# MEASUREMENT AND TRAINING OF DUAL-TASK OF GAIT IN PERSONS WITH MULTIPLE SCLEROSIS

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# DEDICATION

For God,

who gave me the strength and perseverance to complete this work.

For my parents,

who in their own way have always supported on the path I have set for myself.

For my family,

who have constantly encouraged and supported me throughout this journey.

For my all my friends,

who have been fundamental in maintaining my sanity throughout this whole experience.

And for those who I hold closest to my heart,

whose unwavering presence and love have made everything worthwhile.

And my deepest gratitude,

for those who live and battle daily with multiple sclerosis,

for your steadfast strength.

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ABSTRACT

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MEASUREMENT AND TRAINING OF DUAL-TASK OF GAIT
IN PERSONS WITH MULTIPLE SCLEROSIS

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Individuals with multiple sclerosis (MS) present with a wide variability of motor, sensory, and cognitive symptoms that affect their ability to engage in and perform their daily activities. Walking is a motor task that is known to be widely affected by the symptoms of MS and individuals with MS demonstrate difficulties with their ability to ambulate even early on in their disease process. Although it is broadly accepted that walking is heavily influenced by motor and sensory symptoms, recent studies in the area of cognitive-motor interference have identified a relationship between cognitive functioning and motor performance in individuals with MS. The concurrent performance of a motor and cognitive task (dual-task) has been found to adversely affect the gait mechanics of individuals with MS, effectually increasing their risk for falling.

Physical therapists often rely on outcome measures to help quantify an individual's physical performance; however, there is a lack of a standardized dual-task outcome measure that not only measures overall dual-task performance but also measures the single-task performance of the motor and cognitive task. The modified Walking and Remembering Test (mWART) is one such dual-task outcome measure that quantifies dual-task performance relative to the single-task performance of the motor and the cognitive task. Additionally, the mWART adjusts the difficulty of the dual-task cognitive task relative to the individual's single-task cognitive performance.

As we continue to improve our understanding of the underlying mechanisms of cognitive-motor interference and the anatomical correlates of dual-task performance, studies have

emerged to study methods by which we can improve dual-task ability. Although there has been a substantial growth of research in individuals with Parkinson disease, stroke, or dementia, more studies are needed, especially in individuals with MS.

Three studies comprise this dissertation. The first study determined the test-retest reliability and discriminant validity of the mWART. The second study assessed the feasibility and effects of a 6-week gait-specific dual-task training intervention on gait velocity, cadence, and step length. Finally, the third study evaluated the effects of the training intervention on walking capacity, self-perceived walking ability, and subjective fatigue. The participants were tested on 2 separate days to collect the average baseline data for Study One and Study Two. Participants were randomly allocated to a 6-week dual-task training group or a 6-week single-task training group for Study Two and Study Three.

Study One results revealed good to excellent test-retest reliability of the mWART for single-task gait velocity ($ICC_{2,k}$ = .961, $p$ < .001), dual-task gait velocity ($ICC_{2,k}$ = .968, $p$ < .001), and single-task digit span recall ($ICC_{2,k}$ = .829, $p$ = .004) for individuals with MS. The mWART was also able to discriminate based on single-task gait velocity ($p$ = .001) and dual-task gait velocity ($p$ = .002) between individuals with MS and without MS. To assess spatiotemporal gait parameters, the Protokinetics ZenoWalkway was used to quantify gait velocity, cadence, and step length in response to the gait-specific dual-task training intervention. Results from the second study revealed that the dual-task training intervention elicited clinically significant improvements in single-task (18.6% improvement) and dual-task gait velocity (13.0% improvement) at post intervention. The dual-task group was the only group able to demonstrate significantly different changes in single-task gait velocity at both post-intervention ($p$ = .018) and follow-up ($p$ = .042). Observationally, the results also suggest that dual-task training supports more robust changes in dual-task performance (3.5% or less change at follow-up compared to post-intervention). The results from the final study revealed clinically meaningful improvements in walking capacity ($p$ = .007, partial $\eta^2$ = .505) and self-perceived walking ability ($p$ = .009, partial $\eta^2$ = .345) following the dual-task training intervention despite there being no significant changes in subjective fatigue.

The overall results indicate the mWART is a valid and reliable clinical measure of dual-task performance in individuals with MS. Additionally, the gait-specific dual-task training intervention detailed within is effective in improve single-task and dual-task performance in individuals with MS and can serve as a framework from which clinicians may initiate dual-task training for their patients with MS.

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# CHAPTER I

# INTRODUCTION

## INTRODUCTION

The relationship between cognition and mobility in persons with neurological conditions has sparked interest in the study of cognitive-motor interference as it relates to balance and gait. Cognitive-motor interference can be observed as a deterioration of motor performance in the presence of a concurrently performed cognitive task. This decline in motor or cognitive performance is known as the dual-task effect or cost (DTC).[1] Considering both the high prevalence of cognitive dysfunction in individuals with multiple sclerosis (MS),[2-4] as well as the persistent mobility difficulties they experience,[5-7] the performance of an everyday motor task such as walking is significantly impacted in the presence of a cognitive task. The demands placed on cognitive resources by both a motor and cognitive task concurrently have been shown to increase gait variability in those with neurological disorders.[8,9] Previous studies have associated the extent of cognitive-motor interference to postural instability,[10,11] gait dysfunction,[12-20] and increased fall risk[12,21-23] in those with MS.

Regardless of the clinical presentation of MS, neuropsychological studies in individuals with MS cite prevalence rates of cognitive dysfunction up to 65%,[2-4] adversely impacting one's daily activities,[24] social functioning,[24,25] employment,[24-26] interpersonal relationships,[24,25,27] mood,[27] general life satisfaction and quality of life.[26-28] While gait impairment has been greatly attributed to MS symptoms such as muscle weakness, pain, spasticity, sensory and visual disturbances, and fatigue,[5,6,29,30] research within the last decade has linked cognitive dysfunction to motor impairments in balance and gait.[1,10-16,18,20,22,31] These studies show that cognitive dysfunction, especially involving information processing efficiency (working memory and processing speed), attention, and executive function, contributes to deficits noted in dual-task walking and increased fall risk. Moreover, these studies have found that cognitive-motor dual-task impacts specific gait parameters, such as speed, step length, cadence, double limb support time, and swing time variability, which are associated with fall risk.

Despite the known prevalence of cognitive-motor interference in persons with neurological conditions and MS, the few existing clinical measures of dual-task performance lack standardization and possess inherent limitations for use in persons with MS. The Stops When Walking Test (SWWT),[32-34] Walking While Talking Test (WWTT),[34-37] and Timed Up-and-Go cognitive (TUG-cog)[38,39] are all clinical tests of dual-task performance, but do not account for the relationship between the relative difficulty of the cognitive task and the individual's cognitive capacity. Additionally, education, literacy levels, and language difficulties would greatly influence the performance and outcomes of these types of tests.[40,41] Equally essential to consider is the verbal component used by current measures of dual-task without considering the structural interference that speech articulation may additionally have on cognitive demands.[40]

Recommendations have been proposed to adjust the level of dual-task difficulty relative to the person's single-task ability.[40] One proposed cognitive task is the use of a titrated digit span for single-task cognitive and dual-task conditions. The Walking and Remembering Test (WART) is a clinical measure initially developed for use in older individuals and later used for those with brain injury.[34,41] The titrated forward digit span included in the measure is tailored to the individual's baseline working memory function (a part of executive function), which is characteristically impaired in persons with MS and is associated with motor performance.[42-44] The WART provides several benefits over other clinical measures, including a cognitive task tailored to baseline performance, use of readily available equipment, the straightforward judgment of accuracy, and the absence of articulation, preventing pacing of walking, or an additive cognitive load.[41] Furthermore, the WART requires the participant to walk at his or her fastest walking speed, providing a sufficiently difficult motor task that could compete with cognitive demands. Inter-rater and test-retest reliability and the preliminary construct validity of the WART have been established in community-dwelling older adults[41]; however, its utility and psychometric properties have not been established for use in persons with MS.

Although promising studies exploring the effectiveness of dual-task interventions in other populations exist,[9] eg, Parkinson's disease (PD), older adults, and stroke, there is a paucity of studies in MS despite the prevalence of cognitive-motor interference in this population.[45,46] Most notably, no published dual-task intervention studies were found that specifically trains only the dual-task gait of individuals with MS. In other populations such as PD, dual-task training has been found to improve gait velocity and step length, as well as gait variability, which is related to fall risk.[9,47,48] These studies suggest that dual-task training is safe and feasible. Unfortunately, too many uncertainties remain, and the existing studies are too heterogeneous to reliably replicate or generalize to different neurological populations.

In a study by Evans et al, the authors examined the effects of a 5-week dual-task intervention in persons with traumatic brain injury and stroke.[49] Although there was a significant effect of the intervention in their sample, the interventions were non-standardized and insufficiently described to replicate reliably. Additionally, the specific dual-task measures they used may have been too cumbersome to administer and score. In a randomized control trial by Schwenk et al, a specific exercise program was effective in improving dual-task performance in older individuals with dementia.[50] However, multiple intervention modalities were implemented, including different aerobic and resistance training regimens, dance, balance training, and throwing or catching a ball. Additionally, there was no true standardization or progression of cognitive tasks during dual-task training. The use of mixed group and individualized training schemes further complicated replication of the study, as well as confounding the results obtained by the authors. The authors noted that the changes in outcomes observed may not be clinically meaningful. Another study in older adults was presented with similar difficulties: non-standardized interventions and measurement tools, contributing to limited reproducibility and reliability of results.[51]

A detailed pilot study by Yogev-Seligmann et al (n = 7) sought to evaluate the feasibility of a dual-task training intervention specific to gait,[47] which has differed from other dual-task training interventions in the literature which have incorporated multiple modalities. The study's 4-week-long program consisted of training three times per week with a total of 25 minutes of walking time in each session (separated into 5 blocks of 5 minutes each). Verbal fluency, serial subtraction, and information processing tasks were randomized during each block. The authors observed improvements retained 1-month later in both gait speed and gait variability, and transfer effects to a non-trained dual-task condition. However, considering the small sample size of this study, results should be interpreted cautiously. Given that persons with MS also have both motor and cognitive impairments, the dual-task intervention protocol developed by Yogev-Seligmann et al could be easily adapted for use in persons with MS.

**PURPOSE**

The purpose of this research investigation was to assess the feasibility of a dual-task training intervention for gait in persons with MS. This investigation utilized 3 separate studies. The first study evaluated the psychometric properties of the modified WART for use in individuals in MS. The second study assessed the effects of a specific dual-task intervention on gait and dual-task performance and whether different disability levels respond differently to the intervention. The third study evaluated the dual-task intervention's effect on walking capacity, self-perceived walking ability, and fatigue.

## STUDY ONE

## RELIABILITY AND VALIDITY OF THE MODIFIED WALKING AND REMEMBERING TEST IN PERSONS WITH MULTIPLE SCLEROSIS

### Specific Aims and Hypotheses

This study aimed to assess the test-retest reliability and discriminant validity of the modified WART (mWART) in individuals with MS. The hypothesis was that the mWART would demonstrate adequate stability over time ($ICC_{2,k}$ > 0.75) and would be able to detect dual-task cost performance.

### Participants

A convenience sample of up to 40 healthy adults and 40 adults with MS (ages 18 to 65 years) was used in the study. Inclusion criteria for both groups included (1) ability to read, speak, and understand English, (2) ability to walk independently with or without an assistive device, (3) independent community-dwelling, (4) no history or presence of other clinically significant musculoskeletal, cardiovascular, respiratory, or neurologic disease. Individuals with MS were required to have a definite diagnosis of MS [Expanded Disability Status Scale (EDSS) ≤6.5], be relapse-free for the past 30 days, and not currently receiving or planning to receive any rehabilitation services during the study. Participants were provided the option to participate or not participate in this and subsequent studies. Participants who experienced a true relapse or exacerbation of their symptoms (>24 hours duration in the absence of infection or fever, or an ambient increase in body temperature) during the study were excluded from the study.

Additionally, participants were asked not to start any new medications specifically targeting gait or fatigue (eg, antispasmodics, potassium-channel blockers, or wakefulness-promoting agents) while enrolled in the study. If participants were already taking such medications, they were asked not to change dosages for the duration of the study.

**Instrumentation**

**EDSS.** The EDSS was initially developed to measure the disability status of persons with MS and has been modified several times to reflect the levels of disability clinically observed more accurately. The EDSS provides a total score from 0 to 10 with 0 indicating a normal neurological exam and 10 indicating death due to MS. Gait and functional systems scores determine the total score on the EDSS. Different levels of disability were defined as follows: mild (EDSS 2.0-3.5), moderate (EDSS 4.0-5.5), and severe (EDSS 6.0-6.5).[16]

**Montreal Cognitive Assessment.** The Montreal Cognitive Assessment (MoCA) screens for mild cognitive dysfunction in older adults and neurological populations. Its construct validity has been established for use in individuals with MS, significantly correlating to neuropsychological measures of learning, delayed recall, executive functioning, and information processing.[52-54] The tool assesses short-term memory, visuospatial abilities, executive functions, attention, concentration, working memory, language, and orientation. It has been found to be more sensitive than the Mini-Mental Status Exam (MMSE) and have a higher ceiling effect than the MMSE.[52-54] A cut-off score of <26 was used to classify those with cognitive impairment.[53]

**WART.** The WART is comprised of 3 distinct tasks: single-task fast walk, single-task cognitive task, and dual-task condition.[41] The titrated forward digit span included in the WART is tailored to the individual's baseline working memory function, which is a component of information processing efficiency and executive function.[42,43] Working memory is characteristically impaired in persons with MS and associated with motor performance changes.[42,43] The mWART eliminates path deviation assessment.[34] The WART requires a stopwatch, cones, tape, and an obstacle-free corridor.

The WART has been validated for use in older adults, and the tool was found to detect dual-task changes in community-dwelling older adults and those with acquired brain injury.[41] It has excellent inter-rater reliability ($ICC_{2,1} \geq 0.97$) for walking time, and digit span accuracy and test-retest reliability is good ($ICC_{2,1} \geq 0.79$). In the study, older adults were slower and remembered shorter digit spans than younger, healthy adults, and demonstrated greater dual-task costs for digit span accuracy.[41] However, due to the higher level of functioning of the older adults included in the study, relative dual-task costs for walking time were not significantly different between the older adult and younger adult groups.[41]

**ProtoKinetics Zeno Walkway.** The ProtoKinetics Zeno Walkway is a pressure-sensitive electronic walkway previously used in individuals with MS to detect and collect pressure data for balance and gait assessments.[55-58] The device and software calculates the center of pressure trajectories and is a reliable and valid tool for measuring spatiotemporal gait parameters (eg, gait velocity, cadence, step length, and double limb support time) based on footfalls.[55]

**Procedures**

Participants attended 2 testing sessions separated by at least 1 week, but no more than 2 weeks. Each session lasted no more than 60 minutes. After screening, intake, and administration of the MoCA by the principal investigator, participants completed the mWART. All testing was performed by a physical therapist in a well-lit, obstacle-free, and level walkway. The Zeno Walkway was placed in the middle of the 10-meter walkway to measure gait velocity. After screening and intake by the examiner, participants completed the mWART, which was scored by the examiner. The participants completed a total of 5 walking trials per baseline assessment session. Ninety-second seated rest breaks and guarding of each participant were provided to ensure the participant's safety. For the practice walking trial, participants were asked to walk at their self-selected comfortable walking speed.

For the single-task walking condition, participants were asked to walk at their fastest possible walking speed along the designated walkway for 2 trials. Gait velocity and time to complete both trials were recorded and averaged to obtain the mean single-task gait velocity. The participant was then allowed to sit in preparation for the digit span testing of the mWART. A digit span is a random sequence of numbers used to measure working memory capacity and requires the participants to repeat a series of digits of increasing length. Included in the mWART are 6 pairs of unique digit spans. Each digit span is a standardized random number sequence starting at a length of four digits, and the length of the digit spans increase by 1 digit in each subsequent pair for a possible 9 digits in the final pair. The participants were then informed that they may use any method except writing or talking to help them remember the numbers. The examiner verbally provided the digit span from the first pair to the participant, and after a delay equivalent to the time it took the participant to walk in the single-task walking condition, the examiner cued the participant to repeat the numbers back to the examiner. The examiner then repeated this process for each subsequent digit span until the participant was only able to recall 1 trial of a digit span correctly from a pair. For example, if the participant was able to correctly recall with 100% accuracy only the first digit span in the fourth pair (7 digits in length), but not the second digit span in that pair, then the digit span testing was stopped. The longest digit span correct for at least 1 trial was used to determine the length of the unique digit span for the dual-task condition and considered 100% correct in assessing cognitive errors.[59]

For the dual-task walking condition, the participant was verbally provided a random digit span equal in length to that found in the digit span testing. The examiner then immediately cued the participant to walk at his or her fastest speed. At the end of the walking trail, the examiner cued the participant to repeat the numbers back to the examiner. Similar to the digit span testing, participants were informed beforehand that they may use any method to remember the numbers, except saying them out loud. Two trials were performed and both gait velocity and digit span accuracy were recorded and averaged by the examiner for both of the trials.

**Data Analysis**

Intra-class correlation coefficients ($ICC_{2,k}$) was calculated to evaluate test-retest reliability of gait velocity and digit span accuracy. ICC values of >0.9 were considered excellent reliability, 0.75-0.90 good reliability, 0.5-0.75 moderate reliability, and values less than 0.5 indicate poor reliability.[60]

Relative dual-task costs (%DTC) were calculated for gait velocity and digit span recall using the following formula[14]: $\%\mathrm{DTC} = \frac{(Single\ Task - Dual\ Task)}{Single\ Task} \times 100$. A %DTC value of greater or less than 0 for gait velocity represented a relative dual-task cost. A %DTC value of greater than 0 for digit span recall represented relative dual-task cost indicating a digit span accuracy of <100%.

To assess discriminant validity, separate mixed-model analysis of variance (ANOVA) with factors of time or condition (test-retest) and group (non-MS vs. MS) were conducted for gait velocity and digit span accuracy. Separate binomial logistic regressions were then performed to determine if gait velocity and digit span performance in single- and dual-task conditions were able to predict group membership. As a secondary analysis, separate mixed-model ANOVAs were performed to compare %DTC for gait velocity and digit span accuracy amongst different EDSS levels: mild (EDSS 2.0-3.5), moderate (EDSS 4.0-5.5), and severe (EDSS 6.0-6.5).[16] All tests utilized a significance level of $\alpha = .05$.

## STUDY TWO

## EFFECTS OF GAIT-SPECIFIC DUAL-TASK TRAINING FOR INDIVIDUALS WITH MULTIPLE SCLEROSIS

### Specific Aims and Hypotheses

The first aim of Study Two was to investigate the feasibility and effects of a 6-week gait-specific dual-task training intervention on both single-task and dual-task gait performance. The second aim was to investigate whether single-task or dual-task training improves cognitive performance on the mWART. The first hypothesis was that there will be a difference after the intervention in single-task and dual-task performance of gait at a significance level of 0.05. The second hypothesis was that there will be a greater effect of the dual-task intervention on cognitive performance over the single-task intervention.

### Participants

A sample of up to 20 persons with MS who participated in Study One was used in Study Two.

### Instrumentation

The Borg Rating of Perceived Exertion (RPE) and visual analog scale for fatigue (VAS-F), pulse oximeter, and blood pressure monitor was be used in Study Two. Additionally, the mWART and the Zeno Walkway was used for assessment. An mp3 player and headphones was used for the intervention to provide dual-task prompts to the participants.

### Procedures

Participants were randomized into 2 groups: dual-task group (DT) and single-task group (ST). Both groups underwent a 6-week-long intervention program consisting of 1-on-1 gait training sessions 3 days per week for 18 total sessions (see Figure 1). Each session was led by a licensed physical therapist with experience in treating individuals with MS. Each training session consisted of 5 different training blocks with each block consisting of four minutes of total gait training time for an entire session walking time of 20 minutes. Each block was then further divided into 2 gait training bouts with 2-minute rests between each bout. Participants were instructed to walk at a self-selected gait speed they could maintain for each 2-minute bout. The ST group was asked to focus on gait performance and walk without any distractors of music, talking, or reading during all bouts. ST group participants were provided with feedback regarding their performance after each bout. In addition to gait training, participants in the DT group performed a randomly selected cognitive task for each bout (6 hours total of DT-specific practice).[61] For each block with the DT group, participants were asked to prioritize either their gait performance or cognitive performance.  For gait-prioritized blocks and the ST group participants, feedback such as "larger steps" or "stand taller" may have been provided. For cognitive-prioritized blocks, feedback such as "try to say more words than last time" or "try to answer more accurately and faster this time" may have also been provided.

| **Dual-Task Training** | **Block 1** | **Block 2** | **Block 3** | **Block 4** | **Block 5** |
|---|---|---|---|---|---|
| Total walk time | 4 min | 4 min | 4 min | 4 min | 4 min |
| Walking sets | 2x2 min bouts<br>2 min rest | 2x2 min bouts<br>2 min rest | 2x2 min bouts<br>2 min rest | 2x2 min bouts<br>2 min rest | 2x2 min bouts<br>2 min rest |
| Task prioritization | None | Gait | Cognitive | Gait | Cognitive |
| Cognitive tasks | Three cognitive tasks randomized within each block:<br>• Serial subtraction by threes<br>• Verbal/phonemic fluency<br>• Simple arithmetic problem with *n*-back task (*n* = 1) | | | | |

**Figure 1.** Dual-task training protocol.

The cognitive tasks incorporated into the DT group intervention targets cognitive domains shown to be impaired in individuals with MS and have been previously described as eliciting cognitive-motor interference in persons with neurological impairment.[2] These include serial subtraction by 3, verbal fluency, and simple arithmetic problems with an n-back task. For serial subtraction by 3, participants verbally performed serial subtraction from a randomly generated 3-digit number by 3. For verbal fluency, participants were tasked to verbalize as many words as possible that begin with a randomly generated letter every 30 seconds. For the simple arithmetic problem task, the participants were asked to solve a series of simple arithmetic problems provided at intervals of 2 seconds and verbalize if their response was larger or smaller than their previous response.

Two-minute rest breaks were initially provided between each bout and were subsequently reduced by 30 seconds every 2 weeks until a 1-minute rest break was achieved during weeks 5 and 6 of the intervention period. After each bout, all participants reported their perceived fatigue on the visual analog scale-fatigue and effort on RPE. Blood pressure was obtained before and after each session. Heart rate was obtained after each walking bout to ensure participants were exercising within acceptable limits; ie, RPE of 11-15, blood pressure under 170/100, and heart rate within 40-60% of heart rate reserve (heart rate reserve = maximum heart rate – resting heart rate).

**Data Analysis**

Descriptive statistics were calculated for primary and secondary outcome variables with percent change ($\Delta x$%) to be reported from pre to post and post to follow-up. Friedman analysis of variance tests were conducted to determine if there were differences in gait velocity, step length, and cadence during a 6-week training program. Pairwise comparisons were performed with a Bonferroni correction for multiple comparisons. Mann-Whitney tests were performed to determine if there were any differences between groups for each time period. A significance level of .05 was set for all tests.

Relative dual-task costs (%DTC)[14] were computed for primary and secondary outcomes to assess performance changes between single-task and dual-task walking conditions. Relative dual-task costs (%DTC) were also calculated using the following formula[14]:

$$\%\mathrm{DTC} = \frac{(Single\ Task - Dual\ Task)}{Single\ Task} \times 100.$$

A %DTC value of greater or less than 0 for gait outcomes represented a relative dual-task cost. A %DTC value of greater than 0 for digit span recall represented relative dual-task cost indicating a digit span accuracy of <100%. A positive %DTC indicated a decrement in performance during the dual-task condition as compared to the single-task condition, while a negative %DTC indicated an improvement in performance during the dual-task condition over the single-task condition.

**STUDY THREE**

**EFFECTS OF A GAIT-SPECIFIC DUAL-TASK TRAINING INTERVENTION ON WALKING CAPACITY AND SELF-PERCEIVED WALKING ABILITY IN PERSONS WITH MULTIPLE SCLEROSIS**

**Specific Aims and Hypotheses**

The primary aim of Study Three was to investigate the effect of a dual-task training program on the walking capacity and ability of individuals with MS as measured by the 2-minute walk test (2MWT) and the 12-Item Multiple Sclerosis Walking Scale (MSWS-12). The second aim was to investigate whether participants experienced improvements in fatigue after the dual-task training program, as measured by the Fatigue Scale for Motor and Cognitive Functions (FSMC). The first hypothesis was that there would be a difference in distance walked on the

2MWT and scores on the MSWS-12 within and between groups at the end of the intervention at a significance level of 0.05. The secondary hypothesis was that there would be a difference in fatigue levels on the FSMC within and between groups at the end of the intervention at a significance level of 0.05.

**Participants**

The participants in Study Two were the same participants for Study Three.

**Instrumentation**

**2MWT.** The 2MWT assesses walking capacity and endurance over a 2-minute period. The test is performed at the fastest possible speed with the option to use an assistive device. Compared to the 6-minute walk test (6MWT), the 2MWT has been found to be less burdensome for persons with MS, especially those with higher EDSS levels.[62,63] The 2MWT is highly correlated with the 6MWT ($R^2 = 0.97$), and in terms of walking distance at 1-minute intervals, there was no significant difference between the 2 tests ($p = 0.82$).[62,63] The 2MWT eliminates the redundancy of the last 4 minutes of the 6MWT and better predicts community ambulation in persons with MS than the Timed 25-Foot Walk Test or 10-meter Walk Test.[62,63]

**MSWS-12.** The MSWS-12 is a 12-item self-report measure of the impact of MS on one's walking ability.[64] It includes questions regarding the amount of support needed to walk, distance able to walk, speed of walking, and concentration required while walking. It demonstrates both excellent validity and reliability and adequate to excellent floor and ceiling effects.[64-66] A cut-off of 75 or greater had a sensitivity of 52 and specificity of 82 in predicting fallers vs. non-fallers.[67]

**FSMC.** The FSMC is a self-report outcome measure for measuring physical and mental fatigue in patients with MS. Both motor and mental subscales have shown good reliability, sensitivity, and specificity, and has been highly intercorrelated with the Modified Fatigue Inventory (MFIS) and Fatigue Severity Scales (FSS).[68] However, the FSMC has demonstrated superior sensitivity and specificity over the MFIS and FSS in persons with MS.[68] The cut-off values provided for identifying mild, moderate, and severe fatigue provide clinicians with the ability to grade fatigue over time.[68]

**Procedures**

The procedures of Study Three was the same as Study Two. 2MWT distances, MSWS-12 scores, and FSMC scores were concurrently collected during Study Two.

**Data Analysis**

For the primary aim, 2 separate mixed-design ANOVAs were be performed for walking distance (meters) on the 2MWT and total score on the MSWS-12 with group (2 levels) and time (4 levels). For the secondary aim, another mixed-design ANOVA was performed for FSMC scores with group (2 levels) and time (4 levels). Primary outcomes were further analyzed with separate mixed-models analyses of covariance for mid-intervention and post-intervention with condition as the between-subjects factor and pre-intervention scores as covariates. A significance level of .05 was set for all tests.

CHAPTER II

REVIEW OF LITERATURE

**INTRODUCTION**

MS is a chronic and progressive demyelinating disease of the central nervous system (CNS), characterized by both inflammatory and neurodegenerative processes.[1-4] In the United States, MS is the most common cause of non-traumatic neurological disability in young adults, with a peak incidence at around 30 years of age.[4-6] In 2017, the estimated prevalence of MS in the United States was 362 cases per 100 000 people, or 913 925 adults,[5] and more than 2.5 million individuals worldwide.[6] Although there is a higher prevalence in those of Northern European ancestry, a higher incidence exists within the African American population.[6] Women are also more affected than men, with a ratio approaching 3:1.[5,6]

MS is characterized by the presence of widespread lesions in the brain and spinal cord, disseminated both temporally and spatially.[2,7] These lesions affect the myelin sheath surrounding the axons of nerve fibers, culminating in the disruption of axonal transmissions and eventual transection of axons. Although the etiology of MS remains unclear, the inflammatory and demyelinating process remains a hallmark feature of MS early in the disease process with neurodegenerative processes manifesting once the compensatory capacity of the CNS is exhausted.[2-4,8] The resulting heterogeneity in MS symptomatology encompasses motor, sensory, cognitive, and neuropsychiatric domains.

Neuropsychological studies on cognitive dysfunction in individuals with MS cite prevalence rates of up to 65%.[9] A study by Rao et al[9] found a cognitive dysfunction prevalence rate of 43% in community-dwelling individuals with MS after controlling for recruitment bias in previous clinic-based studies. With studies citing such high rates of cognitive dysfunction in individuals with MS, recognizing and addressing the impact of cognitive dysfunction on the functioning of individuals with MS throughout their continued care becomes ever more critical. Cognitive dysfunction has direct and indirect adverse effects on the ability of an individual to perform his or her activities of daily living and social and occupational roles.[9-12] Moreover, cognitive dysfunction has is found to be related to poorer physical functioning in individuals with MS.[13,14] Increasing evidence points towards the negative impact that cognitive dysfunction has on an individual's mood, general life satisfaction, and quality of life.[13,15-17]

Up to 90% of individuals with MS report difficulty with mobility and cite that walking impairment is often one of the most disabling symptoms of MS.[15,18] Traditionally, balance and gait dysfunction have been attributed to the loss of neuromuscular function, manifesting in such symptoms as muscle weakness, hypertonicity, spasticity, pain, sensory disturbance, and fatigue.[19-21] However, emerging evidence within the MS literature has begun to establish the relationship between cognitive impairment and mobility, specifically gait.[22] This interaction between cognitive and motor performance is detailed extensively within the dual-task literature in various patient populations.[23-52] This phenomenon of cognitive-motor interference occurs when the simultaneous performance of a cognitive and motor task (dual-task) results in the deterioration of performance in one or both of the tasks, relative to single-task performance.[53] The concept of cognitive-motor dual-tasking is highly relevant to everyday living, as individuals rarely perform only one task at a time (eg, walking while talking, walking while remembering, walking while reading, etc). Consequently, the diminished capacity to dual-task, especially in an open environment such as the community setting, may lead to limitations in mobility, activities, and community-level participation.

The purposes of this literature review are to describe the nature and prevalence of motor and cognitive dysfunction in individuals with MS, describe the current literature examining the relationship between cognitive dysfunction and motor performance within the dual-task paradigm, describe how dual-task cost is clinically measured, and discuss current interventions aimed at improving dual-task ability in individuals with MS.

**PATHOPHYSIOLOGY OF MS**

The pathophysiological process of MS contributes to a heterogeneous clinical picture with symptoms encompassing multiple domains. Classically, MS is characterized by an acute, high inflammatory stage followed by a progressive neurodegenerative stage. The pathological process of MS involves the breakdown of the blood-brain barrier, multifocal inflammation, demyelination, oligodendrocyte loss, reactive gliosis, and axonal degeneration.[1-3] Individual variations in areas of inflammation and axonal damage exist and impact the variability in sensorimotor and cognitive symptomatology. However, with recent advances in magnetic resonance imaging (MRI) and developments in our understanding of immune and neurobiological processes, our knowledge of the pathogenesis of MS has similarly expanded. Multiple factors, such as genetic components, environmental factors, and more recently, the human microbiome, have been proposed to explain the pathogenesis and pathological process of MS.[1-3]

MS has been proposed as a dysimmune or autoimmune disease process, in which the disease develops from the autoimmune activation against specific CNS antigens.[1-3] This dysimmune process involves activation of specific T cells (CD4+ and CD8+ T cells), white blood cells that play an essential role in the adaptive immune system. These particular T cells become primed against myelin-specific antigens and components, and from this immune-dependent mechanism of damage, axonal demyelination within the central nervous system ensues.[1-3,54]

Numerous studies hypothesize that the exposure to specific pathogens (eg, Epstein-Barr virus, measles, human herpesvirus-6, etc) may induce myelin-reactive pathogenic T cells.[1-3] This phenomenon of cross-reactivity or "molecular mimicry" with CNS myelin antigens may trigger a faulty autoimmune response, which leads to myelin degradation. Recent evidence points towards both cell-mediated and humoral immunity in MS disease pathology as evidenced by clonal expansion of both T and B cells.[54] This role of humoral immunity in MS pathology may also partly explain why immunosuppressive therapies targeting B cell function and proliferation are successful in treating patients with relapsing and progressive forms of MS.[54]

**Clinical Courses of Multiple Sclerosis**

There are four widely accepted clinical phenotypes of MS: relapsing-remitting MS (RR-MS), secondary-progressive MS (SP-MS), primary-progressive MS (PP-MS), and relapsing-progressive MS (RP-MS). In more recent years, disease modifiers ("active/not active" and "active/not active with/without progression") were developed to facilitate the description and improve the specificity of the previously developed broad classification scheme.[55] Generally, these clinical phenotypes comprise a 3-stage process: (1) a pre-clinical stage in which the disease process is triggered, (2) a highly active, but self-limiting inflammatory clinical stage characterized by neurological dysfunction affecting motor, sensory, and cognitive functions, and (3) a progressive clinical stage in which there is continued neurological decline with the individual with MS experiencing gradual worsening of his or her symptoms (see Figure 2).[1]

Although more recent epidemiological studies in MS are showing shifts in the prevalence of the different clinical courses of MS, it is widely accepted that approximately 85% of individuals with MS are diagnosed with RR-MS.[4] RR-MS is characterized by active lesions which manifest clinical symptoms and neurological disability. These relapses in RR-MS usually resolve with time or with pharmacological intervention, and the individual with MS may return to a pre-relapse clinical level or sustain some extent of residual deficits (see Figure 3A). These acute lesions lead to the transection of axons within the deep gray matter and white matter of the brain and spinal cord.[1-3] Axonal loss occurs at the onset of disease and continues throughout the disease process. This continued axonal loss along with other factors contribute to the transition of RR-MS to SP-MS when the CNS exhausts its ability to compensate for neuronal loss.[1-3] Epidemiological studies have shown that 50% of individuals with RR-MS convert to SP-MS within 10 years of diagnosis and 90% convert to SP-MS within 25 years of diagnosis.[4]

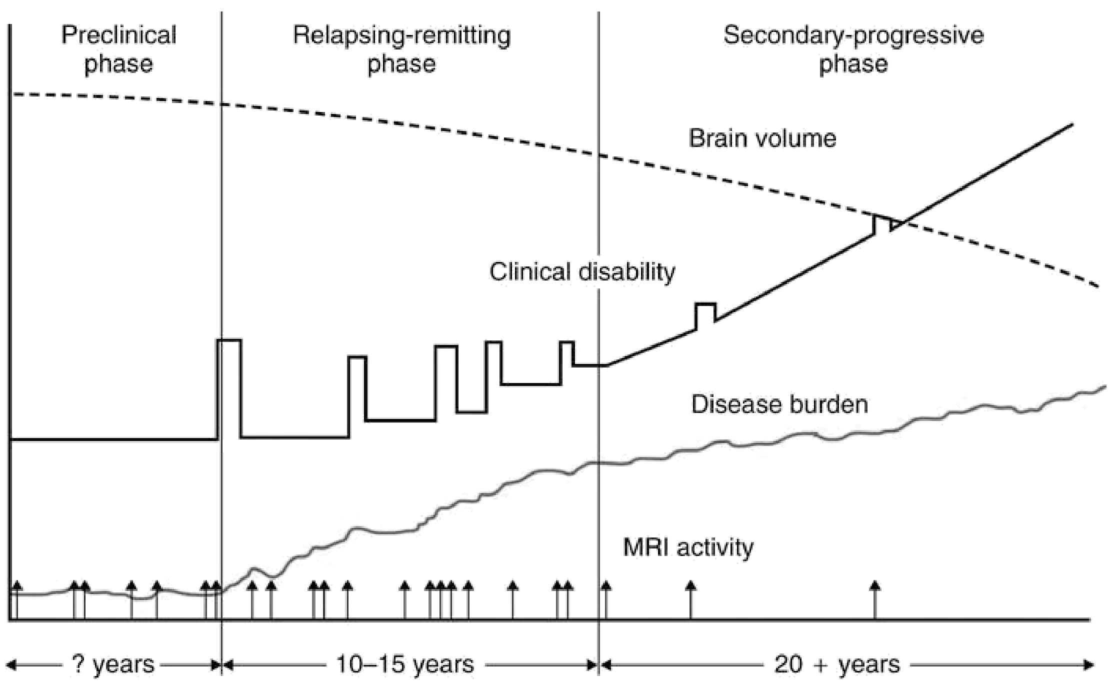


**Figure 2.** The natural history of relapsing-remitting MS.

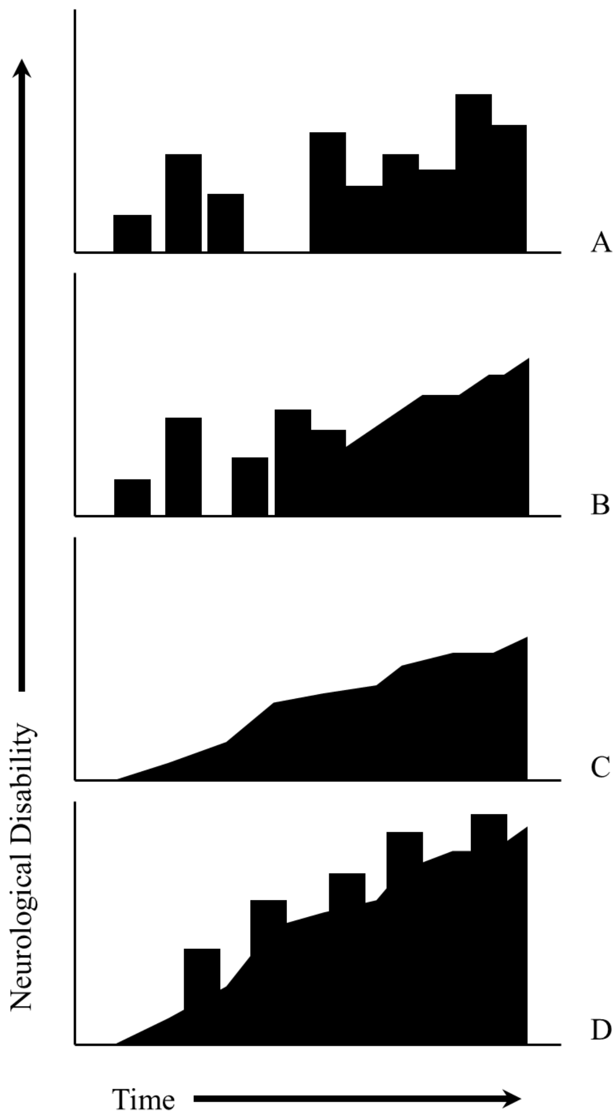


**Figure 3.** Clinical Courses of MS. (A) relapsing-remitting MS, (B) secondary-progressive MS, (C) primary-progressive MS, (D) progressive-relapsing MS.

In contrast to RR-MS, SP-MS is characterized by chronic lesions and significant cortical atrophy. Unlike RR-MS, a high inflammatory process and active lesions are rare in SP-MS, and instead, progressive neurological disability is a clinical hallmark of SP-MS (see Figure 3B). Relapses in this stage are not clinically apparent and typically occur at a subclinical level. This neurodegenerative stage of an initial relapsing course of MS is attributed to several factors and changes identified in individuals with MS, including chronic smoldering inflammation, microglial activation and infiltrate, ion channel dysfunction, energetic failure, hypoxic injury, glutamate excitotoxicity, mitochondrial dysfunction, oxidative injury, and neuronal loss by apoptosis and necrosis.[3,56] The pathological process of SP-MS shares these very same immune-independent mechanisms of CNS damage with PP-MS.

In contrast to SP-MS, a progressive decline from disease onset is the characteristic hallmark of PP-MS. Approximately 10% of individuals diagnosed with have PP-MS.[4] In this particular clinical course, relapses are not clinically apparent, and the individual characteristically follows a course of gradual neurological and functional decline with time (see Figure 3C).[3,57] In 5% of individuals diagnosed with MS, however, their clinical course can be characterized by both relapses and progressive decline at disease onset (PR-MS; see Figure 3D). In most instances of progressive MS, the course is SP-MS, and the individual merely experiences subclinical relapses, though, on some occasions, the disease course does truly begin as a primary progressive disease course (PP-MS).[1]

In comparison to RR-MS, which is characterized by the infiltration of peripheral immune cells into the CNS, progressive MS involves a compartmentalized pathological process in the brain. The pathological process in relapsing MS is primarily driven by a dysfunctional peripheral immune system, while damage to the CNS in progressive MS involves both immune-dependent and immune-independent mechanisms.[1,57] Immune-dependent components of the disease may trigger various disease processes that become self-maintaining and immune-independent.[1-3,57,58] These processes include mitochondrial injury, oxidative stress, ion channel dysfunction, glutamate excitotoxicity, excess intra-axonal calcium, tissue hypoxia, and axonal transport dysfunction.[3,57] These immune-independent mechanisms of progressive MS may partly explain why immunomodulatory treatments for RR-MS are largely ineffective in treating progressive forms of MS.[1]

## OVERVIEW OF MOTOR AND COGNITIVE DYSFUNCTION IN MS

The pathophysiological process of MS leads to lesions in the brain and spinal cord, disseminated both in space and time. The direct and compounded effects of these lesions contribute to the heterogeneous clinical presentation and individual variability in MS symptomatology. Motor and cognitive faculties are both affected in MS, and although individual variability does exist amongst individuals with MS, the development of classifications of these motor and cognitive deficits has permitted the identification and study of MS-related symptom patterns and trends.

### Motor Dysfunction in MS

The North American Research Committee on Multiple Sclerosis (NARCOMS), a multi-national database that collects data from over 35 000 patient volunteers with MS, identified 11 different patient-specific domains commonly affected in MS. The NARCOMS database identifies mobility or gait disability, hand function, fatigue, bladder/bowel function, spasticity, and tremor/discoordination as the principal motor symptoms associated with MS.[18]

**Mobility and Gait Dysfunction.** Individuals with MS rate their walking ability as their most valuable bodily function—with vision rated as their second most valuable bodily function.[59] An evaluation of the NARCOMS database reveals that 35% of individuals with MS experience some extent of gait disability within the first year of diagnosis.[18] An additional 15% of individuals with MS require the use of an assistive device, such as a cane or walker, to safely ambulate.[18] This number reflects the high prevalence of gait dysfunction experienced by individuals with MS early in their disease process, and this prevalence rate rises with disease progression and disease duration. By 15 years post-diagnosis, 84% of individuals with MS will experience gait dysfunction[18]; another study cites prevalence rates of mobility impairments of up to 85%.[19] Moreover, by this 15-year time frame, more than 50% of individuals with MS will require an assistive device to ambulate.[60] It then comes to no surprise that individuals with MS, regardless of disease duration, rate their walking ability as their most valuable bodily function.

Studies investigating gait impairment in MS reveal that individuals with MS generally demonstrate slower gait velocity, shorter step lengths, a wider base of support, greater step time, and greater time in double-limb support compared to individuals without MS.[60] Additionally, individuals with MS demonstrate significant gait variability (the variations in gait parameters between steps), most notably in step length and step time compared to individuals without MS.[60] These variabilities in gait parameters are positively correlated with disability on the Expanded Disability Status Scale (EDSS).[60,61] This observation of gait variability raises clinical concerns, as gait variability has been associated with increased fall risk in several different clinical populations.[62,63]

**Fatigue.** Before the introduction of a taxonomy for fatigue in 2013, the definition of fatigue was heterogeneous, generally conceptualizing a perceived feeling of excessive tiredness or lack of energy that was disproportionate to, or regardless of, the effort exerted.[64] This generalized definition of fatigue created inherent problems in the assessment and treatment of fatigue and fatigue-related symptoms. In 2013, a taxonomy was introduced to better differentiate between the 2 primary dimensions of fatigue: subjective fatigue and objective fatigability.[65] While objective fatigability can be directly measured by an external observer, subjective fatigue typically relies on self-reported measures of fatigue perception.[64]

The exact pathoetiology and pathophysiology of fatigue currently remain unknown; however, multiple factors contribute to both the perception of fatigue and objective fatigability in individuals with MS. The origins of fatigue can be separated into 2 different categories: primary fatigue and secondary fatigue.[66] Primary fatigue is considered a direct result of the pathophysiological processes that accompany MS. These processes include structural changes in white and grey matter, immunological and inflammatory processes, maladaptive network recruitment, functional reorganization of neural circuits, neuroendocrine involvement, and peripheral abnormalities, and metacognition of interoception of dyshomeostatic stress (self-monitoring and self-perception of bodily states, function, and movement).[64,66] Secondary fatigue is a result of variables and processes that occur secondary or tertiary to the pathophysiological process of MS, and these include sleep disorders, reduced physical activity, psychological factors, depression, and other symptoms (eg, pain).[66]

Fatigue is a prevalent symptom of MS, cannot be predicted by measures of neurological impairment, and is independent of clinical course.[67,68] Up to 82% of individuals with MS experience fatigue within their first year of diagnosis, and prevalence rates for fatigue reach up to 94% within 15 years of diagnosis.[18] In individuals who experience fatigue, 40% experience fatigue daily and 60% report that their fatigue worsens their other MS-related symptoms (eg, spasticity, weakness, cognitive function, etc).[67] The importance of recognizing fatigue in those with MS is highlighted by its strong correlation with mental health status, functional mobility status, and general health status.[67,68]

**Spasticity.** Spasticity is a motor disorder that is a velocity-dependent increase in tonic stretch reflexes, characterized by hyperexcitability of the stretch reflex due to loss of central regulatory inhibitory pathways.[69] The location and extent of spasticity vary from individual to individual, depending on the anatomical locations of damage in the central nervous system.[69] More than 50% of those with MS experience some extent of spasticity within their first year of diagnosis. This number increases drastically to 86% within 15 years of diagnosis.[18]

Spasticity can be a functionally disabling symptom of MS, contributing to postural and gait deficits. Specifically, those individuals with MS who have a higher degree of spasticity demonstrate greater levels of postural deficits.[70] Furthermore, spasticity is related to lower levels of mobility, and individuals with MS who have spasticity demonstrate a reduction in gait speed, gait endurance, and self-reported walking ability.[71] Of most concern is the twofold increased risk of falling for those individuals with MS who have spasticity.[72]

**Tremor and Dyscoordination.** More than 48% of individuals with MS experience tremor or coordination difficulties within the first year of their diagnosis, and this prevalence increases to 88% within 15 years of diagnosis.[18] Tremor and coordination deficits are primarily related to focal or multifocal damage to the cerebellum and to the pathways or connections that relay information between the cerebellum and other areas of the central nervous system.[73] Tremors and coordination deficits are related to increased difficulty with both upper extremity, and lower extremity functioning, specifically as these functions relate to the performance of ADLs.[73] Dyscoordination can also adversely affect gait, affecting both inter-limb coordination and multi-joint coordination of the lower extremities during walking.[74] These changes and difficulties with coordinating movements are associated with increased falls and fall risk in those with MS.[75]

### Cognitive Dysfunction in MS

According to the NARCOMS database, within the first year of diagnosis, approximately 63% of individuals with MS experience mild to severe cognitive dysfunction. This data is consistent with past neuropsychological studies that cite prevalence rates of 65%. Although there is a significant prevalence of cognitive dysfunction in those with MS and cognitive functioning is highly relevant to an individual's wellbeing, cognitive dysfunction in MS remains mostly overlooked and often undertreated.[11] Cognitive dysfunction presents as one of the most common, but "invisible" symptoms facing individuals with MS, negatively impacting the ability to perform their activities of daily living and occupational roles, physical functioning, mood, and quality of life.

The domains of cognition most affected in individuals with MS vary by lesion load and individual pathology, contingent upon focal and diffuse brain damage within the white and deep gray matter of the brain. Neuropsychological studies, however, have discovered common areas of cognitive dysfunction in individuals with MS. Memory, information processing efficiency, attention, executive function, and visuospatial skills are all significantly impacted in MS.[11,76,77] Although inconsistencies do exist amongst neuropsychological studies regarding the most affected cognitive domains in MS, there appears to be a consensus that both memory and information processing efficiency are 2 of the most commonly affected cognitive domains in individuals with MS.[9,11,77]

**Memory.** The severity of memory-related deficits in MS varies widely from individual to individual. Research has identified that a staggering 40% to 65% of individuals with MS experience memory impairment during their disease process.[11,77] Further studies regarding the specific areas of memory that are involved in MS are needed, but current studies show that long-term memory appears to be the most affected in individuals with MS. Long-term memory is the ability to learn new information, store it, and recall it at a later time.[11,77] The underlying cause of long-term memory impairment remains unclear but is generally understood to be primarily a dysfunction in the process of initial learning of information.[11,77] Surprisingly, previous studies show that both recall and recognition in individuals with MS are similar to that of healthy individuals without MS after the information has been acquired.[11,77] Individuals with MS, however, require more considerable amounts of repetition of information to reach a learning threshold for appropriate information acquisition.[11] Factors such as poor executive functioning, slow processing speed, susceptibility to interference, and perceptual deficits contribute to this deficit in the initial learning of information.[11] The implications of this distinguishing feature between individuals with MS and without MS may extend to the ability to relearn or acquire motor skills, such as gait.

**Information Processing Efficiency.** More than 50% of individuals with MS present with impaired processing efficiency compared to healthy non-MS controls.[11,78] Information processing efficiency is a result of a multifactorial and complex interaction of multiple cognitive systems. Information processing efficiency refers to the ability of an individual to receive and maintain information (working memory), and subsequently process and respond to that information (information processing speed).[11] The ability to process information is composed of 3 significant steps: (1) the transmission of afferent input, (2) the completion of cognitive tasks, and (3) the creation of motor output.[79] The speed at which these steps need to occur to accomplish a specific task or demand underlies the intrinsic interaction between information processing speed and other cognitive domains, such as working memory, executive functioning, learning, and memory.[79] Individuals with MS demonstrate impaired information processing efficiency, with difficulties noted in both information processing speed and working memory.[11,78,79]. Findings from previous students reveal that as higher demands are placed on the working memory of an individual with MS, the more prominent the deficits in cognitive processes become. These deficits, especially in working memory, are apparent in individuals in the early stages of MS, but those with progressive MS tend to exhibit greater impairments in information processing speed.[11]

An impairment in information processing efficiency typically presents concurrently with other cognitive deficits and is understood to affect the functioning of other cognitive domains.[11,79] For instance, impairments in information processing efficiency (working memory and information processing speed) and visual memory suggest dysfunction in initial learning stemming from delayed processing of information as compared to other factors, such as faulty information retrieval.[11,77,78] This impairment in information processing efficiency also affects motor functioning and mobility. Slower information processing speed is associated with increased gait variability and fall risk in individuals with MS.[80,81] Moreover, information processing speed and working memory seem to be highly associated with attention, impairing performance on both sustained and divided attention tasks.[11]

**Attention.** It has been shown that slower information processing speed has a deleterious effect on attention, particularly sustained and divided attention.[82] Because of attention's role in the initial learning of information, impaired attention has been linked to memory dysfunction.[82] Critically, attention's relationship to memory and executive function (the ability for complex goal-directed behavior and adaption to changing demands) highlights the interrelationship amongst the various cognitive domains affected in MS. Deficits in divided attention, particularly, have been demonstrated with tasks of cognitive-motor interference or dual-tasking, even early in the MS disease process. Impaired divided attention, in turn, has been correlated to increased gait variability and fall risk in individuals with MS.[83]

**Natural History of Cognitive Dysfunction in MS**

There is a common misconception that cognitive dysfunction in MS occurs solely in the later, more advanced stages of the disease process.[10] Although longitudinal and cross-sectional studies find that greater neurological disability and disease duration are factors in the extent of cognitive dysfunction, studies have also identified that even individuals with a sub-clinical course of MS [clinically isolated syndrome (CIS)] and early stage of RR-MS demonstrate some degree of cognitive dysfunction.[10,84] Most importantly, cognitive dysfunction may exist in the absence of neurological or functional disability, as measured by the EDSS. [10,84]

A study in individuals who have relapsing, secondary-progressive, primary progressive, and CIS cites an overall prevalence of 47.5% of cognitive dysfunction.[85] Approximately 27.3% of all individuals with CIS present with some extent of cognitive dysfunction.[85] Specifically, complex attention and information processing speed are found to be the most impaired in individuals with CIS.[76,85] It seems that regardless of the clinical course, in the early stages of the disease process, divided attention and information processing speed are two cognitive domains that demonstrate the most extensive deterioration within the first 6 years of diagnosis.[86] Although cognitive dysfunction may not exhibit a strong relationship between neurological disability and disease duration, the prevalence and neuropsychological profile of cognitive dysfunction may be dependent on the disease course (CIS: 27.3%, RR-MS: 40.0%, PP-MS: 56.5%, SP-MS: 82.8%).[85] Specifically, in a review of 47 studies that included a total of 4460 individuals, those diagnosed with PP-MS consistently exhibited greater cognitive impairment than their RR-MS counterparts.[87] Moreover, this review supports previous findings that neurological disability cannot significantly explain the variance in cognitive impairment.[87]

The methodological heterogeneity of longitudinal studies that have examined the prevalence and progression of cognitive impairment in MS makes it difficult to assess the prognosis of those individuals presenting with cognitive dysfunction. Such limitations include the duration of studies, attrition rates, sampling bias, and small sample sizes. However, findings by Amato et al[76] reveal that in the long-term, progressive neurological and physical disability are directly associated with cognitive decline, suggesting an eventual convergence of both neurological and cognitive impairment. And though the overall rate of cognitive decline may remain stable over time, cognitive dysfunction is largely variable and progressive, with those presenting with cognitive dysfunction early in the disease course exhibiting a greater degree of cognitive deterioration over time.[88] With such prevalence of cognitive dysfunction even in the early stages of MS, cognitive dysfunction has demonstrated large associations with detrimental effects on quality of life and overall mobility in these individuals.

**Cognitive Dysfunction, Quality of Life and Mobility**

**Quality of Life.** Cognitive dysfunction is shown to be associated with health-related quality of life (HRQoL) in individuals with MS.[11-14,17,89] Individuals with MS who have cognitive dysfunction score significantly lower on the Sickness Impact Profile (SIP) than their non-cognitively impaired counterparts.[14] The SIP is a general measure used to evaluate the impact of a particular disease on both the physical and emotional functioning of the individual based on how they are feeling that particular day. Higher scores on the SIP indicate worse health, while lower scores on the SIP indicate better health. Cognition is a significant predictor of physical HRQoL, suggesting that individuals with cognitive dysfunction are less able to engage in meaningful physical activities of daily living, such as recreational activity, social interaction, task completion, and workplace demands. [14] In another study by Hughes and colleagues, the authors conclude that cognitive dysfunction may interfere with re-integration into the home and community.[89] Specifically, individuals who subjectively report cognitive dysfunction are less able to participate in activities pertaining to the home or household management, which included shopping, housework, caring for children, and social arrangements.[89] Moreover, higher levels of dysfunction in attention and information processing speed are significantly associated with less social participation, including participation in leisure and recreational activities.[11-14,17,89]

Regardless of demographic and clinical characteristics, cognitive dysfunction negatively impacts community integration for individuals with MS who self-report cognitive dysfunction and score poorly on neuropsychological tests. Benedict et al and Ruet et al both report that cognitive dysfunction is associated with vocational disability.[13,17] Specifically, cognitive dysfunction at baseline is predictive of vocational status up to 7 years after initial diagnosis of MS independent of neurological disability (EDSS).[17] Approximately 81.5% of study participants were gainfully employed, but after 7 years, 37.5% of participants had changed their employment status in some way (restricted work duties, reduced hours, stopped working, or received disability benefits).[17] The authors attribute this change in vocational status specifically to impairments in information processing speed, verbal memory, and executive function, even after controlling for demographic and clinical variables.[13] Overall, cognitive dysfunction has a negative impact on the quality of life of an individual with MS, affecting social participation and vocational roles.

**Mobility.** In a cross-sectional study by Sandroff et al, the authors were able to provide further understanding regarding the associations between aerobic capacity, muscular strength, and cognitive function.[90] Regardless of disease course and disability level, aerobic capacity is a significant predictor of information processing speed, especially in those individuals with defined mild neurological disability (EDSS <4.0).[90] Additionally, muscular strength is also significantly associated with information processing speed in those with mild neurological disability.[90] Findings from the 2015 Sandroff study led to the conclusion that those with higher disability levels (EDSS of 4.0 or greater) may have already surpassed the threshold at which exercise may have significant positive effects on cognitive processing and executive functioning.

Information processing speed is found to be related to fall frequency in a sample of individuals with MS.[81] A study by Sosnoff et al examined the relationship between one-time fallers and recurrent fallers on measures of mobility and cognitive function.[81] Both groups in the study demonstrated no significant differences on measures of balance, mobility, and walking. However, the authors demonstrated that recurrent fallers have significantly lower mean scores on neuropsychological measures of information processing speed and executive function, specifically the Paced Auditory Serial Addition Test (recurrent fallers: 41.9 ± 11.0, single-time fallers: 51.1 ± 6.1, $p < .01$, $d = -1.0$) and Symbol Digits Modalities Test (recurrent fallers: 46.4 ± 7.2, single-time fallers: 52.9 ± 4.9, $p < .01$, $d = -1.1$).[81] These findings suggest that although balance and mobility are impaired in both one-time fallers and recurrent fallers, information processing speed may have a role in differentiating fall frequency in individuals with MS and detecting those most at risk for recurrent falls. Additionally, information processing speed is known to be an independent predictor of gait speed in a sample of individuals with MS.[80] In particular, worse performance on the SDMT is correlated with slower gait speed, which is also related to increased fall risk.[80]

In a study exploring the intersection of physical function, cognitive performance, aging, and MS, information processing speed as measured by the SDMT was significantly associated with gait speed, walking endurance, and overall functional mobility.[91] Performance on the 6MWT, Six Spot Step Test (SSST), Timed 25-Foot Walk Test (T25FW), and Timed Up & Go

(TUG) are significantly correlated with performance on the SDMT. Specifically, in older adults with MS, performance on the SDMT explains variance in all the functional measures compared to older adults without MS regardless of demographic variables (eg, age, sex, education level).[91] These results support the idea that higher cognitive control plays a vital role in the physical functioning of those with MS, especially those of older age.[91]

## COGNITIVE-MOTOR INTERFERENCE IN MS

Prior research has focused on the independent assessment and treatment of cognitive dysfunction and motor deficits. The substantial growth in studies exploring the relationship and intersection of cognition and physical functioning in MS only occurred within the last decade as the understanding of the cognitive dysfunction and imaging technologies have improved. The earliest dual-task literature in MS is a paper by D'Esposito et al from 1996,[25] in which the authors examined the effects of a cognitive task on finger tapping, humming a melody, or reciting the alphabet. This study was one of the first to demonstrate the presence of dual-task interference and that dual-task performance in those with MS is significantly correlated with performance on neuropsychological tests of working memory.[25] Although the majority of the literature on cognitive-motor interference in individuals with MS has been published within the last decade, cognitive-motor interference has been extensively studied in populations of older adults and individuals with other neurological diagnoses, such as stroke, PD, and Alzheimer's disease. As mentioned previously, the interaction between cognitive and motor performance has been studied within the context of the dual-task paradigm, by which the DTC of one task on the other is assessed.

## The Intersection of Cognition and Motor Performance

Of interest in the rehabilitation literature is the effect of cognitive-motor interference and dual tasking on postural control and gait. Research in this area reveals that our performance of gait is not as automatic as previously understood. Recent studies have found that gait is significantly impacted by the performance of a cognitive task, suggesting that the control of gait and its specific parameters rely heavily on higher-order cognitive systems receiving afferent information and providing input to motor control.[92]

Advances in brain imaging technologies provide greater information and a deeper understanding of the underlying anatomical and functional neurological correlates of cognitive control of posture and gait. A study by Mihara et al found that the introduction of a postural perturbation in a population of healthy adults significantly activated the bilateral dorsolateral prefrontal cortices (DLPFC) of the brain.[93] The DLPFC in this sample of healthy adults was activated prior to the actual administration of the external perturbation during the preparatory trials. Previous studies have demonstrated that postural control requires an extent of attentional demand, in which there is a conflict detection during task performance and the appropriate allocation of attentional resources as necessary to either task.[93-95] A function of the DLPFC is the appropriate selection and allocation of attention to particular tasks, and its activation during the perturbation trials suggests its relevance during attentional allocation to the maintenance of postural stability.[93] Studies have also demonstrated that the DLPFC projects abundant connections to the pontine nuclei and is inherently responsible for the reflexive control of gait and posture.[96-99]

A study using functional near-infrared spectroscopy (fNIRS) by Suzuki et al demonstrated that the PFC is highly involved during both the preparatory and normal phases of gait.[100] Their conclusions were consistent with the results of Mihara et al. The authors hypothesized that because the PFC plays an integral role in working memory and anticipatory or preparatory actions, it then primarily functions to allocate attention to gait functions and gait parameters appropriately.[100] Harada et al found that older adults had to activate their left PFC to a greater extent than their younger counterparts to control gait velocity.[101] Participants with lower walking capacity demonstrated a greater activation level of the PFC, suggesting that this greater activation is a compensatory mechanism in older adults in order to perform at a similar level as their younger counterparts.[101] The findings of Holtzer et al parallel those of Harada et al in that in their cohort of participants, younger, healthy individuals demonstrated increases in bilateral PFC activity while performing a cognitive task during gait.[102] However, in the group of older individuals, there was attenuation in bilateral PFC activation, suggesting that older individuals underutilize the PFC in gait control. This finding supports the idea that the underutilization of the PFC in older individuals adversely affects the appropriate coordination of attentional resources to gait and to cognitive performance during a cognitive-motor dual-task gait condition.[102] Again, since the PFC is known to play a crucial role in working memory and attention, these changes observed in PFC activation during gait and a dual-task condition are related to the brain's capacity to provide regulatory input into postural control and control of gait parameters, such as velocity and cadence.[102]

**Theories for Cognitive-Motor Interference**

Three prevailing, but related theories attempt to explain cognitive-motor interference[29,103,104]: capacity sharing theory, serial bottleneck theory, and self-awareness theory.

The attentional capacity or capacity sharing theory suggests that there is a limit to one's attentional capacity, and once that theoretical threshold is reached during the simultaneous performance of multiple tasks, the performance of one or both tasks will decline. [29,103,104] Typically, people carry out multiple tasks at once routinely until one of these tasks becomes challenging and more effort is required, leading to a decrement in the performance of one or both of the tasks.[104] Individuals with neurological deficits, such as MS, may be especially susceptible to cognitive-motor interference because attentional demands to control motor processes are relatively increased, leaving less attentional resources for the performance of other tasks.[104]

The serial bottleneck theory builds on the capacity sharing theory and suggests that the limited capacity of the cognitive system leads to “bottlenecks” where the flow and processing of information are restricted, causing decrements in performance of one or both tasks.[104] The parallel processing of multiple tasks may be difficult for certain central processing operations. Even in a case of a task that may require only a simple mechanism of operation, when another task requires that same operation, a bottleneck phenomenon results. The performance of one or both is delayed or impaired. Such is the case for more complex tasks (eg, gait) that require the use of multiple or different types of processing mechanisms to efficiently perform.[29,103,104]

The self-awareness theory relates to an individual being aware of his or her limitations and consequently prioritizing demands based on task and environmental demands. This theory is consistent with the model of task prioritization in which there is a competition for attentional resources.[49] In this model of task prioritization, the individual performing the dual-task must prioritize 1 of the 2 tasks, taking into account factors that will minimize danger and maximize pleasure.[49] This task prioritization is observed when an individual dual-tasking adopts a “posture first” or “posture second” strategy.[105] If an individual detects or anticipates a threat to postural stability, then that individual may choose to attend more to posture and stability (“posture first” strategy) to reduce the risk of falling. Although separate theories of cognitive-motor interference have been proposed, the theories are undoubtedly related and contribute to our understanding of how cognitive processes contribute to dual-task interference.

**Sequelae of Cognitive-Motor Interference and Dual-Task in MS**

Several studies in individuals with MS evaluated the effects of cognitive demand on motor outcomes of postural stability and gait. The consensus is that cognition is an independent predictor of DTC of walking in individuals with MS. Individuals with mild MS (EDSS 0-4.5) demonstrate delayed postural reactions during a dual-task condition when they perform a Stroop task.[106] The individuals' postural responses to different external perturbations are attenuated, and they tend to demonstrate compensatory reactions compared to individuals without MS. Additionally, when comparing single-task and dual-task static standing, individuals with MS demonstrate decreased postural sway variability during the dual-task condition (serial subtraction by threes) compared to the single-task condition, which was not observed in the healthy control groups.[106] Although a reduction in sway variability is commonly seen as a favorable postural outcome, diminished sway variability may interfere with the postural control system's ability to respond to a postural perturbation flexibly. This strategy of reduced postural sway assumed by individuals with MS may require less attentional resources because the postural control system would have less to control as it would have if a more variable postural strategy were employed.[106] By assuming a reduced sway variability, the individuals with MS performing a dual-task allows more attentional resources to be directed towards the other competing task(s). In this specific instance, there is a greater reserve capacity that can be retained for the performance of the Stroop task.

Similarly, individuals with MS tend to demonstrate declines in gait performance with the addition of a cognitive task. A study 18 participants with MS showed that those with MS demonstrate a reduction in gait velocity and an increase in swing time variability.[107] Individuals with MS demonstrated a 9% reduction in gait velocity during a dual-task condition involving a titrated digit span task ($p = .001$).[107] Interestingly, however, this DTC increased to 11% with the use of a fixed digit span task ($p < .001$).[107] It would have been insightful if the DTC of cognitive performance had also been measured to see the interaction between motor DTC and cognitive DTC. In addition to alterations in gait velocity, the authors of the study found that a dual-task condition increased swing time variability in those with MS by 19% ($p = .037$), which the authors suggested is related to increased fall risk.[107]

The findings by Hamilton et al have been corroborated by several subsequent studies. In a 2011 study of 78 participants with MS, individuals with MS demonstrated a 12% reduction in gait velocity when walking while performing a semantic fluency task (p < .001).[75] Individuals with MS of moderate and severe disability status (EDSS) demonstrated significantly greater declines in performance ($p < .05$).[75] In a larger sample of participants with MS ($n = 120$), Nogueira et al reported a comparable decrease of 11.6% in dual-task gait velocity ($p < .01$)[108]; however, the authors in this study used a serial subtraction by 3 task as compared to the digit span and semantic fluency tasks performed in previous dual-tasking studies. Allali et al sought to determine the effects of different cognitive tasks on dual-task gait performance in a sample of 25 participants with MS.[109] The authors report significant decrements in dual-task gait velocity ($p < .01$) and step lengths ($p = .01$) while performing a forward digit span, backward digit span, semantic fluency task, and a verbal fluency task.[109] Allali et al further show that dual-task gait velocity and step lengths during backward counting and verbal fluency are significantly correlated with EDSS levels in their sample ($p < .05$).[109] Motl et al extended their research scope to examine the relationship between dual-task performance and functional measures of gait, such as the 6MWT.[110] In addition to finding a significant reduction in gait velocity ($p < .001$), cadence ($p < .001$), and step length ($p < .001$), the authors found a significant relationship between 6MWT distance and DTC for gait velocity ($r = -.41$, $p < .001$) and DTC for step length ($r = -.45$, $p < .001$), which may suggest that improving walking capacity in those with MS may also reduce DTC of gait.[110]

Sosnoff et al report a reduction in gait velocity in a sample of 96 participants with MS while performing a semantic fluency task ($p < .05$).[111] These findings are similar to that of Learmonth et al, in which the authors demonstrate in a sample of 82 participants with MS that dual-task of walking leads to a reduction of 12.5% in gait velocity during an alternate alphabet task, in which participants recite the alphabet but skip every other letter.[112] This latter study also shows the presence of cognitive-motor interference in those with MS regardless of disease disability status. The findings from these 2 studies, however, seem to suggest that a generalized rehabilitative approach to cognitive-motor interference in those with MS may be more beneficial than separately focusing on cognitive and motor task rehabilitation.[111,112] Overall, these observations of cognitive-motor interference in individuals with MS do support the possibility that DTC may be reduced through interventions targeting walking performance, cognitive function, or both.

## MEASUREMENT AND ASSESSMENT OF COGNITIVE-MOTOR INTERFERENCE IN MS

For the scope of this literature review, the cognitive-motor interference of gait will be principally discussed. The phenomenon of cognitive-motor interference may be measured in terms of DTC, which is a calculated relative ratio of single-task to dual-task performance[107]:

$$\%\text{DTC} = \frac{(\text{Single Task } - \text{Dual Task})}{\text{Single Task}} \times 100$$

This formula, which follows procedures outlined by Hamilton et al, considers the performance in the dual-task condition relative to the single-task condition.[107] For an example of %DTC of walking, the single-task condition could be fast gait velocity on the 10-meter walk test (a standardized outcome measure of gait speed), and the dual-task condition would involve performing a cognitive task, such as a serial subtraction by threes, during the 10-meter walk test. If single-task gait velocity was 1.25 m/s and the DT gait velocity was 1.0 m/s, then the DTC would be 25%. This calculation may also be performed to determine %DTC of cognitive performance, so long as single-task cognitive performance is measured prior.

Although a standardized formula for measuring DTC exists, a standardized measure that utilizes this formula and reports DTC is lacking. Additionally, there is no consensus on the type of cognitive task to use during a dual-task assessment to optimally and appropriately create an interference effect.

**Dual-Task Outcome Measures**

Despite the known prevalence of cognitive-motor interference in individuals with MS and other neurological conditions, the few existing clinical measures of dual-task performance lack standardization and possess inherent limitations for use in individuals with MS.[113,114] It is also crucial to note that the cognitive tasks of some of these clinical measures may not be sufficiently complex for a dual-task effect to be observed. For example, cognitive tasks such as talking, answering simple questions, or reciting the alphabet may not adequately tax attentional resources to show an observable performance decrement in walking. Furthermore, other measures may include motor tasks too difficult for more disabled individuals to complete. Other than the TUG-cog, no other clinical measures have been validated for use with individuals with MS.

Several measures, such as SWWT,[113,115,116] WWTT,[26,31,113,117] and TUG-cog[38,118] are all clinical tests of dual-task performance that have been used in various special populations. Further information about these measures can be found in Table 1.

Unfortunately, many of these clinical tests do not account for the relative difficulty of the cognitive task in relation to the person's single-task ability.[113,114] The SWWT, for example, utilizes conversation as the cognitive task while walking at a self-selected comfortable speed. For individuals with higher cognitive functioning, this clinical test may not sufficiently challenge cognitive resources for a dual-task effect to be observed. Other clinical tests, such as the TUG-cog, utilizes a serial subtraction by threes as the cognitive task during the dual-task condition. However, the use of serial subtraction by threes poses 2 issues. Firstly, the task may be too easy for those who are used to simple computations or more difficult for those who are mathematically disinclined. Secondly, the use of a verbal component may introduce further structural interference, as speech articulation may impose additional load on cognitive resources. Moreover, factors such as education level, literacy, and language difficulties may greatly influence the performance and outcomes of other measures, such as the WWTT, while other tests may involve a motor task that is too difficult for more impaired individuals to perform (ie, Tandem Walk With Cognitive Task).[114]

**Table 1.** Clinical measures of cognitive-motor dual-task performance[119,120]

| Measure | Walking Task | Cognitive Task | Outcome | Populations Tested |
|---|---|---|---|---|
| Stops While Walking Test | Self-selected speed, with or without aids | Conversation | Stops walking while talking | Older Adults, PD, Stroke[115,116,121] |
| TUG-cog | Stand, walk 3 m, 180° turn, walk 3 m back to chair and sit, with or without aids | Serial subtraction by threes from random number between 20 and 100 | Time for single-task and DT conditions | Older Adults, PD, MS[38,118] |
| Walking While Talking Test | Self-selected speed for 20 ft, 180° turn and return 20 ft | 1 – recite alphabet<br>2 – alternate alphabet task | Time for single-task and DT conditions | Older Adults, Brain Injury, PD, AD[26,31,117,122] |
| Multiple Tasks Test | Stand, self-selected speed, turn, sit down, adding obstacles, carrying tray, using slippery soles, tapping floor, reducing environment light | Simple conversational questions | Hesitations or stops in multiple task conditions and comparing to single-task walking and conversation | Older Adults, PD[27,123] |
| Walking and Remembering Test | Fast self-selected speed 20ft within 7.5 in walkway. Modified WART eliminates 7.5 in walkway. | Titrated Digit Span | DTC gait: Time for single-task and DT conditions; steps outside of walkway<br>DTC cognitive: percentage of digits correctly recalled subtracted from 100% | Older Adults, Brain Injury[39,119,122] |
| Tandem Walk with Cognitive Task | Fast self-selected speed walking tandem 20 ft, turn, and return 20 ft | Recite phonetic alphabet or other similarly complex task | DTC gait: time for single-task and DT conditions | Brain Injury[31] |
| Dual-Task Questionnaire | N/A | N/A | 10-questions related to everyday difficulties related to DT. Overall average rating from 0 to 4, with higher score indicating increased DT difficulties | Brain Injury[43] |

Recommendations were proposed to mitigate these methodological issues inherent in these dual-task measures, especially as they relate to adjusting the dual-task difficulty relative to the person's single-task ability. A previous review by Leone et al recommends that the cognitive task used in a dual-task measure should be adjusted relative to the individual's single-task ability and that it should, if possible, avoid verbal fluency and mathematical calculations.[114] The authors note that verbal fluency may be relatively simple initially, but becomes more difficult as the test progresses, varying the attentional load required during dual-task performance. Those individuals with language difficulties or lower literacy levels may also be disadvantaged by the use of verbal fluency during the dual-task assessment. Mathematical calculation, however, poses a similar issue—one that may relate to educational level.

One proposed solution is the use of a titrated digit span for single-task and dual-task conditions. A titrated digit span tests an individual's working memory, which is the ability of an individual to receive and maintain information and a component of information processing efficiency and executive functioning. Additionally, the use of a titrated digit span can be performed during a walking task and does not present any bias to those with limited literacy or educational levels. Finally, the task of recalling the digit span at the end of the test eliminates articulation during walking, preventing verbal pacing of walking or reducing the challenge to attentional capacity any further.[113,114]

**The Walking and Remembering Test.** The WART is a clinical measure originally developed by McCulloch et al for those with older individuals,[113] but has since been validated in those with acquired brain injury (see Appendix A).[39,122] The titrated forward digit span included in the measure is tailored to the individual's baseline working memory function, which is characteristically impaired in individuals with MS and associated with motor performance changes.[25,83] The WART provides several other potential benefits mentioned earlier, including the use of readily available equipment, a straightforward judgment of accuracy, absence of speech articulation, and mitigation of pacing of walking and additional cognitive loads. Furthermore, the WART recommends the test participant walk at his or her fastest possible walking speed as opposed to a self-selected walking speed, which may not provide a sufficiently demanding load that could compete with secondary cognitive demands. In essence, other clinical dual-task measures that utilize self-selected comfortable walking speed may leave sufficient “reserve capacity” for other tasks to be performed.[103] Reliability and preliminary validity of the WART have been established in community-dwelling older adults.

The WART is composed of 3 separate, distinct tasks. The first part of the WART is a single-task walking condition. The individual is asked to walk at his or her fastest walking speed along a 20-ft walkway. The test allows for different walkway lengths to be used, as long as the distance of the walkway is standardized between tests.[124] The individual is asked to walk twice, the 2 times are averaged, and the averaged time is considered the walking time for the single-task walking condition. A modified version of the WART has also been introduced.[122] The mWART utilizes the same procedures; however, path deviation is not measured during the mWART.

For the single-task walking condition, participants are asked to walk at their fastest possible walking speed along the designated walkway for 2 trials. Gait speeds for both trials are recorded and averaged to obtain the participants’ mean single-task gait speed. For the second part of the mWART, a digit span test is administered in sitting. A digit span is a random sequence numbers used to measure working memory capacity and requires the participants to repeat a series of digits of increasing length. Included in the mWART are 6 pairs of unique digit spans.

Each digit span is a standardized random number sequence starting at a length of 4 digits, and the length of the digit spans increase by 1 digit in each subsequent pair for a possible 9 digits in the final pair. The participant is given the following instructions[124]:

> I'm going to say some numbers that I want you to remember after a brief delay. Listen carefully to the numbers and use any method except writing or talking to help you remember them. When I give you the cue 'now', repeat the numbers back to me.

With these instructions, the participants are informed that they may use any method except writing or talking to help them remember the numbers. The examiner verbally provides the digit span from the first pair to the participant, and after a delay equivalent to the time it took the participant to walk in the single-task walking condition, the examiner cues the participant to repeat the numbers back to the examiner. The examiner repeats this process for each subsequent digit span until the participant is only able to recall 1 trial of a digit span correctly from a pair. For example, if the participant is able to correctly recall with 100% accuracy only the first digit span in the fourth pair (7 digits in length), but not the second digit span in that pair, then the digit span testing is stopped, and this trial is recorded. The longest digit span correctly recalled for at least 1 trial is used to determine the length of the unique digit span for the dual-task condition and considered 100% correct in assessing cognitive errors.[124]

For the dual-task walking condition, the following instructions are provided to the participant[124]:

> Now we are going to combine walking with remembering numbers. We will do this task twice. I am going to say some numbers that I want you to remember until we get to the

end of the walking path. You may use any method you choose to remember the numbers, except saying them out loud. Walk as quickly as you can but take care not to step off the path. I will walk beside you and time you from when you first step onto the path. Continue walking until I say ‘now’, then repeat the numbers you have been concentrating on while you were walking.

With these instructions, the participants are verbally provided a unique digit span equal in length to that found in the digit span testing. The examiner immediately cues the participant to walk at his or her fastest speed, and at the end of the walking trial, the examiner cues the participant to repeat the numbers back to the examiner. Similar to the digit span testing, participants are informed beforehand that they may use any method to remember the numbers, except saying them out loud. Two trials, each with unique digit spans, are performed, and both gait velocity and digit span accuracy are recorded and averaged by the examiner for both of the trials.

Inter-rater reliability is excellent in both young adults and community-dwelling older adults with $ICC_{2,1}$ of $\geq .97$ for walking time and digit span accuracy.[113] Agreement between raters is also excellent (93%) for younger adults and good (76%) for older adults. Although lower, test-retest reliability is still good for walking times with $ICC_{2,1}$ of $\geq .79$.[113] Other findings found older adults performing worse than younger adults on single-task walking and digit span recall, and during dual-task walking and digit span recall. However, the DTC for walking time did not differ significantly between the 2 groups.[113]

For those with acquired brain injury, the WART is a feasible tool for assessing dual-task performance demonstrating similar dual-task costs for cognitive task performance between those with acquired brain injury and young adults.[39] The WART median relative dual-task costs for walking speed is greater for those with acquired brain injury, .18, 95% CI [.01,.24] than young adults, .002, 95% CI [−.02,.05]. Those with acquired brain injury also demonstrate greater difficulty with step accuracy compared to young adults.[39]

Considering the prevalence of cognitive-motor interference in individuals with MS and its effects on both postural stability and gait functioning, a need for valid and reliable measures of dual-task performance exists. Other than the TUG-cog, no other dual-task measure has been validated and found to be reliable in detecting dual-task interference in individuals with MS. The WART presents as a promising measure of dual-task performance as it includes both the single-task and dual-task performance of walking and digit span accuracy, which is lacking with the TUG-cog and other measures of dual-tasking.

## DUAL-TASK TRAINING IN MS

Although cognitive-motor interference in individuals with MS is well documented in the literature, the majority of dual-task training studies have been performed in other special populations.[23,52,125] Specifically, its effects have been explored in persons with PD, Alzheimer's disease, traumatic brain injury, and stroke. Recent systematic reviews and meta-analyses have had difficulty recommending with strong confidence dual-task training for those with dual-task deficits stemming from neurological dysfunction.[23] Specifically, there are currently a limited number of randomized control trials (RCTs) in the area of dual-task training, and many studies lack a control group for comparison of effects. Thus, any observed changes may be attributed to spontaneous recovery or due to the passage of time.[23] However, the results of current dual-task training interventions in these populations do hold promise for improving gait, and cognitive performance, which in turn may influence falls risk and overall functional independence.

A systematic review by Fritz et al reported that dual-task training generally results in improvements of both balance and gait performance in those with neurological deficits.[23] Parameters for dual-task training interventions vary considerably amongst the included studies. Frequency, intensity, and duration of the interventions range from single 30-minute weekly training sessions to a cumulative 180-minutes per week for 16 weeks, and only 3 small RCTs are included in the review. However, treatment effects and forest plots indicate that dual-task training is favored over comparison groups in the studies included in their systematic review. When considering the effects on dual-task training in different neurological populations, the authors cite effect sizes for dual-task training intervention ranging from 0.66 to 2.07 for improvements on balance or gait parameters.[23] Individuals with PD, for example, demonstrate improvements in 6MWT, single-gait speed, step length, step amplitude, and cadence.[23] These individuals also demonstrate improvements in dual-task gait speed, step length, and stride time variability, which are all maintained after the intervention. The authors also report improvements in both single-task and dual-task balance performance on measures of computerized dynamic posturography.[23]

Additionally, individuals with Alzheimer's disease show similar outcomes following dual-task training, demonstrating improved single-task step length, single-task balance on the Berg Balance Scale (effect size: 1.67), reduced postural sway, and reduced %DTC of gait velocity and step lengths.[23] Interestingly both clinical groups also demonstrate improvements in cognitive performance based on neuropsychological tests. Individuals with PD improve their performance on the Trail Making Test, demonstrating 31% fewer errors following a dual-task training intervention.[23] Similarly, those with Alzheimer's disease improve their performance on the Frontal Assessment Battery (Hedges standardized mean differences ranging from 1.96-3.07).[23] Overall, the authors conclude that dual-task training may have the potential to improve both the single-task and dual-task performance of gait, but also result in modest improvements on balance and cognitive functioning.

In those with brain injury and stroke, the systematic review written by Fritz et al in 2015 documented extremely limited available evidence in stroke and brain injury at the time. More recent systematic reviews and meta-analyses, published in 2017 and 2019 by Ghai et al and He et al, respectively, were able to include additional studies and controlled trials concerning individuals with stroke and brain injury diagnoses. Ghai et al documented that in participants with chronic stroke, 30-minute dual-task training sessions provided 3 days per week for 8 weeks results in significant improvements on the Functional Reach Test with a large effect size (Hedge's $g$: 0.32) and 95% CI [−.22,0.86] cm reported indicating a beneficial effect on postural stability.[125] In a systematic review by He et al, dual-task training in participants with stroke improved single-task walking function (effect size: 0.14-2.24) based on spatiotemporal gait parameters and clinical measures of mobility (Timed Up-and-Go, Dynamic Gait Index) compared to single-task mobility training.[52] However, the authors did find that the effects on dual-task measures of walking function were inconsistent amongst the included studies. Additionally, cognitive-motor dual-task balance training is effective in improving single-task balance (effect size: 0.27-1.82), but the effects on dual-task balance were not studied.[52] Overall, both systemic reviews suggest that there is some evidence that dual-task training can improve single-task performance on balance and gait measures in those with chronic stroke.

The above 3 systematic reviews document inherent limitations to their analyses based on the limited methodological quality of studies that are included in each of their respective reviews. All 3 reviews state that the overall methodological quality of the included studies was low with limited RCTs available.[23,52,125] Most studies that are included have a high risk of bias due to lack of blinding of assessors or participants, which may introduce bias in favor of the dual-task training intervention. Additionally, the overall sample sizes of the included studies are low, reducing statistical power, and perhaps introducing a high possibility of type II error. Systematic differences related to participant characteristics, such as age, sex, disease severity, and duration of disease, also contribute to difficulties in generalizing and interpreting the results of the included studies. Considering that these dual-task interventions include measures of single-task and/or dual-task performance, most of the studies fail to present or assess changes in actual %DTC of motor or cognitive performance. Moreover, differences in dual-task interventions, protocols, and limited long-term follow-up continue to hinder the generalizability of results and reproducibility for further research studies on clinical translation. Due to the limited number of studies currently available, none of the systematic reviews include studies examining the effects of dual-task training interventions in individuals with MS. To date, only 4 dual-task training interventional studies in MS exist in the literature.[126-129]

There continues to be a lack of evidence pertaining to methods of mitigating the effects of cognitive-motor interference in MS. Of the four dual-task training studies available, only one pilot study incorporates gait-specific dual-task training as its sole intervention. In the small pilot study by Peruzzi et al,[127] the authors sought to examine the effects of using a virtual reality-based treadmill training program on improving gait and endurance in a group of 8 participants with MS. The study included only participants with relapsing-remitting MS with a mean age of 44.3 ± 8.1 years. These participants were of relatively moderate disability (mean EDSS: 4.8 ± 0.9), moderate disease duration (11.6 ± 5.5 years), mild ambulation impairment (mean Ambulation Index: 3.5 ± 0.7), and intact cognitive status (mean Mini-Mental State Examination: 28.3 ± 1.9). The intervention consisted of participants walking on a treadmill while watching a virtual reality environment in which they were required to pass obstacles that appeared on the trail. Participants in the study attended the intervention twice per week for 6 weeks and were supervised by a physical therapist. Each session lasted approximately 45 minutes, broken up into three 10-minute training bouts with 5-minute rests between each bout. Participants were asked to walk over-ground at their self-selected gait speed, and this speed was used to determine the that participants' starting treadmill speed. Participants initially walked at 80% of their over-ground self-selected gait speed, and treadmill speeds were increased by 10% every week for progression. Outcome measures included the 6MWT and Four Square Step Test. Spatiotemporal parameters of gait (gait speed and stride length) were also collected during single-task and dual-task conditions (performing serial subtraction by 3 during comfortable walking speed).

The authors found that single-task gait speed improved by 10% at post-intervention and 11% at follow-up 4 weeks post-intervention ($p$ = .197), while single-task stride length increased by 7% at post-intervention and 11% ($p$ = .135) at follow-up.[127] On the other hand, dual-task gait speed demonstrated greater magnitudes of improvement, having significantly improved by 18% at post-intervention and 26% at follow-up ($p$ = .021).[127] Dual-task stride length also significantly improved at post-intervention and follow-up ($p$ = .008).[127] On performance measures, the participants in the study demonstrated a mean 8% increase in walk distance on the 6MWT at post-intervention and a mean increase of 23% at follow-up, reflecting improved walking capacity.[127] Additionally, the time to complete the Four Square Step Test decreased significantly by 22% at post-intervention ($p$ = .02) and by 37% at follow-up ($p$ = .02).[127]

The findings from Peruzzi et al provide preliminary evidence that a dual-task training program, specifically virtual reality treadmill-based training, may result in improvements of gait and mobility during both single-task and dual-task conditions. However, the study has several limitations that limit its interpretability, including a small sample size, a homogeneous cohort of participants, and a lack of a control group for comparative analysis. Of course, these limitations are understandably inherent in any pilot or feasibility trial.

In another study by Kramer et al, the authors examined the effects of a 3-week exergaming regimen on tests of balance and gait under single-task and dual-task conditions.[126] A cohort of 61 participants were included in the study with 21 participants randomized to the exergaming group, 20 participants to the Posturomed group, and 20 participants to the conventional training group. Of the 61 participants, 44 were women, and 17 were men with a mean age of 47 ± 9 years and an EDSS score of 3 ± 1.[126] The training interventions consisted of 9 total supervised sessions lasting 30 minutes each. The exergaming group engaged in playing Wii Sports, Wii Sport Resort, and Wii Fit games. While playing these games on the Wii platform, the participants also stood on an unstable surface (Posturomed) that moved in response to the participants' upper extremity movements or balance reactions. Meanwhile, the Posturomed-only group participated in 5 different single-task balance exercises on the Posturomed device. The conventional training group participated in conventional balance training exercises on a stable surface. Outcome measures for balance included different conditions of Romberg stance and single-limb stance on a force plate. The authors also analyzed spatiotemporal parameters of gait (gait velocity and step-to-step coefficient of variance). All groups showed similar improvements after the training on tests of balance and gait; however, significant differences were found between dual-task and single-task conditions only for the exergaming training group ($t = 2.9$, $p = .01$).[126]

Findings from Kramer et al demonstrate the potential beneficial effects of exergaming and its influence on both single-task and dual-task performance. However, the study does present with limitations, albeit much fewer than those of Peruzzi et al. The participants included in the Kramer study included those of relatively lower disability levels (EDSS 3 ± 1), which limits generalizability to those with more moderate or severe levels of disability. Additionally, the authors do not disclose the clinical course of MS of the participants, again limiting generalizability to the different clinical presentations and clinical courses of MS. Finally, the different interventions in the study may be difficult to replicate due to the need for specific equipment (Wii console and games, Posturomed device) and lack of specificity of frequency, intensity, and progression of the exercises or activities of each group. Nonetheless, the results from the study are consistent with Peruzzi et al in that dual-task training utilizing virtual reality or exergaming strategies may improve dual-task deficits in those with MS.

A more methodologically sound study by Sosnoff et al explored the feasibility and effects of a 12-week, 24 sessions dual-task balance and gait training program on measures of balance, walking, and cognitive performance.[128] A total of 14 participants with MS completed the post-intervention assessment, with 8 participants randomized into the dual-task training group and 6 participants randomized into the control or conventional training group. The participants in the dual-task training group had a mean age of 48 ± 14.2 years. Of the 8 participants in the dual-task group, 5 were female, 7 had relapsing-remitting MS, and 1 had benign MS. The participants had a mean disease duration of 11.9 ± 11.7 years and a median EDSS of 1.75.[128] There were no significant differences found between groups for each of the demographic variables. Both groups underwent training sessions twice per week, each session lasting for 1 hour. Both groups received an individualized progressive protocol of both balance and gait exercises. The balance training component of the intervention protocol included 10 different exercises that were performed prior to gait exercises and lasted 30 minutes in duration. Each exercise was performed twice by both groups; however, the dual-task training group performed a concomitant cognitive task that has been matched to the single-task abilities of the participants. For the second half of the training intervention, both groups participated in treadmill training. Both groups walked for 10 minutes during the first session and progressed to walking 30 minutes by the end of the 12-week intervention. In addition to walking on the treadmill, the dual-task group also performed walking with a cognitive task. Walking speed on the treadmill was based on that participant's comfortable walking speed and was progressed by 10% each week thereafter. The dual-task group performed cognitive tasks that targeted verbal fluency, discrimination and decision making, working memory, mental tracking, and visuospatial cognition, all of which have been shown to be impaired in individuals with MS, as well as elicit cognitive-motor interference. Outcome measures for the study were single-task and dual-task gait speed, cognitive performance, balance performance on the Berg Balance Scale, and balance confidence on the Activities Specific Balance Confidence Scale.

The authors found that the dual-task training regimen was safe and feasible to be completed by those with MS. They also found that adherence to the training program was high, with a high level of retention. However, no differences were found between groups in single-task gait speed [$F(1,13) = 0.15$, $p = .71$, $\eta^2 = .01$], although there was a trend for the dual-task training group to improve to a greater degree in dual-task gait speeds during alternating letters [$F(1,13) = 3.5$, $p = .09$, $\eta^2 = .24$] and serial subtractions [$F(1,13) = 3.1$, $p = .11$, $\eta^2 = .22$] compared to the conventional training group.[128] Similarly, no significant differences were found in cognitive performance measures during dual-task trials. The dual-task training group did, however, demonstrate a trend for having greater improvement on the Brief Visuospatial Memory Test-Revised [$F(1,13) = 3.3$, $p = .10$, $\eta^2 = .23$].[128] Unfortunately, the authors also found no significant differences between groups in balance function [$F(1,13) = 1.2$, $p = .30$, $\eta^2 = .10$] and balance confidence [$F(1,13) = 0.0$, $p = .98$, $\eta^2 = .00$].[128]

Despite a lack of difference between groups, improvements were found on all measures regardless of group assignment. The study demonstrates that dual-task training may alter dual-task walking performance, which is consistent with previous studies in MS. However, compared to the previously cited studies, the intervention by Sosnoff et al requires only the use of a treadmill for dual-task training. Additionally, the authors' intervention incorporates a gait-specific dual-task training component to target dual-task gait performance. The authors describe several limitations that may once again limit the external validity and interpretability of their results. Firstly, their pilot study is a feasibility trial, which like Peruzzi et al, has a small sample size, reducing the study's power to find a significant difference. Sosnoff et al did not examine or report %DTC of motor or cognitive performance.

Additionally, the balance and gait exercises that they incorporated into their protocol may not have been of sufficient intensity or duration to elicit significant changes and improvements in balance or gait performance. The participants in the study were also of generally lower disability status (EDSS of 1.75), and changes in dual-task interference may not have been observed in this sample compared to those of higher EDSS and subsequent dual-task interference. Nonetheless, the observations from this study provide valuable data upon which to build future, larger-scale studies.

A recent multi-center randomized control trial of 40 individuals with MS demonstrated that both single-task and dual-task training significantly improved motor and cognitive performance. However, only dual-task training contributed to better dual-task walking compared to the single-task group.[129] The study utilized an 8-week training intervention of 20 forty-five minute dual-task sessions that consisted of walking or stepping practice while performing 11 different cognitive tasks of varying complexity delivered through a unique computer-based application developed specifically for the study. In contrast, the single-task group intervention consisted of 21 different gait and balance exercises that were performed. The single task group performed the 21 different exercises, with each exercise duration lasting anywhere from 30 seconds to 2 minutes, and the progression of the single-task intervention was based on therapist judgment. The dual-task group performed all exercises for 2 minutes and encouraged variable-priority training. The therapist provided feedback on performance after every dual-task exercise.

Twenty individuals were randomized into each group with the dual-task training group demographic variables not differing significantly between groups. The dual-task training group had a mean age of 51.4 ± 9.3 years, a mean of 9.6 ± 7.7 years of disease duration, a mean EDSS of 3.4 ± 1.0, and a mean Mini-Mental State Examination score of 28.5 ± 1.3.[129] In the dual-task group, 60% were female, 65% had relapsing-remitting MS, 20% had secondary-progressive MS, and 15% had primary-progressive MS.[129] The %DTCs for 9 different cognitive-motor dual-task conditions were assessed for the primary outcomes of the walk-digit span, walk-subtraction, walk-vigilance, cup-digit span, cup-subtraction, cup-vigilance, obstacles-digit span, obstacles-subtraction, and obstacles-vigilance. Secondary outcome measures included the Brief Repeatable Battery of Neuropsychological Tests, Selective Reminding Test, Spatial Recall Test, Symbol Digital Modalities Test, Paced Auditory Serial Addition Test, Timed 25 Foot-Walk Test, TUG, Dynamic Gait Index, 2MWT, Multiple Sclerosis Impact Scale-29, the Falls Efficacy Scale, Dual-Task Questionnaire, and the Modified Fatigue Impact Scale. Additionally, the authors measured adherence to the training intervention and administered the Intrinsic Motivation Inventory.

Overall, the study found that regardless of group assignment, improvements were observed in absolute dual-task gait speed.[129] However, only the dual-task training group demonstrated improvements in relative dual-task performance, reducing their %DTC during walking while performing a digit span or serial subtraction task. No changes were found in %DTC of cognitive performance for either group. Improvements in the dual-task group demonstrated retention at follow-up, suggesting improved motor learning and control over single-task training.[129]

Although the study presents more promising results of dual-task training, the study does present with several methodological uncertainties. These include the study's use of a novel training computer-based application, which may not be universally available or accessible; the use of drastically different training regimens for each group, limiting the interpretability of comparisons between-group differences; the lack of a standardized dual-task outcome measure; the analysis and results of 22 different outcomes raise questions regarding statistical credibility. Nevertheless, the study builds upon the previous literature on dual-task training in MS, contributing to the findings that dual-task training not only improves both single-task and dual-task gait performance but also induces longer-term or more robust improvements to motor learning compared to single-task training.

## FUTURE DIRECTIONS

Current evidence has established the presence of cognitive-motor interference and dual-task interference in individuals with MS. Within this dual-task paradigm, the performance of one task demonstrates significant decrements when another task is performed. Of initial concern is the current lack of standardized outcome measures that assess dual-task performance in both the motor and cognitive domains, specifically allowing the clinician to determine both the %DTC of motor and cognitive performance. The lack of valid and reliable measures of dual-task performance limits the ability for researchers to provide a standardized comparison across groups and studies and limits the ability for clinicians and other researchers to reproduce and interpret the results of current dual-task training studies. Thus, a clinical measure of dual-tasking that incorporates these characteristics is needed for use in individuals with MS—one that also takes into account the baseline cognitive abilities of the individual, sufficiently provides a challenging motor task, targets a cognitive domain typically impaired in individuals with MS, and is relatively accessible and simple to administer. The WART is a promising tool that has the potential to fill this gap and provide both researchers and clinicians a valid and reliable method of assessing dual-task performance in individuals with MS.

Despite the well-known deficits of dual-task performance in those with MS, there is a paucity of research that explores different avenues by which to mitigate cognitive-motor interference and dual-task decrements in performance. The current literature on dual-task training in those with MS has consisted of interventions that employed multiple modes of training, confounding contributions of specific interventions or exercises on improvements in absolute and relative measures of dual-task. Walking ability is considered the most valuable body function by those with MS. Yet, there is currently no study that explores the effects of a gait only dual-task intervention on measures of gait performance that are known to be affected by cognitive-motor interference (ie, gait velocity, step length, cadence) or walking ability (ie, 2MWT, Multiple Sclerosis Walking Scale-12 [MSWS-12]) in individuals with MS. The study by Peruzzi et al is the only study that attempts to explore the effects of a gait-specific intervention on dual-task performance; however, the study lacked a comparison group to determine if the changes observed differed from conventional therapy or rehabilitation approaches.

### Other Clinical Measures

**MoCA.** The MoCA screens for mild cognitive dysfunction in older adults and those with neurological deficits (see Appendix B). Its construct validity has been established for use in MS, significantly correlating to neuropsychological measures of learning, delayed recall, executive functioning, and information processing.[130-132] The tool assesses short-term memory, visuospatial abilities, executive functions, attention, concentration, working memory, language, and orientation. It is more sensitive than the MMSE and has a higher ceiling effect than the MMSE.[130,131] A cutoff score of <26 has been identified to classify those with cognitive impairment.[132]

**2MWT.** The 2MWT assesses walking capacity and endurance over 2 minutes and is performed at the fastest possible speed (see Appendix C). Individuals performing the test have the option to use an assistive device if it is a part of their normal method of walking. Because of its relative brevity in walking duration, the 2MWT is less burdensome for individuals with MS[133,134]. However, although the 2MWT is much shorter than the 6MWT, the 2MWT is highly correlated with the 6MWT ($R^2 = 0.97$).[133,134] Moreover, in terms of walking distance at 1-minute intervals, there is no significant difference between the 2 tests ($p = 0.82$).[133,134] The 2MWT effectively eliminates the redundancy of the last 4 minutes of the 6MWT while better predicting community ambulation in persons with MS as compared to shorter tests of walking ability, ie, the Timed 25-

Foot Walk Test or 10-meter Walk Test.[133,134] An improvement of 31.5 ft on the 2MWT is needed for a minimally important change (MIC) from the patient's perspective, while a change of 22.6 ft is required for a MIC from the therapist's perspective ($p < .05$).[135]

**MSWS-12.** The MSWS-12 is a 12-item self-report measure that asks the responder to assess the impact of MS on his or her walking ability in the past 2 weeks (see Appendix D).[136] The 12 items on the MSWS-12 assess constructs such as walking, running, balance, task difficulty, required effort, and concentration while walking. Each item is graded on a Likert scale, ranging from 1-5, with a score of "1" indicating "Not at all" and a score of "5" indicating "Extremely" in regards to how MS has affected the different aspects of the responder's walking ability. Scores from each item are then summed for a total possible 60 points. The total score is then transformed into a 0-100 scale with possible scores ranging from 20-100. The MSWS-12 demonstrates both excellent validity and reliability and adequate to excellent floor and ceiling effects.[136-138] A cut-off score of 75% or greater had a sensitivity of 52 and specificity of 82 in predicting fallers vs. non-fallers.[72] An decrease of 10.4 points on the MSWS-12 is indicative of a MIC from the patient's perspective, while a decrease of 11.4 points is indicative of a MIC from the therapist's perspective.[135]

**The Fatigue Scale for Motor and Cognitive Functions.** The Fatigue Scale for Motor and Cognitive Functions (FSMC) is a self-report outcome measure of physical and mental fatigue in patients with MS over 2 weeks (see Appendix E). Each item is rated on a Likert scale ranging from 1-5, with a score of "1" indicating that the item "Does Not Apply At All" and a score of "5" indicating that the item "Applies Completely". Scores are then summed and can range from 20-100 with higher values indicating greater fatigue levels. The FSMC can be used to measure motor fatigue only, cognitive fatigue only, or both as a summed score. Both subscales separately demonstrate good reliability, sensitivity, and specificity, and are highly intercorrelated with the Modified Fatigue Inventory (MFIS) and Fatigue Severity Scales (FSS).[139] However, the FSMC demonstrates superior sensitivity and specificity over the MFIS and FSS in persons with MS. The cut-off values for identifying mild, moderate, and severe fatigue provide clinicians with the ability to grade fatigue over time (see Appendix E).

**Dual-Task Training Intervention**

The dual-task training intervention developed for this study was based on the findings and recommendations of previous studies on dual-task training and motor learning.[44,140,141] The dual-task training will consist of a 6-week long intervention consisting of 1-on-1 over-ground gait training sessions with a physical therapist 3 days per week (18 total sessions). Each training session will consist of 4 different training blocks with each block consisting of 4 minutes of total gait training time for a total session walking time of 20 minutes (see Figure 4).

Each block is further divided into 2 gait training bouts with 2-minute rests between each bout. Participants will be instructed to walk at a self-selected gait speed that they believe they will be able to maintain for each 2-minute bout. On the other hand, the single-task training group will be asked to focus on gait performance and walk without any distractors of music, talking, or reading during all bouts. The single-task training group participants will be provided with feedback regarding knowledge of performance after each bout. In addition to the gait training they will receive, participants in the dual-task training group will perform a randomly selected cognitive task for each bout for a total of 6 hours total of dual-task-specific practice.[142] For each block with the dual-task training group, participants will be asked to prioritize either gait performance or cognitive performance.

| Dual-Task Training | Block 1 | Block 2 | Block 3 | Block 4 | Block 5 |
|---|---|---|---|---|---|
| Total walk time | 4 min | 4 min | 4 min | 4 min | 4 min |
| Walking sets | 2x2 min bouts<br>2 min rest | 2x2 min bouts<br>2 min rest | 2x2 min bouts<br>2 min rest | 2x2 min bouts<br>2 min rest | 2x2 min bouts<br>2 min rest |
| Task prioritization | None | Gait | Cognitive | Gait | Cognitive |
| Cognitive tasks | Three cognitive tasks randomized within each block:<br>• Serial subtraction by threes, verbal/phonemic fluency, and simple arithmetic problem with an *n*-back task (*n* = 1) | | | | |

**Figure 4.** Cognitive-Motor Dual-Task Gait Training Intervention.

The cognitive tasks incorporated into the DT group intervention targets cognitive domains shown to be impaired in individuals with MS and have been previously described as eliciting cognitive-motor interference in persons with neurological impairment.[11] These cognitive tasks include serial subtraction by 3, verbal or phonemic fluency, and simple arithmetic problems with an n-back task. For serial subtraction by 3, participants will verbally perform serial subtraction from a randomly generated 3-digit number by 3. For verbal fluency, participants will be tasked with verbalizing as many words as possible that begin with a randomly generated letter every 30 seconds. Words that are proper nouns or different forms of a verb will not be considered. For the simple arithmetic problem task, the participants will be asked to solve a series of simple arithmetic problems provided at intervals of 2 seconds and verbalize if their response was larger or smaller than their previous response.

Two-minute rest breaks will be initially provided between each bout and will subsequently be reduced by 30 seconds every 3 weeks until a 1-minute rest break is achieved during weeks 5 and 6 of the intervention period. After each bout, all participants will report their perceived fatigue on the visual analog scale-fatigue and effort on RPE. Blood pressure and heart rate will be obtained to ensure participants were exercising within acceptable limits, ie, RPE of 11-15, blood pressure under 170/100, and heart rate within 40-60% of heart rate reserve (heart rate reserve = maximum heart rate – resting heart rate).

**CONCLUSIONS**

In conclusion, despite the prevalence and deleterious effects of cognitive-motor interference in individuals with MS, there continues to be a need for standardized measures of dual-task performance. The current paucity of valid and reliable clinical measures of dual-task performance makes generalizability of research challenging and application in the clinic by the clinician difficult. Thus, the first study of this dissertation sought to examine the psychometric properties and utility of the WART for use in individuals with MS.

Considering the prevalence of cognitive-motor interference in those with MS, as well as the effects of dual-task on gait and cognitive performance, little is currently known concerning methods by which to mitigate dual-task effects on performance. The second and third studies of this dissertation, therefore, examined the effects of a gait-specific dual-task training intervention on single-task and dual-task gait and cognitive performance, walking capacity, self-perceived walking ability, and subjective fatigue in individuals with MS.

CHAPTER III

RELIABILITY AND VALIDITY OF THE MODIFIED

WALKING AND REMEMBERING TEST IN

PERSONS WITH MULTIPLE SCLERSOSIS

**INTRODUCTION**

The control of gait and locomotion is no longer thought to be solely accomplished by automatic processes of the central nervous system. Current evidence from the early 2000s demonstrate that higher-order cognitive processes heavily influence the normal control of gait and locomotion and underpin the relationship between cognitive function and walking.[1,2] Particularly, deficits in information processing speed, memory, attention, and executive function have been found to adversely affect domains such as postural stability,[3,4] gait function,[5-13] fall risk,[9,14-16] and health-related quality of life.[17-23] The interaction between cognitive function and walking can be observed within the dual-task paradigm, specifically as cognitive-motor interference, which is the deterioration in the performance of one task in the presence of a simultaneous task.[24-26] This difference between dual-task performance (motor and cognitive) and single-task performance relative to single-task performance is measured as dual-task cost (%DTC).[6]

Deficits in both gait and cognitive function are well-established components MS symptomatology. Approximately 50% of individuals with MS experience some extent of gait dysfunction within the first year of their diagnosis.[27] This prevalence rate increases to 78% within 10 years of diagnosis, with more than half demonstrating moderate to severe gait disability.[27] In addition to gait dysfunction, 63% of persons with MS report problems with cognitive impairment within their first year of diagnosis, which increases to approximately 78% within 10 years of diagnosis, with almost half of these individuals demonstrating moderate to severe cognitive difficulties.[27] Consequently, those with MS experience deficits not only in walking and cognition separately but also in dual-task walking.[13]

The effects of cognitive-motor interference on gait performance in individuals with MS are also well established in the literature. Individuals with MS demonstrate reduced gait velocity, reduced step, and stride lengths, reduced cadence, and increased double limb support time during dual-task walking conditions.[5-9,11,12,14] Individuals with MS already experience motor and sensory deficits that contribute to pervasive balance and gait dysfunction, increasing risk of falls compared to those without MS.[28,29] Of greatest concern are findings from previous reports which demonstrate that gait-related performance deterioration during dual-task walking is related to increased fall risk in those with MS.[8,9,14,30]

Despite the known prevalence of cognitive-motor interference in persons with neurological conditions and MS, the few existing clinical measures of dual-task performance lack standardization and possess inherent limitations for use in individuals with MS.[25,31] Several measures, such as the SWWT,[31-33] WWTT,[31,34-36] and TUG-cog[37,38] are all clinical tests of dual-task performance that have been used in various non-clinical and clinical populations. Unfortunately, these clinical tests of dual-task performance do not account for the relative difficulty of the cognitive task in relation to the person's single-task ability.[25,31] Many of these tests only measure motor dual-task performance and do not account for cognitive dual-task performance. Factors such as education level, literacy, and language difficulties may greatly influence the performance and outcomes of these types of measures.[25] For example, the effect of a verbal component on some of these clinical dual-task measures necessitates further consideration, as the structural interference that speech articulation imposes may further load cognitive resources unrelated to the primary cognitive task.

Recommendations have been proposed to attempt to mitigate these methodological issues inherent in existing dual-task measures, especially as they relate to adjusting the difficulty of the dual-task to the person's single-task ability. A previous review recommended that the cognitive task that is used by a measure should be adjusted relative to the individual's single-task ability and that it should, if possible, avoid the cognitive tasks of verbal fluency and mathematical calculations to avoid complications with language or educational level.[25] One proposed solution is the use of a titrated forward digit span (a random sequence of numbers of a certain length) for single-task and dual-task conditions. The WART is a clinical measure of dual-task performance initially developed for older individuals,[31] but has since been validated in those with acquired brain injury.[39,40] The titrated forward digit span included in the WART is tailored to the participants' baseline working memory function. The titrated forward digit span measures the participant's working memory function, which is a component of information processing efficiency and executive function.[41,42] Working memory is characteristically impaired in persons with MS and associated with motor performance changes.[41,42]

The WART provides several other potential benefits over other clinical dual-task measures, including the use of readily available equipment, straightforward judgment of accuracy, absence of speech articulation, mitigation of pacing of walking, and limiting additional cognitive loads. Furthermore, each participant must walk at his or her fastest possible speed on the WART as opposed to walking at a self-selected comfortable speed. The use of a self-selected comfortable walking speed may not provide a sufficiently demanding load that could compete with secondary cognitive demands. Fundamentally, the other clinical dual-task measures that utilize self-selected comfortable walking speed, such as the SWWT and WWTT, may leave enough "reserve capacity" for other tasks to be performed.[43] The reliability and validity of the

WART have been established in community-dwelling older adults; however, its clinical utility and psychometric properties have not been explored for use in individuals with MS.

The purpose of this study was to evaluate the psychometrics of the WART for use in individuals with MS. Test-rest reliability and discriminant validity of the WART were assessed in participants with MS and without MS Specifically, the study examined if differences existed in gait velocity between single-task and dual-task conditions by group. Secondary analyses sought to determine if a relationship existed between disability level and dual-task performance, cognitive status, and dual-task performance.

## METHODS

This study was approved by the institutional review boards of Texas Woman's University Institute of Health Sciences – Houston Center (#20068) and The University of Texas Health Science Center at Houston (HSC-MS-18-0050).

### Participants

Prospective participants were recruited between 2018 and 2019 from the Greater Houston area through physician and rehabilitation across The Institute for Rehabilitation and Research (TIRR) and Memorial Hermann Rehabilitation Networks, the Greater Houston Chapter of the National Multiple Sclerosis Society, clinicaltrials.gov, and electronic and physical flyers sent to local MS support groups and physician clinics. English-speaking participants between the age of 18 years and 65 years were recruited. To be eligible for the study, participants were required to be able to walk independently with or without an assistive device; community-dwelling; have no history or presence of other clinically significant musculoskeletal, cardiovascular, respiratory or neurologic disease; and not currently receiving or scheduled to receive any rehabilitation during the study.

Participants with MS were required to have a neurologist-confirmed diagnosis of MS (EDSS $\leq 6.5$) and be relapse-free for the past 30 days. Additionally, participants were asked not to start any new medications that specifically target gait function or fatigue, eg, antispasmodics, potassium-channel blockers, or wakefulness-promoting agents, while enrolled in the study. If participants were already taking medication for gait or fatigue, they were asked not to modify their dosages for the duration of the study.

### Measures

**EDSS.** The EDSS was initially developed to measure the disability status of persons with MS and has been modified several times to more accurately reflect the levels of disability that are clinically observed.[44] The EDSS provides a total score from 0 to 10 with 0 indicating a normal neurological exam and 10 indicating death due to MS.[44] Gait and functional systems scores determine the total score on the EDSS.

**MoCA.** The MoCA screens for mild cognitive dysfunction in older adults and neurological populations. Its construct validity has been established for use in individuals with MS and is significantly correlated to neuropsychological measures of learning, delayed recall, executive functioning, and information processing.[45-47] The tool assesses short-term memory, visuospatial abilities, executive functions, attention, concentration, working memory, language, and orientation. It has been found to be more sensitive than the MMSE and has a higher ceiling effect than the MMSE.[45,46] A cutoff score of <26 has been identified to classify those with cognitive impairment.[47]

**WART.** The WART is comprised of 3 distinct tasks: single-task walking (fast pace) to obtain gait velocity (cm/s), digit-span testing to obtain the longest digit span the participant can remember, and dual-task walking (fast pace) to determine gait velocity (cm/s) and digit span recall accuracy (percent of digits correctly recalled).[31] Although path deviation may also be assessed with the WART, the mWART that is used for this study eliminates path deviation assessment.[40] The total length of the walkway used for the mWART in this study was 12 m (39.4 ft) with strips of brightly colored tape placed at the 1-m and 11-m mark to demarcate the 10 m testing zone.

The WART has been validated for use in older adults and the tool was found to detect dual-task changes in community-dwelling older adults and those with acquired brain injury.[31] It has excellent inter-rater reliability ($ICC_{2,1} \geq .97$) for walking time and digit span accuracy, and test-retest reliability is good ($ICC_{2,1} \geq .79$). Older adults were slower and remembered shorter digit spans than younger, healthy adults, and demonstrated greater dual-task costs for digit span accuracy.[31] However, due to the higher level of functioning of the older adults included in their study, relative dual-task costs for walking time were not significantly different between the older adult and younger adult groups.[31]

**ProtoKinetics Zeno Walkway.** The ProtoKinetics Zeno Walkway is a pressure-sensitive electronic walkway previously used in individuals with MS to detect and collect pressure data for balance and gait assessments.[48-51] The device and software calculates the center of pressure trajectories and is reliable and valid for measuring spatiotemporal gait parameters (eg, gait velocity, cadence, step length, double limb support time, etc) based on footfalls.[48]

## Procedures

Approvals from the institutional review boards were obtained. Prospective participants contacted the primary investigator, who screened the potential participants based on the inclusion criteria. At the laboratory, all participants were provided with both a written and a verbal explanation of the study procedures and were provided sufficient opportunity to ask any questions related to their participation in the study. After written consent was provided, participants were provided with a demographic questionnaire concerning relevant past medical history, assistive device use, falls history, and medications, as well as a release, to contact their physician if necessary.

Participants attended 2 testing sessions separated by at least 1 week, but no more than 2 weeks. All testing was performed by a physical therapist in a well-lit, obstacle-free, and level walkway. The Zeno Walkway was placed in the middle of the walkway to measure gait velocity. After screening and intake by the examiner, participants completed the mWART, which was scored by the examiner. The participants completed a total of 5 walking trials per testing session. Ninety-second seated rest breaks were provided by the examiner between walking bouts, and appropriate guarding of each participant was provided to ensure the participant's safety. For the practice walking trial, participants were asked to walk at their self-selected comfortable walking speed.

For the single-task walking condition, participants were asked to walk at their fastest possible walking speed along the designated walkway for 2 trials. Gait speeds for both trials were recorded and averaged to obtain the participants' mean single-task gait speed. For the second part of the mWART, a digit span test is administered in sitting. A digit span is a random sequence of numbers used to measure working memory capacity and requires the participants to repeat a series of digits of increasing length. Included in the mWART are 6 pairs of unique digit spans. Each digit span is a standardized random number sequence starting at a length of 4 digits, and the length of the digit spans increase by 1 digit in each subsequent pair for a possible 9 digits in the final pair. The participants were informed that they could use any method except writing or talking to help them remember the numbers. The examiner verbally provided the digit span from the first pair to the participant, and after a delay equivalent to the time it took the participant to walk in the single-task walking condition, the examiner cued the participant to repeat the numbers back to the examiner. The examiner repeated this process for each subsequent digit span until the participant was only able to recall 1 trial of a digit span correctly from a pair. For example, if the participant was able to correctly recall with 100% accuracy only the first digit span in the fourth pair (7 digits in length), but not the second digit span in that pair, then the digit span testing was stopped. The longest digit span correct for at least 1 trial was used to determine the length of the unique digit span for the dual-task condition and considered 100% correct in assessing cognitive errors.[52]

For the dual-task walking condition, the participants were verbally provided a unique digit span equal in length to that determined during the digit span testing. The examiner then immediately cued the participant to walk at his or her fastest speed. At the end of the walking trial, the examiner cued the participant to repeat the numbers back to the examiner. Similar to the digit span testing, participants were informed beforehand that they could use any method to remember the numbers, except saying them out loud. Two dual-task walking trials each with unique digit spans were performed and both gait velocity and digit span accuracy were recorded and averaged by the examiner for both of the trials.

**Statistical Analysis**

Data was entered into Microsoft Excel (2016) and exported to SPSS v25 (IBM, Chicago IL) for data analysis. Student *t*-Test and Fisher's Exact Test were used to compare, respectively, parametric or non-parametric data. Intra-class correlation coefficients ($ICC_{2,k}$) were calculated to evaluate test-retest reliability of gait velocity and digit span accuracy. ICC values of >0.9 are considered excellent reliability, 0.75-0.90 good reliability, 0.5-0.75 moderate reliability, and values less than 0.5 indicate poor reliability.

Relative dual-task costs (%DTC) were calculated for both gait velocity and digit span recall using the following formula[6]: $\%\mathrm{DTC} = \frac{(Single\ Task - Dual\ Task)}{Single\ Task} \times 100$. A %DTC value of greater or less than 0 for gait velocity represents a relative dual-task cost. A %DTC value of greater than 0 for digit span recall represents relative dual-task cost indicating a digit span accuracy of <100%.

To assess discriminant validity, separate mixed-model analysis of variance (ANOVA) with factors of time or condition (test-retest) and group (non-MS vs. MS) were conducted for gait velocity and digit span accuracy. Separate binomial logistic regressions were then performed to determine if gait velocity and digit span performance in single- and dual-task conditions were able to predict group membership. As a secondary analysis, separate mixed-model ANOVAs were performed to compare %DTC for gait velocity and digit span accuracy amongst different EDSS levels: mild (EDSS 2.0-3.5), moderate (EDSS 4.0-5.5), and severe (EDSS 6.0-6.5).[8] All tests utilized a significance level of $\alpha = .05$.

## RESULTS

Demographic characteristics for the 18 total participants are detailed in Table 2. No significant differences were found between groups for age and sex; however, the number of falls in the past 6 months was found to be significant between groups.

**Table 2.** Demographic and clinical characteristics of participants ($n$ = 18)

| **Variable** | **MS ($n$ = 12)** | **Non-MS ($n$ = 6)** | ***p*-value** |
|---|---|---|---|
| Age (years)[a] | 51.1 ± 13.4 (30-65) | 41.5 ± 17.2 (23-63) | $t$ = 1.31, $p$ = .21 |
| Sex ($n$) | | | |
| Male | 1 | 2 | $p$ = .245 |
| Female | 11 | 4 | |
| Mobility aids used ($n$) | | | |
| Cane | 2 | 0 | |
| Rollator | 3 | 0 | |
| None | 7 | 6 | |
| Clinical course ($n$) | | | |
| RRMS | 9 | | |
| SPMS | 3 | | |
| EDSS[b] | 5.0 (4-6) | | |
| Years since diagnosis[a] | 12.5 ± 8.5 (3.0-32.0) | | |
| MoCA | 23.5 ± 3.0 (18.0-28.0) | | |
| ≥1 fall in the past 6 months ($n$) | 7 | 0 | ***p* = .038**[†] |

Abbreviations: RRMS, relapsing-remitting MS; SPMS, secondary-progressive MS.
[a]age and years since diagnosis are reported in mean ± SD (range).
[b]EDSS reported as median (IQR).
[†]significant at $p$ < .05.

### Test-Retest Reliability

$ICC_{2,k}$ values for single-task gait velocity, dual-task gait velocity, single-task digit span, and dual-task digit span between sessions for both groups are found in Table 3. All components of the measure suggest good to excellent reliability, except for the dual-task digit span condition, which suggests poor reliability.

**Table 3.** $ICC_{2,k}$ values for test-retest reliability of the mWART

| | **MS** | | **Non-MS** | |
|---|---|---|---|---|
| **Variable** | **$ICC_{2,k}$** | ***p*-value** | **$ICC_{2,k}$** | ***p*-value** |
| Single-task gait velocity | .961 | **<.001**$^{\dagger}$ | .903 | **.010**$^{\dagger}$ |
| Dual-task gait velocity | .968 | **<.001**$^{\dagger}$ | .874 | **.023**$^{\dagger}$ |
| Single-task digit span | .829 | **.004**$^{\dagger}$ | .828 | **.035**$^{\dagger}$ |
| Dual-task digit span | .439 | .154 | .816 | .057 |

$^{\dagger}$significant at $p < .05$.

### Gait Velocity

Descriptive statistics for gait velocity are located in Table 4. Both groups demonstrated similar increases in single-task gait velocity at the second assessment. There was a significant main effect of group for single-task gait velocity [$F(1,16) = 18.64$, $p = .001$, partial $\varepsilon^2 = .054$] and dual-task gait velocity [$F(1,16) = 13.67$, $p = .002$, partial $\varepsilon^2 = .46$] with the group without MS demonstrating faster gait velocity. However, no significant effects of time [single task: $F(1,16) = 2.26$, $p = .15$, partial $\varepsilon^2 = .12$; dual-task: $F(1,16) = 0.15$, $p = .71$, partial $\varepsilon^2 = .009$] or interaction were found for both conditions [single-task: $F(1,16) = 6.77$, $p = .82$, partial $\varepsilon^2 = 0.003$); dual-task: $F(1,16) = 1.81$, $p = .20$, partial $\varepsilon^2 = .10$].

A binomial logistic regression was performed to determine the effect of single-task gait velocity and dual-task gait velocity on the likelihood that participants have MS. The logistic regression model for single-task gait velocity was statistically significant, $\chi^2(1) = 22.915$, $p < .0005$. The model explained 100.0% (Nagelkerke $R^2$) of the variance in group membership and correctly classified 100.0% of cases. The logistic regression model for dual-task gait velocity was also statistically significant, $\chi^2(1) = 18.194$, $p < .0005$. The model explained 88.3% (Nagelkerke $R^2$) of the variance in group membership and correctly classified 94.4% of cases.

**Table 4.** Gait velocity and digit span scores

| | **MS** | | **Non-MS** | | **Group main effect *p*-value** |
|---|---|---|---|---|---|
| | **Time 1** | **Time 2** | **Time 1** | **Time 2** | |
| Gait velocity (cm/s) | | | | | |
| Single-task | 94.5 ± 45.5 (6.5-146.6) | 101.3 ± 48.5 (10.2-167.2) | 180.7 ± 16.1 (162.6-210.5) | 185.7 ± 20.2 (166.7-222.2) | **.001**† |
| Dual-task | 95.3 ± 44.7 (5.9-145.4) | 101.8 ± 49.9 (8.0-173.8) | 173.8 ± 16.4 (157.5-204.1) | 170.2 ± 19.1 (155.0-198.0) | **.002**† |
| Digit span (n) | | | | | |
| Single-task | 5.9 ± 1.3 (4.0-8.0) | 6.1 ± 1.1 (5.0-8.0) | 6.5 ± 1.5 (5.0-9.0) | 6.0 ± 1.3 (5.0-8.0) | .68 |
| Dual-task | 3.8 ± 3.7 (1.0-8.0) | 4.7 ± 1.2 (3.0-7.0) | 5.3 ± 1.5 (3.5-7.0) | 5.3 ± 1.7 (3.5-7.0) | .50 |

All values displayed as mean ± SD (range).
†significant at $p < .05$.

**Digit Span Scores**

Descriptive statistics for digit span scores are located in Table 4. There were no significant differences found between groups or time for single-task and dual-task digit span lengths. No significant main effects of group [$F(1,6) = .18$, $p = .68$, partial $\varepsilon^2 = .01$], time [$F(1,16) = .57$, $p = .50$, partial $\varepsilon^2 = .03$], or interaction effects [$F(1,16) = 1.88$, $p = .19$, partial $\varepsilon^2 = .10$] were found for single-task digit span scores. No significant effects of group [$F(1,16) =

2.53, $p$ = .13, partial $\varepsilon^2$ = .14], time [$F$(1,16) = .88, $p$ = .36, partial $\varepsilon^2$ = .057], or interaction effects [$F$(1,16) = 1.28, $p$ = .27, partial $\varepsilon^2$ = .07] were found for dual-task digit span scores.

A binomial logistic regression was performed to determine the effect of single-task digit span scores and dual-task digit span scores on the likelihood that participants have MS. The logistic regression model for single-task digit span scores was statistically non-significant, $\chi^2(1) = 0.20$, $p = .65$. The model explained 1.5% (Nagelkerke $R^2$) of the variance in group membership and correctly classified 66.7% of cases. The logistic regression model for dual-task digit span score was also statistically non-significant, $\chi^2(1) = 2.61$, $p = .11$. The model explained 18.7% (Nagelkerke $R^2$) of the variance in group membership and correctly classified 72.2% of cases.

**Relative Dual-Task Costs**

Those with MS demonstrated %DTCs of gait velocity averaging −1.2% to 2.1%, while the non-MS group demonstrated %DTCs of gait velocity averaging 3.7% to 8.2% (see Table 5). No significant main effects or interaction effects were found for %DTCs for gait velocity [group: $F$(1,16) = 2.50, $p$ = .13, partial $\varepsilon^2$ = .14; time: $F$(1,16) = 2.93, $p$ = .11, partial $\varepsilon^2$ = .004; group x time: $F$(1,16) = 0.06, $p$ = .81, partial $\varepsilon^2$ = .004].

Greater %DTCs were found for those with MS at both assessment periods compared to those without MS (see Table 5). Generally, those with MS recalled fewer digits during the dual-task condition compared to those without MS, who were able to recall a greater number of digits. However, no significant main effects or interaction effects were found for %DTCs for digit span score [group: $F$(1,16) = 3.12, $p$ = .10, partial $\varepsilon^2$ = .16; time: $F$(1,16) = 1.49, $p$ = .24, partial $\varepsilon^2$ = .09; group x time: $F$(1,16) = 0.18, $p$ = .67, partial $\varepsilon^2$ = .01].

**Table 5.** Mean relative dual-task costs (%DTC) for gait velocity and digit span

| | **MS** | | **Non-MS** | |
|---|---|---|---|---|
| **Variable** | **Time 1** | **Time 2** | **Time 1** | **Time 2** |
| Gait velocity | −1.2 ± 9.5 (−16.3-11.1) | 2.1 ± 8.8 (−8.4-21.2) | 3.7 ± 5.7 (−5.1-11.81) | 8.2 ± 6.4 (3.0-14.5) |
| Digit span | 34.5 ± 29.6 (0.0-80.0) | 22.2 ± 16.2 (0.0-50.0) | 18.2 ± 11.8 (0.0-30.0) | 12.3 ± 13.9 (0.0-30.0) |

All values displayed as mean ± SD (range).

**Disability Level & %DTC**

Significant differences were found for %DTC for gait velocity for participants with MS by EDSS level [$F(2,9) = 5.3$, $p = .03$] (see Table 6). Post-hoc analysis found significantly higher %DTC for mild vs severe EDSS level (mean difference = 11.72, 95% CI [−0.86,24.3)], $p = .04$) and for moderate vs severe EDSS level (mean difference = 11.28, 95% CI [0.21,22.34], $p = .046$). However, no significant differences were found for %DTC for digit span scores by EDSS level [$F(2,9) = .02$, $p = .99$].

**Table 6.** Differences in %DTC by disability level for gait velocity and digit span

| | **EDSS level** | | | |
|---|---|---|---|---|
| **Variable** | **Mild** | **Moderate** | **Severe** | ***p*-value** |
| Gait velocity | −3.62 ± 1.80 (−4.85 - [−1.56]) | −3.18 ± 7.13 (-9.89-4.66) | 8.10 ± 5.33 (-3.85-15.50) | **.030**† |
| Digit span | 27.29 ± 10.27 (15.63-35.00) | 29.48 ± 19.83 (5.00-55.00) | 27.83 ± 21.73 (14.29-60.00) | .985 |

All values displayed as mean ± SD (range).
†significant at $p < .05$.

## DISCUSSION

In line with previous studies of the WART, the study findings support the test-retest reliability of the mWART over 2 weeks for those with MS and without MS. Participants included in this study, however, had a mean age of 51.1 ± 13.4 years for the MS group and 41.5 ± 17.2 years for the non-MS group. Included in the MS group were participants with RR-MS (*n* = 9) and SP-MS (*n* = 3). The dual-task digit span condition for those with MS demonstrated the poorest reliability compared to the other conditions, and results pertaining to improvements on this part of the measure may require greater consideration. This poor reliability in dual-task digit span could be related to the heterogeneous symptomatology of MS that can vary day-to-day depending on factors such as motor or cognitive fatigue.[53-55] In turn, this day-to-day variation could adversely affect motor performance, cognitive performance, or both. Specifically, if fatigued, those with MS may sacrifice cognitive performance to ensure safety with mobility tasks, such as walking, which may account for the difference and poor test-rest reliability observed between the 2 assessment periods. This observed difference is especially important as there are no instructions included in the mWART specifying task prioritization during the dual-task walking condition. This finding may suggest that clinical measures should be repeated, and scores compared and averaged to obtain a more reliable picture of the individual's overall performance.

As expected, there were differences in baseline gait velocity between those with MS and without MS during both single- and dual-task conditions. Logistic regression analyses also found that both single-task and dual-task gait velocity were able to predict the likelihood of a participant having MS. However, these observations with gait velocity were not reflected in single-task and dual-task cognitive performance on the digit span task. Those with MS tended to walk at a slower gait velocity than their non-MS counterparts, but these results were stable over time. The finding that participants with MS walk slower than their non-MS counterparts raises the question of the potentially greater impact a slower gait velocity has on functional independence. A small reduction in speed for individuals that already walk at a slower gait velocity may reach a lower threshold for associated outcomes or comorbidities.[56] Both groups also demonstrated the non-significant differences in digit span lengths for each condition and may relate to the dual-task costs identified during each assessment period.

Both groups demonstrated similar changes in %DTC of gait velocity. Although statistically non-significant, the MS group demonstrated less %DTC of gait velocity as compared to the non-MS group. When %DTCs for digit span recall is considered, however, the MS group demonstrated a larger %DTC of digit span recall compared to their non-MS counterparts. In respect to the MS group's median disability level (EDSS 5.0), as well as the mean length of diagnosis (12.5 years), the participants with MS included in this study may have developed compensatory mechanisms that prioritize motor performance over cognitive performance, which may account for why the participants with MS had less %DTC of gait performance, but greater %DTC of cognitive performance. For those with greater motor deficits, this compensatory mechanism of prioritizing motor performance over cognitive performance may be important to their ability to maintain their balance or safety during walking and prevent adverse events such as falls.[57] Fifty-eight percent of the participants with MS in this study fell at least once in a 6-month period. Considering falls in MS are more often attributed to distraction or attentional deficits,[58] this compensatory mechanism is not necessarily a negative phenomenon and should not be discouraged by clinicians.

Unexpectedly, the performance of the MS group under dual-task conditions did not differ from the performance of the non-MS group. This finding, however, is consistent with results from a recent meta-analysis that found dual-task performance did not differ in magnitude between those with and without MS, emphasizing that cognitive-motor interference is largely a universal process between those with and without MS. The authors of the meta-analysis did concede that although similar changes in dual-task performance were observed between those with and without MS, differences in neural activation during dual-task conditions may exist. Those with MS may require greater activation of specific neural structures in order to perform under dual-task conditions compared to those without MS similarly. The results of this current study, however, further suggest that those with higher disability levels (EDSS 5.0-6.5) demonstrate greater %DTC of gait velocity as compared to those with lower levels of disability (EDSS 2.0-4.5). This finding may be related to both the differences in the level of motor impairment and method of task prioritization between those with higher and lower disability levels. However, this finding did not extend to cognitive performance as previous studies suggest that cognitive impairment may exist independently from that of neurological or functional disability.[59,60]

The limitations of this study are that the sample sizes for both groups were smaller than the recommended sample size of 30 per group.[61] Additionally, the sample sizes were unequal between groups. The small sample size limits the power of the study to find differences that may have existed if sample sizes for both groups were larger. Participants with MS included in the study only included those with a relapsing course of MS (RR-MS and SP-MS). Caution should be taken when generalizing these results to individuals with progressive forms of MS (ie, PP-MS). Finally, the participants with MS included in this study were of higher EDSS level (EDSS median: 5.0) and lower cognitive status (MoCA mean: 23.5/30). The MoCA was used only as a screening tool for cognitive impairment in the sample of persons with MS. More comprehensive and sensitive measures of cognitive capacity are necessary to better draw conclusions about the relationship of cognition impairment and the mWART. Additional studies are warranted to explore further the mWART's reliability and validity in a more heterogeneous sample of persons with MS. These future studies may also explore other sources of variability, such as cognitive status and clinical course, as well as further explore the mWART's relationship to fall risk in those with MS.

The current study provides preliminary evidence of test-retest and discriminant validity of the mWART for use in individuals with MS. The mWART is an easily administered clinical measure and provides several benefits over other current measures of dual-task performance: tests at a higher mobility level than self-selected comfortable walking speed, tailors the difficulty of the cognitive task to the individual's working memory capacity, and provides a measure of both single-task and dual-task motor and cognitive performance.

## CLINICAL RELEVANCE

- The mWART is reliable and valid over time in those with MS but should be performed more than once to account for the day-to-day variability of symptoms in those with MS.
- Gait and cognitive performance under single-task and dual-task conditions do not differ between participants with MS and those without MS, suggesting that dual-task interference is a shared phenomenon and not unique to MS only.
- Single-task and dual-task gait velocity, but not cognitive performance on the mWART were able to differentiate between participants with MS and those without MS.
- Further studies are required to further explore the reliability and validity of the mWART in a larger and more heterogeneous sample of persons with MS.

## COMPETING INTERESTS

The authors declared that there is no conflict of interest.

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CHAPTER IV

# GAIT-SPECIFIC DUAL-TASK TRAINING FOR INDIVIDUALS WITH MULTIPLE SCLEROSIS

## INTRODUCTION

Individuals with MS present with both motor and cognitive impairments that typically interfere with their daily functioning, social engagement, general life satisfaction, and quality of life.[1-7] Recent studies have examined the relationship between motor functioning and cognitive impairment in individuals with MS, especially as it relates to balance and gait.[8-17] Previous research that has focused on individuals with MS and other neurological diagnoses has found that the concomitant performance of a motor and cognitive task (dual-task) results in cognitive-motor interference.[18,19] Considering the high prevalence of cognitive impairment in individuals with MS,[4,20-23] as well as the persistent motor deficits they experience, the performance of an everyday mobility task such as walking is significantly impacted in the presence of an additional cognitive load. This increased demand exerted by both the motor and cognitive task on finite cognitive resources in those with MS has been shown to contribute to balance impairment,[8,9] gait dysfunction,[10-17,24] and increased fall risk.[24-26]

While gait dysfunction has been greatly attributed to MS symptoms such as muscle weakness, pain, spasticity, sensory disturbances, and fatigue,[27-31] research within the last decade has associated cognitive dysfunction with motor impairments in balance and gait, an interaction known as cognitive-motor interference.[11,32-34] Studies have demonstrated that cognitive impairment is a significant predictor of gait variability and falls in patients with MS.[24-26] Studies specifically examining cognitive-motor interference in individuals with MS have found that cognitive-motor dual-tasking adversely impacts specific spatiotemporal gait parameters, such as gait velocity, step length, cadence, double limb support time, and swing time variability, all of which are associated with increased fall risk.[19,35-38] These findings demonstrate the possible direct influence of cognitive impairment on gait function and overall mobility status.

Although studies exploring the effectiveness of dual-task interventions in neurological populations exist[19]; eg, PD,[39-43] older adults,[44,45] and stroke,[46] there is a paucity of studies on individuals diagnosed with MS despite the prevalence of both motor and cognitive impairments in this population. In populations such as those with Parkinson disease, dual-task training has been found to improve gait velocity, step length, gait variability, and fall risk.[19,39-43] Additionally, in individuals with stroke, dual-task training improves postural stability, single-task walking performance, and overall mobility based on functional measures of mobility as compared to single-task training.[47,48] However, despite the prevalence of cognitive-motor interference in individuals with MS and the reported benefits of dual-task training in other populations with neurological diagnoses, no study was identified within the MS literature that examined the effects of a gait-specific dual-task training intervention on dual-task of gait performance.

Specifically, current studies investigating dual-task interventions for individuals with MS incorporate multiple modes of dual-task training interventions, which may have consisted of balance training, therapeutic exercises, group exercise, gait training, and aerobic training. These multiple modes of interventions result in the ambiguity of the effects of the single intervention strategies.[49-52] These previous studies were unable to distinguish the specific intervention that may have contributed to improvements in both single-task and dual-task outcomes. The use of non-standardized interventions, mixed groups, and individualized regimens further complicated reproducibility and clinical utility of study findings. The use of non-standardized dual-task measures also added to the difficulty of reproducibility of the studies' findings.

By demonstrating improvements in dual-task gait performance following a gait-specific dual-task training intervention, guidance can be provided to clinicians on how to structure dual-task interventions for their patients with MS. The purpose of this research investigation was to assess the feasibility and effect of a 6-week, 18 sessions, gait-specific dual-task intervention on %DTC, and measures of dual-task gait (gait velocity, cadence, and step length) and cognitive performance in individuals with MS.

**METHODS**

This study was a single-blinded randomized control trial exploring the feasibility and effects of a 6-week intervention utilizing a dual-task of gait training protocol (experimental condition) as compared to a gait training protocol (control condition) on single-task and dual-task of gait parameters: gait velocity, cadence, and step length (#NCT03536299). All procedures for the study were approved by the institutional review boards of Texas Woman's University Institute of Health Sciences – Houston Center (#20068) and The University of Texas Health Science Center at Houston (HSC-MS-18-0050).

**Participants**

Prospective participants were recruited from 2018-2019 through various avenues: physician and rehabilitation clinics across TIRR and Memorial Hermann Rehabilitation Networks, the Greater Houston Chapter of the National Multiple Sclerosis Society, clinicaltrials.gov, and electronic flyers sent to local MS support groups and physician clinics around the Greater Houston Area. Individuals with MS between the ages of 18 and 65 years were recruited. To be included in the study, the participants were required to have the ability to speak and understand English; have a neurologist confirmed diagnosis of MS (EDSS $\leq 6.5$ ); be relapse-free for the past 30 days, be able to walk independently with or without an assistive device; be community-dwelling; have no history or presence of other clinically significant musculoskeletal, cardiovascular, respiratory, or neurologic disease; and not currently receiving or scheduled to receive any rehabilitation services during the study. Additionally, participants were asked not to start any new medications specifically targeting gait or fatigue (eg, antispasmodics, potassium-channel blockers, or wakefulness-promoting agents), while enrolled in the study. If participants were already taking such medications, they were asked not to change dosages for the duration of the study.

**Procedures**

Approvals from the institutional review boards were obtained. Interested participants contacted the primary investigator, who screened the potential participants based on the inclusion criteria. All testing was performed at the Texas Woman's University Institute of Health Sciences – Houston Center's Motion Analysis Laboratory. All participants were provided with both a written and verbal explanation of the study procedures and were provided sufficient opportunity to ask any questions related to their participation in the study. After consent was obtained, participants were provided with a demographic questionnaire concerning their MS clinical course, years since diagnosis, assistive device use, falls history, medications, and past medical history, as well as a release to contact their neurologist to confirm EDSS level.

Randomization of study participants into DT or ST groups was completed using a random number generator in Microsoft Excel (2016). Blood pressure and heart rate were obtained before and after the session to ensure patients were safe to perform the assessments. The same assessments were provided at each assessment period by the primary investigator, a licensed physical therapist. Participants completed 2 initial outcome assessments at the laboratory at least 1 week apart prior to initiating the 6-week intervention period. These assessments included the administration of the mWART. The walking trials of the mWART were performed over a 10-meter distance with the central portion of the walking track covered by the Protokinetics Zeno™ Walkway Gait Analysis System (Protokinetics LLC, Havertown PA), which has been found to be reliable and valid in measuring the center of pressure trajectories and spatiotemporal gait parameters (eg, gait velocity, cadence, step length, double limb support time) based on footfalls.[53] Gait velocity, cadence, and step length were processed by the accompanying PKMAS software (Protokinetics LLC, Havertown PA).[53]

Data from these 2 initial assessments were then averaged to provide the data for baseline outcomes. The participants completed a post-intervention assessment upon the termination of the 6-week intervention and a follow-up outcome assessment within 4 weeks of the termination of the 6-week intervention period.

**Measures**

Cognitive status was measured with the MoCA, which is a tool used to screen for mild cognitive impairment in older adults and neurological populations.[54-57] The MoCA assesses short-term memory, visuospatial abilities, executive functions, attention, concentration, working memory, language, and orientation. The MoCA has been found to be a valid screening tool for mild cognitive impairment in individuals with MS and a cut-off score of <26 has been identified to classify those with cognitive impairment.

The outcome measures for this study were gait velocity (cm/s), cadence (steps/min), step length (cm), and cognitive performance during the WART. The WART is a clinical tool used to measure dual-task walking performance and cost using a titrated digit span (working memory).[58]

The mWART is comprised of 3 distinct tasks, each performed twice: single-task fast walk, single-task cognitive task, and dual-task fast walk. The WART has been found to be a useful measure for measuring dual-task cost in healthy adults, older adults, and those with acquired brain injury.[58-60] The mWART eliminates the path deviation assessment included in the original version of the WART.[59]

For the single-task walking condition, participants were asked to walk at their fastest possible walking speed along the designated walkway for 2 trials. Gait speeds for both trials were recorded and averaged to obtain the participants' mean single-task gait speed. For the second part of the mWART, a digit span test is administered in sitting. A digit span is a random sequence of numbers of used to measure working memory capacity and requires the participants to repeat a series of digits of increasing length. Included in the instructions of the mWART are 6 pairs of unique digit spans. Each digit span is a standardized random number sequence starting at a length of 4 digits, and the length of the digit spans increase by 1 digit in each subsequent pair for a possible 9 digits in the final pair. The participants were informed that they could use any method except writing or talking to help them remember the numbers. The examiner verbally provided the digit span from the first pair to the participant, and after a delay equivalent to the time it took the participant to walk in the single-task walking condition, the examiner cued the participant to repeat the numbers back to the examiner. The examiner repeated this process for each subsequent digit span until the participant was only able to recall 1 trial of a digit span correctly from a pair. For example, if the participant was able to correctly recall with 100% accuracy only the first digit span in the fourth pair (7 digits in length), but not the second digit span in that pair, then the digit span testing was stopped. The longest digit span correct for at least 1 trial was used to determine the length of the unique digit span for the dual-task condition and considered 100% correct in assessing cognitive errors.[61]

For the dual-task walking condition, the participants were verbally provided a unique digit span equal in length to that determined during the digit span testing. The examiner then immediately cued the participant to walk at his or her fastest speed. At the end of the walking trial, the examiner cued the participant to repeat the numbers back to the examiner. Similar to the digit span testing, participants were informed beforehand that they could use any method to remember the numbers, except saying them out loud. Two dual-task walking trials each with unique digit spans were performed and both gait velocity and digit span accuracy were recorded and averaged by the examiner for both of the trials.

**Interventions**

Participants were randomized into 2 groups: DT and ST. Both groups underwent a 6-week intervention program consisting of 1-on-1 gait training sessions 3 days per week for 18 total sessions (see Figure 5). Each session was led by a licensed physical therapist with experience in treating individuals with MS. Each training session consisted of 5 different training blocks with each block consisting of 4 minutes of total gait training time for an entire session walking time of 20 minutes. Each block was further divided into 2 gait training bouts with 2-minute rests between each bout. Participants were instructed to walk at a self-selected gait speed they could maintain for each 2-minute bout. The ST group was asked to focus on gait performance and walk without any distractors of music, talking, or reading during all bouts. ST group participants were provided with feedback regarding gait performance after each bout. For example, participants may have been instructed to "take larger steps," "walk in a straight line," "pick up your foot more," or other cues to address the participants' specific gait deviations. In addition to the same gait training protocol, participants in the DT group performed a randomly selected cognitive task for each bout (6 hours total of dual-task–specific practice).[62] For each block with the DT group, participants were asked to prioritize either their gait performance or cognitive performance.

| **Dual-Task Training** | **Block 1** | **Block 2** | **Block 3** | **Block 4** | **Block 5** |
|---|---|---|---|---|---|
| Total walk time | 4 min | 4 min | 4 min | 4 min | 4 min |
| Walking sets | 2x2 min bouts<br>2 min rest | 2x2 min bouts<br>2 min rest | 2x2 min bouts<br>2 min rest | 2x2 min bouts<br>2 min rest | 2x2 min bouts<br>2 min rest |
| Task prioritization | None | Gait | Cognitive | Gait | Cognitive |
| Cognitive tasks | Three cognitive tasks randomized within each block:<br>• Serial subtraction by threes<br>• Verbal/phonemic fluency<br>• Simple arithmetic problem with *n*-back task ($n$ = 1) | | | | |

**Figure 5.** Dual-task training protocol.

The cognitive tasks incorporated into the DT group intervention targeted cognitive domains shown to be impaired in individuals with MS and have been previously described as eliciting cognitive-motor interference in persons with neurological impairment.[4] These included serial subtraction by 3, verbal fluency, and simple arithmetic problems with an *n*-back. An *n*-back task is a task of working memory in which the *n* refers to how many previous stimuli that the participant must remember. For serial subtraction by 3, participants verbally performed serial subtraction from a randomly generated 3-digit number by 3. For verbal fluency, participants were tasked to verbalize as many words as possible that begin with a randomly generated letter every 30 seconds. For the simple arithmetic problem task, the participants were asked to solve a series of simple arithmetic problems provided at intervals of 2 seconds and verbalize if their response was larger or smaller than their previous response (*n*-back task of $n = 1$).

Two-minute rest breaks were initially provided between each bout and were subsequently reduced by 30 seconds every 2 weeks until a 1-minute rest break was achieved during weeks 5 and 6 of the intervention period. After each bout, all participants reported their perceived fatigue on the visual analog scale-fatigue and effort on RPE. Blood pressure was obtained before and after each session. Heart rate was also obtained after each walking bout to ensure participants were exercising within acceptable limits, ie, RPE of 11-15, blood pressure under 170/100, and heart rate within 40-60% of heart rate reserve (heart rate reserve = maximum heart rate – resting heart rate).

**Statistical Analysis**

Data was entered into Microsoft Excel (2016) and exported into SPSS v25 (IBM, Chicago IL) for analysis. For demographic characteristics, the Mann-Whitney test or Fisher's Exact test, and Student *t* tests were used to compare the median for non-parametric variables and the mean for parametric demographic variables, respectively. Descriptive statistics were calculated for primary and secondary outcome variables with percent change ($\Delta x$%) reported from pre to post and post to follow-up. Friedman analysis of variance tests were run to determine if there were differences in gait velocity, step length, and cadence during the 6-week training program. Pairwise comparisons were performed with a Bonferroni correction for multiple comparisons. Mann-Whitney tests were performed to determine if there were any differences between groups for each primary outcome. A significance level of .05 was set for all tests.

%DTCs[11] were computed for gait velocity, cadence, and step length to assess performance changes between single-task and dual-task walking conditions. Relative dual-task costs (%DTC) were calculated using the following formula[11]:

$$\%\mathrm{DTC} = \frac{(Single\ Task - Dual\ Task)}{Single\ Task} \times 100.$$

A %DTC value of greater or less than zero for gait outcomes represents a relative dual-task cost. A positive %DTC indicates a decrement in performance during the dual-task condition as compared to the single-task condition, while a negative %DTC indicates an improvement in performance during the dual-task condition over the single-task condition.

**RESULTS**

A total of 28 individuals with MS were assessed for eligibility. After screening, 14 participants were enrolled and randomized into the 2 groups and underwent baseline assessment. The flow diagram in Figure 6 provides an overview of the 11 total participants who underwent randomization into the DT group (*n* = 6) and ST group (*n* = 5). After enrollment, 1 participant withdrew because of work-related conflicts, 1 withdrew due to drive distance and time commitment, and 1 was withdrawn by the primary investigator after failing to attend sessions.

The sample characteristics for each group are reported in Table 7. There were no significant differences found between groups for age, sex, MS clinical course, years since diagnosis, EDSS, and MoCA scores at pre-intervention. None of the participants who were enrolled in the study and underwent the 2 intervention protocols reported any adverse events, such as falls, excessive fatigue, prolonged soreness, or pain directly associated with the intervention.

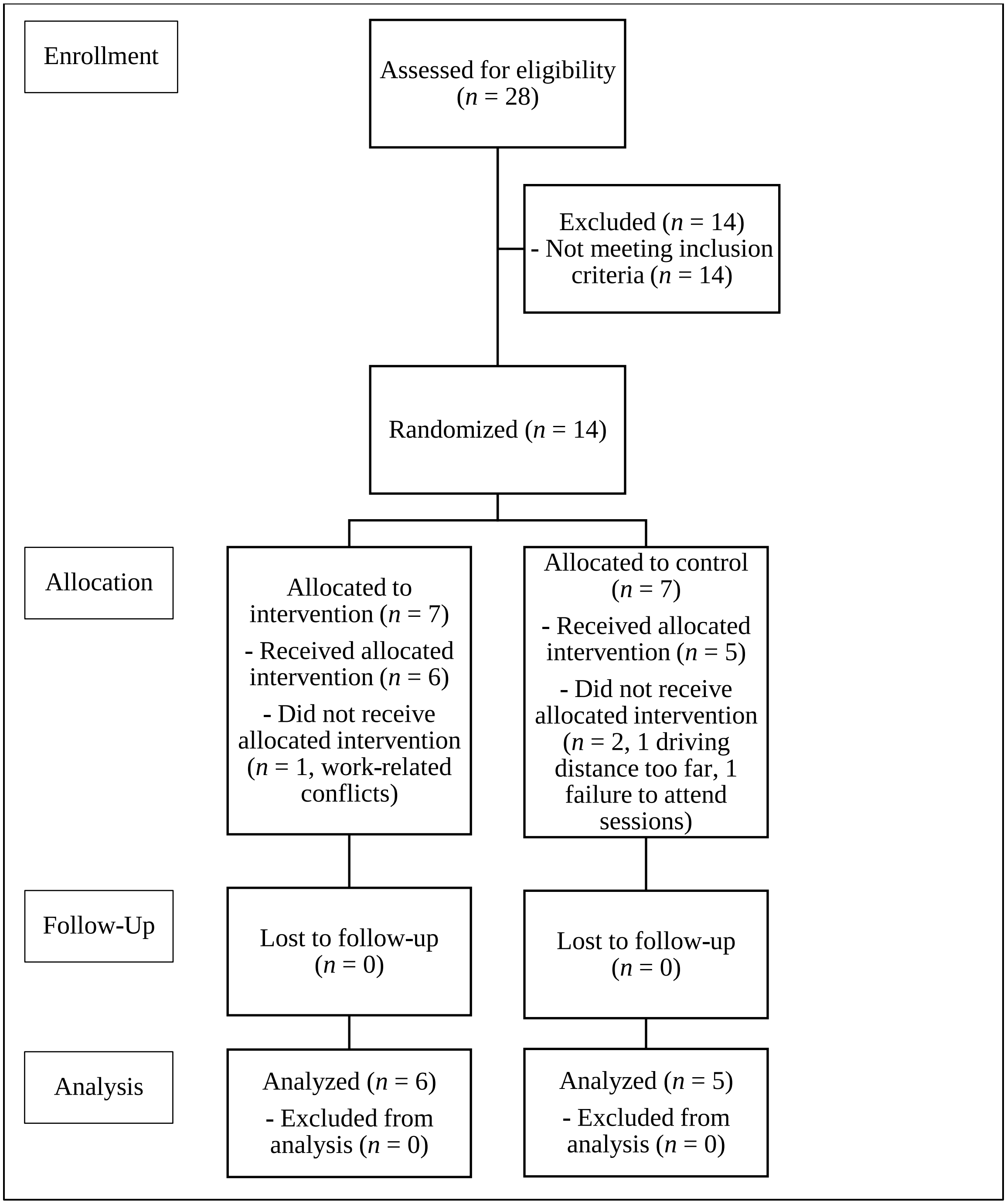


**Figure 6.** Flow diagram from enrollment to analysis of participants.

**Table 7**. Demographic and clinical characteristics of participants in both groups ($n$ = 11)

| **Variable** | **DT Group ($n$ = 6)** | **ST Group ($n$ = 5)** | ***p*-value** |
|---|---|---|---|
| Age, years[a] | 50.0 ± 15.2 (30-65) | 54.8 ± 12.2 (36-65) | $t$ = .57, $p$ = .58 |
| Sex | Female = 6 Male = 0 | Female = 4 Male = 1 | Test statistic NA, $p$ = .46 |
| MS clinical course | RRMS = 5 SPMS = 1 | RRMS = 3 SPMS = 2 | $U$ = 11.50, $p$ = .54 |
| Years since diagnosis[a] | 11.0 ± 7.20 (3-22) | 16.2 ± 9.9 (6-32) | $t$ = 1.01, $p$ = .34 |
| EDSS[b] | 4.25 (2.38-5.63) | 6.0 (5-6) | $U$ = 7.50, $p$ = .18 |
| MoCA[a] | 23.2 ± 2.3 (20.0-27.0) | 22.9 ± 3.5 (18.0-27.0) | $t$ = −0.152, $p$ = .88 |

Abbreviations: RRMS, relapsing-remitting MS; SPMS, secondary-progressive MS.
[a]Age, years since diagnosis, and MoCA scores are reported in mean ± SD (range).
[b]EDSS is reported as median (IQR).

### Gait Velocity

Descriptive statistics for the outcome measures are reported in Table 8 and Table 9. Descriptive analyses for both groups demonstrated improvements at post-intervention with gait velocity in both dual-task and single-task walking conditions. The DT group, however, demonstrated a greater percent change (18.6%) compared to the ST group (9.7%) in the single-task condition (see Table 10). Both groups demonstrated a decrement in dual-task gait velocity at follow-up, but the DT group demonstrated mildly better retention of dual-task gait velocity (DT: −3.5%, ST: −8.0%), while the ST group demonstrated better retention of single-task gait velocity (DT: −2.6%, ST: 0.2%).

**Table 8.** Primary measures and %DTC of gait and cognitive performance on the mWART for the dual-task group

| | Pre | | | Post | | | Follow-up | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **ST** | **DT** | **%DTC** | **ST** | **ST-task** | **%DTC** | **ST** | **DT** | **%DTC** |
| Gait velocity, cm/s | 112.0 ± 58.6 (25.6-180.1) | 114.32 ± 59.7 (24.3-188.5) | −1.7 ± 5.7 (−8.77-5.3) | 132.8 ± 60.4 (28.5-192.0) | 129.2 ± 64.7 (21.8-198.2) | 6.2 ± 10.4 (−3.24-23.7) | 129.4 ± 57.9 (25.8-189.7) | 124.7 ± 56.9 (35.5-193.7) | 3.6 ± 4.2 (−0.52-9.0) |
| Cadence, steps/min | 110.7 ± 33.4 (49.6-135.5) | 111.5 ± 34.1 (48.6-139.7) | −0.5 ± 2.7 (−4.4-2.2) | 117.7 ± 35.2 (48.6-146.2) | 115.9 ± 37.2 (44.2-148.3) | 2.5 ± 5.1 (−3.1-9.1) | 116.9 ± 33.1 (52.3-141.1) | 113.2 ± 33.3 (49.6-136.8) | 3.4 ± 3.8 (−1.32-9.6) |
| Step length, cm | 56.4 ± 19.0 (30.8-80.9) | 57.3 ± 18.8 (30.5-81.9) | −1.8 ± 3.3 (−5.7-2.5) | 63.9 ± 17.4 (35.9-85.1) | 61.9 ± 19.7 (29.2-85.6) | 4.5 ± 7.2 (−0.9-18.6) | 63.4 ± 15.9 (42.5-85.0) | 62.9 ± 15.7 (42.6-85.4) | 0.6 ± 2.0 (−0.5-4.6) |
| Cognitive performance | 6.0 ± 1.2 (4.5-7.5) | 4.0 ± 1.0 (2.5-5.0) | 32.4 ± 16.8 (5.56-54.6) | 6.7 ± 1.0 (5.0-8.0) | 4.8 ± 0.8 (4.0-6.0) | 27.1 ± 17.4 (0.0-42.86) | 6.5 ± 1.2 (5.0-8.0) | 5.2 ± 1.2 (5.0-8.0) | 19.9 ± 14.1 (0.0-43.8) |

All values are reported a mean ± SD (range).

**Table 9.** Primary measures and %DTC of gait and cognitive performance on the mWART for the single-task group

| | Pre | | | Post | | | Follow-up | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **ST** | **DT** | **%DTC** | **ST** | **ST-task** | **%DTC** | **ST** | **DT** | **%DTC** |
| Gait velocity, cm/s | 84.4 ± 48.3 (8.4-140.8) | 83.7 ± 47.8 (7.0-134.8) | 3.4 ± 10.1 (−9.1-16.7) | 92.6 ± 48.7 (12.1-139.4) | 95.9 ± 50.8 (16.5-149.4) | −8.8 ± 16.0 (−36.1-4.0) | 92.8 ± 51.4 (16.7-151.5) | 88.2 ± 45.6 (15.0-132.2) | 2.8 ± 6.3 (−3.28-12.8) |
| Cadence, steps/min | 91.4 ± 45.8 (20.8-135.3) | 90.5 ± 47.7 (17.6-134.0) | 3.6 ± 7.2 (−3.7-15.6) | 98.6 ± 47.0 (28.5-139.7) | 99.1 ± 47.3 (31.3-144.3) | −1.5 ± 5.3 (−9.7-3.2) | 100.3 ± 48.1 (33.4-146.4) | 95.7 ± 43.6 (33.1-137.7) | 3.5 ± 4.2 (−1.2-9.3) |
| Step length, cm | 50.5 ± 20.8 (20.6-76.5) | 49.8 ± 19.5 (19.3-72.0) | 1.2 ± 5.6 (-5.0-6.2) | 52.8 ± 18.6 (24.7-76.0) | 55.5 ± 16.4 (32.2-76.5) | −8.0 ± 12.7 (−30.2-0.7) | 52.1 ± 16.6 (26.9-70.5) | 52.7 ± 14.3 (31.0-69.6) | 3.0 ± 7.4 (−15.4-3.7) |
| Cognitive performance | 5.6 ± 0.7 (5.0-6.0) | 4.1 ± 1.3 (2.0-5.5) | 27.7 ± 18.7 (15.0-60.0) | 5.6 ± 0.5 (5.0-6.0) | 5.5 ± 0.7 (4.5-6.0) | 2.0 ± 4.5 (0.0-10.0) | 5.8 ± 0.4 (5.0-6.0) | 5.1 ± 0.9 (4.0-6.0) | 11.7 ± 16.2 (0.0-33.3) |

All values are reported a mean ± SD (range).

**Table 10.** Percent change for measures of gait and cognitive performance on the mWART

| Group | Variable | $\Delta x$% Pre-Post | $\Delta x$% Post -Follow-up |
|---|---|---|---|
| DT | Single-task gait velocity, cm/s | **18.6**† | −2.6 |
| | Dual-task gait velocity, cm/s | **13.0**† | −3.5 |
| | Single-task cadence, steps/min | 6.3 | −0.7 |
| | Dual-task cadence, steps/min | 3.9 | −2.3 |
| | Single-task step length, cm | 13.3 | −0.8 |
| | Dual-task step length, cm | 8.0 | 1.6 |
| | Single-task cognitive performance | 11.7 | −3.0 |
| | Dual-task cognitive performance | 20.0 | 8.3 |
| ST | Single-task gait velocity, cm/s | 9.7 | 0.2 |
| | Dual-task gait velocity, cm/s | **14.6**† | −8.0 |
| | Single-task cadence, steps/min | 7.9 | 1.7 |
| | Dual-task cadence, steps/min | 9.5 | −3.4 |
| | Single-task step length, cm | 4.6 | −1.3 |
| | Dual-task step length, cm | 11.4 | −5.0 |
| | Single-task cognitive performance | 0.0 | 3.6 |
| | Dual-task cognitive performance | 34.1 | −7.3 |

†Exceeds clinically meaningful difference of 12%[63]

Single-task gait velocity for the dual-task group was significantly different at the 3 different assessment time points during the training intervention, $\chi^2(2) = 9.48$, $p = .009$ (see Table 11). Post hoc analysis revealed significant differences in single-task gait velocity from pre (median = 118.96 cm/s) to post-intervention (median = 144.86 cm/s, $p = .02$) and follow-up (median = 140.73 cm/s, $p = .04$) to pre-intervention. No significant differences were found between groups at any assessment point (see Table 12).

**Table 11.** Within-groups differences (Friedman test) for gait velocity, cadence, and step length

| Group | Condition | Variable | Pre | Post | Follow-up | *p*-value |
|---|---|---|---|---|---|---|
| DT | Single-task condition | Gait velocity, cm/s | 118.96 | 144.86 | 140.73 | **.009**† |
| | | Cadence, steps/min | 125.30 | 128.57 | 127.63 | .309 |
| | | Step length, cm | 56.43 | 66.94 | 64.18 | **.006**† |
| | | Digit span, n | 6.00 | 7.00 | 7.00 | **.023** |
| | Dual-task condition | Gait velocity, cm/s | 117.97 | 137.37 | 133.89 | .260 |
| | | Cadence, steps/min | 124.01 | 126.83 | 125.88 | .738 |
| | | Step length, cm | 56.75 | 64.96 | 63.68 | **.032**† |
| | | Digit span, n | 4.13 | 4.75 | 5.00 | .538 |
| ST | Single-task condition | Gait velocity, cm/s | 84.74 | 97.59 | 87.63 | .247 |
| | | Cadence, steps/min | 103.42 | 108.41 | 103.83 | .091 |
| | | Step length, cm | 48.31 | 52.00 | 50.72 | .549 |
| | | Digit span, n | 5.50 | 6.00 | 6.00 | .670 |
| | Dual-task condition | Gait velocity, cm/s | 86.80 | 95.88 | 89.40 | .074 |
| | | Cadence, steps/min | 101.95 | 104.97 | 105.04 | .074 |
| | | Step length, cm | 50.52 | 53.55 | 51.88 | **.015**† |
| | | Digit span, n | 4.25 | 6.00 | 5.00 | .080 |

All values are reported as medians.
†significant at $p < .05$.

**Table 12.** Between-groups differences for gait velocity, cadence, and step length

| | | Single-task condition | | | Dual-task condition | | |
|---|---|---|---|---|---|---|---|
| **Time** | **Variable** | **DT** | **ST** | ***p*-value** | **DT** | **ST** | ***p*-value** |
| Pre- | Gait velocity, cm/s | 118.96 | 94.74 | .537 | 117.97 | 86.80 | .429 |
| | Cadence, steps/min | 125.30 | 103.42 | .537 | 124.01 | 101.95 | .537 |
| | Step length, cm | 56.43 | 48.31 | .792 | 56.75 | 50.52 | .792 |
| | Digit span, n | 6.00 | 5.50 | .662 | 4.13 | 4.25 | .931 |
| Post- | Gait velocity, cm/s | 144.86 | 97.59 | .177 | 137.37 | 95.88 | .247 |
| | Cadence, steps/min | 128.57 | 108.41 | .662 | 126.83 | 104.97 | .662 |
| | Step length, cm | 66.94 | 52.00 | .329 | 64.96 | 53.55 | .662 |
| | Digit span, n | 7.00 | 6.00 | .082 | 4.75 | 6.00 | .177 |
| Follow-up | Gait velocity, cm/s | 140.73 | 87.63 | .247 | 133.89 | 89.40 | .329 |
| | Cadence, steps/min | 127.63 | 103.83 | 1.000 | 125.88 | 105.04 | .792 |
| | Step length, cm | 64.18 | 50.72 | .247 | 63.68 | 51.88 | .329 |
| | Digit span, n | 7.00 | 6.00 | .329 | 5.00 | 5.00 | .931 |

All values are reported as medians.

### Cadence

Although both groups demonstrated improvements in cadence at post-intervention in single-task and dual-task conditions, these improvements in cadence were statistically non-significant. The ST groups demonstrated greater improvements at post-intervention for both dual-task (DT: 3.9%, ST: 9.5%) and single-task (DT: 6.3%, ST: 7.9%) conditions (see Table 10). Both groups showed a decrease in cadence at follow-up during the dual-task condition (DT: −2.3%, ST: −3.4%), but the ST group improved slightly at follow-up compared to the DT group during the ST condition (DT: −0.7%, ST: 1.7%). No significant differences were found between groups and at the 3 different assessment time points (see Table 12).

**Step Length**

Both groups demonstrated improved step lengths at post-intervention (see Table 10). The DT group demonstrated a greater percent change over the ST group in the single-task condition (DT: 13.3%, ST:4.6%), while the ST group demonstrated a greater percent change over the DT in the dual-task condition (DT: 8.0%, ST: 11.4%). The ST group demonstrated decrements at follow-up for both walking conditions (dual-task condition: −5.0%, single-task condition: −1.3%), while the DT group demonstrated relative retention of step length in both conditions (dual-task condition: 1.6%, single-task condition: −0.8%).

Step length for the dual-task group was statistically significantly different at the different time points during the training intervention for the single-task condition [$\chi^2(2) = 10.174$, $p = .006$] and dual-task condition [$\chi^2(2) = 6.870$; $p = .032$] (see Table 11). Post hoc analysis revealed statistically significant differences in single-task step length from pre (median = 56.43 cm) to post-intervention (median = 66.94, $p = .007$) and in dual-task step length from pre (median = 56.75 cm) to post-intervention (median = 64.96 cm; $p = .042$).

Step length for the single-task group was statistically significantly different at the different time points during the training intervention for the dual-task condition [$\chi^2(2) = 8.400$, $p = .015$]. Post hoc analysis revealed statistically significant differences in single-task step length from pre (median = 50.52 cm) to post-intervention (median = 53.55 cm; $p = .013$). No significant differences were found between groups at any assessment point (see Table 12).

**Cognitive Performance**

For the secondary analysis of cognitive performance, both groups demonstrated improvements in cognitive performance on the titrated digit span of the mWART at post-intervention (see Table 10). The DT group was able to remember a greater number of digits compared to the ST group in the single-task condition (DT: 11.7%, ST: 0.0%). Though the ST group showed no change in single task cognitive performance, they did demonstrate improvements in recalling the number of digits in the dual-task condition (34.1%). The DT group demonstrated a greater degree of retention at follow-up over the ST group for dual-task performance (DT: 8.3%, ST: −7.3%). No significant differences were found for between-groups analyses for digit span recall.

**Relative Dual-Task Costs**

The DT group demonstrated a slightly higher mean %DTC at post-intervention for gait velocity (6.2 ± 10.4 cm/s), cadence (2.5 ± 5.1 steps/min), and step length (4.5 ± 7.2 cm; see Table 8). However, the DT group showed less cognitive %DTC at post-intervention (27.1% ± 17.4%) compared to pre-intervention (32.4% ± 16.8%), which was retained at follow-up (19.9% ± 14.1%). At follow-up, the DT group demonstrated reduced %DTC of gait velocity (3.6% ± 4.2%) and step length (3.4% ± 3.8%) but increased %DTC for cadence (3.4% ± 3.8%). The ST group demonstrated improvements in mean %DTC at post-intervention for gait velocity (−8.8% ± 16.0%), cadence (3.5% ± 4.2%), and step length (−3.0% ± 7.4%). The ST group demonstrated improvements in mean %DTC of cognitive performance by post-intervention (2.0% ± 4.5%) compared to pre-intervention (27.7% ± 18.7%), but improvements were not retained at follow-up (11.7% ± 16.2%). At follow-up, however, the ST group demonstrated increases in all gait %DTC (gait velocity: 2.8% ± 6.3%, cadence: 3.5% ± 4.2%, step length: −3.0% ± 7.4%).

Dual-task costs were significantly different at the different time points during the training intervention for cadence [$\chi^2(2) = 6.870$, $p = .032$] and step length [$\chi^2(2) = 6.870$, $p = .032$] (see Table 13). Post hoc analysis revealed statistically significant differences in cadence from pre (median = 0.05%) to follow-up (median = 3.39%; $p = .042$) and in step length from pre (median = −1.72%) to post-intervention (median = 2.54%; *p* = .042). A significant difference between groups in %DTC of step length was found only at post-intervention (see Table 14). Medians %DTC of step lengths were statistically significantly higher in the DT group (2.54%) than in the ST group (−2.98%), $U = 3.00$, $z = 5.477$, $p = .030$. Median %DTC for digit span were also significantly higher in the DT group (31.25%) than the ST group (0.00%), $U = 27.00$, $z = 5.209$, $p = .030$.

**Table 13.** Within-groups differences for %DTC of gait velocity, cadence, and step length

| Group | Variable | Pre | Post | Follow-up | *p*-value |
|---|---|---|---|---|---|
| Dual-task group | Gait velocity | −3.18 | 4.59 | 2.29 | .119 |
| | Cadence | 0.05 | 1.24 | 3.39 | **.032**† |
| | Step length | −1.72 | 2.54 | −0.18 | **.032**† |
| | Digit span | 34.17 | 31.25 | 20.00 | .727 |
| Single-task group | Gait velocity | 4.27 | −6.54 | 2.84 | .449 |
| | Cadence | 1.42 | −0.44 | 2.68 | .819 |
| | Step length | 3.53 | −2.98 | −1.99 | .449 |
| | Digit span | 20.83 | 0.00 | 0.00 | .135 |

All values are reported as medians %DTC.
†significant at $p < .05$.

**Table 14.** Between-groups differences for %DTC gait velocity, cadence, and step length

| **Time** | **Variable** | **DT** | **ST** | ***p*-value** |
|---|---|---|---|---|
| Pre | Gait velocity | −3.18 | 4.27 | .537 |
| | Cadence | 0.05 | 1.42 | .329 |
| | Step length | −1.72 | 3.53 | .247 |
| | Digit span | 34.27 | 20.83 | .931 |
| Post | Gait velocity | 4.59 | 6.54 | .126 |
| | Cadence | 1.24 | −0.44 | .329 |
| | Step length | 2.54 | −2.98 | **.030**† |
| | Digit span | 31.25 | 0.00 | **.030**† |
| Follow-up | Gait velocity | 2.29 | 2.84 | .931 |
| | Cadence | 3.40 | 2.68 | 1.00 |
| | Step length | −0.18 | −1.99 | .429 |
| | Digit span | 20.00 | 0.00 | .537 |

All values are reported as median percentages (%DTC).
†significant at $p < .05$.

## DISCUSSION

The findings from this study demonstrate that a 6-week long gait-specific dual-task training program is safe and well-tolerated by individuals with MS and showed beneficial effects on gait parameters and cognitive performance on the mWART. This study can serve as a general framework from which further larger-scale studies can be developed, as well as one that clinicians can utilize for clinical-decision making to assist them with integrating dual-task training into their plans of care.

The current study found that the gait-specific dual-task training intervention improved single-task and dual-task gait performance, especially gait velocity, which has been well-established in the literature as being correlated to functional independence and fall risk.[64,65] In regards to walking tests in MS, a change of 12% is generally indicative of clinically meaningful difference,[63] and the results from this study demonstrated improvements in dual-task walking for the DT group (13.0%) and ST group (14.6%) that reached clinical meaningfulness. Additionally, the DT group demonstrated a clinically meaningful improvement of 18.6% in single-task gait velocity. The DT group demonstrated statistically significant improvements mostly in single-task performance, especially in gait velocity and step lengths, while only demonstrating statistically significant improvements in dual-task step length. The current study found concomitant improvements in both cadence and step lengths for both groups at post-intervention, which may explain the improvements observed in gait velocity. Both groups seemed to have adopted a motor strategy that generally led to greater changes in step length over cadence to increase gait velocity. This observation is consistent with the findings of a recent study that suggested that walking with larger strides as opposed to a faster cadence may mitigate the risk of tripping and the consequent loss of postural stability.[66] Results suggest that individuals who underwent dual-task training tended to demonstrate greater improvements in single-task gait performance, while those who underwent single-task training tended to demonstrate greater improvements in dual-task performance on measures of gait performance. However, no significant differences were found between groups. This unexpected finding could be a result of several factors.

The ST group received a greater proportion of gait training during their sessions compared to the DT group. Unlike the DT group, which had alternating prioritized walking blocks of gait and cognitive performance, the ST group only trained gait and had all 5 blocks prioritized to gait performance. Effectively, this may have allowed the participants in the ST group to practice improving their walking ability to a greater extent than the DT group. These individuals may then have developed a more automatic control for gait compared to the DT group.[67] Individuals in the ST group may have been able to distribute attentional resources more efficiently, as they did not require as extensive of an allocation of attentional resources to gait. The ST group's cognitive performance improvement of 34.1% in the dual-task walking condition supports this observation.

Compared to the ST group, the DT group were trained in cognitive-motor dual-task walking, where dual-task prioritization was distributed equally within a session. Consequently, the DT group has less training focused on improving their gait (50% less than the ST group). Interestingly, however, is the observation of the DT group's greater retention of improvements at follow-up assessment compared to the ST group. This finding may support the hypothesis that dual-task gait training may allow for the development of more robust motor control strategies in response to cognitive-motor interference during gait-related tasks.[68,69]

Of interest are the changes observed in both groups on the measures of cognitive performance on the mWART. While the ST group demonstrated no change in single-task cognitive performance—meaning they neither remembered more digits nor reported more errors, the DT group demonstrated improvements in single-task cognitive performance, remembering a greater number of digits. This finding could be attributed to the nature of the dual-task training intervention, in which the DT group performed cognitive tasks concurrently with gait training regardless of block prioritization. In contrast, the ST group showed improved cognitive performance during dual-task conditions, but demonstrated a decrease at follow-up, while the DT group demonstrated retention at follow-up. Again, these findings may relate to greater gait automaticity that the ST group developed, and the more robust changes seen in the DT group.

The findings for relative measures of gait and cognitive performance (%DTC) for both groups mirror the unexpected findings for the absolute measures. The DT group demonstrated significant increases in %DTC compared to the ST group at post-intervention for gait parameters. The increases seen in %DTC of gait for the DT group should not be necessarily seen as detrimental, as the DT group's measures of gait performance improved post-intervention. They were able to walk with improved gait mechanics and, by doing so, may have meant a greater need to reallocate attentional resources appropriately, as they may not have developed gait automaticity like the ST group. This is demonstrated through the concurrent increases in %DTC gait parameters and the reduction of cognitive performance at post-intervention for the DT group. At follow-up, the ST group demonstrated increases in %DTC of both gait and cognitive performance compared to the DT group. This observation may be attributed to an adaptive response of sacrificing cognitive performance to maximize safety and gait performance since the ST group's improvements may not have been robust.

These study findings suggest that compared to single-task training, dual-task training may induce improvements that are less in magnitude, but more robust longer-term, while single-task training may improve dual-task performance better short-term. These observations lead to clinical and research questions regarding the appropriate timing, application, and rationale of dual-task interventions in the clinic.[43] However, results from this study should be interpreted with caution as the study's small sample size and lack of more statistically powerful comparative analyses limits interpretability and generalizability.

Previous studies conducted in individuals who have MS have shown that cognitive-motor interference has a detrimental effect on both the gait and cognitive performance during a dual-task activity.[18] However, there is minimal evidence that pertains to methods by which the effects of cognitive-motor interference may be mitigated. Currently, only 3 interventional studies related to dual-task training in MS were found. Only 4 interventional studies on dual-task training in MS were found that included a component of gait or walking training. A small pilot study by Peruzzi et al found promising improvements post-intervention in gait speed (18%) and stride length (10%) following a 6-week, 12 sessions, virtual reality-based treadmill training intervention.[49] The authors found that these improvements were maintained 4 weeks later. However, the results of this study should be taken with caution because of the study's small sample size, lack of control group, and lack of blinding. A more methodologically sound study but Sosnoff et al explored the feasibility and effects of a 12-week, 24 sessions dual-task balance and gait training program on measures of balance, walking, and cognitive performance.[51] Following the intervention, the authors did not find any significant differences between groups on measures of balance or cognitive performance, but the authors did find a trend for improvements in dual-task gait velocity in the dual-task training group. Measures of %DTC were not examined by the authors. The study's small sample size, possible low exercise intensity, low cognitive task difficulty, and lack of follow-up limit the interpretations of its results and larger intervention studies focusing on dual-task rehabilitation are warranted. Additionally, the inclusion of balance exercises in the intervention limits the interpretation of contributions to dual-task gait improvements.

A 2019 multi-center randomized control trial of 40 individuals with MS demonstrated that both single-task and dual-task training significantly improved motor and cognitive performance, but only dual-task training contributed to better dual-task walking compared to the single-task group.[52] The study utilized an 8-week, 20 sessions dual-task training intervention that consisted of walking or stepping practice while performing 11 different cognitive tasks of varying complexity delivered through a special computer-based application developed specifically for the study. The single-task group intervention consisted of 21 different gait and balance exercises. Improvements in the dual-task group demonstrated retention at follow-up, suggesting improved motor learning and control over single-task training. The study's use of a novel training application, lack of use of a standardized dual-task outcome measure, and considerable different interventions between groups limit the generalizability of its results.

The results of the current study indicate that a 6-week dual-task training may improve single-task and dual-task of gait, and cognitive performance is consistent with previous studies. Unlike previous dual-task training studies in individuals with MS, which consisted of multiple modes of exercise and dual-tasking, the present study utilized a gait-specific training program for both the ST and DT groups to better determine its feasibility and effects on single-task and double-task spatiotemporal gait performance and cognitive performance. Another strength of this study is the use of 1-on-1 sessions with a physical therapist, who was able to provide immediate feedback on gait and cognitive performance after each walking bout. This may have allowed the participants to engage feedforward mechanisms necessary to correct performance errors on each subsequent bout.[70] Moreover, this study did not require any equipment outside that which is readily available in most clinics. The use of over-ground gait training may have also been more salient and eliminated the need for a treadmill.[71] The intervention could also serve as a general framework on which clinicians can base and initiate dual-task training programs for those with MS.

This study has several limitations. Primarily, the sample size was small, resulting in challenges with power and limiting the generalizability of the results. Reasons for the small sample size include difficulty with the recruitment of individuals with MS, as well as personnel, financial, and scheduling constraints, which limited the number of prospective. The use of non-parametric statistical analyses may have also contributed to an underpowered study. Future studies with larger sample sizes are needed for more robust comparative statistical. Although the intervention protocol was standardized for both groups, there was no standardized progression of the protocol's gait training outside of reduced rest times. Additionally, there was no standardized progression of the cognitive tasks outside the feedback that was provided by the physical therapist in response to participant performance errors. This may have created an intervention whose intensity and duration were insufficient to induce optimal training effects for longer-term changes. Most participants for both groups were female and had relapsing-remitting multiple sclerosis, further limiting the generalizability of the study. Future studies should address these limitations to strengthen methodological comparability. Finally, the ST group had a higher EDSS level, which meant that the capacity to improve their gait was more limited than the DT group, which had a lower EDSS level.

To our knowledge, this is the first study to evaluate the feasibility and effects of a gait-specific dual-task training intervention on measures of absolute and relative measures of dual-task gait and dual-task performance in individuals with MS. Results from this study provide valuable information upon which future studies can build concerning dual-task rehabilitation interventions. Randomized control trials with larger sample sizes are warranted to elucidate the external validity of dual-task interventions better and guide clinical decision-making.

## CLINICAL RELEVANCE

- A gait-specific dual-task training intervention for people with MS elicits clinically significant improvements in single-task and dual-task gait velocity, as well as robust more robust dual-task performance changes.
- However, this intervention lacked the sample size to perform more statistically powerful comparative analyses for generalizability.
- This study provides a general framework that can help guide clinicians when developing dual-task interventions for patients with MS.


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CHAPTER V

EFFECTS OF A GAIT-SPECIFIC DUAL-TASK INTERVENTION ON WALKING CAPACITY AND SELF-PERCEIVED WALKING ABILITY IN PERSONS WITH MULTIPLE SCLEROSIS

## INTRODUCTION

Individuals with MS present with both motor and cognitive impairments that typically interfere with their daily functioning, social engagement, general life satisfaction, and quality of life.[1-7] Recent studies have examined the relationship between motor functioning and cognitive impairment in individuals with MS, especially in how this relationship affects balance and gait.[8-17] Previous research in individuals with MS has found that the concomitant performance of a motor and cognitive task (dual-task) results in what is known as cognitive-motor interference.[18,19] Considering the high prevalence of cognitive impairment in individuals with MS,[4,20-23] as well as their persistent motor deficits, the performance of an everyday mobility task such as walking can be significantly impacted in the presence of an additional cognitive load. This increased demand exerted by both the motor and cognitive task on the finite cognitive resources of those with MS has been shown to contribute to balance impairment,[8,9] gait dysfunction,[10-17,24] and increased fall risk.[24-26]

While gait dysfunction has been greatly attributed to MS symptoms such as muscle weakness, pain, spasticity, sensory disturbances, and fatigue,[27-31] research within the last decade has further linked cognitive dysfunction to motor impairments in balance and gait. These studies show that cognitive impairment, especially within the domains of information processing efficiency (information processing speed and working memory), attention, and executive function, contributes to deficits in dual-task walking and increased fall risk.[24-26] Studies in MS and other neurological diseases reveal that cognitive-motor dual-tasking impacts specific spatiotemporal gait parameters, such as gait velocity, step length, cadence, double limb support time, and swing time variability, which are all associated with increased fall risk.[19,32-35] These studies demonstrate how the cognitive capacity of individuals with MS influences their ability to walk and be independent with functional mobility.

Previous studies have explored the impact of dual-task interventions on specific gait parameters, balance outcomes, and other functional measures in MS and other neurological diseases[19,36-41]; however, there is minimal evidence available regarding the effects of dual-task gait interventions on measures of walking capacity and self-perceived walking ability in individuals with MS. Recent systematic reviews and meta-analyses have shown the positive effects of exercise and gait rehabilitation on improving walking performance in those with MS.[42-44] Interventional studies examining the effects of exercise on walking performance ranged from 4 to 26 weeks in duration,[42-44] while gait-specific training interventions (ie, robot-assisted gait training, conventional gait training) ranged anywhere from 9 to 18 session.[42-44] Although there is a wealth of information on exercise and gait training in improving measures of walking in individuals with MS, the impact of gait-specific dual-task training on walking measures for endurance and self-perceived walking ability has yet to be explored. By demonstrating improvements in functional gait following a gait-specific dual-task training intervention, clinicians are then afforded with a method by which they can effectively treat gait-specific and functional outcomes together rather than separately.

The purpose of this research investigation was to assess the feasibility of a gait-specific dual-task intervention on overall walking capacity and self-perceived walking ability as measured by the 2MWT and the MSWS-12, respectively. The secondary aim sought to examine the intervention's impact on subjective fatigue as measured by the Fatigue Scale for Motor and Cognitive Functions.

## METHODS

A single-blinded randomized control trial explored the feasibility of a 6-week dual-task intervention utilizing a gait training protocol (dual-task condition) compared to a single-task gait training protocol (single-task condition) on measures of walking capacity and self-perceived walking ability (ClinicalTrials.gov Identifier: #NCT03536299). The study was approved by the institutional review boards of Texas Woman's University Institute of Health Sciences – Houston Center (#20068) and The University of Texas Health Science Center at Houston (HSC-MS-18-0050).

### Participants

Prospective participants were recruited through various avenues: clinics across TIRR and Memorial Hermann Rehabilitation Networks, the Greater Houston Chapter of the National Multiple Sclerosis Society, clinicaltrials.gov, and electronic flyers sent to local MS support groups and MS-specific physician clinics around the Greater Houston Area from 2018-2019. Individuals with MS between the ages of 18 years and 65 years were recruited. Inclusion criteria require the participants to have a neurologist-confirmed diagnosis of MS [Expanded Disability Status Scale (EDSS) ≤6.5]; be relapse-free for the past 30 days from recruitment, be able to walk independently with or without an assistive device; be community-dwelling; have no history or presence of other clinically significant musculoskeletal, cardiovascular, respiratory, or neurologic disease; and not currently receiving or scheduled to receive any rehabilitation services during the study. Additionally, participants were asked not to start any new medications specifically targeting gait or fatigue, eg, antispasmodics, potassium-channel blockers, or wakefulness-promoting agents, while enrolled in the study. If participants were already taking such medications, they were asked not to change dosages for the duration of the study.

**Procedures**

Interested participants contacted the primary investigator, who screened potential participants based on the inclusion criteria. At the initial laboratory session, all participants were provided with both a written and verbal explanation of the study procedures and were provided sufficient opportunity to ask any questions related to their participation in the study. After consent was obtained, participants were provided with a demographic questionnaire concerning their MS clinical course, years since diagnosis, assistive device use, falls history, medications, and past medical history, as well as a release to contact their neurologist to confirm EDSS level. All testing was performed in the laboratory, and training sessions were conducted in the clinic.

Randomization of study participants into DT or ST groups was completed using a random number generator in Microsoft Excel (2016). Participants completed 2 initial outcome assessments at least 1 week apart prior to initiating a 6-week intervention period. Data from the 2 initial assessments were then averaged to provide the baseline data for the following measures: 2MWT, MSWS-12, and Fatigue Scale for Motor and Cognitive Functions. The participants then completed a mid-intervention outcome assessment after week 3 of the intervention, a post-intervention assessment upon the termination of the 6-week intervention, and a follow-up outcome assessment 4 weeks after the termination of the 6-week intervention period. Assessments were provided in a standardized order.

**Measures**

Primary outcome measures for this study were the 2MWT and MSWS-12. The 2MWT assesses walking capacity and endurance over 2 minutes and is performed at the fastest possible speed with the option to use an assistive device. The 2MWT is highly correlated with the 6MWT

($R^2 = 0.97$), and in terms of walking distance at 1-minute intervals, there is no significant difference between the 2 tests ($p = 0.82$).[45,46] The 2MWT is less burdensome than the 6MWT for individuals with MS, especially for those with higher disability[45,46] The 2MWT eliminates the redundancy of the last 4 minutes of the 6MWT and better predicts community ambulation in persons with MS than the Timed 25-Foot Walk Test or 10-meter Walk Test.[45,46] An improvement of 31.5 ft on the 2MWT is needed for a MIC from the patient's perspective.[47] The MSWS-12 is a 12-item self-report measure of the impact of MS on one's walking ability.[48] Scores from each item are summed for a total possible 60 points. The total score is then transformed into a 20-100 scale with higher scores indicating higher walking disability. The MSWS-12 demonstrates both excellent validity and reliability and adequate to excellent floor and ceiling effects.[48-50] A cut-off score of 75% or greater had a sensitivity of 52 and specificity of 82 in predicting fallers vs. non-fallers.[28] An improvement of -10.4 points is necessary to observe a MIC from the patient's perspective.[47]

The secondary measure included the participant's self-reported fatigue over 2 weeks. The Fatigue Scale for Motor and Cognitive Functions (FSMC) is a self-report outcome measure for measuring physical and mental fatigue in patients with MS. Scores are summed and scores range from 20-100 with higher values indicating greater fatigue severity. The FSMC can be used to measure motor fatigue only, cognitive fatigue only, or both as a summed score. Both subscales have shown good reliability, sensitivity, and specificity, and have been highly correlated with the MFIS and FSS.[51] However, the FSMC demonstrated superior sensitivity and specificity over the MFIS and FSS in persons with MS and cut-off values for identifying mild, moderate, and severe fatigue provide clinicians with the ability to grade fatigue over time.[51]

**Interventions**

Participants were randomized into 2 groups: DT and ST. Both groups underwent a 6-week-long intervention program consisting of 1-on-1 gait training sessions with a licensed physical therapist 3 days per week (18 total sessions). Each training session consisted of 4 different training blocks with each block consisting of 4 minutes of total gait training time for an entire session walking time of 20 minutes (see Figure 7).

| **Dual-Task Training** | **Block 1** | **Block 2** | **Block 3** | **Block 4** | **Block 5** |
|---|---|---|---|---|---|
| Total walk time | 4 min | 4 min | 4 min | 4 min | 4 min |
| Walking sets | 2x2 min bouts 2 min rest | 2x2 min bouts 2 min rest | 2x2 min bouts 2 min rest | 2x2 min bouts 2 min rest | 2x2 min bouts 2 min rest |
| Task prioritization | None | Gait | Cognitive | Gait | Cognitive |
| Cognitive tasks | Three cognitive tasks randomized within each block:<br>• Serial subtraction by threes<br>• Verbal/phonemic fluency<br>• Simple arithmetic problem with *n*-back task (*n* = 1) | | | | |

**Figure 7.** Dual-task training protocol.

Each block was further divided into 2 gait training bouts with 2-minute rests between each bout. Participants were instructed to walk at a self-selected gait speed they could maintain for each 2-minute bout. The ST group was asked to focus on gait performance and walk without any distractors of music, talking, or reading during all bouts. ST group participants were provided with feedback regarding knowledge of performance after each bout. In addition to gait training, participants in the DT group performed a randomized cognitive task for each bout (6 hours total of dual-task–specific practice).[52] For each block with the DT group, participants were asked to prioritize either their gait performance (eg, "I want you to focus on walking with even steps.") or cognitive performance (eg, "I want you to focus on answering the questions as accurately as you can.").

The cognitive tasks incorporated into the DT group intervention targeted cognitive domains shown to be impaired in individuals with MS and have been previously described as eliciting cognitive-motor interference in persons with neurological impairment.[4] These included serial subtraction by 3, verbal fluency, and simple arithmetic problems with an *n*-back task. For serial subtraction by 3, participants verbally performed serial subtraction from a randomly generated 3-digit number by 3. For verbal fluency, participants were tasked to verbalize as many words as possible that begin with a randomly generated letter every 30 seconds. For the simple arithmetic problem task, the participants were asked to solve a series of simple arithmetic problems provided at intervals of 2 seconds and verbalize if their response was larger or smaller than their previous response.

Two-minute rest breaks were initially provided between each bout and these rest breaks were subsequently reduced by 30 seconds every 2 weeks until a 1-minute rest break was achieved during weeks 5 and 6 of the intervention period. After each bout, all participants reported their perceived fatigue on the visual analog scale-fatigue and effort on RPE. Blood pressure was taken before and after each session, and heart rate was obtained after every bout to ensure participants were exercising within acceptable limits, ie, RPE of 11-15, blood pressure under 170/100, and heart rate within 40-60% of heart rate reserve (heart rate reserve = maximum heart rate – resting heart rate).

**Statistical Analysis**

Data were entered into Microsoft Excel (2016) and exported into SPSS v25 (IBM, Chicago IL) for data analysis. For group comparisons of demographic variables, the Mann-

Whitney test or Student *t* test was used to compare, respectively, the median for non-parametric variables or the mean for parametric demographic variables. The effects of the intervention on primary and secondary outcomes were analyzed using multiple mixed-design analyses of variance with treatment group (2 levels) as a between-subjects factor and assessment time (4 levels) as a within-subjects factor. Primary outcomes were further analyzed with separate mixed-models analyses of covariance for mid-intervention and post-intervention with the condition as the between-subjects factor and pre-intervention scores as covariates. A significance value of $\alpha = .05$ was set for all tests.

**RESULTS**

The flow diagram in Figure 8 provides an overview of the 11 total participants who underwent randomization into the DT group ($n$ = 6) and ST group ($n$ = 5). A total of 28 individuals with MS were assessed for eligibility. After screening, 14 participants were enrolled, randomized into the 2 groups, and underwent baseline assessment. After enrollment, 1 participant withdrew because work-related conflicts, 1 withdrew due to drive distance and time commitment, and 1 was withdrawn by the primary investigator after failing to attend sessions. None of the participants who were enrolled in the study and underwent the intervention protocol reported any adverse events (eg, falls, excessive fatigue, pain) directly associated with the intervention.

The sample characteristics for each group are reported in Table 15. There were no significant differences found between groups for age, sex, MS clinical course, years since diagnosis, and EDSS.

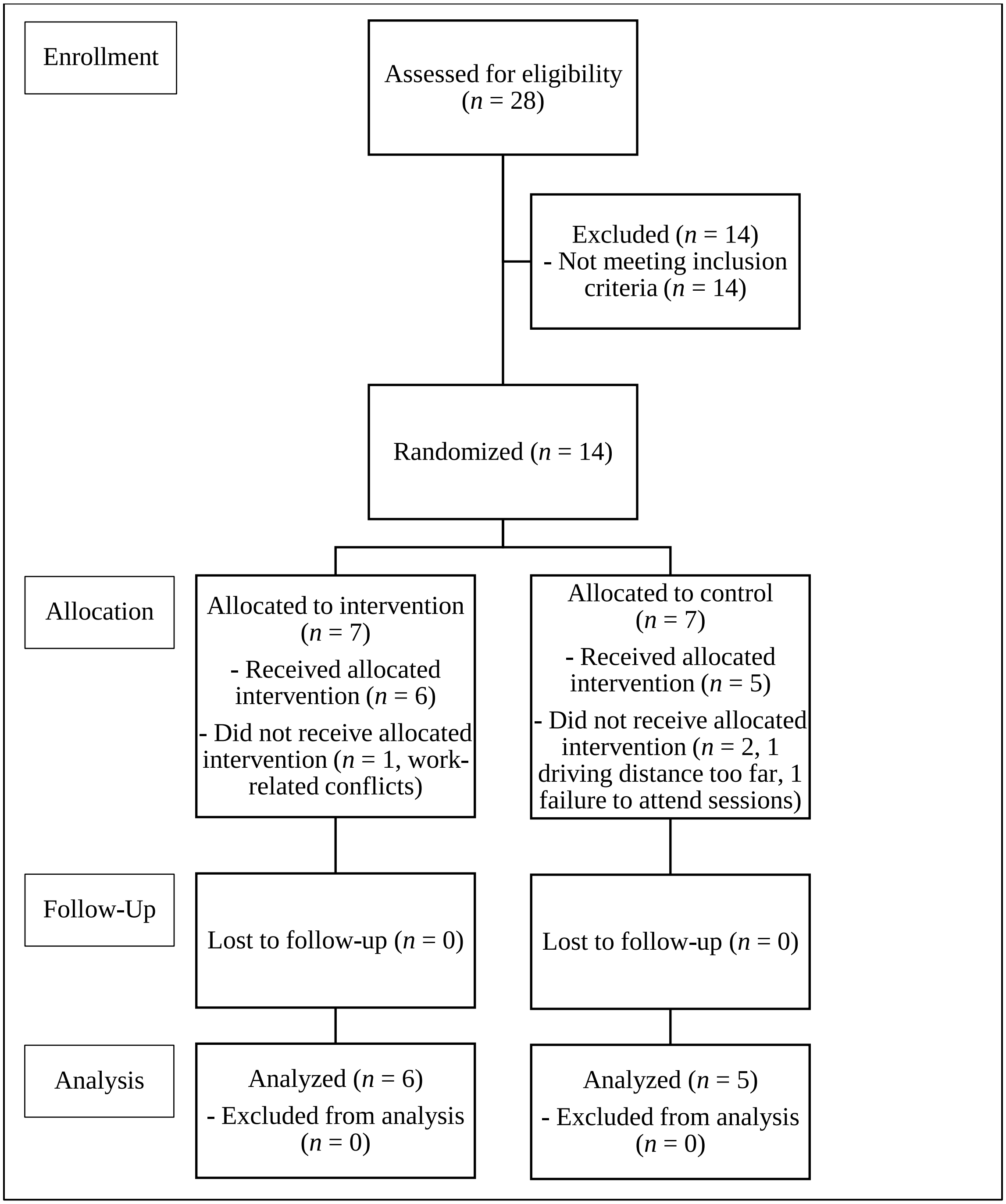


**Figure 8.** Flow diagram from enrollment to analysis of participants.

**Table 15.** Descriptive statistics of demographic and clinical characteristics of participants in both groups (*n* = 11)

| Variable | DT Group (*n* = 6) | ST Group (*n* = 5) | *p*-value |
|---|---|---|---|
| Age, years[a] | 50.0 ± 15.2 (30-65) | 54.8 ± 12.2 (36-65) | *t* = .57, *p* = .58 |
| Sex | Female = 6 Male = 0 | Female = 4 Male = 1 | *U* = 12.00, *p* = .66 |
| MS clinical course | RRMS = 5 SPMS = 1 | RRMS = 3 SPMS = 2 | *U* = 11.50, *p* = .54 |
| Years since diagnosis[a] | 11.0 ± 7.20 (3-22) | 16.2 ± 9.9 (6-32) | *t* = 1.01, *p* = .34 |
| EDSS[b] | 4.25 (2.38-5.63) | 6.0 (5-6) | *U* = 7.50, *p* = .18 |

Abbreviations: RRMS, relapsing remitting MS; SPMS, secondary progressive MS.
[a]Age and years since diagnosis are reported in mean ± SD (range).
[b]EDSS is reported as median (IQR).

**Walking Capacity**

No significant interaction effect was found for time x group, $F(1.35,12.13) = 0.09$, $p = .846$, partial $\eta^2 = .01$, $\varepsilon^2 = .45$ (see Table 16). Statistical analyses revealed no significant main effect of group on the 2MWT [$F(1,9)=1.57$, $p = .243$, partial $\eta^2 = .15$]. However, the main effect of time showed a statistically significant difference in the 2MWT distance [$F(1.35,12.13) = 9.18$, $p = .007$, partial $\eta^2 = .51$, $\varepsilon^2 = .45$]. Specifically, a mean increase in the 2MWT distance of 77.53 ft, 95% CI [154.48,0.59] was found to be significant between baseline and mid-intervention, $p = .048$ (see Figure 9). The mean differences on the 2MWT at the post-intervention for group (DT = 95.2 ft, ST = 92.8 ft) and all participants (94.0 ft) exceeded the minimal important change for 2MWT improvement (MIC = 31.5 ft) from the patient perspective. For post-intervention to follow-up, a mean difference of −27.88 ft was found non-significant, 95% CI [-64.85,9.08].

Separate mixed-models ANCOVA revealed that mid-intervention and post-intervention 2MWT scores were influenced by pre-intervention scores [mid-intervention: $F(1,8) = 46.19$,

$p$ < .001, partial $\varepsilon^2$ = .85; post-intervention: $F(1,8)$ = 29.63, $p$ = .001, partial $\varepsilon^2$ = .79]; however, when pre-intervention scores were adjusted for, no significant differences were found between groups at mid-intervention, $F(1,8)$ = 0.08, $p$ = .782, partial $\varepsilon^2$ = .01, or post-intervention, $F(1,8)$ = 0.00, $p$ = .953, partial $\varepsilon^2$ = .00 (see Table 19).

**Table 16.** Comparative analysis of 2MWT distance for both groups ($n$ = 11)

| | **Pre** | **Mid** | **Post** | **Follow-up** | ***p*-value**[a] |
|---|---|---|---|---|---|
| DT | 379.3 ± 210.4<br>(82.5-663.0) | 449.2 ± 207.2<br>(102.0-688.0) | 474.5 ± 219.3<br>(90.0-720.0) | 442.3 ± 200.5<br>(119.0-442.3) | $p$ = .007[†] |
| ST | 232.0 ± 137.9<br>(26.0-392.0) | 317.2 ± 182.4<br>(40.0-524.0) | 324.8 ± 179.4<br>(50.0-502.0) | 301.2 ± 168.8<br>(43.0-496.0) | |
| *p*-value[b] | $p$ = .243 | | | | |

All values are reported as mean ± SD (range).
[a]Main effect of time.
[b]Main effect of group.
[†]Significant at $p$ < .05.

## Self-Perceived Walking Ability

No significant interaction effect was found for time x group [$F(3,27)$ = 0.27, $p$ = .850, partial $\eta^2$ = .03] (see Table 17). Statistical analysis revealed no significant main effect of group for scores on the MSWS-12 [$F(1,9)$ = 0.01, $p$ = .910, partial $\eta^2$ = .00]. There was a significant main effect of time for the MSWS-12 [$F(3,27)$ = 4.73, $p$ = .009, partial $\eta^2$ = .35]. Follow-up pairwise comparisons revealed a significant difference between baseline and mid-intervention (mean difference = 16.54, 95% CI [0.03,33.05], $p$ = .050), and baseline and post-intervention (mean difference = 11.62, 95% CI [0.34,22.90], $p$ = .043); see Figure 10). For post-intervention to follow-up, a mean difference of 5.33% was found non-significant, 95% CI [−8.35,19.02].

**Table 17.** Comparative analysis of MSWS-12 scores for both groups ($n$ = 11)

| | Pre | Mid | Post | Follow-up | $p$-value[a] |
|---|---|---|---|---|---|
| DT | 65.3 ± 25.7 (20.0-90.0) | 47.5 ± 17.4 (20.0-73.3) | 53.3 ± 18.3 (20.0-73.3) | 61.7 ± 25.1 (20.0-85.0) | $p$ = .009† |
| ST | 64.6 ± 14.8 (42.5-78.2) | 49.3 ± 19.6 (26.7-75.0) | 53.3 ± 13.3 (38.3-70.0) | 55.7 ± 14.2 (45.0-80.0) | |
| $p$-value[b] | $p$ = .910 | | | | |

All values are reported as mean ± SD (range).
[a]Main effect of time.
[b]Main effect of group.
†Significant at $p < .05$.

Separate mixed-models ANCOVA revealed that mid-intervention and post-intervention MSWS-12 scores were influenced by pre-intervention scores [mid-intervention: $F(1,8) = 6.93$, $p = .030$, partial $\varepsilon^2 = .46$; post-intervention: $F(1,8) = 23.77$, $p = .001$, partial $\varepsilon^2 = .75$]; however, when pre-intervention scores are adjusted for, significant differences were found between groups at mid-intervention, $F(1,8) = 0.07$, $p = .805$, partial $\varepsilon^2 =.01$, or post-intervention, $F(1,8) = 0.01$, $p = .938$, partial $\varepsilon^2 = .00$ (see Table 19).

**Fatigue**

No significant interaction effect was found for time x group [$F(3,27) = 0.39$, $p = .763$, partial $\eta^2 = .04$] (see Table 18). For both groups, mean scores on the FSMC ranged from 71.46 at baseline to 69.47 at post-intervention. Statistical analysis found no significant main effect of group [$F(1,9) = 0.17$, $p = .690$, partial $\eta^2 = .02$] or time [$F(3,27) = 0.54$, $p = .657$, partial $\eta^2 = .06$].

**Table 18.** Comparative analysis of FSMC scores for both groups ($n$ = 11)

| | Pre | Mid | Post | Follow-up | *p*-value[a] |
|---|---|---|---|---|---|
| DT | 73.9 ± 16.3 (51.0-95.5) | 68.8 ± 13.7 (51.0-89.0) | 72.0 ± 19.6 (46.0-95.0) | 72.3 ± 16.2 (52.0-91.0) | $p$ = .657 |
| ST | 69.0 ± 18.1 (44.0-92.5) | 97.8 ± 20.4 (40.0-97.0) | 66.2 ± 20.3 (36.0-93.0) | 66.6 ± 21.7 (38.0-98.0) | |
| *p*-value[b] | $p$ = .690 | | | | |

All values are reported as mean ± SD (range).
[a]Main effect of time.
[b]Main effect of group.

**Table 19.** Adjusted intervention means for mid-intervention and post-intervention 2MWT distance and MSWS-12 scores with pre-intervention as covariate

| | 2MWT (ft) | | MSWS-12 (%) | |
|---|---|---|---|---|
| **Group** | **Mid** | **Post** | **Mid** | **Post** |
| DT | 382.3 ± 34.2 [303.5,461.1] | 408.3 ± 42.2 [296.7,511.9] | 47.3 ± 5.8 [33.9,60.8] | 53.1 ± 3.5 [45.0,61.3] |
| ST | 397.5 ± 37.7 [310.5,484.5] | 404.3 ± 46.7 [296.7,511.9] | 49.5 ± 6.4 [34.8,64.3] | 53.6 ± 3.9 [44.6,62.5] |

All values reported as mean ± SE [95% CI].

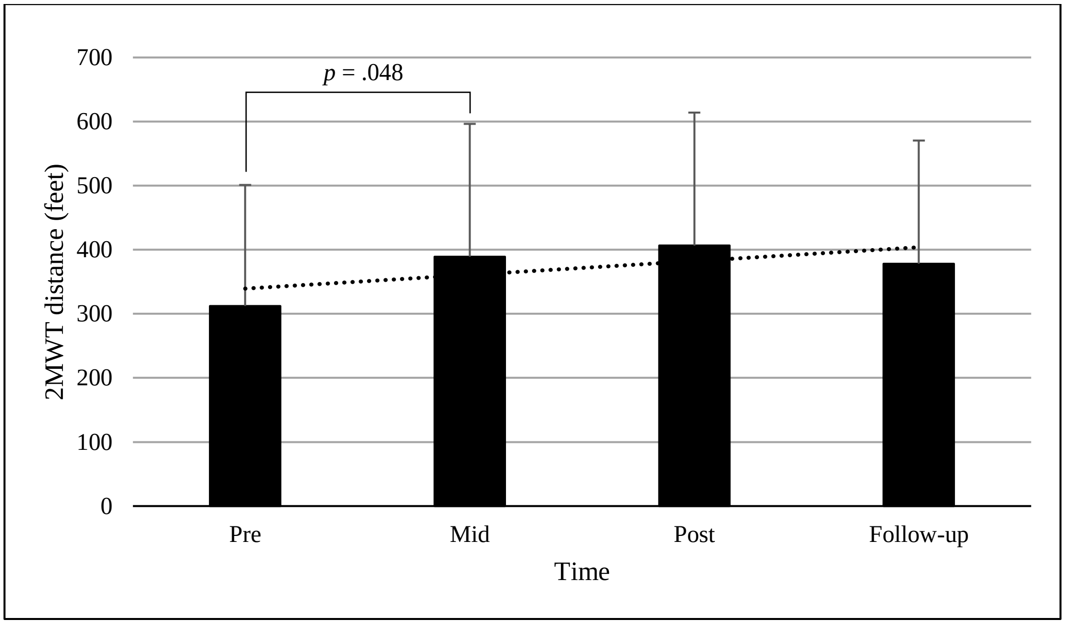


**Figure 9.** Main effect of time for 2MWT distance.

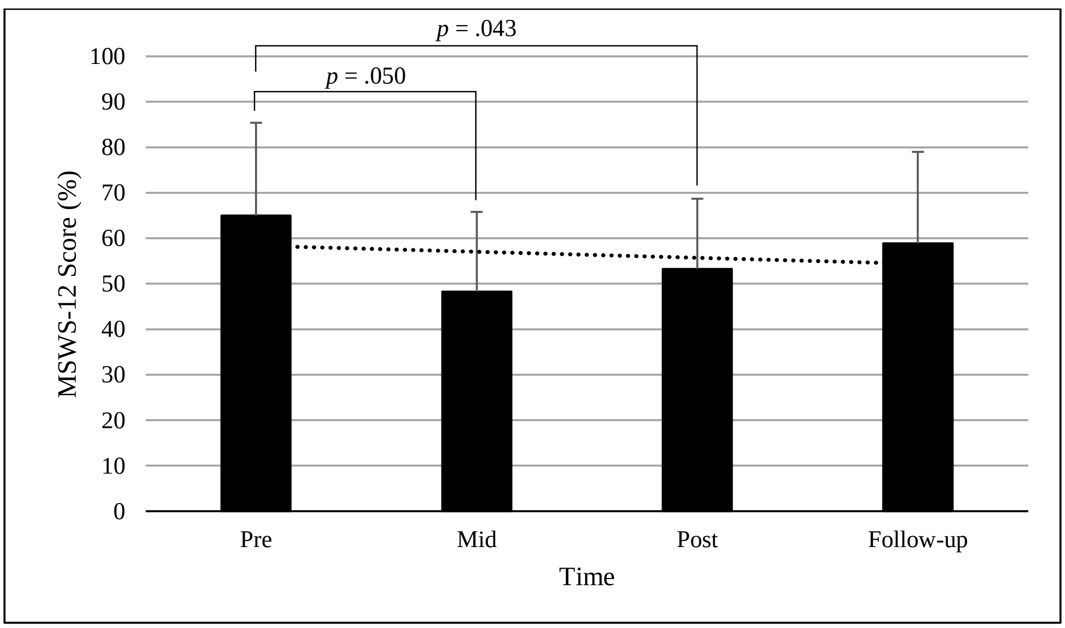


**Figure 10.** Main effect of time for MSWS-12 scores.

## DISCUSSION

Results from this study expand on previous studies investigating the dual-task paradigm by examining the effects on function that occur after a dual-tasking intervention. The present study demonstrates that a task-specific dual-task of gait training program was safe and effective in improving the walking capacity and self-perceived walking abilities in individuals with mild to moderate MS. However, the single-task gait training intervention also produced similar effects on improving walking distance on the 2MWT and self-perceived walking ability on the MSWS-12.

Although not statistically significant from pre- to post-intervention, a trend for improvement was observed on the distances walked on the 2MWT. The mean differences on the 2MWT at the post-intervention for each group (DT = 95.2 ft, ST = 92.8 ft) and all participants (94.0 ft) exceeded the minimal important change for 2MWT improvement (MIC = 31.5 ft) from the patient perspective. This improvement suggests that regardless of dual-task or single-task gait intervention, individuals with MS seem to improve their walking capacity and distance walked on the 2MWT by similar magnitudes. The reduction in the MSWS-12 scores also reflects this concept, with mean differences on the MSWS-12 at post-intervention for group (DT = −12.0, ST = −11.3) and all participants (−11.6, $p = 0.043$) exceeding its minimal important change for improvement (MIC = −10.4) from the patient perspective. These observations may indicate that the intervention's intensity and duration were sufficient to produce a meaningful short-term change in walking performance and ability. Additionally, when considering 2MWT post-intervention to 1-month follow-up assessments, the mean differences for group (DT = −32.2 ft, ST = −23.6 ft) and all participants (−27.9 ft) were statistically significant; however, the DT group exceeded the 2MWT's MIC, while the ST group was trending towards the 2MWT's MIC of 31.5 ft. However, the mean differences from post-intervention to follow-up assessment for the MSWS-12 revealed both statistically and clinically non-significant changes for both groups.

Overall, these findings suggest that the observed improvements in walking endurance may not be maintained long-term, but self-perceived walking ability may be more robust to change over time. These results are unsurprising as participants were asked not to change their activity outside of their regular daily routine while enrolled in the study, and discontinuation of the gait training program without any carryover into self-management may explain this phenomenon. This further suggests that a more extended intervention program that incorporates a home exercise program or a daily physical activity/step goal may be required to induce longer-term changes, as well as habit formation. A previous study found that new habits may require 66 days to be retained and become automatic.[53] Clinically, this is important as continued physical activity and exercise, especially after a bout of rehabilitation, are important to enhance the retention of improvements in those with MS. However, these results should be interpreted with caution as the study's small sample size and low power may inhibit interpretability.

No changes in the FSMC were found in this study in response to the intervention program. However, the FSMC is a measure of subjective fatigue and while it did not demonstrate any significant difference from pre-intervention and post-intervention regardless of the training intervention, improvements in objective fatigability were evident, as based on the improvements on the 2MWT. Fatigue in MS is multifactorial,[54] and although the intervention attempted to mitigate controllable factors, factors such as stress, affective disorders, sleep disorders, medications, seasonal weather, and outdoor temperatures could not be controlled. Additionally, the intervention did not include any components of cognitive-behavioral therapy, specific fatigue management strategies, or combined strengthening and aerobic exercise, which have been shown to positively affect fatigue levels in those with MS.[55,56] Additionally, the responsiveness to change of the FSMC has not yet been studied.

Although previous studies have established the detrimental effect of cognitive-motor interference in those with MS, there is little evidence on examining ways to mitigate interference during walking tasks. Only 2 interventional studies on dual-task training in MS were found that included a component of gait or walking training. A small pilot study by Peruzzi et al examined the effects of a 6-week, 12-session, virtual reality-based treadmill training program and found promising improvements in gait speed (18%), stride length (10%), and 6MWT distance (8%) which were maintained up to 4 weeks after the intervention.[57] However, due to the small sample size, lack of control group, and lack of blinding, results from the study should still be interpreted with caution. In a feasibility trial conducted by Sosnoff et al, the authors sought to examine the effects of a 12-week, 24-session dual-task balance and gait training program on balance and walking function.[58] The authors found that their intervention program resulted in changes that were trending toward improvement on measures of dual-task gait velocity but found no difference on measures of balance or cognitive performance.[58] Measures of dual-task costs were not examined by the authors. The study's small sample size, possible low exercise intensity, low cognitive tasks difficulty, and lack of follow-up limit the interpretations of its results and larger intervention studies focusing on dual-task rehabilitation are warranted. Additionally, the inclusion of balance exercises in the intervention limits the interpretation of contributions to dual-task gait improvements.

A recent multi-center randomized control trial of 40 individuals with MS demonstrated that both single-task and dual-task training significantly improved motor and cognitive performance, but only dual-task training contributed to a greater degree of improvements in dual-task walking compared to the single-task group.[59] The study utilized an 8-week, 20 sessions dual-task training intervention that consisted of walking or stepping practice while performing 11 different cognitive tasks of varying complexity delivered through a unique computer application developed specifically for the study. In contrast, the single-task group intervention consisted of 21 different gait and balance exercises. Improvements in the dual-task group demonstrated were maintained at follow-up assessment, suggesting improved motor learning and control over single-task training. The study's use of a novel training application, lack of use of a standardized dual-task outcome measure, and considerably different interventions between groups limit the generalizability of its results.

The results from the current 6-week intervention study are consistent with the findings of previous studies on dual-task training effects on gait outcomes. Unlike other studies, which incorporated multiple modes of dual-task training, this study utilized a gait-specific training program to better determine its direct effects on functional gait outcomes. Additionally, in comparison to the other studies, each 1-on-1 session in the current study was led by a licensed physical therapist who provided immediate feedback on gait and cognitive performance after each bout of walking, which may have allowed the participant to engage feedforward mechanisms necessary to correct their performance on each subsequent bout. Moreover, this study intervention did not require any equipment and could, therefore, be readily implemented in the clinic. The intervention could be easily adapted to meet the needs of the clinician and patient in a variety of settings and could also serve as a general framework on which to base and initiate gait-specific training programs for those with MS.

This study has several limitations. Primarily, the sample size was small, resulting in challenges with power, which limits the generalizability of the findings. Reasons for the small sample size include difficulty with recruitment of individuals with MS, as well as financial and time constraints, which limited the number of enrolled participants. Based on the results of this study, a sample of 62 participants with 31 participants per group would be needed in a future study to find significant group differences on walking outcomes (Bonferroni adjusted $\alpha = .067$, 80% power). Although the intervention protocol was standardized for all participants, there was no standardized progression of the gait training protocol other than the reduction of rest times every 2 weeks. This possibly created an intervention whose intensity and duration were insufficient to induce optimal training effects for long-term changes. Additionally, the majority of participants for both groups were female and had relapsing-remitting multiple sclerosis, further limiting the generalizability of the study. Finally, the DT group demonstrated greater walking capacity at pre-testing compared to the ST group, reflecting the lower level of disability in the DT group. Future studies should address these limitations to strengthen methodological comparability.

To our knowledge, this is the first study to evaluate the feasibility and effects of a gait-specific dual-task training intervention on measures of walking capacity, self-reported walking ability, and self-reported fatigue in individuals with MS. Results from the study have provided valuable information that future studies can expand upon for dual-task rehabilitation interventions. Additional randomized controlled trials with larger sample sizes are needed to elucidate the external validity of dual-task interventions better and guide clinical decision-making.

**CLINICAL RELEVANCE**

- A gait-specific dual-task training intervention for people with MS may improve walking capacity and self-perceived walking ability.
- However, this intervention alone was insufficient to observe changes in self-reported fatigue.
- This study provides a general framework to help guide clinicians who are wishing to incorporate dual-task training into their interventions to improve overall walking function.

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## COMPETING INTERESTS

The authors declared that there is no conflict of interest.

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# CHAPTER VI

# CLINICAL IMPLICATIONS OF DUAL-TASK MEASUREMENT & TRAINING IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

## STATEMENT OF THE PROBLEM

MS is the most common cause of non-traumatic neurological disability in young adults and contributes to the motor and cognitive deficits that can affect an individual's ability to function independently.[1-3] Specifically, multiple sclerosis can significantly alter an individual's ability to ambulate safely by adversely affecting the individual's gait pattern and increasing his or her risk for falling. Up to 65% of people with MS demonstrate cognitive deficits and up to 90% of people with MS and mobility deficits.[4-6] The individual variability in the pathological process of MS underlies the heterogeneity of both cognitive and motor deficits and contributes to the difficulties with dual-task ability.[7-11] Individuals with MS present with detrimental changes in dual-task gait performance, especially in gait velocity, step length, cadence, and gait variability, which are associated with an increased risk for falls.[7-11] Additionally, this phenomenon of cognitive-motor interference, which is measured as dual-task cost, is significantly associated with measures of functional gait.[12]

Currently, we were not able to find evidence of an appropriate clinical measure to assess dual-task gait and dual-task cognitive performance.[13,14] The majority of clinical measures of dual-task do not appropriately consider the individual's dual-task cognitive performance relative to single-task cognitive performance, nor do they provide an appropriately challenging motor and cognitive task. Moreover, we were unable to find sufficient clinical research of strong methodological quality that seeks to explore interventions and methods to mitigate cognitive-motor interference or reduce the dual-task cost of gait performance. The current studies sought to answer some of these questions within the MS dual-tasking literature.

## REVIEW OF METHODOLOGY

The aim of the first study was to assess the test-retest reliability and discriminant validity of a clinical measure of dual-task performance, the mWART in individuals with MS and individuals without MS. The second study sought to investigate the feasibility and effects of a 6-week gait-specific dual-task training intervention on both single-task and dual-task gait performance of gait velocity, cadence, and step length. The aim of the final study was to determine the effects of the dual-task intervention on validated measures of walking capacity, self-perceived walking ability, and self-reported fatigue.

## SUMMARY OF FINDINGS

The first study found that the mWART is a reliable and valid tool over time for both individuals with MS and without MS. The mWART demonstrated good to excellent test-retest reliability for single-task gait velocity and digit span recall, as well as dual-task velocity. However, dual-task cognitive performance demonstrated poor test-retest reliability. This finding suggests that the clinical measure should be repeated or to account for the day-to-day variability of symptoms in those with MS. Moreover, the study found that single-task and dual-task gait velocity, but not cognitive performance was able to differentiate between participants with MS and without MS. Further studies, however, are required to explore the reliability and validity of the mWART in a larger, more heterogeneous sample of persons with MS and without MS.

The second study found that a gait-specific dual-task training intervention for people with MS improves single-task and dual-task gait performance, specifically gait velocity, and may provide a more robust and longer-lasting effect than single-task training. Clinically meaningful changes were found at post-intervention for single-task and dual-task gait velocity following the dual-task intervention. Only dual-task gait velocity improved at a clinically meaningful difference at post-intervention following single-task training. The dual-task training group demonstrated greater %DTC for gait parameters at post-intervention as compared to the single-task training group, which could be explained by task prioritization following the specific intervention. Specifically, the single-task group, which engaged in only single-task gait training, may have been able to develop more gait automaticity than the dual-task group. However, the decline of these improvements at follow-up for the single-task group as compared to the dual-task group suggests a less robust effect of single-task training.

The third study found that the specific dual-task training intervention may improve walking capacity on the 2MWT and self-perceived walking ability on the MSWS-12. These improvements on the 2MWT and MSWS-12 were found to surpass the minimal important change for each measure at post-intervention. However, the changes observed in walking capacity had significantly declined at follow-up compared to post-intervention, and self-perceived walking ability improvements were maintained at follow-up. This may suggest that a longer intervention program that incorporates a home exercise program or daily physical activity goal may be required to induce longer-term changes and facilitate habit formation.

## CLINICAL RELEVANCE

The results of these studies may provide clinicians with more confidence in reliably and validly measuring dual-task gait performance. Findings from the intervention studies may also provide clinicians with greater guidance when implementing a gait-specific dual-task training intervention to improve both single-task and dual-task gait performance, walking capacity, and self-perceived walking ability. The intervention developed for these studies are specific to individuals with MS to assist with mitigating concerns with fatigue and over-exertion, while still providing a sufficient intensity to produce clinically meaningful change. The intervention used in this study may be adapted and used in a variety of settings and could serve as a general framework from which to initiate gait-specific training programs for individuals with MS.

**IMPLICATIONS FOR FUTURE STUDIES**

There are several recommendations for future studies. Firstly, increasing the study sample size would greatly increase statistical power and improve the generalizability of the results. Additionally, larger sample sizes would allow for the use of more robust methods of statistical analyses. However, future studies may explore how the length or duration of the intervention affects outcomes. Would a more extended intervention produce greater improvements in gait and functional measures, or would an intervention program of the same length but with more frequent training sessions produce greater improvements? Measuring participants after the intervention protocol is concluded would help to determine whether changes that have occurred following dual-task training extend beyond the 6-week training intervention.

Conventional physical therapy plans of care typically include a home exercise program as an integral component of rehabilitation, so future studies may also wish to explore the effects of incorporating a home exercise program with the dual-task intervention on gait and functional outcomes. Future studies may also explore how standardized progression of the cognitive and motor task affects gait and functional outcomes.

Another recommendation for future studies with a more heterogeneous and larger sample size is to compare the effects of dual-task training on different levels of disability based on the Expanded Disability Status Scale or a patient-derived disability outcome, such as the Patient Determined Disease Steps. Future studies concerning dual-task performance should also incorporate more specific and sensitive neuropsychological measures to assess cognitive dysfunction in individuals with MS. These studies may also explore the effects of different interventions such as cognitive rehabilitation on both motor and cognitive dual-task performance.

# REFERENCES

## Chapter I


1. Wajda DA, Sosnoff JJ. Cognitive-motor interference in multiple sclerosis: a systematic review of evidence, correlates, and consequences. *Biomed Res Int.* 2015;2015:720856.
2. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol.* 2008;7(12):1139-1151.
3. Rao SM. Cognitive function in patients with multiple sclerosis: impairment and treatment. *Int J MS Care*. 2004;6(1):9-22.
4. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology.* 1991;41(5):685-691.
5. Cameron MH, Wagner JM. Gait abnormalities in multiple sclerosis: pathogenesis, evaluation, and advances in treatment. *Curr Neurol Neurosci Rep.* 2011;11(5):507-515.
6. Comber L, Galvin R, Coote S. Gait deficits in people with multiple sclerosis: A systematic review and meta-analysis. *Gait Posture.* 2017;51:25-35.
7. Kister I, Bacon TE, Chamot E, et al. Natural history of multiple sclerosis symptoms. *Int J MS Care.* 2013;15(3):146-158.
8. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM. Dual-tasking effects on gait variability: the role of aging, falls, and executive function. *Mov Disord.* 2006;21(7):950-957.
9. Fritz NE, Cheek FM, Nichols-Larsen DS. Motor-cognitive dual-task training in persons with neurologic disorders: a systematic review. *J Neurol Phys Ther.* 2015;39(3):142-153.

10. Negahban H, Mofateh R, Arastoo AA, et al. The effects of cognitive loading on balance control in patients with multiple sclerosis. *Gait Posture.* 2011;34(4):479-484.

11. Jacobs JV, Kasser SL. Effects of dual tasking on the postural performance of people with and without multiple sclerosis: a pilot study. *J Neurol.* 2012;259(6):1166-1176.

12. D'Orio VL, Foley FW, Armentano F, Picone MA, Kim S, Holtzer R. Cognitive and motor functioning in patients with multiple sclerosis: neuropsychological predictors of walking speed and falls. *J Neurol Sci.* 2012;316(1-2):42-46.

13. Nogueira LA, Dos Santos LT, Sabino PG, Alvarenga RM, Santos Thuler LC. Factors for lower walking speed in persons with multiple sclerosis. *Mult Scler Int.* 2013;2013:875648.

14. Hamilton F, Rochester L, Paul L, Rafferty D, O'Leary CP, Evans JJ. Walking and talking: an investigation of cognitive-motor dual tasking in multiple sclerosis. *Mult Scler.* 2009;15(10):1215-1227.

15. Kalron A, Dvir Z, Achiron A. Walking while talking--difficulties incurred during the initial stages of multiple sclerosis disease process. *Gait Posture.* 2010;32(3):332-335.

16. Sosnoff JJ, Boes MK, Sandroff BM, Socie MJ, Pula JH, Motl RW. Walking and thinking in persons with multiple sclerosis who vary in disability. *Arch Phys Med Rehabil.* 2011;92(12):2028-2033.

17. Learmonth YC, Sandroff BM, Pilutti LA, et al. Cognitive motor interference during walking in multiple sclerosis using an alternate-letter alphabet task. *Arch Phys Med Rehabil.* 2014;95(8):1498-1503.

18. Allali G, Laidet M, Assal F, Armand S, Lalive PH. Walking while talking in patients with multiple sclerosis: the impact of specific cognitive loads. *Neurophysiol Clin.* 2014;44(1):87-93.

19. Motl RW, Sosnoff JJ, Dlugonski D, Pilutti LA, Klaren R, Sandroff BM. Walking and cognition, but not symptoms, correlate with dual task cost of walking in multiple sclerosis. *Gait Posture.* 2014;39(3):870-874.

20. Sosnoff JJ, Socie MJ, Sandroff BM, et al. Mobility and cognitive correlates of dual task cost of walking in persons with multiple sclerosis. *Disabil Rehabil.* 2014;36(3):205-209.

21. Wajda DA, Motl RW, Sosnoff JJ. Dual task cost of walking is related to fall risk in persons with multiple sclerosis. *J Neurol Sci.* 2013;335(1-2):160-163.

22. Sosnoff JJ, Balantrapu S, Pilutti LA, Sandroff BM, Morrison S, Motl RW. Cognitive processing speed is related to fall frequency in older adults with multiple sclerosis. *Arch Phys Med Rehabil.* 2013;94(8):1567-1572.

23. Bollaert RE, Sandroff BM, Stine-Morrow EAL, Sutton BP, Motl RW. The intersection of physical function, cognitive performance, aging, and multiple sclerosis: a cross-sectional comparative study. *Cogn Behav Neurol.* 2019;32(1):1-10.

24. Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology.* 1991;41(5):692-696.

25. Hoogs M, Kaur S, Smerbeck A, Weinstock-Guttman B, Benedict RH. Cognition and physical disability in predicting health-related quality of life in multiple sclerosis. *Int J MS Care.* 2011;13(2):57-63.

26. Ruet A, Deloire M, Hamel D, Ouallet JC, Petry K, Brochet B. Cognitive impairment, health-related quality of life and vocational status at early stages of multiple sclerosis: a 7-year longitudinal study. *J Neurol.* 2013;260(3):776-784.

27. Benedict RH, Wahlig E, Bakshi R, et al. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *J Neurol Sci.* 2005;231(1-2):29-34.

28. Glanz BI, Healy BC, Rintell DJ, Jaffin SK, Bakshi R, Weiner HL. The association between cognitive impairment and quality of life in patients with early multiple sclerosis. *J Neurol Sci.* 2010;290(1-2):75-79.

29. Givon U, Zeilig G, Achiron A. Gait analysis in multiple sclerosis: characterization of temporal-spatial parameters using GAITRite functional ambulation system. *Gait Posture.* 2009;29(1):138-142.

30. Sherwood J, Inouye C, Anderson E, et al. 6-minute walk test. *Med Sci Sports Exerc.* 2016;48:31-32.

31. Sosnoff JJ, Wajda DA, Sandroff BM, Roeing KL, Sung J, Motl RW. Dual task training in persons with Multiple Sclerosis: a feasability randomized controlled trial. *Clin Rehabil.* 2017;31(10):1322-1331.

32. Bloem BR, Grimbergen YAM, Cramer M, Valkenburg VV. "Stops walking when talking" does not predict falls in Parkinson's disease. *Annals of Neurology.* 2000;48(2):268.

33. Hyndman D, Ashburn A. "Stops walking when talking" as a predictor of falls in people with stroke living in the community. *J Neurol Neurosurg Psychiatry.* 2004;75(7):994-997.

34. McCulloch KL, Buxton E, Hackney J, Lowers S. Balance, attention, and dual-task performance during walking after brain injury: associations with falls history. *J Head Trauma Rehabil.* 2010;25(3):155-163.

35. Camicioli R, Howieson D, Lehman S, Kaye J. Talking while walking the effect of a dual task in aging and Alzheimer's disease. *Neurology.* 1997;48(4):955-958.

36. McCulloch K. Attention and dual-task conditions: physical therapy implications for individuals with acquired brain injury. *J Neurol Phys Ther.* 2007;31(3):104-118.

37. Verghese J, Xue X. Identifying frailty in high functioning older adults with normal mobility. *Age Ageing.* 2010;39(3):382-385.

38. Campbell CM, Rowse JL, Ciol MA, Shumway-Cook A. The effect of cognitive demand on Timed Up and Go performance in older adults with and without Parkinson disease. *J Neurol Phys Ther.* 2003;27(1):2-7.

39. Hofheinz M, Schusterschitz C. Dual task interference in estimating the risk of falls and measuring change: a comparative, psychometric study of four measurements. *Clin Rehabil.* 2010;24(9):831-842.

40. Leone C, Patti F, Feys P. Measuring the cost of cognitive-motor dual tasking during walking in multiple sclerosis. *Mult Scler.* 2015;21(2):123-131.

41. McCulloch KL, Mercer V, Giuliani C, Marshall S. Development of a clinical measure of dual-task performance in walking: reliability and preliminary validity of the Walking and Remembering Test. *J Geriatr Phys Ther.* 2009;32(1):2-9.

42. Brecl Jakob G, Remsak T, Sega Jazbec S, Horvat Ledinek A, Rot U. Step initiation interferes with working memory in nondisabled patients with the earliest multiple sclerosis-A dual-task study. *Gait Posture.* 2017;51:201-207.

43. D'Esposito M, Onishi K, Thompson H, Robinson K, Armstrong C, Grossman M. Working memory impairments in multiple sclerosis: Evidence from a dual-task paradigm. *Neuropsychology.* 1996;10(1):51-56.

44. Johannsen L, Li KZ, Chechlacz M, Bibi A, Kourtzi Z, Wing AM. Functional neuroimaging of the interference between working memory and the control of periodic ankle movement timing. *Neuropsychologia.* 2013;51(11):2142-2153.

45. Learmonth YC, Ensari I, Motl RW. Cognitive motor interference in multiple sclerosis: insights from a systematic quantitative review. *Arch Phys Med Rehabil.* 2017;98(6):1229-1240.

46. Wajda DA, Mirelman A, Hausdorff JM, Sosnoff JJ. Intervention modalities for targeting cognitive-motor interference in individuals with neurodegenerative disease: a systematic review. *Expert Rev Neurother.* 2017;17(3):251-261.

47. Yogev-Seligmann G, Giladi N, Brozgol M, Hausdorff JM. A training program to improve gait while dual tasking in patients with Parkinson's disease: a pilot study. *Arch Phys Med Rehabil.* 2012;93(1):176-181.

48. Veldkamp R, Baert I, Kalron A, et al. Structured cognitive-motor dual task training compared to single mobility training in persons with multiple sclerosis, a multicenter RCT. *J Clin Med.* 2019;8(12):2177.

49. Evans JJ, Greenfield E, Wilson BA, Bateman A. Walking and talking therapy: improving cognitive-motor dual-tasking in neurological illness. *J Int Neuropsychol Soc.* 2009;15(1):112-120.

50. Schwenk M, Zieschang T, Oster P, Hauer K. Dual-task performances can be improved in patients with dementia: a randomized controlled trial. *Neurology.* 2010;74(24):1961-1968.

51. Falbo S, Condello G, Capranica L, Forte R, Pesce C. Effects of physical-cognitive dual task training on executive function and gait performance in older adults: a randomized controlled trial. *Biomed Res Int.* 2016;2016:5812092.

52. Dagenais E, Rouleau I, Demers M, et al. Value of the MoCA test as a screening instrument in multiple sclerosis. *Can J Neurol Sci.* 2013;40(3):410-415.

53. Freitas S, Batista S, Afonso AC, et al. The Montreal Cognitive Assessment (MoCA) as a screening test for cognitive dysfunction in multiple sclerosis. *Appl Neuropsychol Adult.* 2018;25(1):57-70.

54. Charvet LE. The Montreal Cognitive Assessment (MoCA) in multiple sclerosis: relation to clinical features. *J Mult Scler.* 2015;02(02).

55. Lynall RC, Zukowski LA, Plummer P, Mihalik JP. Reliability and validity of the protokinetics movement analysis software in measuring center of pressure during walking. *Gait Posture.* 2017;52:308-311.

56. Wajda DA, Moon Y, Motl RW, Sosnoff JJ. Preliminary investigation of gait initiation and falls in multiple sclerosis. *Arch Phys Med Rehabil.* 2015;96(6):1098-1102.

57. Kirkland MC, Wallack EM, Rancourt SN, Ploughman M. Comparing three dual-task methods and the relationship to physical and cognitive impairment in people with multiple sclerosis and controls. *Mult Scler Int.* 2015;2015:650645.

58. Fritz NE, Keller J, Calabresi PA, Zackowski KM. Quantitative measures of walking and strength provide insight into brain corticospinal tract pathology in multiple sclerosis. *Neuroimage Clin.* 2017;14:490-498.

59. Weightman MM, McCulloch K. Dual-task Assessment and Intervention. *Mild Traumatic Brain Injury Rehabilitation Toolkit.* 2014:321.

60. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med.* 2016;15(2):155-163.

61. Erickson KI, Colcombe SJ, Wadhwa R, et al. Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. *Neurobiol Aging.* 2007;28(2):272-283.

62. Gijbels D, Eijnde BO, Feys P. Comparison of the 2- and 6-minute walk test in multiple sclerosis. *Mult Scler.* 2011;17(10):1269-1272.

63. Gijbels D, Dalgas U, Romberg A, et al. Which walking capacity tests to use in multiple sclerosis? A multicentre study providing the basis for a core set. *Mult Scler.* 2012;18(3):364-371.

64. Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). *Neurology.* 2003;60(1):31-36.

65. Pilutti LA, Dlugonski D, Sandroff BM, et al. Further validation of multiple sclerosis walking scale-12 scores based on spatiotemporal gait parameters. *Arch Phys Med Rehabil.* 2013;94(3):575-578.

66. Motl RW, Snook EM. Confirmation and extension of the validity of the Multiple Sclerosis Walking Scale-12 (MSWS-12). *J Neurol Sci.* 2008;268(1-2):69-73.

67. Nilsagard Y, Lundholm C, Denison E, Gunnarsson LG. Predicting accidental falls in people with multiple sclerosis -- a longitudinal study. *Clin Rehabil.* 2009;23(3):259-269.

68. Penner IK, Raselli C, Stocklin M, Opwis K, Kappos L, Calabrese P. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler.* 2009;15(12):1509-1517.

Chapter II

1. Baecher-Allan C, Kaskow BJ, Weiner HL. Multiple sclerosis: mechanisms and immunotherapy. *Neuron.* 2018;97(4):742-768.

2. Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. *Nat Rev Immunol.* 2015;15(9):545-558.

3. Mahad DH, Trapp BD, Lassmann H. Pathological mechanisms in progressive multiple sclerosis. *Lancet Neurol.* 2015;14(2):183-193.

4. Ransohoff RM, Hafler DA, Lucchinetti CF. Multiple sclerosis-a quiet revolution. *Nat Rev Neurol.* 2015;11(3):134-142.

5. Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: A population-based estimate using health claims data. *Neurology.* 2019;92(10):e1029-e1040.

6. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. *Lancet Neurol.* 2010;9(5):520-532.

7. Alonso A, Hernan MA. Temporal trends in the incidence of multiple sclerosis: a systematic review. *Neurology.* 2008;71(2):129-135.

8. Bjartmar C, Trapp BD. Axonal degeneration and progressive neurologic disability in multiple sclerosis. *Neurotox Res.* 2003;5(1-2):157-164.

9. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology.* 1991;41(5):685-691.

10. Amato MP, Portaccio E, Goretti B, et al. Cognitive impairment in early stages of multiple sclerosis. *Neurol Sci.* 2010;31(Suppl 2):S211-214.

11. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol.* 2008;7(12):1139-1151.

12. Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology.* 1991;41(5):692-696.

13. Benedict RH, Wahlig E, Bakshi R, et al. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *J Neurol Sci.* 2005;231(1-2):29-34.

14. Hoogs M, Kaur S, Smerbeck A, Weinstock-Guttman B, Benedict RH. Cognition and physical disability in predicting health-related quality of life in multiple sclerosis. *Int J MS Care.* 2011;13(2):57-63.

15. Hemmett L, Holmes J, Barnes M, Russell N. What drives quality of life in multiple sclerosis? *QJM.* 2004;97(10):671-676.

16. Kobelt G, Berg J, Lindgren P, Fredrikson S, Jonsson B. Costs and quality of life of patients with multiple sclerosis in Europe. *J Neurol Neurosurg Psychiatry.* 2006;77(8):918-926.

17. Ruet A, Deloire M, Hamel D, Ouallet JC, Petry K, Brochet B. Cognitive impairment, health-related quality of life and vocational status at early stages of multiple sclerosis: a 7-year longitudinal study. *J Neurol.* 2013;260(3):776-784.

18. Kister I, Bacon TE, Chamot E, et al. Natural history of multiple sclerosis symptoms. *Int J MS Care.* 2013;15(3):146-158.
19. Comber L, Galvin R, Coote S. Gait deficits in people with multiple sclerosis: A systematic review and meta-analysis. *Gait Posture.* 2017;51:25-35.
20. Givon U, Zeilig G, Achiron A. Gait analysis in multiple sclerosis: characterization of temporal-spatial parameters using GAITRite functional ambulation system. *Gait Posture.* 2009;29(1):138-142.
21. Sherwood J, Inouye C, Anderson E, et al. 6-minute walk test. *Med Sci Sports Exerc.* 2016;48:31-32.
22. Learmonth YC, Ensari I, Motl RW. Cognitive motor interference in multiple sclerosis: insights from a systematic quantitative review. *Arch Phys Med Rehabil.* 2017;98(6):1229-1240.
23. Fritz NE, Cheek FM, Nichols-Larsen DS. Motor-cognitive dual-task training in persons with neurologic disorders: a systematic review. *J Neurol Phys Ther.* 2015;39(3):142-153.
24. Rochester L, Rafferty D, Dotchin C, Msuya O, Minde V, Walker RW. The effect of cueing therapy on single and dual-task gait in a drug naive population of people with Parkinson's disease in northern Tanzania. *Mov Disord.* 2010;25(7):906-911.
25. D'Esposito M, Onishi K, Thompson H, Robinson K, Armstrong C, Grossman M. Working memory impairments in multiple sclerosis: Evidence from a dual-task paradigm. *Neuropsychology.* 1996;10(1):51-56.
26. Camicioli R, Howieson D, Lehman S, Kaye J. Talking while walking the effect of a dual task in aging and Alzheimer's disease. *Neurology.* 1997;48(4):955-958.

27. Bloem BR, Valkenburg VV, Slabbekoorn M, van Dijk JG. The multiple tasks test. Strategies in Parkinson's disease. *Exp Brain Res.* 2001;137(3-4):478-486.

28. Szameitat AJ, Schubert T, Muller K, Von Cramon DY. Localization of executive functions in dual-task performance with fMRI. *J Cogn Neurosci.* 2002;14(8):1184-1199.

29. Yogev G, Giladi N, Peretz C, Springer S, Simon ES, Hausdorff JM. Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? *Eur J Neurosci.* 2005;22(5):1248-1256.

30. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM. Dual-tasking effects on gait variability: the role of aging, falls, and executive function. *Mov Disord.* 2006;21(7):950-957.

31. McCulloch K. Attention and dual-task conditions: physical therapy implications for individuals with acquired brain injury. *J Neurol Phys Ther.* 2007;31(3):104-118.

32. Beauchet O, Annweiler C, Allali G, Berrut G, Herrmann FR, Dubost V. Recurrent falls and dual task-related decrease in walking speed: is there a relationship? *J Am Geriatr Soc.* 2008;56(7):1265-1269.

33. Canning CG, Ada L, Woodhouse E. Multiple-task walking training in people with mild to moderate Parkinson's disease: a pilot study. *Clin Rehabil.* 2008;22(3):226-233.

34. Evans JJ, Greenfield E, Wilson BA, Bateman A. Walking and talking therapy: improving cognitive-motor dual-tasking in neurological illness. *J Int Neuropsychol Soc.* 2009;15(1):112-120.

35. Silsupadol P, Lugade V, Shumway-Cook A, et al. Training-related changes in dual-task walking performance of elderly persons with balance impairment: a double-blind, randomized controlled trial. *Gait Posture.* 2009;29(4):634-639.

36. Brauer SG, Morris ME. Can people with Parkinson's disease improve dual tasking when walking? *Gait Posture.* 2010;31(2):229-233.

37. Fok P, Farrell M, McMeeken J. Prioritizing gait in dual-task conditions in people with Parkinson's. *Hum Mov Sci.* 2010;29(5):831-842.

38. Hofheinz M, Schusterschitz C. Dual task interference in estimating the risk of falls and measuring change: a comparative, psychometric study of four measurements. *Clin Rehabil.* 2010;24(9):831-842.

39. McCulloch KL, Buxton E, Hackney J, Lowers S. Balance, attention, and dual-task performance during walking after brain injury: associations with falls history. *J Head Trauma Rehabil.* 2010;25(3):155-163.

40. Schwenk M, Zieschang T, Oster P, Hauer K. Dual-task performances can be improved in patients with dementia: a randomized controlled trial. *Neurology.* 2010;74(24):1961-1968.

41. Fok P, Farrell M, McMeeken J. The effect of dividing attention between walking and auxiliary tasks in people with Parkinson's disease. *Hum Mov Sci.* 2012;31(1):236-246.

42. Montero-Odasso M, Muir SW, Speechley M. Dual-task complexity affects gait in people with mild cognitive impairment: the interplay between gait variability, dual tasking, and risk of falls. *Arch Phys Med Rehabil.* 2012;93(2):293-299.

43. Plummer-D'Amato P, Cohen Z, Daee NA, Lawson SE, Lizotte MR, Padilla A. Effects of once weekly dual-task training in older adults: a pilot randomized controlled trial. *Geriatr Gerontol Int.* 2012;12(4):622-629.

44. Yogev-Seligmann G, Giladi N, Brozgol M, Hausdorff JM. A training program to improve gait while dual tasking in patients with Parkinson's disease: a pilot study. *Arch Phys Med Rehabil.* 2012;93(1):176-181.

45. de Andrade LP, Gobbi LT, Coelho FG, Christofoletti G, Costa JL, Stella F. Benefits of multimodal exercise intervention for postural control and frontal cognitive functions in individuals with Alzheimer's disease: a controlled trial. *J Am Geriatr Soc.* 2013;61(11):1919-1926.

46. Menant JC, Schoene D, Sarofim M, Lord SR. Single and dual task tests of gait speed are equivalent in the prediction of falls in older people: a systematic review and meta-analysis. *Ageing Res Rev.* 2014;16:83-104.

47. Fernandes A, Rocha N, Santos R, Tavares JM. Effects of dual-task training on balance and executive functions in Parkinson's disease: A pilot study. *Somatosens Mot Res.* 2015;32(2):122-127.

48. Kirkland MC, Wallack EM, Rancourt SN, Ploughman M. Comparing three dual-task methods and the relationship to physical and cognitive impairment in people with multiple sclerosis and controls. *Mult Scler Int.* 2015;2015:650645.

49. Plummer P, Eskes G. Measuring treatment effects on dual-task performance: a framework for research and clinical practice. *Front Hum Neurosci.* 2015;9:225.

50. Plummer P, Osborne MB. What are we attempting to improve when we train dual-task performance? *J Neurol Phys Ther.* 2015;39(3):154-155.

51. Strouwen C, Molenaar E, Munks L, et al. Training dual tasks together or apart in Parkinson's disease: results from the DUALITY trial. *Mov Disord.* 2017;32(8):1201-1210.

52. He Y, Yang L, Zhou J, Yao L, Pang MYC. Dual-task training effects on motor and cognitive functional abilities in individuals with stroke: a systematic review. *Clin Rehabil.* 2018;32(7):865-877.

53. Plummer P, Eskes G, Wallace S, et al. Cognitive-motor interference during functional mobility after stroke: state of the science and implications for future research. *Arch Phys Med Rehabil.* 2013;94(12):2565-2574 e2566.

54. Ziemssen T, De Stefano N, Sormani MP, Van Wijmeersch B, Wiendl H, Kieseier BC. Optimizing therapy early in multiple sclerosis: An evidence-based view. *Mult Scler Relat Disord.* 2015;4(5):460-469.

55. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology.* 2014;83(3):278-286.

56. Friese MA, Schattling B, Fugger L. Mechanisms of neurodegeneration and axonal dysfunction in multiple sclerosis. *Nat Rev Neurol.* 2014;10(4):225-238.

57. Correale J, Gaitan MI, Ysrraelit MC, Fiol MP. Progressive multiple sclerosis: from pathogenic mechanisms to treatment. *Brain.* 2017;140(3):527-546.

58. Lassmann H, van Horssen J, Mahad D. Progressive multiple sclerosis: pathology and pathogenesis. *Nat Rev Neurol.* 2012;8(11):647-656.

59. Heesen C, Bohm J, Reich C, Kasper J, Goebel M, Gold SM. Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable. *Mult Scler.* 2008;14(7):988-991.

60. Socie MJ, Motl RW, Pula JH, Sandroff BM, Sosnoff JJ. Gait variability and disability in multiple sclerosis. *Gait Posture.* 2013;38(1):51-55.

61. Meyer-Moock S, Feng YS, Maeurer M, Dippel FW, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. *BMC Neurol.* 2014;14(1):58.

62. Brach JS, Studenski SA, Perera S, VanSwearingen JM, Newman AB. Gait variability and the risk of incident mobility disability in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci.* 2007;62(9):983-988.

63. Hausdorff JM. Gait variability: methods, modeling and meaning. *J Neuroeng Rehabil.* 2005;2(1):19.

64. Manjaly ZM, Harrison NA, Critchley HD, et al. Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2019;90(6):642-651.

65. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: Proposal for a unified taxonomy. *Neurology.* 2013;80(4):409-416.

66. Kos D, Kerckhofs E, Nagels G, D'Hooghe M B, Ilsbroukx S. Origin of fatigue in multiple sclerosis: review of the literature. *Neurorehabil Neural Repair.* 2008;22(1):91-100.

67. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. *Can J Neurol Sci.* 2015;21(1):9-14.

68. Garg H, Bush S, Gappmaier E. Associations between fatigue and disability, functional mobility, depression, and quality of life in people with multiple sclerosis. *Int J MS Care.* 2016;18(2):71-77.

69. Sheean G. The pathophysiology of spasticity. *Eur J Neurol.* 2002;9 Suppl 1(s1):3-9; dicussion 53-61.

70. Sosnoff JJ, Shin S, Motl RW. Multiple sclerosis and postural control: the role of spasticity. *Arch Phys Med Rehabil.* 2010;91(1):93-99.

71. Sosnoff JJ, Socie MJ, Boes MK, et al. Mobility, balance and falls in persons with multiple sclerosis. *PLoS One.* 2011;6(11):e28021.

72. Nilsagard Y, Lundholm C, Denison E, Gunnarsson LG. Predicting accidental falls in people with multiple sclerosis -- a longitudinal study. *Clin Rehabil.* 2009;23(3):259-269.

73. Koch M, Mostert J, Heersema D, De Keyser J. Tremor in multiple sclerosis. *J Neurol.* 2007;254(2):133-145.

74. Shafizadeh M, Watson P, Mohammadi B. Intra-limb coordination in gait pattern in health people and multiple sclerosis patients. *Clinical Kinesiology.* 2013;67(3).

75. Sosnoff JJ, Boes MK, Sandroff BM, Socie MJ, Pula JH, Motl RW. Walking and thinking in persons with multiple sclerosis who vary in disability. *Arch Phys Med Rehabil.* 2011;92(12):2028-2033.

76. Amato MP, Zipoli V, Portaccio E. Multiple sclerosis-related cognitive changes: a review of cross-sectional and longitudinal studies. *J Neurol Sci.* 2006;245(1-2):41-46.

77. Rao SM. Cognitive function in patients with multiple sclerosis: impairment and treatment. *Int J MS Care.* 2004;6(1):9-22.

78. Archibald CJ, Fisk JD. Information processing efficiency in patients with multiple sclerosis. *J Clin Exp Neuropsychol.* 2000;22(5):686-701.

79. Costa SL, Genova HM, DeLuca J, Chiaravalloti ND. Information processing speed in multiple sclerosis: Past, present, and future. *Mult Scler.* 2017;23(6):772-789.

80. D'Orio VL, Foley FW, Armentano F, Picone MA, Kim S, Holtzer R. Cognitive and motor functioning in patients with multiple sclerosis: neuropsychological predictors of walking speed and falls. *J Neurol Sci.* 2012;316(1-2):42-46.

81. Sosnoff JJ, Balantrapu S, Pilutti LA, Sandroff BM, Morrison S, Motl RW. Cognitive processing speed is related to fall frequency in older adults with multiple sclerosis. *Arch Phys Med Rehabil.* 2013;94(8):1567-1572.

82. Downing PE. Interactions between visual working memory and selective attention. *Psychol Sci.* 2000;11(6):467-473.

83. Brecl Jakob G, Remsak T, Sega Jazbec S, Horvat Ledinek A, Rot U. Step initiation interferes with working memory in nondisabled patients with the earliest multiple sclerosis-A dual-task study. *Gait Posture.* 2017;51:201-207.

84. Feuillet L, Reuter F, Audoin B, et al. Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. *Mult Scler.* 2007;13(1):124-127.

85. Potagas C, Giogkaraki E, Koutsis G, et al. Cognitive impairment in different MS subtypes and clinically isolated syndromes. *J Neurol Sci.* 2008;267(1-2):100-106.

86. Hankomaki E, Multanen J, Kinnunen E, Hamalainen P. The progress of cognitive decline in newly diagnosed MS patients. *Acta Neurol Scand.* 2014;129(3):184-191.

87. Johnen A, Landmeyer NC, Burkner PC, Wiendl H, Meuth SG, Holling H. Distinct cognitive impairments in different disease courses of multiple sclerosis-A systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2017;83:568-578.

88. Deloire M, Ruet A, Hamel D, Bonnet M, Brochet B. Early cognitive impairment in multiple sclerosis predicts disability outcome several years later. *Mult Scler.* 2010;16(5):581-587.

89. Hughes AJ, Hartoonian N, Parmenter B, et al. Cognitive impairment and community integration outcomes in individuals living with multiple sclerosis. *Arch Phys Med Rehabil.* 2015;96(11):1973-1979.

90. Sandroff BM, Pilutti LA, Benedict RH, Motl RW. Association between physical fitness and cognitive function in multiple sclerosis: does disability status matter? *Neurorehabil Neural Repair.* 2015;29(3):214-223.

91. Bollaert RE, Sandroff BM, Stine-Morrow EAL, Sutton BP, Motl RW. The intersection of physical function, cognitive performance, aging, and multiple sclerosis: a cross-sectional comparative study. *Cogn Behav Neurol.* 2019;32(1):1-10.

92. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord.* 2008;23(3):329-342; quiz 472.

93. Mihara M, Miyai I, Hatakenaka M, Kubota K, Sakoda S. Role of the prefrontal cortex in human balance control. *Neuroimage.* 2008;43(2):329-336.

94. MacDonald AW, 3rd, Cohen JD, Stenger VA, Carter CS. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science.* 2000;288(5472):1835-1838.

95. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture.* 2002;16(1):1-14.

96. Auvinet B, Touzard C, Montestruc F, Delafond A, Goeb V. Gait disorders in the elderly and dual task gait analysis: a new approach for identifying motor phenotypes. *J Neuroeng Rehabil.* 2017;14(1):7.

97. Drew T, Prentice S, Schepens B. Cortical and brainstem control of locomotion. *Prog Brain Res.* 2004;143:251-261.

98. Ramnani N, Behrens TE, Johansen-Berg H, et al. The evolution of prefrontal inputs to the cortico-pontine system: diffusion imaging evidence from Macaque monkeys and humans. *Cereb Cortex.* 2006;16(6):811-818.

99. Kim LH, Sharma S, Sharples SA, Mayr KA, Kwok CHT, Whelan PJ. Integration of descending command systems for the generation of context-specific locomotor behaviors. *Front Neurosci.* 2017;11:581.

100. Suzuki M, Miyai I, Ono T, Kubota K. Activities in the frontal cortex and gait performance are modulated by preparation. An fNIRS study. *Neuroimage.* 2008;39(2):600-607.

101. Harada T, Miyai I, Suzuki M, Kubota K. Gait capacity affects cortical activation patterns related to speed control in the elderly. *Exp Brain Res.* 2009;193(3):445-454.

102. Holtzer R, Mahoney JR, Izzetoglu M, Izzetoglu K, Onaral B, Verghese J. fNIRS study of walking and walking while talking in young and old individuals. *J Gerontol A Biol Sci Med Sci.* 2011;66(8):879-887.

103. Wajda DA, Mirelman A, Hausdorff JM, Sosnoff JJ. Intervention modalities for targeting cognitive-motor interference in individuals with neurodegenerative disease: a systematic review. *Expert Rev Neurother.* 2017;17(3):251-261.

104. Pashler H. Dual-task interference in simple tasks: data and theory. *Psychol Bull.* 1994;116(2):220-244.

105. Patel P, Lamar M, Bhatt T. Effect of type of cognitive task and walking speed on cognitive-motor interference during dual-task walking. *Neuroscience.* 2014;260:140-148.

106. Negahban H, Mofateh R, Arastoo AA, et al. The effects of cognitive loading on balance control in patients with multiple sclerosis. *Gait Posture.* 2011;34(4):479-484.

107. Hamilton F, Rochester L, Paul L, Rafferty D, O'Leary CP, Evans JJ. Walking and talking: an investigation of cognitive-motor dual tasking in multiple sclerosis. *Mult Scler.* 2009;15(10):1215-1227.

108. Nogueira LA, Dos Santos LT, Sabino PG, Alvarenga RM, Santos Thuler LC. Factors for lower walking speed in persons with multiple sclerosis. *Mult Scler Int.* 2013;2013:875648.

109. Allali G, Laidet M, Assal F, Armand S, Lalive PH. Walking while talking in patients with multiple sclerosis: the impact of specific cognitive loads. *Neurophysiol Clin.* 2014;44(1):87-93.

110. Motl RW, Sosnoff JJ, Dlugonski D, Pilutti LA, Klaren R, Sandroff BM. Walking and cognition, but not symptoms, correlate with dual task cost of walking in multiple sclerosis. *Gait Posture.* 2014;39(3):870-874.

111. Sosnoff JJ, Socie MJ, Sandroff BM, et al. Mobility and cognitive correlates of dual task cost of walking in persons with multiple sclerosis. *Disabil Rehabil.* 2014;36(3):205-209.

112. Learmonth YC, Sandroff BM, Pilutti LA, et al. Cognitive motor interference during walking in multiple sclerosis using an alternate-letter alphabet task. *Arch Phys Med Rehabil.* 2014;95(8):1498-1503.

113. McCulloch KL, Mercer V, Giuliani C, Marshall S. Development of a clinical measure of dual-task performance in walking: reliability and preliminary validity of the Walking and Remembering Test. *J Geriatr Phys Ther.* 2009;32(1):2-9.

114. Leone C, Patti F, Feys P. Measuring the cost of cognitive-motor dual tasking during walking in multiple sclerosis. *Mult Scler.* 2015;21(2):123-131.

115. Bloem BR, Grimbergen YAM, Cramer M, Valkenburg VV. “Stops walking when talking” does not predict falls in Parkinson's disease. *Annals of Neurology.* 2000;48(2):268.

116. Hyndman D, Ashburn A. “Stops walking when talking” as a predictor of falls in people with stroke living in the community. *J Neurol Neurosurg Psychiatry.* 2004;75(7):994-997.

117. Verghese J, Xue X. Identifying frailty in high functioning older adults with normal mobility. *Age Ageing.* 2010;39(3):382-385.

118. Campbell CM, Rowse JL, Ciol MA, Shumway-Cook A. The effect of cognitive demand on Timed Up and Go performance in older adults with and without Parkinson disease. *J Neurol Phys Ther.* 2003;27(1):2-7.

119. Allali G, Laidet M, Assal F, Chofflon M, Armand S, Lalive PH. Dual-task assessment in natalizumab-treated multiple sclerosis patients. *Eur Neurol.* 2014;71(5-6):247-251.

120. Monjezi S, Negahban H, Tajali S, Yadollahpour N, Majdinasab N. Effects of dual-task balance training on postural performance in patients with Multiple Sclerosis: a double-blind, randomized controlled pilot trial. *Clin Rehabil.* 2017;31(2):234-241.

121. Beauchet O, Annweiler C, Dubost V, et al. Stops walking when talking: a predictor of falls in older adults? *Eur J Neurol.* 2009:786-795.

122. McCulloch K, Blakley K, Freeman L. Clinical tests of walking dual-task performance after acquired brain injury (ABI): feasibility and dual-task cost comparisons to a young adult group. *J Neurol Phys Ther.* 2005;29(4):213.

123. Bloem BR, Valkenburg VV, Slabbekoorn M, Willemsen MD. The Multiple Tasks Test: development and normal strategies. *Gait Posture.* 2001;14(3):191-202.

124. Weightman M, McCulloch K. Dual-task assessment and intervention. In: *Mild traumatic brain injury rehabilitation toolkit.* Fort Sam Houston, Texas: Borden Institute; 2014:321-333.

125. Ghai S, Ghai I, Effenberg AO. Effects of dual tasks and dual-task training on postural stability: a systematic review and meta-analysis. *Clin Interv Aging.* 2017;12:557-577.

126. Kramer A, Dettmers C, Gruber M. Exergaming with additional postural demands improves balance and gait in patients with multiple sclerosis as much as conventional balance training and leads to high adherence to home-based balance training. *Arch Phys Med Rehabil.* 2014;95(10):1803-1809.

127. Peruzzi A, Cereatti A, Della Croce U, Mirelman A. Effects of a virtual reality and treadmill training on gait of subjects with multiple sclerosis: a pilot study. *Mult Scler Relat Disord.* 2016;5:91-96.

128. Sosnoff JJ, Wajda DA, Sandroff BM, Roeing KL, Sung J, Motl RW. Dual task training in persons with Multiple Sclerosis: a feasability randomized controlled trial. *Clin Rehabil.* 2017;31(10):1322-1331.

129. Veldkamp R, Baert I, Kalron A, et al. Structured cognitive-motor dual task training compared to single mobility training in persons with multiple sclerosis, a multicenter RCT. *J Clin Med.* 2019;8(12):2177.

130. Dagenais E, Rouleau I, Demers M, et al. Value of the MoCA test as a screening instrument in multiple sclerosis. *Can J Neurol Sci.* 2013;40(3):410-415.

131. Charvet LE. The Montreal Cognitive Assessment (MoCA) in multiple sclerosis: relation to clinical features. *J Mult Scler.* 2015;02(02).

132. Freitas S, Batista S, Afonso AC, et al. The Montreal Cognitive Assessment (MoCA) as a screening test for cognitive dysfunction in multiple sclerosis. *Appl Neuropsychol Adult.* 2018;25(1):57-70.

133. Gijbels D, Dalgas U, Romberg A, et al. Which walking capacity tests to use in multiple sclerosis? A multicentre study providing the basis for a core set. *Mult Scler.* 2012;18(3):364-371.

134. Gijbels D, Eijnde BO, Feys P. Comparison of the 2- and 6-minute walk test in multiple sclerosis. *Mult Scler.* 2011;17(10):1269-1272.

135. Baert I, Freeman J, Smedal T, et al. Responsiveness and clinically meaningful improvement, according to disability level, of five walking measures after rehabilitation in multiple sclerosis: a European multicenter study. *Neurorehabil Neural Repair.* 2014;28(7):621-631.

136. Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). *Neurology.* 2003;60(1):31-36.

137. Pilutti LA, Dlugonski D, Sandroff BM, et al. Further validation of multiple sclerosis walking scale-12 scores based on spatiotemporal gait parameters. *Arch Phys Med Rehabil.* 2013;94(3):575-578.

138. Motl RW, Snook EM. Confirmation and extension of the validity of the Multiple Sclerosis Walking Scale-12 (MSWS-12). *J Neurol Sci.* 2008;268(1-2):69-73.

139. Penner IK, Raselli C, Stocklin M, Opwis K, Kappos L, Calabrese P. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler.* 2009;15(12):1509-1517.

140. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J Speech Lang Hear Res.* 2008;51(1):S225-239.

141. Latimer-Cheung AE, Martin Ginis KA, Hicks AL, et al. Development of evidence-informed physical activity guidelines for adults with multiple sclerosis. *Arch Phys Med Rehabil.* 2013;94(9):1829-1836 e1827.

142. Erickson KI, Colcombe SJ, Wadhwa R, et al. Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. *Neurobiol Aging.* 2007;28(2):272-283.

Chapter III

1. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord.* 2008;23(3):329-342; quiz 472.

2. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc.* 2012;60(11):2127-2136.

3. Negahban H, Mofateh R, Arastoo AA, et al. The effects of cognitive loading on balance control in patients with multiple sclerosis. *Gait Posture.* 2011;34(4):479-484.

4. Jacobs JV, Kasser SL. Effects of dual tasking on the postural performance of people with and without multiple sclerosis: a pilot study. *J Neurol.* 2012;259(6):1166-1176.

5. Nogueira LA, Dos Santos LT, Sabino PG, Alvarenga RM, Santos Thuler LC. Factors for lower walking speed in persons with multiple sclerosis. *Mult Scler Int.* 2013;2013:875648.
6. Hamilton F, Rochester L, Paul L, Rafferty D, O'Leary CP, Evans JJ. Walking and talking: an investigation of cognitive-motor dual tasking in multiple sclerosis. *Mult Scler.* 2009;15(10):1215-1227.
7. Kalron A, Dvir Z, Achiron A. Walking while talking--difficulties incurred during the initial stages of multiple sclerosis disease process. *Gait Posture.* 2010;32(3):332-335.
8. Sosnoff JJ, Boes MK, Sandroff BM, Socie MJ, Pula JH, Motl RW. Walking and thinking in persons with multiple sclerosis who vary in disability. *Arch Phys Med Rehabil.* 2011;92(12):2028-2033.
9. D'Orio VL, Foley FW, Armentano F, Picone MA, Kim S, Holtzer R. Cognitive and motor functioning in patients with multiple sclerosis: neuropsychological predictors of walking speed and falls. *J Neurol Sci.* 2012;316(1-2):42-46.
10. Learmonth YC, Sandroff BM, Pilutti LA, et al. Cognitive motor interference during walking in multiple sclerosis using an alternate-letter alphabet task. *Arch Phys Med Rehabil.* 2014;95(8):1498-1503.
11. Allali G, Laidet M, Assal F, Armand S, Lalive PH. Walking while talking in patients with multiple sclerosis: the impact of specific cognitive loads. *Neurophysiol Clin.* 2014;44(1):87-93.
12. Motl RW, Sosnoff JJ, Dlugonski D, Pilutti LA, Klaren R, Sandroff BM. Walking and cognition, but not symptoms, correlate with dual task cost of walking in multiple sclerosis. *Gait Posture.* 2014;39(3):870-874.

13. Sosnoff JJ, Socie MJ, Sandroff BM, et al. Mobility and cognitive correlates of dual task cost of walking in persons with multiple sclerosis. *Disabil Rehabil.* 2014;36(3):205-209.

14. Wajda DA, Motl RW, Sosnoff JJ. Dual task cost of walking is related to fall risk in persons with multiple sclerosis. *J Neurol Sci.* 2013;335(1-2):160-163.

15. Sosnoff JJ, Balantrapu S, Pilutti LA, Sandroff BM, Morrison S, Motl RW. Cognitive processing speed is related to fall frequency in older adults with multiple sclerosis. *Arch Phys Med Rehabil.* 2013;94(8):1567-1572.

16. Bollaert RE, Sandroff BM, Stine-Morrow EAL, Sutton BP, Motl RW. The intersection of physical function, cognitive performance, aging, and multiple sclerosis: a cross-sectional comparative study. *Cogn Behav Neurol.* 2019;32(1):1-10.

17. Heesen C, Bohm J, Reich C, Kasper J, Goebel M, Gold SM. Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable. *Mult Scler.* 2008;14(7):988-991.

18. Hemmett L, Holmes J, Barnes M, Russell N. What drives quality of life in multiple sclerosis? *QJM.* 2004;97(10):671-676.

19. Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology.* 1991;41(5):692-696.

20. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol.* 2008;7(12):1139-1151.

21. Heine M, van de Port I, Rietberg MB, van Wegen EE, Kwakkel G. Exercise therapy for fatigue in multiple sclerosis. *Cochrane Database Syst Rev.* 2015(9):CD009956.

22. Benedict RH, Wahlig E, Bakshi R, et al. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *J Neurol Sci.* 2005;231(1-2):29-34.

23. Hoogs M, Kaur S, Smerbeck A, Weinstock-Guttman B, Benedict RH. Cognition and physical disability in predicting health-related quality of life in multiple sclerosis. *Int J MS Care.* 2011;13(2):57-63.

24. Al-Yahya E, Dawes H, Smith L, Dennis A, Howells K, Cockburn J. Cognitive motor interference while walking: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2011;35(3):715-728.

25. Leone C, Patti F, Feys P. Measuring the cost of cognitive-motor dual tasking during walking in multiple sclerosis. *Mult Scler.* 2015;21(2):123-131.

26. Learmonth YC, Ensari I, Motl RW. Cognitive motor interference in multiple sclerosis: insights from a systematic quantitative review. *Arch Phys Med Rehabil.* 2017;98(6):1229-1240.

27. Kister I, Bacon TE, Chamot E, et al. Natural history of multiple sclerosis symptoms. *Int J MS Care.* 2013;15(3):146-158.

28. Cattaneo D, De Nuzzo C, Fascia T, Macalli M, Pisoni I, Cardini R. Risks of falls in subjects with multiple sclerosis. *Arch Phys Med Rehabil.* 2002;83(6):864-867.

29. Matsuda PN, Shumway-Cook A, Bamer AM, Johnson SL, Amtmann D, Kraft GH. Falls in multiple sclerosis. *PM R.* 2011;3(7):624-632; quiz 632.

30. Etemadi Y. Dual task cost of cognition is related to fall risk in patients with multiple sclerosis: a prospective study. *Clin Rehabil.* 2017;31(2):278-284.

31. McCulloch KL, Mercer V, Giuliani C, Marshall S. Development of a clinical measure of dual-task performance in walking: reliability and preliminary validity of the Walking and Remembering Test. *J Geriatr Phys Ther.* 2009;32(1):2-9.

32. Bloem BR, Grimbergen YAM, Cramer M, Valkenburg VV. "Stops walking when talking" does not predict falls in Parkinson's disease. *Annals of Neurology.* 2000;48(2):268.

33. Hyndman D, Ashburn A. "Stops walking when talking" as a predictor of falls in people with stroke living in the community. *J Neurol Neurosurg Psychiatry.* 2004;75(7):994-997.

34. Verghese J, Xue X. Identifying frailty in high functioning older adults with normal mobility. *Age Ageing.* 2010;39(3):382-385.

35. Camicioli R, Howieson D, Lehman S, Kaye J. Talking while walking the effect of a dual task in aging and Alzheimer's disease. *Neurology.* 1997;48(4):955-958.

36. McCulloch K. Attention and dual-task conditions: physical therapy implications for individuals with acquired brain injury. *J Neurol Phys Ther.* 2007;31(3):104-118.

37. Hofheinz M, Schusterschitz C. Dual task interference in estimating the risk of falls and measuring change: a comparative, psychometric study of four measurements. *Clin Rehabil.* 2010;24(9):831-842.

38. Campbell CM, Rowse JL, Ciol MA, Shumway-Cook A. The effect of cognitive demand on Timed Up and Go performance in older adults with and without Parkinson disease. *J Neurol Phys Ther*. 2003;27(1):2-7.

39. McCulloch K, Blakley K, Freeman L. Clinical tests of walking dual-task performance after acquired brain injury (ABI): feasibility and dual-task cost comparisons to a young adult group. *J Neurol Phys Ther.* 2005;29(4):213.

40. McCulloch KL, Buxton E, Hackney J, Lowers S. Balance, attention, and dual-task performance during walking after brain injury: associations with falls history. *J Head Trauma Rehabil.* 2010;25(3):155-163.

41. D'Esposito M, Onishi K, Thompson H, Robinson K, Armstrong C, Grossman M. Working memory impairments in multiple sclerosis: Evidence from a dual-task paradigm. *Neuropsychology.* 1996;10(1):51-56.

42. Brecl Jakob G, Remsak T, Sega Jazbec S, Horvat Ledinek A, Rot U. Step initiation interferes with working memory in nondisabled patients with the earliest multiple sclerosis-A dual-task study. *Gait Posture.* 2017;51:201-207.

43. Wajda DA, Mirelman A, Hausdorff JM, Sosnoff JJ. Intervention modalities for targeting cognitive-motor interference in individuals with neurodegenerative disease: a systematic review. *Expert Rev Neurother.* 2017;17(3):251-261.

44. Meyer-Moock S, Feng YS, Maeurer M, Dippel FW, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. *BMC Neurol.* 2014;14(1):58.

45. Dagenais E, Rouleau I, Demers M, et al. Value of the MoCA test as a screening instrument in multiple sclerosis. *Can J Neurol Sci.* 2013;40(3):410-415.

46. Charvet LE. The Montreal Cognitive Assessment (MoCA) in multiple sclerosis: relation to clinical features. *J Mult Scler.* 2015;02(02).

47. Freitas S, Batista S, Afonso AC, et al. The Montreal Cognitive Assessment (MoCA) as a screening test for cognitive dysfunction in multiple sclerosis. *Appl Neuropsychol Adult.* 2018;25(1):57-70.

48. Lynall RC, Zukowski LA, Plummer P, Mihalik JP. Reliability and validity of the protokinetics movement analysis software in measuring center of pressure during walking. *Gait Posture.* 2017;52:308-311.

49. Wajda DA, Moon Y, Motl RW, Sosnoff JJ. Preliminary investigation of gait initiation and falls in multiple sclerosis. *Arch Phys Med Rehabil.* 2015;96(6):1098-1102.

50. Kirkland MC, Wallack EM, Rancourt SN, Ploughman M. Comparing three dual-task methods and the relationship to physical and cognitive impairment in people with multiple sclerosis and controls. *Mult Scler Int.* 2015;2015:650645.

51. Fritz NE, Keller J, Calabresi PA, Zackowski KM. Quantitative measures of walking and strength provide insight into brain corticospinal tract pathology in multiple sclerosis. *Neuroimage Clin.* 2017;14:490-498.

52. Weightman MM, McCulloch K. Dual-task Assessment and Intervention. *Mild Traumatic Brain Injury Rehabilitation Toolkit.* 2014:321.

53. Garg H, Bush S, Gappmaier E. Associations between fatigue and disability, functional mobility, depression, and quality of life in people with multiple sclerosis. *Int J MS Care.* 2016;18(2):71-77.

54. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. *Can J Neurol Sci.* 2015;21(1):9-14.

55. Wolkorte R, Heersema DJ, Zijdewind I. Reduced dual-task performance in MS patients is further decreased by muscle fatigue. *Neurorehabil Neural Repair.* 2015;29(5):424-435.

56. Middleton A, Fritz SL, Lusardi M. Walking speed: the functional vital sign. *J Aging Phys Act.* 2015;23(2):314-322.

57. Plummer P, Osborne MB. What are we attempting to improve when we train dual-task performance? *J Neurol Phys Ther.* 2015;39(3):154-155.

58. Mazumder R, Murchison C, Bourdette D, Cameron M. Falls in people with multiple sclerosis compared with falls in healthy controls. *PLoS One.* 2014;9(9):e107620.

59. Amato MP, Portaccio E, Goretti B, et al. Cognitive impairment in early stages of multiple sclerosis. *Neurol Sci.* 2010;31(Suppl 2):S211-214.

60. Feuillet L, Reuter F, Audoin B, et al. Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. *Mult Scler.* 2007;13(1):124-127.

61. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med.* 2016;15(2):155-163.

Chapter IV

1. Heesen C, Bohm J, Reich C, Kasper J, Goebel M, Gold SM. Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable. *Mult Scler.* 2008;14(7):988-991.

2. Hemmett L, Holmes J, Barnes M, Russell N. What drives quality of life in multiple sclerosis? *QJM.* 2004;97(10):671-676.

3. Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology.* 1991;41(5):692-696.

4. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol.* 2008;7(12):1139-1151.

5. Heine M, van de Port I, Rietberg MB, van Wegen EE, Kwakkel G. Exercise therapy for fatigue in multiple sclerosis. *Cochrane Database Syst Rev.* 2015(9):CD009956.

6. Benedict RH, Wahlig E, Bakshi R, et al. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *J Neurol Sci.* 2005;231(1-2):29-34.

7. Hoogs M, Kaur S, Smerbeck A, Weinstock-Guttman B, Benedict RH. Cognition and physical disability in predicting health-related quality of life in multiple sclerosis. *Int J MS Care.* 2011;13(2):57-63.

8. Negahban H, Mofateh R, Arastoo AA, et al. The effects of cognitive loading on balance control in patients with multiple sclerosis. *Gait Posture.* 2011;34(4):479-484.

9. Jacobs JV, Kasser SL. Effects of dual tasking on the postural performance of people with and without multiple sclerosis: a pilot study. *J Neurol.* 2012;259(6):1166-1176.

10. Nogueira LA, Dos Santos LT, Sabino PG, Alvarenga RM, Santos Thuler LC. Factors for lower walking speed in persons with multiple sclerosis. *Mult Scler Int.* 2013;2013:875648.

11. Hamilton F, Rochester L, Paul L, Rafferty D, O'Leary CP, Evans JJ. Walking and talking: an investigation of cognitive-motor dual tasking in multiple sclerosis. *Mult Scler.* 2009;15(10):1215-1227.

12. Kalron A, Dvir Z, Achiron A. Walking while talking--difficulties incurred during the initial stages of multiple sclerosis disease process. *Gait Posture.* 2010;32(3):332-335.

13. Sosnoff JJ, Boes MK, Sandroff BM, Socie MJ, Pula JH, Motl RW. Walking and thinking in persons with multiple sclerosis who vary in disability. *Arch Phys Med Rehabil.* 2011;92(12):2028-2033.

14. Learmonth YC, Sandroff BM, Pilutti LA, et al. Cognitive motor interference during walking in multiple sclerosis using an alternate-letter alphabet task. *Arch Phys Med Rehabil.* 2014;95(8):1498-1503.

15. Allali G, Laidet M, Assal F, Armand S, Lalive PH. Walking while talking in patients with multiple sclerosis: the impact of specific cognitive loads. *Neurophysiol Clin.* 2014;44(1):87-93.

16. Motl RW, Sosnoff JJ, Dlugonski D, Pilutti LA, Klaren R, Sandroff BM. Walking and cognition, but not symptoms, correlate with dual task cost of walking in multiple sclerosis. *Gait Posture.* 2014;39(3):870-874.

17. Sosnoff JJ, Socie MJ, Sandroff BM, et al. Mobility and cognitive correlates of dual task cost of walking in persons with multiple sclerosis. *Disabil Rehabil.* 2014;36(3):205-209.

18. Wajda DA, Sosnoff JJ. Cognitive-motor interference in multiple sclerosis: a systematic review of evidence, correlates, and consequences. *Biomed Res Int.* 2015;2015:720856.

19. Fritz NE, Cheek FM, Nichols-Larsen DS. Motor-cognitive dual-task training in persons with neurologic disorders: a systematic review. *J Neurol Phys Ther.* 2015;39(3):142-153.

20. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology.* 1991;41(5):685-691.

21. Amato MP, Portaccio E, Goretti B, et al. Cognitive impairment in early stages of multiple sclerosis. *Neurol Sci.* 2010;31(Suppl 2):S211-214.

22. Feuillet L, Reuter F, Audoin B, et al. Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. *Mult Scler.* 2007;13(1):124-127.

23. Potagas C, Giogkaraki E, Koutsis G, et al. Cognitive impairment in different MS subtypes and clinically isolated syndromes. *J Neurol Sci.* 2008;267(1-2):100-106.

24. D'Orio VL, Foley FW, Armentano F, Picone MA, Kim S, Holtzer R. Cognitive and motor functioning in patients with multiple sclerosis: neuropsychological predictors of walking speed and falls. *J Neurol Sci.* 2012;316(1-2):42-46.

25. Wajda DA, Motl RW, Sosnoff JJ. Dual task cost of walking is related to fall risk in persons with multiple sclerosis. *J Neurol Sci.* 2013;335(1-2):160-163.

26. Sosnoff JJ, Balantrapu S, Pilutti LA, Sandroff BM, Morrison S, Motl RW. Cognitive processing speed is related to fall frequency in older adults with multiple sclerosis. *Arch Phys Med Rehabil.* 2013;94(8):1567-1572.

27. Cameron MH, Wagner JM. Gait abnormalities in multiple sclerosis: pathogenesis, evaluation, and advances in treatment. *Curr Neurol Neurosci Rep.* 2011;11(5):507-515.

28. Nilsagard Y, Lundholm C, Denison E, Gunnarsson LG. Predicting accidental falls in people with multiple sclerosis -- a longitudinal study. *Clin Rehabil.* 2009;23(3):259-269.

29. Givon U, Zeilig G, Achiron A. Gait analysis in multiple sclerosis: characterization of temporal-spatial parameters using GAITRite functional ambulation system. *Gait Posture.* 2009;29(1):138-142.

30. Comber L, Galvin R, Coote S. Gait deficits in people with multiple sclerosis: A systematic review and meta-analysis. *Gait Posture.* 2017;51:25-35.

31. Sherwood J, Inouye C, Anderson E, et al. 6-minute walk test. *Med Sci Sports Exerc.* 2016;48:31-32.

32. Leone C, Patti F, Feys P. Measuring the cost of cognitive-motor dual tasking during walking in multiple sclerosis. *Mult Scler.* 2015;21(2):123-131.

33. Plummer P, Eskes G, Wallace S, et al. Cognitive-motor interference during functional mobility after stroke: state of the science and implications for future research. *Arch Phys Med Rehabil.* 2013;94(12):2565-2574 e2566.

34. Prosperini L, Castelli L, Sellitto G, et al. Investigating the phenomenon of "cognitive-motor interference" in multiple sclerosis by means of dual-task posturography. *Gait Posture.* 2015;41(3):780-785.

35. Yogev G, Giladi N, Peretz C, Springer S, Simon ES, Hausdorff JM. Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? *Eur J Neurosci.* 2005;22(5):1248-1256.

36. Hausdorff JM, Balash J, Giladi N. Effects of cognitive challenge on gait variability in patients with Parkinson's disease. *J Geriatr Psychiatry Neurol.* 2003;16(1):53-58.

37. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM. Dual-tasking effects on gait variability: the role of aging, falls, and executive function. *Mov Disord.* 2006;21(7):950-957.

38. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord.* 2008;23(3):329-342; quiz 472.

39. Yogev-Seligmann G, Giladi N, Brozgol M, Hausdorff JM. A training program to improve gait while dual tasking in patients with Parkinson's disease: a pilot study. *Arch Phys Med Rehabil.* 2012;93(1):176-181.

40. Brauer SG, Morris ME. Can people with Parkinson's disease improve dual tasking when walking? *Gait Posture.* 2010;31(2):229-233.

41. dos Santos Mendes FA, Pompeu JE, Modenesi Lobo A, et al. Motor learning, retention and transfer after virtual-reality-based training in Parkinson's disease--effect of motor and cognitive demands of games: a longitudinal, controlled clinical study. *Physiotherapy.* 2012;98(3):217-223.

42. Canning CG, Ada L, Woodhouse E. Multiple-task walking training in people with mild to moderate Parkinson's disease: a pilot study. *Clin Rehabil.* 2008;22(3):226-233.

43. Strouwen C, Molenaar E, Munks L, et al. Training dual tasks together or apart in Parkinson's disease: results from the DUALITY trial. *Mov Disord.* 2017;32(8):1201-1210.

44. de Andrade LP, Gobbi LT, Coelho FG, Christofoletti G, Costa JL, Stella F. Benefits of multimodal exercise intervention for postural control and frontal cognitive functions in individuals with Alzheimer's disease: a controlled trial. *J Am Geriatr Soc.* 2013;61(11):1919-1926.

45. Falbo S, Condello G, Capranica L, Forte R, Pesce C. Effects of physical-cognitive dual task training on executive function and gait performance in older adults: a randomized controlled trial. *Biomed Res Int.* 2016;2016:5812092.

46. Evans JJ, Greenfield E, Wilson BA, Bateman A. Walking and talking therapy: improving cognitive-motor dual-tasking in neurological illness. *J Int Neuropsychol Soc.* 2009;15(1):112-120.

47. Ghai S, Ghai I, Effenberg AO. Effects of dual tasks and dual-task training on postural stability: a systematic review and meta-analysis. *Clin Interv Aging.* 2017;12:557-577.

48. He Y, Yang L, Zhou J, Yao L, Pang MYC. Dual-task training effects on motor and cognitive functional abilities in individuals with stroke: a systematic review. *Clin Rehabil.* 2018;32(7):865-877.

49. Peruzzi A, Cereatti A, Della Croce U, Mirelman A. Effects of a virtual reality and treadmill training on gait of subjects with multiple sclerosis: a pilot study. *Mult Scler Relat Disord.* 2016;5:91-96.

50. Kramer A, Dettmers C, Gruber M. Exergaming with additional postural demands improves balance and gait in patients with multiple sclerosis as much as conventional balance training and leads to high adherence to home-based balance training. *Arch Phys Med Rehabil.* 2014;95(10):1803-1809.

51. Sosnoff JJ, Wajda DA, Sandroff BM, Roeing KL, Sung J, Motl RW. Dual task training in persons with Multiple Sclerosis: a feasability randomized controlled trial. *Clin Rehabil.* 2017;31(10):1322-1331.

52. Veldkamp R, Baert I, Kalron A, et al. Structured cognitive-motor dual task training compared to single mobility training in persons with multiple sclerosis, a multicenter RCT. *J Clin Med.* 2019;8(12):2177.

53. Lynall RC, Zukowski LA, Plummer P, Mihalik JP. Reliability and validity of the protokinetics movement analysis software in measuring center of pressure during walking. *Gait Posture.* 2017;52:308-311.

54. Ismail Z, Rajji TK, Shulman KI. Brief cognitive screening instruments: an update. *Int J Geriatr Psychiatry.* 2010;25(2):111-120.

55. Dagenais E, Rouleau I, Demers M, et al. Value of the MoCA test as a screening instrument in multiple sclerosis. *Can J Neurol Sci.* 2013;40(3):410-415.

56. Kirkland MC, Wallack EM, Rancourt SN, Ploughman M. Comparing three dual-task methods and the relationship to physical and cognitive impairment in people with multiple sclerosis and controls. *Mult Scler Int.* 2015;2015:650645.

57. Charvet LE. The Montreal Cognitive Assessment (MoCA) in multiple sclerosis: relation to clinical features. *J Mult Scler.* 2015;02(02).

58. McCulloch KL, Mercer V, Giuliani C, Marshall S. Development of a clinical measure of dual-task performance in walking: reliability and preliminary validity of the Walking and Remembering Test. *J Geriatr Phys Ther.* 2009;32(1):2-9.

59. McCulloch KL, Buxton E, Hackney J, Lowers S. Balance, attention, and dual-task performance during walking after brain injury: associations with falls history. *J Head Trauma Rehabil.* 2010;25(3):155-163.

60. McCulloch KL. Poster 61. *Arch Phys Med Rehabil.* 2005;86(10):e21.

61. Weightman MM, McCulloch K. Dual-task Assessment and Intervention. *Mild Traumatic Brain Injury Rehabilitation Toolkit.* 2014:321.

62. Erickson KI, Colcombe SJ, Wadhwa R, et al. Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. *Neurobiol Aging.* 2007;28(2):272-283.

63. Learmonth YC, Dlugonski DD, Pilutti LA, Sandroff BM, Motl RW. The reliability, precision and clinically meaningful change of walking assessments in multiple sclerosis. *Mult Scler.* 2013;19(13):1784-1791.

64. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *JAMA.* 2011;305(1):50-58.

65. Espy DD, Yang F, Bhatt T, Pai YC. Independent influence of gait speed and step length on stability and fall risk. *Gait Posture.* 2010;32(3):378-382.

66. Wang WF, Lien WC, Liu CY, Yang CY. Study on tripping risks in fast walking through cadence-controlled gait analysis. *J Healthc Eng.* 2018;2018:2723178.

67. Kal E, Winters M, van der Kamp J, et al. Is implicit motor learning preserved after stroke? A systematic review with meta-analysis. *PLoS One.* 2016;11(12):e0166376.

68. Wajda DA, Mirelman A, Hausdorff JM, Sosnoff JJ. Intervention modalities for targeting cognitive-motor interference in individuals with neurodegenerative disease: a systematic review. *Expert Rev Neurother.* 2017;17(3):251-261.

69. Silsupadol P, Lugade V, Shumway-Cook A, et al. Training-related changes in dual-task walking performance of elderly persons with balance impairment: a double-blind, randomized controlled trial. *Gait Posture.* 2009;29(4):634-639.

70. Pisotta I, Molinari M. Cerebellar contribution to feedforward control of locomotion. *Front Hum Neurosci.* 2014;8:475.

71. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J Speech Lang Hear Res.* 2008;51(1):S225-239.

Chapter V

1. Heesen C, Bohm J, Reich C, Kasper J, Goebel M, Gold SM. Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable. *Mult Scler.* 2008;14(7):988-991.

2. Hemmett L, Holmes J, Barnes M, Russell N. What drives quality of life in multiple sclerosis? *QJM.* 2004;97(10):671-676.

3. Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology.* 1991;41(5):692-696.

4. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol.* 2008;7(12):1139-1151.

5. Heine M, van de Port I, Rietberg MB, van Wegen EE, Kwakkel G. Exercise therapy for fatigue in multiple sclerosis. *Cochrane Database Syst Rev.* 2015(9):CD009956.

6. Benedict RH, Wahlig E, Bakshi R, et al. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *J Neurol Sci.* 2005;231(1-2):29-34.

7. Hoogs M, Kaur S, Smerbeck A, Weinstock-Guttman B, Benedict RH. Cognition and physical disability in predicting health-related quality of life in multiple sclerosis. *Int J MS Care.* 2011;13(2):57-63.

8. Negahban H, Mofateh R, Arastoo AA, et al. The effects of cognitive loading on balance control in patients with multiple sclerosis. *Gait Posture.* 2011;34(4):479-484.

9. Jacobs JV, Kasser SL. Effects of dual tasking on the postural performance of people with and without multiple sclerosis: a pilot study. *J Neurol.* 2012;259(6):1166-1176.

10. Nogueira LA, Dos Santos LT, Sabino PG, Alvarenga RM, Santos Thuler LC. Factors for lower walking speed in persons with multiple sclerosis. *Mult Scler Int.* 2013;2013:875648.

11. Hamilton F, Rochester L, Paul L, Rafferty D, O'Leary CP, Evans JJ. Walking and talking: an investigation of cognitive-motor dual tasking in multiple sclerosis. *Mult Scler.* 2009;15(10):1215-1227.

12. Kalron A, Dvir Z, Achiron A. Walking while talking--difficulties incurred during the initial stages of multiple sclerosis disease process. *Gait Posture.* 2010;32(3):332-335.

13. Sosnoff JJ, Boes MK, Sandroff BM, Socie MJ, Pula JH, Motl RW. Walking and thinking in persons with multiple sclerosis who vary in disability. *Arch Phys Med Rehabil.* 2011;92(12):2028-2033.
14. Learmonth YC, Sandroff BM, Pilutti LA, et al. Cognitive motor interference during walking in multiple sclerosis using an alternate-letter alphabet task. *Arch Phys Med Rehabil.* 2014;95(8):1498-1503.
15. Allali G, Laidet M, Assal F, Armand S, Lalive PH. Walking while talking in patients with multiple sclerosis: the impact of specific cognitive loads. *Neurophysiol Clin.* 2014;44(1):87-93.
16. Motl RW, Sosnoff JJ, Dlugonski D, Pilutti LA, Klaren R, Sandroff BM. Walking and cognition, but not symptoms, correlate with dual task cost of walking in multiple sclerosis. *Gait Posture.* 2014;39(3):870-874.
17. Sosnoff JJ, Socie MJ, Sandroff BM, et al. Mobility and cognitive correlates of dual task cost of walking in persons with multiple sclerosis. *Disabil Rehabil.* 2014;36(3):205-209.
18. Wajda DA, Sosnoff JJ. Cognitive-motor interference in multiple sclerosis: a systematic review of evidence, correlates, and consequences. *Biomed Res Int.* 2015;2015:720856.
19. Fritz NE, Cheek FM, Nichols-Larsen DS. Motor-cognitive dual-task training in persons with neurologic disorders: a systematic review. *J Neurol Phys Ther.* 2015;39(3):142-153.
20. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology.* 1991;41(5):685-691.
21. Amato MP, Portaccio E, Goretti B, et al. Cognitive impairment in early stages of multiple sclerosis. *Neurol Sci.* 2010;31(Suppl 2):S211-214.

22. Feuillet L, Reuter F, Audoin B, et al. Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. *Mult Scler.* 2007;13(1):124-127.

23. Potagas C, Giogkaraki E, Koutsis G, et al. Cognitive impairment in different MS subtypes and clinically isolated syndromes. *J Neurol Sci.* 2008;267(1-2):100-106.

24. D'Orio VL, Foley FW, Armentano F, Picone MA, Kim S, Holtzer R. Cognitive and motor functioning in patients with multiple sclerosis: neuropsychological predictors of walking speed and falls. *J Neurol Sci.* 2012;316(1-2):42-46.

25. Wajda DA, Motl RW, Sosnoff JJ. Dual task cost of walking is related to fall risk in persons with multiple sclerosis. *J Neurol Sci.* 2013;335(1-2):160-163.

26. Sosnoff JJ, Balantrapu S, Pilutti LA, Sandroff BM, Morrison S, Motl RW. Cognitive processing speed is related to fall frequency in older adults with multiple sclerosis. *Arch Phys Med Rehabil.* 2013;94(8):1567-1572.

27. Cameron MH, Wagner JM. Gait abnormalities in multiple sclerosis: pathogenesis, evaluation, and advances in treatment. *Curr Neurol Neurosci Rep.* 2011;11(5):507-515.

28. Nilsagard Y, Lundholm C, Denison E, Gunnarsson LG. Predicting accidental falls in people with multiple sclerosis -- a longitudinal study. *Clin Rehabil.* 2009;23(3):259-269.

29. Givon U, Zeilig G, Achiron A. Gait analysis in multiple sclerosis: characterization of temporal-spatial parameters using GAITRite functional ambulation system. *Gait Posture.* 2009;29(1):138-142.

30. Comber L, Galvin R, Coote S. Gait deficits in people with multiple sclerosis: A systematic review and meta-analysis. *Gait Posture.* 2017;51:25-35.

31. Sherwood J, Inouye C, Anderson E, et al. 6-minute walk test. *Med Sci Sports Exerc.* 2016;48:31-32.

32. Yogev G, Giladi N, Peretz C, Springer S, Simon ES, Hausdorff JM. Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? *Eur J Neurosci.* 2005;22(5):1248-1256.

33. Hausdorff JM, Balash J, Giladi N. Effects of cognitive challenge on gait variability in patients with Parkinson's disease. *J Geriatr Psychiatry Neurol.* 2003;16(1):53-58.

34. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM. Dual-tasking effects on gait variability: the role of aging, falls, and executive function. *Mov Disord.* 2006;21(7):950-957.

35. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord.* 2008;23(3):329-342; quiz 472.

36. Yogev-Seligmann G, Giladi N, Brozgol M, Hausdorff JM. A training program to improve gait while dual tasking in patients with Parkinson's disease: a pilot study. *Arch Phys Med Rehabil.* 2012;93(1):176-181.

37. Brauer SG, Morris ME. Can people with Parkinson's disease improve dual tasking when walking? *Gait Posture.* 2010;31(2):229-233.

38. de Andrade LP, Gobbi LT, Coelho FG, Christofoletti G, Costa JL, Stella F. Benefits of multimodal exercise intervention for postural control and frontal cognitive functions in individuals with Alzheimer's disease: a controlled trial. *J Am Geriatr Soc.* 2013;61(11):1919-1926.

39. Schwenk M, Zieschang T, Oster P, Hauer K. Dual-task performances can be improved in patients with dementia: a randomized controlled trial. *Neurology.* 2010;74(24):1961-1968.

40. Falbo S, Condello G, Capranica L, Forte R, Pesce C. Effects of physical-cognitive dual task training on executive function and gait performance in older adults: a randomized controlled trial. *Biomed Res Int.* 2016;2016:5812092.

41. Evans JJ, Greenfield E, Wilson BA, Bateman A. Walking and talking therapy: improving cognitive-motor dual-tasking in neurological illness. *J Int Neuropsychol Soc.* 2009;15(1):112-120.

42. Pearson M, Dieberg G, Smart N. Exercise as a therapy for improvement of walking ability in adults with multiple sclerosis: a meta-analysis. *Arch Phys Med Rehabil.* 2015;96(7):1339-1348 e1337.

43. Learmonth YC, Ensari I, Motl RW. Physiotherapy and walking outcomes in adults with multiple sclerosis: systematic review and meta-analysis. *Phys Ther Rev.* 2016;21(3-6):160-172.

44. Xie X, Sun H, Zeng Q, et al. Do patients with multiple sclerosis derive more benefit from robot-assisted gait training compared with conventional walking therapy on motor function? A meta-analysis. *Front Neurol.* 2017;8:260.

45. Gijbels D, Dalgas U, Romberg A, et al. Which walking capacity tests to use in multiple sclerosis? A multicentre study providing the basis for a core set. *Mult Scler.* 2012;18(3):364-371.

46. Gijbels D, Eijnde BO, Feys P. Comparison of the 2- and 6-minute walk test in multiple sclerosis. *Mult Scler.* 2011;17(10):1269-1272.

47. Baert I, Freeman J, Smedal T, et al. Responsiveness and clinically meaningful improvement, according to disability level, of five walking measures after rehabilitation in multiple sclerosis: a European multicenter study. *Neurorehabil Neural Repair.* 2014;28(7):621-631.

48. Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). *Neurology.* 2003;60(1):31-36.

49. Pilutti LA, Dlugonski D, Sandroff BM, et al. Further validation of multiple sclerosis walking scale-12 scores based on spatiotemporal gait parameters. *Arch Phys Med Rehabil.* 2013;94(3):575-578.

50. Motl RW, Snook EM. Confirmation and extension of the validity of the Multiple Sclerosis Walking Scale-12 (MSWS-12). *J Neurol Sci.* 2008;268(1-2):69-73.

51. Penner IK, Raselli C, Stocklin M, Opwis K, Kappos L, Calabrese P. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler.* 2009;15(12):1509-1517.

52. Erickson KI, Colcombe SJ, Wadhwa R, et al. Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. *Neurobiol Aging.* 2007;28(2):272-283.

53. Lally P, van Jaarsveld CHM, Potts HWW, Wardle J. How are habits formed: Modelling habit formation in the real world. *Eur J Soc Psychol.* 2010;40(6):998-1009.

54. Manjaly ZM, Harrison NA, Critchley HD, et al. Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2019;90(6):642-651.

55. Latimer-Cheung AE, Pilutti LA, Hicks AL, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. *Arch Phys Med Rehabil.* 2013;94(9):1800-1828 e1803.

56. Rooney S, Moffat F, Wood L, Paul L. Effectiveness of fatigue management interventions in reducing severity and impact of fatigue in people with progressive multiple sclerosis: a systematic review. *Int J MS Care.* 2019;21(1):35-46.

57. Peruzzi A, Cereatti A, Della Croce U, Mirelman A. Effects of a virtual reality and treadmill training on gait of subjects with multiple sclerosis: a pilot study. *Mult Scler Relat Disord.* 2016;5:91-96.

58. Sosnoff JJ, Wajda DA, Sandroff BM, Roeing KL, Sung J, Motl RW. Dual task training in persons with Multiple Sclerosis: a feasability randomized controlled trial. *Clin Rehabil.* 2017;31(10):1322-1331.

59. Veldkamp R, Baert I, Kalron A, et al. Structured cognitive-motor dual task training compared to single mobility training in persons with multiple sclerosis, a multicenter RCT. *J Clin Med.* 2019;8(12):2177.

Chapter VI

1. Ransohoff RM, Hafler DA, Lucchinetti CF. Multiple sclerosis-a quiet revolution. *Nat Rev Neurol.* 2015;11(3):134-142.

2. Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: A population-based estimate using health claims data. *Neurology.* 2019;92(10):e1029-e1040.

3. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. *Lancet Neurol.* 2010;9(5):520-532.

4. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology.* 1991;41(5):685-691.

5. Hemmett L, Holmes J, Barnes M, Russell N. What drives quality of life in multiple sclerosis? *QJM.* 2004;97(10):671-676.

6. Kister I, Bacon TE, Chamot E, et al. Natural history of multiple sclerosis symptoms. *Int J MS Care.* 2013;15(3):146-158.

7. Fritz NE, Cheek FM, Nichols-Larsen DS. Motor-cognitive dual-task training in persons with neurologic disorders: a systematic review. *J Neurol Phys Ther.* 2015;39(3):142-153.

8. Yogev G, Giladi N, Peretz C, Springer S, Simon ES, Hausdorff JM. Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? *Eur J Neurosci.* 2005;22(5):1248-1256.

9. Hausdorff JM, Balash J, Giladi N. Effects of cognitive challenge on gait variability in patients with Parkinson's disease. *J Geriatr Psychiatry Neurol.* 2003;16(1):53-58.

10. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM. Dual-tasking effects on gait variability: the role of aging, falls, and executive function. *Mov Disord.* 2006;21(7):950-957.

11. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord.* 2008;23(3):329-342; quiz 472.

12. Motl RW, Sosnoff JJ, Dlugonski D, Pilutti LA, Klaren R, Sandroff BM. Walking and cognition, but not symptoms, correlate with dual task cost of walking in multiple sclerosis. *Gait Posture.* 2014;39(3):870-874.

13. McCulloch KL, Mercer V, Giuliani C, Marshall S. Development of a clinical measure of dual-task performance in walking: reliability and preliminary validity of the Walking and Remembering Test. *J Geriatr Phys Ther.* 2009;32(1):2-9.

14. Leone C, Patti F, Feys P. Measuring the cost of cognitive-motor dual tasking during walking in multiple sclerosis. *Mult Scler.* 2015;21(2):123-131.

# APPENDIX A

## The Walking and Remembering Test

Date: ____________

ID: ____________

## Walking and Remembering Test (WART)

Marked, narrowed 12-in wide, 10-meter walkway, with additional, 1-meter from start to end of walkway for acceleration and deceleration.

### Step 1: Single-Task Walking (Fast pace)

"Please walk as fast as you can from here to the next mark while keeping in between the lines of the path. Avoid running; this is a test of your fast walking."

Trial 1 (sec): ________ Trial 2 (sec): ________ **Average (sec): ________**

### Step 2: Single Task Digit Span Testing

Determine the longest digit span the participant can recall after a delay equivalent to the average time to walk in STEP 1 (above). The longest digit span correct for at least one trial is used in the dual-task condition and is considered to be 100% correct for assessing cognitive errors. Discontinue testing after the patient scores 0 correct on both trials. Administer both trials of each item even if the participant passes Trial 1. Score 0 to 1 point for each response.

"I'm going to say some numbers that I want you to remember after a brief delay. Listen carefully to the numbers, and use any method except writing or talking to help you remember them. When I give you the cue 'now', repeat the numbers to me."

| Item/Trial | | Digit Span |
|---|---|---|
| 1. | Trial 1 | 6-4-3-9 |
| | Trial 2 | 7-2-8-6 |
| 2. | Trial 1 | 4-2-7-3-1 |
| | Trial 2 | 7-5-8-3-6 |
| 3. | Trial 1 | 6-1-9-4-7-3 |
| | Trial 2 | 3-9-2-4-8-7 |
| 4. | Trial 1 | 5-9-1-7-4-2-8 |
| | Trial 2 | 4-1-7-9-3-8-6 |
| 5. | Trial 1 | 5-8-1-9-2-6-4-7 |
| | Trial 2 | 3-8-2-9-5-1-7-4 |
| 6. | Trial 1 | 2-7-5-8-6-2-5-8-4 |
| | Trial 2 | 7-1-3-9-4-2-5-6-8 |

**Dual-task condition:** __________ (number of digits)

Date: ______________

ID: ______________

**Step 3: Dual-Task Walking (Fast Pace)**

Use the longest digit span from STEP 2 the participant was able to recall at least once with the time delay for the dual-task testing, then combine the two tasks.

"Now we are going to combine walking with remembering numbers. We will do this task twice. I am going to say some numbers that I want you to remember until we get to the end of the walking path. You may use any method you choose to remember the numbers, except saying them out loud. Walk as quickly as you can but take care not to step off the path. I will walk beside you and time you from when you first step onto the path. Continue walking until I saw 'now', the repeat the numbers you have been concentrating on while you were walking."

Trial 1 Digits presented: 5 1 9 6 3 8 4 1 9 3

Digits recalled: ____________________________

Steps off path: ____________________________

Seconds to complete trial (to nearest tenth of a second): ________________

Trial 2 Digits presented: 8 7 1 9 2 4 3 6 9 5

Digits recalled: ____________________________

Steps off path: ____________________________

Seconds to complete trial (to nearest tenth of a second): ________________

**Average Dual-Task Walk Time in seconds (to nearest tenth of a second): ________________**

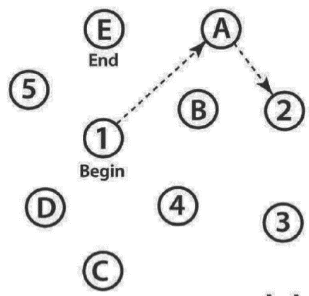
APPENDIX B

Montreal Cognitive Assessment

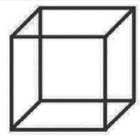
**MONTREAL COGNITIVE ASSESSMENT (MOCA)**
Version 7.1 Original Version

**Participant ID:** **Date:**

## VISUOSPATIAL / EXECUTIVE




[ ]



Copy cube

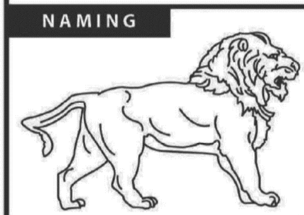
[ ]

Draw CLOCK (Ten past eleven)
( 3 points )

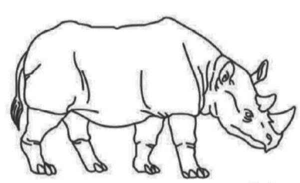
[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

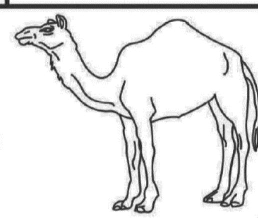
## NAMING



[ ]



[ ]



[ ]

___/3

## MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

| | FACE | VELVET | CHURCH | DAISY | RED |
|---|---|---|---|---|---|
| 1st trial | | | | | |
| 2nd trial | | | | | |

No points

## ATTENTION

Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2
___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B
___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts,** 2 or 3 correct: **2 pts,** 1 correct: **1 pt,** 0 correct: **0 pt**
___/3

## LANGUAGE

Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]
___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)
___/1

## ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler
___/2

## DELAYED RECALL

| | FACE | VELVET | CHURCH | DAISY | RED | |
|---|---|---|---|---|---|---|
| Has to recall words **WITH NO CUE** | [ ] | [ ] | [ ] | [ ] | [ ] | Points for UNCUED recall only |
| **Optional** Category cue | | | | | | |
| Multiple choice cue | | | | | | |

___/5

## ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City
___/6

 **www.mocatest.org** Norm



TOTAL ___/30
Add 1 point if ≤ 12 yr edu

Administered by: ______________________

APPENDIX C

2-Minute Walk Test

Date: ____________

ID: ____________

## 2MWT | 2-Minute Walk Test

### General Information

- Individual walks without assistance for 2 minutes and the distance is measured.
- Start timing when the individual is instructed to "Go".
- Stop timing at 2 minutes
- Assistive devices can be used but should be kept consistent and documented from test to test.
- If physical assistance is required to walk, this should not be performed
- A measuring wheel is helpful to determine distance walked.
- Should be performed at the fastest speed possible

### Set-up and equipment

- Ensure the hallway free of obstacles
- Stopwatch

### Participant Instructions

"Cover as much ground as possible over 2 minutes. Walk continuously if possible, but do not be concerned if you need to slow down or stop to rest. The goal is to feel at the end of the test that more ground could not have been covered in the 2 minutes."

Assistive Device: ______________________________

Bracing: ______________________________

| Date | Distance (ft) | RPE - pre | RPE - post | VAS-F - pre | VAS-F - post | BP (HR) - pre | BP (HR) - post |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

APPENDIX D

12-Item Multiple Sclerosis Walking Scale

Date: ____________

ID: ____________

## MSWS-12 | 12-Item Multiple Sclerosis Walking Scale

Instructions

The following questions ask for your views about the impact of MS on your walking ability **during the past two weeks.** For each statement, please **circle** the **one** number that **best** describes your situation.

Please answer **all** questions.

| ***In the past two weeks, how much has your MS...*** | Not at all | A little | Moderately | Quite a lot | Extremely |
|---|---|---|---|---|---|
| 1. Limited your ability to walk? | 1 | 2 | 3 | 4 | 5 |
| 2. Limited your ability to run? | 1 | 2 | 3 | 4 | 5 |
| 3. Limited your ability to climb up and down stairs? | 1 | 2 | 3 | 4 | 5 |
| 4. Made standing when doing things more difficult? | 1 | 2 | 3 | 4 | 5 |
| 5. Limited your balance when standing or walking? | 1 | 2 | 3 | 4 | 5 |
| 6. Limited how far you are able to walk? | 1 | 2 | 3 | 4 | 5 |
| 7. Increased the effort needed for you to walk? | 1 | 2 | 3 | 4 | 5 |
| 8. Made it necessary for you to use support when walking indoors (eg holding on to furniture, using a stick, etc.)? | 1 | 2 | 3 | 4 | 5 |
| 9. Made it necessary for you to use support when walking outdoors (eg using a stick, a frame, etc.)? | 1 | 2 | 3 | 4 | 5 |
| 10. Slowed down your walking? | 1 | 2 | 3 | 4 | 5 |
| 11. Affected how smoothly you walk? | 1 | 2 | 3 | 4 | 5 |
| 12. Made you concentrate on your walking? | 1 | 2 | 3 | 4 | 5 |

**Total Score: ____/60 = ____%**

APPENDIX E

Fatigue Scale for Motor and Cognitive Functions

Date: ____________

ID: ____________

**FSMC | FATIGUE SCALE FOR MOTOR AND COGNITIVE FUNCTIONS**

Instructions

The following questionnaire is about problems in everyday life which are directly associated with an extreme form of tiredness (fatigue). This extreme form of tiredness refers to an overwhelming state of lethargy, exhaustion and lack of energy which comes on abruptly and is unrelated to any obvious external causes. *It does not mean the sort of isolated episodes which everyone might experience in the course of the day, after exertion, or after a sleepless night!*

Please read each statement carefully. Then decide to what extent each statement applies to you and your everyday life. Please try not to base your answers on the way you are feeling at the moment; **instead try to give us a picture of the way you feel in normal day-to-day life.** Please put a cross in the appropriate circle (only one cross per statement please!).

| | Does not apply at all | Does not apply much | Slightly applies | Applies a lot | Applies com-pletely |
|---|---|---|---|---|---|
| 1. When I concentrate for a long time, I get exhausted sooner than other people of my age. | ○ | ○ | ○ | ○ | ○ |
| 2. When I am experiencing episodes of exhaustion, my movements become noticeably clumsier and less coordinated. | ○ | ○ | ○ | ○ | ○ |
| 3. Because of my episodes of exhaustion, I now need more frequent and/or longer rests during physical activity than I used to. | ○ | ○ | ○ | ○ | ○ |
| 4. When I am experiencing episodes of exhaustion, I am incapable of making decisions. | ○ | ○ | ○ | ○ | ○ |
| 5. When faced with stressful situations, I now find that I get physically exhausted quicker than I used to. | ○ | ○ | ○ | ○ | ○ |
| 6. Because of my episodes of exhaustion, I now have considerably less social contact than I used to. | ○ | ○ | ○ | ○ | ○ |
| 7. Because of my episodes of exhaustion, I now find it more difficult to learn new things than I used to. | ○ | ○ | ○ | ○ | ○ |
| 8. The demands of my work exhaust me mentally more quickly than they used to. | ○ | ○ | ○ | ○ | ○ |

Date: ____________

ID: ____________

| | Does not apply at all | Does not apply much | Slightly applies | Applies a lot | Applies com-pletely |
|---|---|---|---|---|---|
| 9. I feel the episodes of exhaustion particularly strongly in my muscles. | ○ | ○ | ○ | ○ | ○ |
| 10. I no longer have the stamina for long periods of physical activity that I used to have. | ○ | ○ | ○ | ○ | ○ |
| 11. My powers of concentration decrease considerably when I'm under stress. | ○ | ○ | ○ | ○ | ○ |
| 12. When I am experiencing episodes of exhaustion, I am less motivated than others to start activities that involve physical effort. | ○ | ○ | ○ | ○ | ○ |
| 13. My thinking gets increasingly slow when it is hot. | ○ | ○ | ○ | ○ | ○ |
| 14. When I am experiencing an episode of exhaustion, my movements become noticeably slower. | ○ | ○ | ○ | ○ | ○ |
| 15. Because of my episodes of exhaustion, I now feel less like doing things which require concentration. | ○ | ○ | ○ | ○ | ○ |
| 16. When an episode of exhaustion comes on, I am simply no longer able to react quickly. | ○ | ○ | ○ | ○ | ○ |
| 17. When I am experiencing episodes of exhaustion, certain words simply escape me. | ○ | ○ | ○ | ○ | ○ |
| 18. When I am experiencing episodes of exhaustion, I lose concentration considerably quicker than I used to. | ○ | ○ | ○ | ○ | ○ |
| 19. When it is hot, my main feeling is one of extreme physical weakness and lack of energy. | ○ | ○ | ○ | ○ | ○ |
| 20. During episodes of exhaustion, I am noticeably more forgetful. | ○ | ○ | ○ | ○ | ○ |

Please make sure that you have put a cross by each statement. Thank you.

Date: ___________

ID: ___________

## FSMC | Fatigue Scale for Motor and Cognitive Functions

### Scoring form

| | Motor | Cognitive |
|---|---|---|
| 1 | | |
| 2 | | |
| 3 | | |
| 4 | | |
| 5 | | |
| 6 | | |
| 7 | | |
| 8 | | |
| 9 | | |
| 10 | | |
| 11 | | |
| 12 | | |
| 13 | | |
| 14 | | |
| 15 | | |
| 16 | | |
| 17 | | |
| 18 | | |
| 19 | | |
| 20 | | |
| Subtotal | | |
| Total | | |

APPENDIX F

Demographic and Medical History Questionnaire

**Participant Initials** ☐☐☐ **Participant ID** ☐☐☐☐☐ ☐☐ Month ☐☐ Day ☐☐ Year

## Demographics & Medical History

| **First Name*:** |
|---|
| **Middle Name (or initial):** |
| **Last Name*:** |

**Birthdate*:** ☐☐ / ☐☐ / ☐☐☐☐
Month Day Year

**Sex*:** (check one)
- ☐ **Male**
- ☐ **Female**
- ☐ **Unknown/Not Reported/Other**

**Ethnicity*:** (check one)
- ☐ **Hispanic**
- ☐ **Non-Hispanic**
- ☐ **Unknown or Not Reported**

**Race*:** (check all that apply)
- ☐ **American Indian or Alaska Native**
- ☐ **Asian**
- ☐ **Black or African American**
- ☐ **Native Hawaiian or Other Pacific Islander**
- ☐ **White or Caucasian**
- ☐ **Unknown or Not Reported**

**Contact Information:**

| **Address:** | | **Unit #:** |
|---|---|---|
| **City:** | **State:** | **Zip:** |
| **Phone Number:** ☐ Home ☐ Work ☐ Cell ☐ Other | **Alternate Phone Number:** ☐ Home ☐ Work ☐ Cell ☐ Other | **Email address:** |
| **Preferred method of contact:** | | |

**Emergency Contact:**

| **Name:** | | |
|---|---|---|
| **Address:** | | **Unit #:** |
| **City:** | **State:** | **Zip:** |
| **Phone Number:** ☐ Home ☐ Work ☐ Cell ☐ Other | **Alternate Phone Number:** ☐ Home ☐ Work ☐ Cell ☐ Other | **Email address:** |
| **Preferred method of contact:** | | |

*indicates required field



UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-18-0050
IRB APPROVAL DATE: 03/12/2018

1. **Weight:** __________ **Height:** __________
2. **Year of diagnosis:** __________ **Date of last relapse**: _________________
3. **MS subtype:**

   ☐ Relapsing-remitting ☐ Primary progressive

   ☐ Secondary progressive ☐ Progressive relapsing
4. **EDSS level** (if known): __________
5. **Are you currently walking either in your home or in the community?**

   ☐ YES ☐ NO
6. **Do you use an assistive device (e.g., cane, walker, Bioness, AFO) to help you walk at home and/or in the community**?

   ☐ YES ☐ NO
7. **If YES to 6, with which type(s) of device(s) do you use to walk? (please select all that apply)**

   ☐ Single point cane

   ☐ Small base quad cane

   ☐ Large base quad cane

   ☐ Forearm crutches: ☐ Left ☐ Right ☐ Both

   ☐ Axillary crutches: ☐ Left ☐ Right ☐ Both

   ☐ Hemiwalker

   ☐ Walker (no wheels)

   ☐ Rolling walker, 2 wheels

   ☐ Rolling walker, 4 wheels

   ☐ Rollator

   ☐ Left BioNESS: ☐ ankle ☐ thigh ☐ both

   ☐ Right BioNESS: ☐ ankle ☐ thigh ☐ both

   ☐ Ankle-foot orthosis (AFO): ☐ Right ☐ Left ☐ Both

   ☐ Knee ankle-foot orthosis (KAFO): ☐ Right ☐ Left ☐ Both

   ☐ Other: ________________________________________
8. **Are you currently participating in a formal rehabilitation program, e.g. physical therapy, occupational therapy, speech therapy?**

   ☐ YES ☐ NO



UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-18-0050
IRB APPROVAL DATE: 03/12/2018

9. **If NO to 8, do you plan to participate in a formal rehabilitation program within the next two to three months?**

☐ YES ☐ NO

---

This next section will ask about your history of falls. Please answer as accurately as possible.

**Please note that a "fall" is defined as an unplanned or unexpected landing to the floor or lower surface, such as a chair or bed.**

10. **Have you fallen in the past 6 months?** ☐ YES ☐ NO
11. **If YES to 10, how many times have you fallen down in the past 6 months?**

    ☐ 1 ☐ 2 ☐ Other: ________
12. **Have any of your falls resulted in any type of injury? This would include bruises, broken bones, cuts/scrapes, etc.**

    ☐ YES ☐ NO
13. **If YES to 12, how many of your falls led to an injury requiring medical attention?**

    ☐ 1 ☐ 2 ☐ Other: _________
14. **If YES to 12, which injuries did you develop from your fall and required medical attention? (please select all that apply)**

    ☐ Bruising
    ☐ Broken bone
    ☐ Cuts/scrapes
    ☐ Bleeding
    ☐ Severe pain
    ☐ Altered or loss of consciousness
    ☐ Head injury
    ☐ Other: ________________________

15. **Allergies:** ____________________________________________________________

    ____________________________________________________________

16. **Medications. What medications are you currently taking?**

| Medication | Frequency | Dose | Route (oral, infusion, injection, etc.) | Condition being treated |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

17. Past Medical History. Other than your history of MS, what other significant medical history do you have?

☐ heart disease
☐ irregular heart rhythm
☐ atrial fibrillation
☐ high blood pressure
☐ high cholesterol
☐ heart failure
☐ angina
☐ stroke

☐ spinal cord injury
☐ seizure
☐ epilepsy
☐ problems with vision
☐ problems with hearing
☐ dizziness/vertigo
☐ asthma
☐ COPD
☐ other breathing disorder:

☐ Diabetes Type II
☐ Diabetes Type II
☐ cancer
☐ hepatitis
☐ peripheral vascular disease
☐ non-healing wound on ________________
☐ osteoporosis
☐ hip fracture
☐ vertebral fracture
☐ Rheumatoid arthritis
☐ osteoarthritis
☐ sickle Cell Disease
☐ blood disorder
☐ knee replacement (circle: Right or Left)
☐ hip replacement (circle: Right or Left)
☐ Other:

______________________________________

______________________________________

______________________________________

**Form Completed By:** ____________________________________________ **Date:** ________________

APPENDIX G

Institutional Review Board Approval Letters

UTHealth
The University of Texas
Health Science Center at Houston

Committee for the Protection of Human Subjects
6410 Fannin Street, Suite 1100
Houston, Texas 77030

**Dr. Gregory Brusola**
**UT-H - GEN - Comm Protection Human Subj**

**NOTICE OF APPROVAL TO BEGIN RESEARCH** **March 12, 2018**

**HSC-MS-18-0050** - Measurement and Training of Dual-Task of Gait in Persons with Multiple Sclerosis

**Number of Subjects Approved: Target:** 80 **/Screen:** 100

**PROVISIONS**: This approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered by the Committee for the Protection of Human Subjects, e.g. study documents, informed consent, etc.

**APPROVED:** By Expedited Review and Approval

**REVIEW DATE:** **03/08/2018**

**APPROVAL DATE:** 03/12/2018

**EXPIRATION DATE:** 02/28/2019

**CHAIRPERSON:** L. Maximilian Buja, MD L. Maximilian Buja

Subject to any provisions noted above, you may now begin this research.

**CHANGES:** The principal investigator (PI) must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. **ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.**

**INFORMED CONSENT DETERMINATION:**
Signed Informed Consent Required

**INFORMED CONSENT:** When Informed consent is required, it must be obtained by the PI or designee(s), using the format and procedures approved by the CPHS. The PI is responsible to instruct the designee in the methods approved by the CPHS for the consent process. The individual obtaining informed consent must also sign the consent document. Please note that only copies of the stamped approved informed consent form can be used when obtaining consent.

**HEALTH INSURANCE PORTABILITY and ACCOUNTABILITY ACT (HIPAA):**
**HIPAA Authorization required:**
HIPAA Authorization within consent form

**UNANTICIPATED RISK OR HARM, OR ADVERSE DRUG REACTIONS:** The PI will immediately inform the CPHS of any unanticipated problems involving risks to subjects or others, of any serious harm to subjects, and of any adverse drug reactions.

**RECORDS:** The PI will maintain adequate records, including signed consent and HIPAA documents if required, in a manner that ensures subject confidentiality.

**Institutional Review Board**
Office of Research
6700 Fannin, Houston, TX 77030
713-794-2480
irb-houston@twu.edu
http://www.twu.edu/irb.html

DATE: April 11, 2018

TO: Mr. Gregory Brusola
Physical Therapy - Houston

FROM: Institutional Review Board (IRB) - Houston

*Re: Approval for Measurement and Training of Dual-Task of Gait in Persons with Multiple Sclerosis (Protocol #: 20068)*

The above referenced study has been reviewed and approved by the Houston IRB (operating under FWA00000178) on 4/10/2018 using an expedited review procedure. This approval is valid for one year and expires on 4/10/2019. The IRB will send an email notification 45 days prior to the expiration date with instructions to extend or close the study. It is your responsibility to request an extension for the study if it is not yet complete, to close the protocol file when the study is complete, and to make certain that the study is not conducted beyond the expiration date.

If applicable, agency approval letters must be submitted to the IRB upon receipt prior to any data collection at that agency. Please use the consent form with the most recent approval date stamp when obtaining consent from your participants. A copy of the signed consent forms must be submitted with the request to close the study file at the completion of the study.

Any modifications to this study must be submitted for review to the IRB using the Modification Request Form. Additionally, the IRB must be notified immediately of any adverse events or unanticipated problems. All forms are located on the IRB website. If you have any questions, please contact the TWU IRB.

cc. Dr. Peggy Gleeson, Physical Therapy - Houston
Dr. Katy Mitchell, Physical Therapy - Houston
Graduate School

MEMORIAL HERMANN
Clinical Innovation & Research Institute

April 25, 2018

**MEMORIAL HERMANN HEALTHCARE SYSTEM APPROVAL FOR MEMORIAL HERMANN – TIRR KIRBY GLEN**

**Thank you for choosing Memorial Hermann as your service provider for this research study.**

IRB ID: HSC-MS-18-0050 PRINCIPAL INVESTIGATOR: Gregory Brusola, PT, DPT, MSCS, PhD(c)

STUDY TITLE: Measurement and Training of Dual-Task of Gait in Persons with Multiple Sclerosis

NUMBER OF SUBJECTS: 80

---

**Approval is hereby granted by Memorial Hermann Healthcare System to initiate this research study at the Memorial Hermann – TIRR Kirby Glen location. This approval is subject to the Principal Investigator's acceptance of the following stipulations:**

**STUDY-SPECIFIC STIPULATIONS:**
Research Informed Consent:

1. The Joint Commission requires that a copy of the signed consent form for hospital-based studies be in all subjects' hospital medical records. In addition, the MHHS Authorization for Disclosure of Protected Health Information for Research (with IRB approval stamp) must be placed in all subjects' hospital medical records. The informed consent and disclosure form must remain in the subjects' charts.

Data Security and HIPAA:

2. All data security computer devices and Protected Health Information used in this study must be password protected and/or data encrypted.

3. The Principal Investigator will use a "linking log" that contains the subject name, MRN (Medical Record Number) and study number to identify subjects. The MRN must not be used on the data collection tool.

Other Stipulations:

4. Please remember to acknowledge the Memorial Hermann – Texas Medical Center in any publications resulting from this study, and provide a copy of the publication to the Director, Clinical Research Operations for Memorial Hermann Clinical Innovation & Research Institute (Sheila.Ryan@memorialhermann.org). The methods of acknowledgement may include:
   a. Memorial Hermann – Texas Medical Center as an author's affiliation;
   b. mention in an "acknowledgement" section; or
   c. as a footnote.

Please sign and return a copy of this letter to the Memorial Hermann Clinical Innovation & Research Institute to the attention of Eleonora.Balibalita@memorialhermann.org to indicate your acceptance of our terms and policies (guidelines attached).

This study may not be initiated until the letter is signed and returned to the Memorial Hermann Clinical Innovation & Research Institute.

If you have questions or need additional information, please contact the Memorial Hermann Clinical Innovation & Research Institute at (713) 704-5655.