Contribution of Motor and Cognitive Factors to Gait Variability and Fall Risk: From Clinical Assessment to Neural Connectivity

DISSERTATION

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

By

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Abstract

Both motor and cognitive factors contribute to increases in gait variability and fall risk in individuals with neurologic disorders. Tasks requiring simultaneous mobility and cognition (i.e. dual-tasks) have been linked with accidental falls. Although these deficits have been well documented in elderly adults, relapsing remitting multiple sclerosis (RRMS), Parkinson’s disease, traumatic brain injury and stroke, the individual contributions of mobility and cognition have not been explored and there are few studies exploring rehabilitation for these impairments using dual-task training. In order to move toward interventional techniques that effectively improve dual-tasking in individuals with neurologic conditions, a better understanding of tasks that amplify gait variability, the contribution of cognition to mobility and who may benefit from such programs is needed.

Together, a systematic review of the literature and a case study provided evidence to support the importance of the interaction between mobility and cognition, the presence of dual-task deficits, and the feasibility of dual-task training in neurologic disorders. Gaps in the literature identified in the systematic review were used to direct the research questions of this document.

The results of cross-sectional and baseline data from a randomized controlled trial suggest that tasks that amplify gait variability may be related to falls and underlying cognition. Backward walking amplified gait variability in both elderly adults and individuals with RRMS, and a backward walking velocity of <0.6 m/s accurately predicted elderly fallers. Dual-task walking
amplified gait variability in individuals with RRMS, and higher gait variability correlated with lower performance on neuropsychological tests (p<0.01).

Diffusion imaging is a useful tool to examine neural connectivity in individuals with RRMS. The supplemental motor area (SMA) has been implicated in cognitive dual-tasks, but its relationship with motor-cognitive dual-tasks has not been explored. Our baseline imaging work suggests that connectivity of the interhemispheric SMA tract is associated with velocity of dual-task walking in RRMS; regression analysis demonstrates a significant relationship between dual-task walking velocity and SMA axial diffusivity ($r^2=0.436$, p=0.014).

Although work is ongoing to characterize dual-task deficits in individuals with neurologic conditions, our review of the literature suggests that this is an impairment that spans diagnoses and that rehabilitation focused on training both motor and cognitive domains can be successful in improving dual-task deficits. Our case study demonstrated that dual-task deficits can be improved even in individuals with severe impairment. These studies were limited by small sample sizes, the paucity of dual-task training intervention studies to date, differences in measurement tools across studies, making it difficult to compare and generalize results. Our findings were also limited by the preliminary nature of our RRMS dataset.

However, our results provide guidance for future studies to understand the contribution of motor and cognitive factors to gait variability and falls in individuals with neurologic conditions. Rehabilitation of dual-task impairments could improve quality of life, safety and independence in these individuals. Further research is needed to establish appropriate training programs for different diagnoses, effective measuring tools for demonstrating improvement, and predictive factors to explore which individuals can benefit from such programs.
All we have to decide is what to do with the time that is given us.

- J.R.R. Tolkien, The Fellowship of the Ring

For my family and friends who have always been supportive and encouraging when I needed it most.

All my love.
Acknowledgments

I have no notion of loving people by halves, it is not my nature.

- Jane Austen, Northanger Abbey

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**Fields of Study**

**Major Field:** Health and Rehabilitation Sciences

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<td>axial diffusivity</td>
</tr>
<tr>
<td>ADL</td>
<td>activity of daily living</td>
</tr>
<tr>
<td>AP-COP</td>
<td>anterior-posterior center of pressure</td>
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<td>AUC</td>
<td>area under the curve</td>
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<tr>
<td>BBS</td>
<td>Berg Balance Scale</td>
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<tr>
<td>BOS</td>
<td>base of support</td>
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<tr>
<td>BW</td>
<td>backward walking</td>
</tr>
<tr>
<td>BWC</td>
<td>backward walking with a cognitive task</td>
</tr>
<tr>
<td>BWS</td>
<td>body weight support</td>
</tr>
<tr>
<td>CGA</td>
<td>contact-guard assist</td>
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<tr>
<td>CV</td>
<td>coefficient of variation</td>
</tr>
<tr>
<td>CVA</td>
<td>cerebrovascular accident</td>
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<tr>
<td>DT</td>
<td>dual-task or dual-tasking</td>
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<tr>
<td>DTC</td>
<td>dual-task cost</td>
</tr>
<tr>
<td>DTI</td>
<td>diffusion tensor imaging</td>
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<tr>
<td>DTQ</td>
<td>Dual Task Questionnaire</td>
</tr>
<tr>
<td>DTT</td>
<td>dual-task training</td>
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<tr>
<td>Dx</td>
<td>diagnosis</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<tr>
<td>EDSS</td>
<td>Expanded Disability Status Scale</td>
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<tr>
<td>FA</td>
<td>fractional anisotropy</td>
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<tr>
<td>FIM</td>
<td>Functional Independence Measure</td>
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<tr>
<td>FP</td>
<td>fixed priority</td>
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<tr>
<td>FLAIR</td>
<td>fluid attenuated inversion recovery</td>
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<tr>
<td>FW</td>
<td>forward walking</td>
</tr>
<tr>
<td>FWC</td>
<td>forward walking with a cognitive task</td>
</tr>
<tr>
<td>HHA</td>
<td>hand-held assist</td>
</tr>
<tr>
<td>MD</td>
<td>mean diffusivity</td>
</tr>
<tr>
<td>ML-COM</td>
<td>medial-lateral center of mass</td>
</tr>
<tr>
<td>ML-COP</td>
<td>medial-lateral center of pressure</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini Mental State Examination</td>
</tr>
<tr>
<td>MPRAGE</td>
<td>magnetization-prepared rapid gradient-echo</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>MS</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>m/s</td>
<td>meters per second</td>
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<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
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<tr>
<td>PT</td>
<td>physical therapy or physical therapist</td>
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<tr>
<td>PTA</td>
<td>posttraumatic amnesia</td>
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<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RD</td>
<td>radial diffusivity</td>
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<tr>
<td>ROI</td>
<td>region of interest</td>
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<tr>
<td>RRMS</td>
<td>Relapsing Remitting Multiple Sclerosis</td>
</tr>
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</table>
SBA  stand-by assist
SDMT  Symbol Digit Modality Test
SMA  supplementary motor area
ST  single-task
TBI  traumatic brain injury
TMT  Tinetti Mobility Test
TUG  Timed Up and Go
WWTT  Walking While Talking Test
VP  variable priority
Chapter 1: General Introduction

1.1 Introduction

Individuals with neurologic conditions frequently report difficulty performing multiple simultaneous tasks. While this phenomenon has been widely documented in many populations, measurement tools, intervention strategies and the underlying neural connectivity remain largely unexplored. The purpose of this document is to gain a better understanding of the relationship between mobility, cognition and the ability to dual-task (or multi-task).

1.2 The Relationship between Attention, Automaticity and Dual-Task

Automaticity represents a skill that is performed with little demand on attentional resources, whereas a task that is non-automatic would require significant attention to ensure maintenance of performance. Automaticity can change with damage to the nervous system; previously automatic movements may become attention-demanding and place an increased load on cognitive resources. Attention, on the other hand, is the cognitive information processing required to complete a task. This may include directing, shifting, dividing and sustaining attention. Dual-task performance is a method used to measure automaticity by determining the attentional costs of a given task or skill. For example, if tasks are “automatic” and require little attention, multiple tasks can be easily performed concurrently without negatively impacting performance. However, performance of “non-automatic” tasks will be
dependent upon the available attentional resources and may result in deterioration of performance if there is insufficient attention to task, or if the tasks exceed the overall attention capacity.\textsuperscript{5-7} Thus, automaticity is a feature of skilled task performance, while attention is the mechanism by which task performance is maintained. The amount of attention needed for the performance of a task is quantified by measuring dual-task performance. Dual-task performance is typically measured by comparing time to complete the single-task condition to the time to complete the dual-task condition.

1.3 Theories of Dual-Tasking & Divided Attention

There are several theories to explain the phenomenon of divided attention and dual-tasking. The earliest proposed theories were the single-channel theories, including the Bottleneck Theory of Dual-Task and the Filter Theory, which postulate that information is processed serially and that two tasks with similar neural network requirements that are performed concurrently create a “bottleneck” or interference such that performance is decreased in one or both tasks.\textsuperscript{8-10} Single-channel theories are limited in their ability to explain examples of dual-task situations where performance does not decline in either task.\textsuperscript{3}

Several other theories better account for the attention-related limits on dual-task performance: the central resource capacity theory and the multiple resource capacity theory.\textsuperscript{3} In the central resource capacity theory, it is assumed that the information processing capability is finite and limited for each individual; information processing occurs in parallel until this limit in attention is reached,\textsuperscript{11} when performance would deteriorate in either one or both tasks.\textsuperscript{12} In this theory, attentional resources are finite but flexible; they may be influenced by the difficulty of
the task, the novelty of the task or by the motivation of the individual. Indeed, the amount of attention allotted to each task can be controlled by the individual and may be modified by prioritizing one task over another. In contrast, the multiple resource capacity theory proposes that individuals have multiple attentional resources available, each with its own capacity limit, as opposed to a central overall attentional pool. This theory has also been called the Cross-Talk and Neural Theory, with declines in performance (i.e., interference) occurring when simultaneous tasks require overlapping mental processes or neural structures. It further suggests that dual-task related gait changes are influenced by the specific demands of the cognitive task and the difficulty of the motor activity. The commonality between these two theories is that attention has a finite capacity, allowing multiple tasks to be performed without decrement until the limit in attentional resources is reached. Thus, the amount of attention required to maintain performance can be used as an indicator of automaticity and in turn, automaticity can be considered a feature of skilled performance that may be enhanced with practice.

1.4 Dual-Task across Neurologic Populations: The Contribution of Cognitive and Motor Deficits to Dual-Task Deficits and Fall Risk

1.4.1 Baseline Cognitive Deficits

Many individuals report attentional impairments either following or during the course of a neurologic disorder. Indeed 25% of individuals with traumatic brain injury (TBI) and 22-25% of individuals with multiple sclerosis (MS) report specific attentional deficits. Impaired attention and information processing speed have been implicated as sensitive indicators of early cognitive dysfunction in MS. While attention span is generally intact, many of the more complex aspects,
such as selective, divided, or alternating attention, are often impaired.\textsuperscript{16} Divided attention is the ability to respond to multiple stimuli simultaneously and includes motor-motor, motor-cognitive, and cognitive-cognitive tasks. In some neurologic conditions, it has been suggested that the degree of impairment in divided attention is task dependent; indeed individuals with TBI perform more poorly when the divided attention tasks require working memory.\textsuperscript{17} Not surprisingly, cognitive dysfunction has been identified as a risk factor for accidental falls in neurological populations, including those with Parkinson’s disease (PD).\textsuperscript{18}

1.4.2 Baseline Mobility Deficits

Individuals with MS demonstrate increased postural sway in quiet stance, delayed responses to postural perturbations and decreased ability to move toward their limits of stability,\textsuperscript{19} leading to increased fall risk. These deficits have been linked with poor trunk control in both sitting and standing\textsuperscript{19} as well as decreased core stability,\textsuperscript{20} even in those with very low\textsuperscript{21} or no\textsuperscript{22} clinical disability. The majority of falls in both elderly and individuals with PD\textsuperscript{23} occur in the backward direction. Interestingly, eight of ten independently ambulating individuals with MS have delayed postural reactions to backward translations in standing.\textsuperscript{24} This is perhaps explained in part by the fact that poor proprioception underlies imbalance and falls in MS\textsuperscript{19} and that backward walking and stepping requires increased proprioception when compared to forward walking because of the lack of visual cues.\textsuperscript{25} Furthermore, a balance rehabilitation program targeting both sensory and motor strategies improved dynamic balance and reduced fall frequency more effectively than a program aimed at improving motor strategies only or a non-specific general rehabilitation program.\textsuperscript{26}

Deficits in postural control could contribute to the increase in gait variability commonly seen in neurologic disorders. When compared to healthy controls, individuals with MS
demonstrate decreased velocity, step length, cadence and step time, as well as a wider base of support and increased swing time variability in forward walking. In addition, 3D kinematic assessment of gait under single-task conditions revealed reduced hip and knee extension and decreased propulsive force in individuals with MS when compared to healthy controls. Even minimally disabled MS individuals demonstrated prolonged double support phase during stance phase. Individuals with MS produced an arrhythmic gait with variation in stance between legs and an overall increase in sagittal plane hip motion with a reduction in ankle motion. Although variability in gait parameters has been correlated with fall risk in the elderly, Parkinson’s disease, and Alzheimer’s disease, this relationship has not been established in MS. However, an interaction between gait variability and cognition may be appreciated; individuals with MS devote greater cognitive reserve to walking than do healthy controls, resulting in even greater variability in spatiotemporal measures of gait (e.g., step length, velocity) when walking is paired with a cognitive task as compared to both single-task conditions and to healthy controls. This is true even in the early disease stage.

The majority of accidental falls in MS occur during activities of daily life; factors that have been linked to accidental falls were difficulty concentrating, forgetfulness, poor balance, fatigue, and self-reported walking ability. In order to avoid falling, more than 80% of individuals who reported fear of falling reduced their activity level, leading to even further reductions in balance and walking ability. It is then not surprising that poor concentration and difficulty with divided attention have been linked with accidental falls in individuals with MS.
1.4.3 Dual-Task Deficits in Individuals with Neurologic Disorders

**Gait**

Dual-task deficits have been described in MS, PD, Alzheimer’s disease, TBI, acquired brain injury, and elderly fallers. When a secondary cognitive task was added to gait, individuals with PD and MS displayed significantly slower velocity and significantly increased variability in swing time and stride time compared to controls. Swing time is determined predominately by balance control mechanisms and is likely influenced not only by lower performance on executive function tests, but also by the attention-demanding nature of gait, even at a comfortable speed.

Dual-task deficits were amplified in backward walking assessment in PD with greater decrements in velocity, stride length, and swing percent, and a greater increment in stride percent when compared to forward walking dual-tasking. Gait asymmetry (differences between right and left limbs) has been linked to poor attentional resources assigned to gait, indeed, PD subjects demonstrate greater asymmetry and increased variability (differences in step-to-step gait measures within a limb) across all challenging (backward walking and all dual-task) conditions when compared to healthy controls.

**Balance**

Assessment of dual-task ability during balance activities has also been investigated. In individuals with MS; only dual-tasking was able to discriminate between MS and healthy controls in all conditions of postural difficulty (i.e. disturbed visual, vestibular and/or somatosensory inputs). During balance dual-tasks, individuals with MS demonstrated greater postural sway, sway area and sway velocity than age-matched healthy controls.
Executive function is a broad term to describe multiple cognitive processes, including coordination of goal-directed activities, distribution of attention among competing tasks, and performance of novel problem-solving tasks. Impairments in executive function may prevent individuals from allotting appropriate attentional resources to balance and gait, reduce ability to confront and adapt to challenging environments such as obstacles and uneven paths, result in increased gait variability, and may account for the increased fall risk seen in the elderly, PD, and Alzheimer’s disease. Indeed, increasing the complexity of the cognitive task paired with gait resulted in decreasing gait speeds in elderly adults. Interestingly, in MS, gait speed was the variable most affected by dual-task conditions, and the degree of detriment was related not to disease severity or duration but rather to levels of fatigue or general cognitive function.

In summary, dual-tasking in individuals with neurologic conditions is characterized by increased variability during both gait and balance activities. Gait represents an attention-demanding task in individuals with neurologic impairment, and the ability to divide attention is further influenced by level of executive function. Current recommendations from both the animal literature and human trials state that interventions combining motor/physical activity and cognitive therapy focusing on complex and novel tasks should be incorporated into clinical practice to enable patients to move more safely and with a reduced fall risk.

1.5 Strategies to Compensate for Dual-Task Deficits

Individuals cope with dual-tasking during gait by using different strategies; young adults decrease gait speed, elderly non-fallers decrease both gait speed and swing time, and elderly fallers attempt to mimic non-fallers but are ultimately unsuccessful at maintaining a stable
walking pattern, which results in highly variable walking. It has been suggested that individuals with neurological deficits employ a “posture second” strategy rather than a “posture first” strategy when encountered with a dual-task situation.\textsuperscript{9,55} The cognitive secondary task is prioritized over the postural task (i.e. often gait). This leads to impaired multiple-task performance and has been shown to double the risk of sustaining a fall while performing an ADL in PD.\textsuperscript{55} In contrast, decrement in dual-task performance was not related to task prioritization in one study in MS,\textsuperscript{2} but this area has not been well explored. Contradictory evidence suggests that despite gait impairments, individuals with chronic stroke use a posture first strategy only when crossing obstacles on a treadmill with a secondary auditory task,\textsuperscript{56} but utilize the posture second strategy when the secondary task requires working memory, speech or visuospatial cognition during gait.\textsuperscript{57} However, the discrepancy could come from the difference between gait over level ground compared to gait with obstacles, which could potentially apply to walking over irregular terrain while simultaneously negotiating obstacles and having a conversation. This is in agreement with previous literature that suggests the nature and type of primary and secondary task in dual-task performance may also affect the result.\textsuperscript{58} Indeed, attentional demand increased with more challenging postural control tasks,\textsuperscript{59} and the type of cognitive task (arithmetic tasks result in greater coefficients of variation than fluency tasks) resulted in differential dual-task related changes in gait in elderly individuals.\textsuperscript{58}

Taken as a whole, strategies to compensate for dual-task deficits in MS are not well known; rather, gait should be viewed as a complex task utilizing executive function, particularly when additional tasks are performed simultaneously.\textsuperscript{39,60} Thus, in MS, gait speed or variability may prove to be a sensitive marker of fall risk and enhancement of cognitive functioning may reduce fall risk. Clinically, one can infer that individuals with neurologic disorders may need specific
instruction to focus on walking to avoid compromising gait and safety, or perhaps more importantly, they may need to practice specific dual-task training.

1.6 Measurement of Dual-Task Ability

Assessment and treatment with tasks that challenge cognition and uncover or amplify deficits such as increased gait variability or poor balance could identify potential fallers. As previously discussed, dual-tasks have been shown to amplify gait variability in many neurologic populations, including MS. Although backward walking has been explored formally only in individuals with PD, it was also shown to increase gait variability, and should be further explored. To this investigator’s knowledge, dual-task backward walking has only been explored in Parkinson’s disease, but could be a useful assessment in other neurologic populations.

Deficits in dual-task ability highlight its importance in the assessment of motor function in individuals with neurologic disorders. A patient who recovers independence in gait in a quiet, closed environment may not be safe when walking in a more demanding environment where cognitive distractors or uneven terrains are present. In order to appropriately measure improvements in automaticity as a result of rehabilitation, therapists should routinely measure it to ensure the effectiveness of interventions designed to improve automaticity.

1.6.1 Behavioral Measures

GAITRite

The GAITRite System (V3.9, MAP/CIR Inc.) is a 4.88 meter electronic walkway with 16,128 embedded sensors that records footfalls in real time (Figure 1.1). The GAITRite calculates spatiotemporal measures (e.g., velocity, step length, double support) of gait in real time. The GAITRite is reliable and valid for use in individuals with MS. Spatiotemporal impairments
detected by GAITRite have been correlated with associated neurological disability (EDSS).\textsuperscript{27,62}

Temporal and spatial gait measurements from the GAITRite walkway are sampled at the default rate of 60 hertz.

![GAITRite visual output](image)

Figure 1.1 GAITRite visual output from a representative subject walking forward at their comfortable pace. Right feet are represented in purple and left feet are represented in green.

**Timed Up & Go (TUG); TUG Cognitive; TUG Manual**

The Timed Up and Go (TUG) is a common test to examine mobility in elderly adults.\textsuperscript{63} Time to complete the TUG, which requires standing from a chair, walking 10 feet, turning, walking back and sitting down, is correlated with level of mobility\textsuperscript{63} in elderly adults. The TUG has been utilized in MS populations and correlates with longer walking tests.\textsuperscript{64} The TUG manual is the TUG while carrying a glass of water while the TUG cognitive is the TUG while performing a subtraction task. These modifications of the TUG measure dual-task performance and are sensitive and specific for identifying fall risk in elderly.\textsuperscript{65} Older adults who take longer than 13.5 seconds to complete the TUG are classified as “fallers” with a 90% prediction rate.\textsuperscript{65} Those taking >14.5 seconds on the TUG manual and >15 seconds on the TUG cognitive were classified as fallers with a 90% and 86.7% prediction rate, respectively.\textsuperscript{65} The TUG cognitive accurately predicted fallers in MS with a sensitivity of 73%.\textsuperscript{18}
Walking While Talking Test (WWTT)

The WWTT is also a reliable and valid test to identify elderly adults at high risk for falls. The test is performed and timed under three conditions: 1) walk 40 feet with a 180-degree turn at the midpoint; 2) condition 1 + recite the alphabet aloud (WWT-simple); 3) condition 1 + recite alternate letters of the alphabet aloud (WWT-complex). Poor performance on the WWT-simple and complex was strongly predictive of falls; a cut-off of 33 seconds for the WWT-complex predicted fallers with a sensitivity of 38.5% and a specificity of 95.6%. The WWTT has not been validated nor have cut-offs been established in individuals with MS.

Dual Task Questionnaire (DTQ)

The Dual Tasking Questionnaire is a 10 item subjective questionnaire of everyday tasks involving dual-tasking, to be rated for frequency of difficulty from 0-4 (4=highest frequency). It has been shown to be sensitive to the effects of brain injury and Alzheimer’s disease.

1.6.2 Cognitive Measures

One of the most commonly used neuropsychological tests to assess attention and processing speed in individuals with MS is the Symbol Digit Modality Test (SDMT). The SDMT is an easy test to administer clinically. During the SDMT, subjects are presented with nine symbol-digit pairings and asked to match as many symbols to their corresponding number as possible in 90 seconds. The SDMT is a sensitive test of processing speed, visual tracking, rapid decision making, and divided attention. The SDMT is valid and reliable in MS and scores are highly correlated to MRI-derived measures of disease burden in MS patients.

The phonemic fluency word generation task requires participants to generate as many words beginning with the letter “F” as possible in 60 seconds. This is followed by generating
words with A and S. The total number of responses in three 60 second bouts is recorded as the overall score. The word generation task is a test of working memory and executive function.

During the Stroop task, participants are presented with three different conditions: the congruent condition, where the color and the word match (e.g., the word RED printed in red ink); the neutral condition, where color words are written in black ink; and the incongruent condition, where the ink color will be incongruent with the meaning of the word (e.g., the word GREEN printed in blue ink). For each condition the accuracy of stated words or colors provided is recorded as the participant’s score. The Stroop is a test of executive function, selective attention, processing speed, and response inhibition.

1.6.3 Imaging Measures

Magnetic resonance imaging (MRI) is the most commonly used assessment tool for both investigation of underlying pathology and evaluation of disease progression in MS.

Anatomical Scans: T1 MPRAGE, T2 FLAIR

Structural changes in grey and white matter have been widely documented in individuals with MS. Indeed, brain atrophy has been linked to declines in cognitive status in MS and is predictive of both future cognitive impairment in early relapsing-remitting MS (RRMS) and progressive accumulation of physical disability. Interestingly, grey matter volume loss in areas associated with executive function has been significantly associated with deteriorating cognitive performance and white matter lesion progression. Accordingly, increased gray matter volume is positively associated with cardiorespiratory fitness. Higher fitness levels may exert a prophylactic influence on structural decline observed in early RRMS by preserving neuronal integrity and reducing long-term disability.

Diffusion Tensor Imaging (DTI)
The diffusion of molecular water in grey matter is highly isotropic (i.e., the same in all directions), while in white matter, diffusion is often restricted to a particular direction. This anisotropy is dictated by axonal cell membranes, myelin sheaths, neurofilaments, and other structures. Anisotropy is highest in compact white matter pathways where the fiber bundles are oriented in parallel, such as the corpus callosum or pyramidal tracts; a higher fractional anisotropy (FA) value indicates a greater degree of white matter integrity. FA is the most commonly used anisotropy index in the literature and the FA index is normalized to values of 0 (isotropic) to 1 (anisotropic). FA is calculated from the diffusion directions (Figure 1.2) Thus, DTI is a useful way to explore white matter integrity in MS. Compared to healthy controls, individuals with RRMS have lower FA values that correlate well with both motor and cognitive impairment.

Figure 1.2 DTI contrast generation. Diffusion measurements along multiple axes contribute to the shape and orientation of the “diffusion ellipsoid”. From the estimated ellipsoid, the longest axis can be found (eigenvector 1 or e1) which is assumed to correspond with the local fiber orientation. The relative size of each axis determined by the eigenvalues of the tensor ($\lambda_1$, $\lambda_2$, and $\lambda_3$).
In addition, the mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) provide useful information about the tract or white matter region of interest. The AD is equivalent to the primary eigenvalue ($\lambda_1$) and indicates the direction of highest diffusivity and coincides with the fiber tract axis.\textsuperscript{90-91} The RD is calculated by averaging the mean of the other two eigenvalues ($\lambda_2$ and $\lambda_3$). Animal work suggests that the AD may be specific to axonal degeneration while the RD may be modulated by myelin.\textsuperscript{92} The MD is the average of all three eigenvalues, and is therefore not indicative of direction. Diffusion images can also be used to perform tractography, the only available tool for identifying and measuring white matter pathways non-invasively.\textsuperscript{93} Tractography identifies the path along which diffusion is least hindered and thus allows for the exploration of connectivity and for the measurement of diffusivity along a tract of interest.

1.7 Research Aims

Although dual-task deficits have been widely documented in many neurological populations, there is a paucity of evidence exploring the effectiveness of interventions to ameliorate these deficits. Similarly, the interaction between motor and cognitive deficits and the neural connectivity related to dual-task deficits are largely unknown (Figure 1.3).
To address these gaps in knowledge, the objective of this work will be to examine the interaction between motor and cognitive factors contributing to gait variability and falls and to explore the neural connectivity related to dual-task ability. It is hypothesized that motor and cognitive factors contribute to increased gait variability and could increase fall risk in individuals with both minimal and severe baseline deficits. It is further hypothesized that the underlying neural connectivity will be related to functional measures of dual-task, which could improve clinical prediction and rehabilitation of such deficits (Figure 1.4).

Figure 1.3 Schema demonstrating factors contributing to increased gait variability and fall risk.
Figure 1.4 Schema demonstrating the gaps in knowledge identified by our systematic review (Chapter 2) that directed this document’s research goals. Note that the dual-task training in MS study is ongoing and will not be presented here.
The following research goals are proposed to test these hypotheses and lay a foundation for further studies:

1. Describe current rehabilitation models and recommendations to improve motor-cognitive dual-task deficits in individuals with neurologic conditions.
   
   Chapter 2: The Effect of Motor-Cognitive Dual-Task Interventions on Mobility in Neurologic Disorders: A Systematic Review

2. Explore the relationship between gait variability in forward and backward walking and falls in a population with mild impairment (i.e. cross-sectional dataset including young, middle-aged and both healthy and frail elderly adults)

   Chapter 3: Backward Walking Measures Are Sensitive to Age-Related Changes in Mobility and Balance

3. Examine the effect of a dual-task training program on mobility, balance and dual-task ability in an individual with severe impairment following a traumatic brain injury.

   Chapter 4: Dual-Task Training for Balance and Mobility in a Person with Severe Traumatic Brain Injury: A Case Study

4. Explore the interaction between gait variability, cognitive factors (neuropsychological test performance), and falls in individuals with MS and healthy adults.

   Chapter 5: Dual-Task Walking Variability is Associated with Stroop and Dual-Task Questionnaire Performance in Multiple Sclerosis
5. Examine the relationships between neuroimaging measures and clinical measures of dual-task ability to further understanding of the underlying neural connectivity and the potential relationships to dual-task ability.

Chapter 6: SMA Connectivity May Be Associated With Dual-Task Walking in Multiple Sclerosis
1.8 References


2.1 Introduction

Attention is a complex cognitive process contributing to processing speed, working memory, and shifting and dividing attention. Divided attention is the ability to respond to multiple stimuli simultaneously. Dual-tasks are paired stimuli such as a cognitive task and a motor task (e.g., walking while talking) that require divided attention. Deficits in sustained and divided attention are common in neurologic disorders and have specifically been linked with impairments in functional mobility in traumatic brain injury (TBI), acquired brain injury, multiple sclerosis (MS), and aging.

Addition of a secondary cognitive task to mobility tasks such as gait or balance tends to amplify variability in individuals with neurologic disorders. Indeed, under dual-task (DT) conditions, individuals with Parkinson’s disease (PD) and MS demonstrated significantly increased variability in swing time and stride time compared to controls. Because swing time is determined predominately by balance control mechanisms, it is likely influenced not only by altered or diminished executive function, but also by the attention-demanding nature of gait. Impairments in attention may prevent individuals from allotting appropriate attentional
resources to balance and gait, reduce ability to confront and adapt to challenging environments such as obstacles and uneven paths, result in increased gait variability, and account for increased fall risk in the elderly,\textsuperscript{8,11} PD,\textsuperscript{9} and Alzheimer’s disease.\textsuperscript{12} Interestingly, only dual-tasking was able to discriminate between individuals with MS and healthy controls in all conditions of postural difficulty (i.e. disturbed visual, vestibular and/or somatosensory inputs).\textsuperscript{13} During balance dual-tasks, individuals with MS demonstrated greater postural sway,\textsuperscript{14} sway area and variability of sway velocity\textsuperscript{13} than age-matched healthy controls.

It has been suggested that impaired central integration is a primary mechanism of impaired balance and that DT training may be an effective way of addressing central processing deficits.\textsuperscript{15} Despite the documented deterioration in gait and balance under DT conditions, there are few intervention studies that address this deficit. Available studies are marked by variability of both training type and duration. Recently, a virtual reality training program of cognitive-motor dual-tasks in a single individual following a concussion, resulted in improvements in dynamic and static balance.\textsuperscript{16} Similarly, DT training improved balance during cognitive activities to a greater extent than mobility training alone in healthy individuals and those with concussion.\textsuperscript{17,18} Neuropsychological training programs in subacute and chronic severe TBI, focusing either on cognitive dual-tasks\textsuperscript{19} or working memory,\textsuperscript{20} resulted in improvements in reaction times on visual-auditory dual-tasks. The purpose of this systematic review was to examine the relevant literature that addresses motor-cognitive DT training interventions in individuals with neurological deficits.
2.2 Methods

2.2.1 Data Sources and Searches

Two of the authors conducted the literature search, applying the MeSH search terms “nervous system disease(s) OR neurologic disorder(s)” with “rehabilitation OR intervention” and “dual task(s) OR divided attention OR multi task(s)” to the title, abstract or index term fields. These search terms were applied to the following data bases: Biosis, CINAHL, ERIC, PsychInfo, Psychological & Behavioral, PubMed, Scopus, and Web of Knowledge. All databases were searched from their inception until May 2, 2012. Two investigators independently screened the titles of the publications found in the databases. If either investigator believed that a title potentially met the inclusion criteria, or if there was inadequate information to make a decision, a copy of the article was obtained. In addition, two investigators manually searched the reference lists of the retrieved articles for potential studies that may have been overlooked or absent from databases.

2.2.2 Study Selection

Figure 2.1 outlines the number of references considered at each state of the selection process prior to confirming the included trials. A total of 12 studies\textsuperscript{21-32} were identified as eligible for inclusion; the details of excluded studies are shown in Figure 2.1. Inclusion in this review was restricted to studies of adults (>18 years old) with a central neurologic disorder with both a treatment and comparison group or an extended baseline in the case of a repeated measures design. To be included, the training must describe DT training (either cognitive-motor or motor-motor) and include outcomes of either gait/balance or both mobility and cognition. Due to the small number of studies returned, the investigators also opted to include studies of elderly adults with balance impairments or a history of falls.
2.2.3 Data Extraction & Quality Assessment

Data were independently extracted from the included trials by two authors and recorded on a standardized spreadsheet. Extracted information included sample sizes, trial settings, population characteristics (e.g., age, diagnosis, and inclusion criteria), details of the interventions, and outcome data (mean scores, standard deviations and ranges). In one trial, there was insufficient information on the outcomes and study population; the authors of that study were contacted, but no response was received.
Initial electronic search
(conducted by two authors)

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$n=3457$

Duplicates removed (n= 1205)

Excluded (n= 1856)
Excluded by language
Lacked neurologic population
Pediatric population
Unrelated to the study topic
Did not include central nervous system
(articles could be excluded for more than one reason)

Screening of titles
(independently conducted by 2 reviewers)

2252 titles retrieved

Review of abstracts
(independently conducted by 2 reviewers)

$n= 396$

Excluded (n= 379)
Excluded by language
Lacked neurologic population
Pediatric population
Unrelated to study topic
Did not include central nervous system
Observational studies with no intervention
Lack of peer review (abstract only or poster)

Review of full articles
(independently conducted by 2 reviewers)

$n= 17$

Excluded (n= 9)
Lack of neurologic population (healthy subjects only)
Lack of mobility/gait/balance intervention
Lack of control or comparator group

Number added after review of reference lists of full text articles

$n= 4$

Included articles
(independently conducted by 2 reviewers)

$n= 12$

Figure 2.1 Search strategy flowchart
Two reviewers independently assessed the methodological quality of each included study using the PEDro scale.\textsuperscript{33} (Table 2.1) This 10-item rating scale was developed for quality assessment of randomized controlled trials and has demonstrated reliability.\textsuperscript{33} Trials with a rating of at least 6/10 on the PEDro scale were rated as high quality.\textsuperscript{34}

2.2.4 Data Synthesis & Analysis

The included studies were characterized by methodological heterogeneity, thus, we refrained from statistical pooling. Each study was independently evaluated with a standardized rating scale of clinical relevance using the 5 criteria recommended by the Cochrane Back Review Group.\textsuperscript{35} This scale evaluates criteria relevant to physical therapy practice and is suitable for use in the evaluation of neurologic clinical trials as well. (Table 2.1)

1. Are the patients described in detail so that you can decide whether they are comparable to those you see in practice?

2. Are the interventions and treatment settings described well enough so that you can provide the same for your patients?

3. Were all clinically relevant outcomes measured and reported?

4. Is the size of the effect clinically important?

5. Are the likely treatment benefits worth the potential harms?

Presently, there is no established cutoff scores for high and low quality studies with this tool; these data were used in conjunction with the PEDro scores to evaluate the strength of the included studies.
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<th>Trial</th>
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<td>Schwenk et al. 21</td>
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<td>Silsupadol et al. 22</td>
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<td>Yang et al. 23</td>
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<td>Yen et al. 26</td>
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<td>Evans et al. 25</td>
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Table 2.1 Trial ratings on the PEDro Methodological Quality and Clinical Relevance Scales
2.3 Results

2.3.1 Study Characteristics

Table 2.2 presents the characteristics of the included studies. Of the 12 included studies, five were randomized controlled trials,\textsuperscript{21-25} five were quasi-experimental repeated measures designs,\textsuperscript{26-29,32} one was a prospective controlled trial\textsuperscript{30} and one was a case series.\textsuperscript{31} All studies were conducted in an outpatient setting. With the exception of the case series,\textsuperscript{31} sample sizes ranged from five\textsuperscript{28} to 35\textsuperscript{21} patients, with five studies enrolling more than 20 subjects.\textsuperscript{21-24,29} The mean age of patients in the experimental group ranged from 44\textsuperscript{25} to 88\textsuperscript{31} years, and the male-female ratio ranged from 9:1\textsuperscript{25} to 1:7.\textsuperscript{22}

The included studies utilized a wide range of outcome measures to assess the effect of DT training. Table 2.2 outlines all of the outcomes used; here we describe the effect of DT training programs on the most common outcome measures.

2.3.2 Effect of Dual-Task Intervention Programs on Gait

Gait speed for both comfortable\textsuperscript{22,23,26-28,32} and fast\textsuperscript{28,30} walking as well as various spatiotemporal measures of gait (e.g., stride length, stride time and cadence) were measured using equipment including 3D motion capture and the GAITRite electronic walkway. GAITRite measures have been validated for use in PD\textsuperscript{36} and elderly adults.\textsuperscript{37} Across studies, all groups who received DT training improved gait speed on single-task walking. This improvement was significant only when compared to a null control group.\textsuperscript{23,26,27} When compared to an alternative treatment,\textsuperscript{22,30} single-task gait velocity improved across all groups.
<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Design</th>
<th>Participant Characteristics, Inclusion Criteria</th>
<th>Interventions</th>
<th>Comparison Interventions</th>
<th>Outcome Measures</th>
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<tr>
<td>Schwenk et al. (2010)&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Double-Blinded RCT</td>
<td>Dx: Elderly adults with dementia&lt;br&gt;Age: (control) 82.3±7.9; (experimental) 80.4±7.1&lt;br&gt;Gender: (control) 22F, 13M; (experimental) 17F, 9M&lt;br&gt;Inclusion Criteria: MMSE (17-26); Diagnosis of dementia based on international criteria; age &gt;65; no severe neurological, cardiovascular, metabolic or psychiatric disorders.</td>
<td>N=35 Specific dual-task training and additional progressive resistance-balance and functional-balance training; performed in groups of 4-6 persons for 12 weeks (2hr/wk)</td>
<td>N=26 2x/wk for 1 hour of supervised motor placebo group training = flexibility exercises, calisthenics and ball games while seated.</td>
<td>Dual Task Cost (DTC) for maximal gait speed under complex conditions (serial 3 subtraction)&lt;br&gt;Trail Making Test</td>
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Table 2.2 Characteristics of included studies (listed by PEDro score)
Silsupadol et al. (2009)

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<th>PEDro= 8</th>
<th>Clinical= 5</th>
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| **Double-Blinded RCT** | **Dx:** Older adults with balance impairment  
Minimum age: (single-task) 74.71±7.80; (dual-task fixed) 74.38±6.16; (dual-task variable) 76.00±4.65  
Gender: (single-task) 7F, 1M; (dual-task fixed) 6F, 2M; (dual-task variable) 4F, 3M  
Inclusion Criteria: Older than 65yo; independent ambulation for 10m; MMSE≥24; no history of orthopedic, neurologic, cardiac, visual or auditory conditions that could influence balance; ≤52 on the Berg Balance Scale; and/or walked with a self-selected speed of ≤1.1m/s  
All subjects received 45 minutes/session; 3x/week for 4 weeks  
N=7  
Single-task training as in Silsupadol et al 2006  
| N=8  
Single-task training with variable priority as in Silsupadol et al 2006  
| N=8  
Dual-task training with fixed priority as in Silsupadol et al 2006  
| Single & Dual-task gait speed  
Berg Balance Scale  
Activities-specific Balance Confidence Scale  

Continued
Yang et al. (2007)23
PEDro= 8
Clinical= 3

**Single-Blinded RCT**

Dx: Chronic Stroke
Age: (control) 59.17±11.98; (experimental) 59.46±11.83
Gender: (control) 5F,7M; (experimental) 6F,7M.

Inclusion Criteria: single chronic stroke resulting in hemiparetic deficits; gait speed between 58-80cm/s (limited) or minimum 80cm/s (full community ambulatory ability); not presently receiving rehab; able to walk 10m independently; functional use of involved UE; stable medical status; capable of understanding and following directions

N=13
30 min ball exercise program 3x/wk for 4 weeks.

Walking occurred forward, backward, on a circular route, and on an S-shaped route.

N=12
Null control

<table>
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<tr>
<th>Gait Speed</th>
<th>Cadence</th>
<th>Stride Time</th>
<th>Stride Length</th>
<th>Temporal Symmetry Index</th>
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</table>

**Table 2.2 Continued**

| | Yang et al. (2007) | Single-Blinded RCT | N=13 | N=12 | | | |
|---|---|---|---|---|---|---|
| | | Dx: Chronic Stroke | 30 min ball exercise program 3x/wk for 4 weeks. | Null control | | |
| | | Age: (control) 59.17±11.98; (experimental) 59.46±11.83 | 3x/wk for 4 weeks. | | |
| | | Gender: (control) 5F,7M; (experimental) 6F,7M. | | |

1) Walk while holding 1 or 2 balls in both hands
2) Walk to match the rhythm of bouncing 1 ball with 1 hand or both hands
3) Walk while holding 1 ball on 1 hand and concurrently bouncing another ball with the other hand
4) Walk while kicking a basketball (in a net)
5) Walk while holding 1 ball and concurrently kicking a basketball (in net)
6) Walk while bouncing 1 ball and kicking a basketball
7) Walk while reciprocally bouncing 1 ball with both hands

Walking occurred forward, backward, on a circular route, and on an S-shaped route.
### Table 2.2 Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Details</th>
</tr>
</thead>
</table>
| Yen et al. (2011) | Single-Blinded RCT | Dx: Idiopathic PD  
Age: (control) 71.6±5.8; (conventional balance) 70.1±6.9; (virtual reality) 70.4±6.5  
Gender: (control) 5F,9M; (conventional balance) 2F, 12M; (virtual reality) 2F, 12M  
Inclusion Criteria: diagnosis of idiopathic PD (Gelb’s criteria); MMSE>24; Hoehn & Yahr stages II and III; no prior balance/gait training; no uncontrolled chronic diseases |
| | | Training provided 30 minutes per session, 2x/week for 6 weeks  
N=14  
Virtual Reality Group:  
10 minutes of stretching exercises to warm-up followed by 20 minutes of standing on the VR balance board and moving their weight with an ankle strategy to navigate a virtual environment  
N=14  
Conventional Balance Group:  
10 minutes of stretching exercises to warm-up followed by 20 minutes of static stance, dynamic weight shifting and external perturbations. |
| | | N=14  
Null Control |
| | | Sensory Organization Test (conditions 1 through 6) to assess center of pressure and center of gravity sway  
Verbal reaction time during a dual-task while standing= each of the 6 conditions of the SOT + auditory arithmetic subtraction task |

38
<table>
<thead>
<tr>
<th>Evans et al. (2009)</th>
<th>Non-Blinded RCT</th>
<th>Dx: Acquired Brain Injury (control) 5 TBI, 4 CVA; (experimental) 7 TBI, 2 CVA, 1 Tumor</th>
<th>N= 10</th>
<th>30 minute sessions, 1x/week for 5 weeks with a therapist and at-home practice 2 practice sessions/day, 5 days/week for 5 weeks.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEDro= 6</td>
<td>Clinical= 5</td>
<td>Age: (control) 45.11±9.73; (experimental) 44.4±8.51</td>
<td></td>
<td>Walking while: 1) Listening to instrumental music 2) Listening to vocal music 3) Listening to a recording of talk-based radio and then answering recorded questions 4) Verbal fluency task 5) Answer autobiographical questions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gender: (control) 1F,8M; (experimental) 1F,9M</td>
<td></td>
<td>Walking around 2-3 obstacles was introduced with these tasks as they became easier.</td>
</tr>
<tr>
<td>Inclusion Criteria: 18-65 years old; diagnosis of brain injury or other neurologic illness; evidence of performance at least 1 SD below the mean on the Divided Attention &amp; Dual-Tasking test battery; self-reported difficulties with dual-tasking in everyday life</td>
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<tr>
<td></td>
<td></td>
<td>N= 9 Null Control with ~5-10 minute weekly phone calls from a research therapist to review general progress, enquire about difficulties or successes in dual-task situations. Subjects also recorded examples of dual-task difficulties in a diary to simulate awareness-raising that training may have produced.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Walking + clicking a mechanical counter (motor-motor DT)</td>
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<td></td>
<td></td>
<td>Walking + sentence verification task (motor-cognitive DT)</td>
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<tr>
<td></td>
<td></td>
<td>Walking + tone counting (motor-cognitive DT)</td>
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<td></td>
<td></td>
<td>Memory Span &amp; Tracking Task</td>
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<tr>
<td></td>
<td></td>
<td>Test of Everyday Attention Telephone Search while Counting</td>
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<tr>
<td></td>
<td></td>
<td>Dual Tasking Questionnaire</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participant Details</th>
<th>Intervention</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fok et al. (2010)</td>
<td>Test-Retest (Repeated Measures)</td>
<td>Dx: Parkinson's disease</td>
<td>A single training session lasting 30 minutes.</td>
<td>N=6 Null Control; 30 minutes of sitting and reading a magazine</td>
</tr>
<tr>
<td>PEDro= 5 Clincial= 4</td>
<td></td>
<td>Age: (control) 57.7±12.3; (experimental) 66.8±9.0</td>
<td>Participants were given verbal cues to achieve longer stride lengths during comfortable walking.</td>
<td>GAITRite electronic walkway was used to measure Gait Speed and Stride Length during single-task and dual-task walking (walking with serial 3 subtraction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gender: not reported</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Inclusion Criteria: Diagnosis of idiopathic PD; subjective walking difficulties; able to independently ambulate 12m x 25 reps; MMSE≥24.</td>
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<tr>
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<td>N=6 Null Control; 30 minutes of sitting and reading a magazine</td>
</tr>
<tr>
<td>PEDro= 5 Clincial= 4</td>
<td></td>
<td>Age: (control) 73.0±12.0; (experimental) 66.3±11.7</td>
<td>Participants were given verbal cues to achieve longer stride lengths during comfortable walking.</td>
<td>GAITRite electronic walkway was used to measure Gait Speed and Stride Length during single-task and dual-task walking (walking with serial 3 subtraction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gender: not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inclusion Criteria: Diagnosis of idiopathic PD; subjective walking difficulties; able to independently ambulate 12m x 25 reps; MMSE≥24.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canning et al. (2008)</td>
<td>Repeated Measures, baseline-controlled</td>
<td>Dx: Parkinson’s disease Age: 61±8 Gender: 2F,3M</td>
<td>N=5 30 min/week, 1x/week for 3 weeks</td>
<td>Participant perception of fatigue, difficulty, anxiety and confidence on a 10cm visual analogue scale.</td>
</tr>
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</tr>
<tr>
<td>PEDro= 3 Clinical= 4</td>
<td>Inclusion Criteria: Diagnosis of idiopathic PD; Hoehn &amp; Yahr stages I-III; stable response to levodopa medications; subjective report of gait disturbance or UPDRS gait score &lt;3; able to walk independently on level ground; MMSE≥24</td>
<td>30 10-meter walks at participant’s predetermined fast-as-possible pace followed by 10 10-meter walks while practicing each of the additional tasks (cognitive, manual, and cognitive+ manual). During the second and third training sessions, two and four extra 40-meter walks under triple task conditions were added, respectively, and were performed in a narrow public hallway that incorporated obstacles and turns.</td>
<td>Velocity, cadence &amp; stride length measured on GAITRite during walking under the following conditions:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Two paces: a) comfortable b) fast as possible</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Four task conditions a) single b) dual-cognitive c) dual-manual d) triple (cognitive + manual)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Cognitive task: auditory color classification task Manual task: carry a cup filled with water</td>
<td></td>
</tr>
</tbody>
</table>

Continued
Table 2.2 Continued

<table>
<thead>
<tr>
<th>Test/Re-test (Repeated Measures)</th>
<th>Dx: Parkinson's disease</th>
<th>Age (experimental)</th>
<th>Gender:</th>
<th>Clinical</th>
<th>PEDro=3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=20</td>
<td>67 ± 6.5</td>
<td>6F, 14M</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Inclusion Criteria: idiopathic PD; Hoehn & Yahr Stage II-III; walking difficulties identified by the UPDRS motor subscale; able to walk independently for 5 minutes.

The virtual reality program required participants to process multiple stimuli simultaneously and make decisions about obstacle negotiation in two planes while continuing to walk on a treadmill. The virtual reality imposed a cognitive load and demanded attention, response selection, and processing visual stimuli.

Historical active control group of patients with PD who followed a similar program of treadmill training, but without virtual reality.

Stride Length, gait variability, dual task cost and obstacle clearance on the GAITRite and accelerometer during three conditions:

1. Comfortable pace
2. Walk with serial 3 subtraction
3. Walk while negotiating two obstacles (box and line)

6 Minute Walk Test
4 Square Step Test
UPDRS motor subscale
Trail Making Test
PD quality of life questionnaire
Continued
Table 2.2 Continued

<p>| You et al. (2009) | Prospective Controlled Trial (Convenience sample) | Dx: elderly adults with a history of falls Age: (control) 68.0±3.3; (experimental) 70.6±6.8 Gender: (control) 4F,1M; (experimental) 7F,1M | Inclusion Criteria: &gt;1 fall in past year; MMSE≥24; independent ambulation; lack of major neurological, orthopedic or cardiopulmonary disorders | All subjects received 18 sessions for 30 min per session over 6 weeks N=8 Cognitive-motor dual-task intervention combining walking with a memory recall task | N=5 Walking with simple music | Velocity during fast walking Center of Pressure sway in the medial-lateral and anterior-posterior directions Word recall &amp; arithmetic tasks |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Interventions</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silsupadol et al. (2006)</td>
<td>Case Series with random selection to treatment groups</td>
<td>Dx: elderly adults with a history of falls or impaired balance Age: 88.3±5.69 Gender: 2F, 1M</td>
<td>All subjects received 45 minutes/session; 3x/week for 4 weeks N=1 Dual-task training with variable priority; half of the training was completed with a focus on postural task performance and half had a focus on secondary task performance. N=1 Single-task training of balance exercises N=1 Dual-task training with fixed priority; balance exercises with simultaneous auditor and visual discrimination tasks as well as cognitive tasks such as subtraction. Subject was instructed to maintain attention on both postural and secondary tasks at all times.</td>
<td>Berg Balance Scale Dynamic Gait Index Timed Up &amp; Go Activities-specific Balance Confidence Scale # missteps and 3D motion analysis to calculate body kinematics (ML-COM displacement) during a 4m walk under 6 different conditions: 2 single-task: -narrow walking -obstacle crossing 4 dual-task: -narrow walking while counting backward by 3’s -obstacle crossing while counting backward by 3’s -narrow walking with tone discrimination -obstacle crossing with tone discrimination</td>
</tr>
</tbody>
</table>

Continued
| Sveistrup et al. (2003) | Test-Retest | Dx: Moderate or Severe Traumatic Brain Injury Age: not reported Gender: not reported Inclusion Criteria: Diagnosis of moderate to severe TBI sustained at least 6 months earlier; no current participation in acute inpatient rehabilitation; able to stand independently for two minutes | 1 hour sessions, 3x/week for 6 weeks N=5 | Conventional Exercise Group: Balance exercises focusing on stepping, picking up objects, single and double limb stance, moving within the base of support, walking, sit-to-stand, reaching, hopping, jumping, and jogging. N=4 Virtual Reality Exercise Group: requires participants to reach, move within base of support, step, sit-to-stand, hop, jump and jog | N=5 Null Control | Measures of quiet stance and gait speed Activities Balance Confidence Scale Community Balance & Mobility Scale |

Cerebrovascular Accident or Stroke (CVA); Diagnosis (Dx); Dual Task Cost (DTC); Mediolateral Center of Mass (ML-COM); Mini-Mental State Examination (MMSE); Parkinson’s disease (PD); Randomized Controlled Trial (RCT); Traumatic Brain Injury (TBI); United Parkinson’s Disease Rating Scale (UPDRS).
2.3.3 Effect of Dual-Task Intervention Programs on Balance

Balance was assessed using the Berg Balance Scale, a 14 item scale where participants are rated 0-4 on static and dynamic balance tasks. A higher score indicates better balance; the Berg Balance Scale is reliable and valid in MS, and cut off scores have been established for stroke and PD populations. While a case series showed large changes in Berg scores after variable priority DT training, the larger RCT showed no significant differences between treatment and control groups. Variable training was characterized by instructions to prioritize either the motor task or the cognitive task rather than focusing on only one task. Larger improvements were perhaps seen in the case series because the individual receiving variable priority DT training was far more impaired than the other subjects and had room for a larger change with training.

Other studies measured balance with postural sway in quiet stance. The sensory organization test measures static balance and postural sway under 6 conditions: stance on each firm and uneven ground with eyes open, closed and with occluded vision. The sensory organization test has been used in stroke and validated in elderly adults. You et al. found no significant differences between treatment and control groups on anterior-posterior and medial-lateral postural sway in quiet stance in older adults with a history of falls. Values for quiet stance were not reported by Sviestrup et al. and queries to the author received no response. Yen et al. demonstrated a significant difference in two items on the sensory organization test (conditions 5 and 6 with occluded vision or eyes closed on an uneven surface) between the treatment groups and the control group, but no differences between the two treatment groups (DT virtual reality vs. conventional balance training) in individuals with PD.
2.3.4 Effect of Dual-Task Intervention Programs on Cognition

Several studies\textsuperscript{21,25,29,30} measured the effect of DT training on domains of cognition including memory, processing speed and attention. There was no cognitive task common to all of the studies, so comparisons in this outcome could not be assessed. While both Evans et al.\textsuperscript{25} and Schwenk et al.\textsuperscript{21} found no significant differences in cognition following training, You et al.\textsuperscript{30} and Mirelman et al.\textsuperscript{29} reported significant improvements in memory performance and processing speed. This perhaps speaks to the specificity of task training; both Evans and You measured memory domains but the training in You’s study included similar memory dual-tasks as part of the training intervention, while the Evans protocol did not. Baseline level of cognitive dysfunction may also play a role in the benefits gained through training, although this was not explored by any of the studies.

2.3.5 Effect of Dual-Task Intervention Programs on Ability to Dual-Task

By far, the most commonly assessed outcome measure across studies was ability to DT during gait.\textsuperscript{21,23,25-29} While the majority of studies assessed motor-cognitive tasks (e.g., walking while performing arithmetic), several also assessed motor-motor tasks (e.g., walking while carrying a glass).\textsuperscript{23,25,28} A common measure of DT ability during gait is the calculation of the dual-task cost (DTC), which allows one to determine the specific contribution of the secondary task on the primary task, in this case, gait. The formula used to calculate DTC is as follows:

\[
\text{Dual Task Cost (DTC)} = \left[ \frac{(\text{dual task} - \text{single task})}{\text{single task}} \right] \times 100
\]

Following DT training, Schwenk et al.\textsuperscript{21} found reduced DTC for both gait speed and stride length in the intervention group when compared to the control group, where DTC was unchanged. This held true for DT walking when the secondary task was addition or subtraction. Similarly, significant improvements in DT gait speed and stride length were found following
training in PD, chronic stroke, and elderly adults with a history of falls when compared to controls. The type of DT training did not seem to effect the improvement; groups trained with variable task priority and fixed task priority both improved DT walking, as did those who trained with motor-motor tasks rather than motor-cognitive tasks. Greater improvements in gait speed and stride length were seen after training when compared to both null control groups and single-task control groups. Training effects were even seen after short term training programs, such as a single 30 minute session of DT training or three 30-minute sessions of DT training, and these significant increases in stride length and gait velocity were maintained at a delayed retention.

The majority of included studies did not specifically prioritize either the motor or cognitive task during training. However, in studies that did specify allocation of attention, the training effect on DT performance was only maintained at a 12-week follow-up in the participants who received DT training with variable priority (i.e. prioritize first one task and then the other) instructions. This has been previously noted in cognitive-cognitive DT training programs, where individuals trained with variable-priority instructions learned tasks faster and performed better than those who received fixed-priority instructions (i.e. equal attention to both tasks). Fok et al. examined DT walking when subjects were trained to prioritize gait by “focus[ing] 100% on big steps.” Following training, individuals significantly increased gait velocity and gait speed over baseline without an associated decline in secondary task accuracy.

A meta-analysis was not undertaken in this review based on heterogeneity within and among the identified studies. The trials included a wide range of sample sizes, variable alternative treatments, participants of widely different disability levels, and DT training protocols with methodological heterogeneity and vastly variable treatment duration (ranging
from 30 minutes to 24 hours). Given this variability, it was not possible to conclude that the trials were sufficiently homogenous to conduct a meaningful meta-analysis. The mean differences, treatment effect sizes and associated 95% confidence intervals for the individual trials are presented by outcome assessment and comparative treatment in Figure 2.2. Effect sizes greater than zero indicate that the outcome favors the DT training group, while effect sizes less than zero indicate that the outcome favors the comparison group. Confidence intervals that include zero should be interpreted with caution. Unfortunately, only studies providing sufficient data could be included in this figure, thus we were not able to include Yen et al.

2.3.6 Adverse Effects

There were no adverse effects of training reported in any of the included studies.

2.4 Discussion

2.4.1 General Findings

While several case studies have examined DT training in individuals with neurological deficits, there is a paucity of randomized controlled trials in this area. To date, DT training has been formally investigated in elderly adults with dementia, older adults with balance impairment, chronic stroke, PD and brain injury. Based on PEDro scores, there are 7 studies with weak evidence, mostly due to lack of blinding, limited sample size and poor reproducibility. However, if the main conclusions are drawn from the studies scoring a 6 or higher on the PEDro scale, DT training in individuals with neurologic disorders is associated with improvements in balance and ability to DT.
2.4.2 Limitations

Comparison of results across studies was limited by the wide range of neurologic populations and deficits as well as the methods of assessing DT. Many of the studies included null control groups, which does not allow for comparison of DT training to other currently utilized training paradigms. Additionally, the majority of studies used the same task for both training and outcome assessment. Despite the established link between dual-tasking and increased gait variability, none of the studies explored gait variability in their outcome assessments. However, in studies receiving the highest marks for methodological quality, individuals that trained with dual-tasks showed greater improvements in spatiotemporal measures of DT walking than those trained with single-tasks.21,22
<table>
<thead>
<tr>
<th>Comparison Treatment</th>
<th>Outcome Measure</th>
<th>Mean Difference</th>
<th>Effect Size (SMD) and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Balance Training</strong></td>
<td>Balance (Berg)</td>
<td>FP: 1.96, VP: -0.29</td>
<td>SMD: 0.46 (-0.53 to 1.45), 95% CI: -0.1 (-1.1 to 0.9)</td>
</tr>
<tr>
<td></td>
<td>Gait (ST velocity)</td>
<td>FP: 0.13, VP: 0.06</td>
<td>SMD: 0.69 (-0.32 to 1.70), 95% CI: 0.34 (-0.68 to 1.37)</td>
</tr>
<tr>
<td></td>
<td>Gait (DT velocity)</td>
<td>FP: 0.15, VP: 0.14</td>
<td>SMD: 1.03 (-0.01 to 2.08), 95% CI: 0.18 (-1.04 to 1.20)</td>
</tr>
</tbody>
</table>

**General Exercise**

| | Balance (MLCOP) | -0.05 | -0.06 (-1.17 to 1.06), 95% CI: 0.08 (-1.04 to 1.20) |
| | Balance (APCOP) | 0.13 | |
| | Cognition (Memory Recall %) | 16.31 | 1.11 (-0.09 to 2.30) |
| | Gait (ST fast velocity) | -0.07 | -0.30 (-1.42 to 0.83) |
| | Gait (DTC velocity) | 19.01 | 1.14 (0.59 to 1.68) |
| | Gait (DTC stride length) | 14.2 | 1.07 (0.53 to 1.62) |

**Null Control**

| | Cognition (Memory Span & Tracking Task) | -4.75 | -0.59 (-1.51 to 0.33) |
| | Gait (ST velocity) | 42.57 | 1.94 (0.99 to 2.89) |
| | Gait (DT velocity) | 18.15 | 0.82 (0 to 1.63) |
| | Gait (DT stride length) | 13.55 | 0.78 (-0.04 to 1.59) |
| | Gait (DT gait speed) | 6.11 | 1.52 (0.50 to 2.54) |
| | Gait (ST velocity) | 0.15 | 0.56 (-0.60 to 1.71) |
| | Gait (DT velocity) | 0.32 | 1.11 (-0.10 to 2.33) |
| | Gait (DT stride length) | 0.34 | 0.35 (-0.79 to 1.49) |
| | Gait (ST velocity) | 0.09 | 0.66 (-0.50 to 1.82) |
| | Gait (DT velocity) | 0.14 | 0.55 (-0.60 to 1.70) |
| | Gait (DT stride length) | 0.16 | 0.90 (-0.29 to 2.08) |

Figure 2.2 Treatment effects for dual-task (DT) training versus comparison treatments for all trials with full data sets. Treatment effects favoring DT training assigned positive Hedges standardized mean difference (SMD) values.

Anterior-posterior center of pressure (APCOP); dual-task cost (DTC); fixed priority (FP); medial-lateral center of pressure (MLCOP); single-task (ST); variable priority (VP).
2.4.3 Implications for Practice

Descriptive studies have shown that individuals with neurologic conditions often adopt a posture-second strategy, where the cognitive task is given higher priority. This may result in loss of balance, declines in walking, and an increased fall risk.10 In this systematic review, we suggest that a DT training program may be utilized in individuals with neurologic disorders to improve not only gait mechanics, but also prioritization during multi-tasking. Practitioners should consider evaluating patients with neurological disorders for dual-tasking deficits.

2.4.4 Implications for Future Research

While DT training in neurological populations may yield improvements in both balance and gait speed, it has been largely unsuccessful at generalizing to novel dual-task situations. However, a recent pilot study,45 not included in this review due to lack of a control group or extended baseline, suggests that carryover is possible if functional tasks are the focus of training. Future research in the area of DT training should assess the ability of the training paradigm to translate to novel DT situations, particularly during functional tasks encountered by subjects on a daily basis.

2.5 Conclusion

DT training appears to be both feasible and effective for improving spatiotemporal measures of DT gait in individuals with neurologic disorders. More research is needed to define the specific DT interventions that are most effective and to better assess whether some interventions are more appropriate than others for a specific diagnostic group. This is the first review to examine the motor outcomes of DT training across neurologic disorders. Improvement
of DT ability in individuals with neurologic disorders may improve independence and decrease fall risk.
2.6 References


Chapter 3: Backward Walking Measures Are Sensitive to Age-Related Changes in Mobility and Balance

3.1 Introduction

Many falls in elderly occur from backward perturbations or during transitional movements that require a person to move backward, such as turning and stepping backwards to sit in a chair. These falls may be related to deficits in stepping responses to backward perturbations and difficulties with backward walking (BW). In response to unpredictable backward perturbations, elderly individuals were twice as likely to take compensatory steps to maintain balance compared to young adults. Laufer found that healthy elderly had significantly greater reductions in gait speed and stride length during BW than young adults. Increased gait variability was found to correlate with increased fall risk in multiple populations. Hackney et al. demonstrated that gait variability was increased in backward compared to forward walking (FW) in healthy elderly and those with Parkinson’s disease. Several studies have demonstrated that practicing multi-directional stepping either as an exercise program or in the form of tango dancing improves mobility. Taken together these findings suggest that the inability to take effective backward steps may predispose the elderly to declines in functional ambulation and to increased risk of falls.
Since the ability to walk backward is a crucial element of mobility function and deficits might be related to a greater risk for backward falls, assessment of BW may be an important clinical tool. Few studies have compared spatiotemporal gait measures in FW versus BW and only three included elderly participants.⁵,⁶,⁸ No studies to date have examined the characteristics of BW in middle-aged adults or elderly with declines in functional mobility; thus, it is not known whether the decline in BW is a slow, progressive change related to aging or a more abrupt decline related to cumulative changes in the neuromuscular system.

The purpose of this study was to compare spatiotemporal measures and their coefficients of variation (CVs) of BW and FW 1) in young (18-34 y.o.), middle-aged (35-64 y.o.) and elderly (65 y.o. and older) and 2) in elderly fallers and non-fallers; and 3) to compare the strength of the relationship between age and BW and FW measures to determine the utility of BW performance as a clinical measure of safety and functional mobility. We hypothesized that BW spatiotemporal measures would be equivalent between young and middle-aged adults and would be significantly more impaired in elderly fallers than non-fallers. We also hypothesized that age would be more closely related to BW spatiotemporal measures than to FW measures. Assessment of BW measures may assist healthcare professionals in decision making for fall prevention interventions, assistive device prescription, and assessment of intervention efficacy in the elderly.

3.2 Methods

This cross-sectional study was approved by the Institutional Review Board. All participants were consented prior to participation.
A convenience sample of 130 adults, including 37 young, 31 middle-aged and 62 elderly participated in the study. Young and middle-aged participants were recruited from among students and faculty. Elderly participants were recruited at three facilities with independent and assisted-living units. Assisted living residents made up 25% of the elderly sample and 50% of the elderly used an assistive device for walking outside their home. Twice as many elderly were recruited to allow further analysis of differences between those with and without a history of reported falls. All participants were able to ambulate >10 feet without an assistive device and/or physical assistance and demonstrated understanding of the purpose of the study. Individuals who were pregnant or had orthopedic or neurologic conditions that altered their walking were excluded.

Spatiotemporal gait measures were collected using the GAITRite System (V3.9, MAP/CIR Inc.). GAITRite measures are valid and reliable in the elderly. \(^1\) Demographic data including pre-existing diagnoses, weekly types and amounts of exercise, self-reported fall history (number of falls the past 6 months), \(^1\) and assistive device use were collected. Elderly participants were also tested on the Tinetti Mobility Test (TMT) to better describe their functional mobility status. \(^1\) Participants were asked to walk at a comfortable pace across the GAITRite walkway for 3 trials each of FW and BW. Participants were instructed to walk 2 meters before and after the walkway to allow for acceleration and deceleration. Participants completed all trials without an assistive device, wearing a gait belt and were guarded.

3.2.1 Data Analysis

The dependent variables considered in this study included average GAITRite results from trials of each direction, coefficient of variation (CV) values were calculated to assess the variability of gait measures in BW and FW. Data for each of the gait measures and CVs were
analyzed using one-way repeated-measures ANOVA with Tukey’s post-hoc tests to detect
differences between BW and FW and between age groups. The p-value was set at 0.05 to
control for type I error rate. Participant age served as the grouping variable in the ANOVA, while
BW and FW were the within subject or repeated variable. The group (age) effect, direction
(BW/FW) effect and the interaction of the two effects were analyzed. The interaction of age
group and direction was tested for all gait variables and their associated CVs to determine if the
various age groups performed significantly different in BW and FW.

Correlational analysis was performed to examine the relationship between age and
performance in forward and backward gait. Differences in spatiotemporal measures of FW and
BW between elderly fallers and elderly non-fallers were determined using independent t-tests.
This final analysis included only the elderly age group. Statistical analyses were performed using
SPSS version 19.0.

3.3 Results

Young adult [mean age = 24.1 ± 2.5 SD (range 21–31), 10 males], middle-aged [mean age
= 47.3± 7.9 (range 35- 61), 4 males] and elderly -[mean age = 85.3 ±6.7(range 66-98), 12 males]
individuals participated in the study. Two elderly did not meet inclusion criteria due to health
issues and were unable to participate. Ninety percent of elderly participants reported exercising
(most commonly walking) at least once a week (mean = 4x/week). Tinetti Mobility Test scores
for elderly fallers [n = 12; mean age = 86.3±4.7; mean TMT scores = 21.3 ± 5.8 (range 8-28)] were
significantly lower (p<.05, 2 tailed Mann Whitney U test) than non-fallers [n = 50; mean age = 85.4± 7.1; mean TMT = 25 ± 2.8 (range 17-28)] indicating that fallers on average had greater
mobility impairments than non-fallers. In the repeated measures ANOVA, the interaction
between the participant’s age group and walking direction was significant for the average and CV of gait measures across trials. The F statistics and p-values for the interaction terms are in Table 3.1.

3.3.1 Gait Across Age Groups

Gait parameters varied with age and differed from BW to FW (Table 3.2). Velocity was similar between young and middle-aged in both BW (1.13 m/s ± .2; 1.03 m/s ± .2) and FW (1.49 m/s ± .2; 1.48 m/s ± .2), but was significantly (p<.001) lower in elderly individuals compared to the other groups. Declines in velocity were greater in BW (50% young versus elderly, 54% middle-aged versus elderly) than FW (34% young versus elderly, 30% middle-aged versus elderly). Elderly participants also had significantly (p<.001) shorter stride length, increased double support and stance percent, and decreased swing percent than the young and middle-aged individuals in both BW and FW. Base of support (BOS) was significantly wider (p<.001) for elderly compared to the young group (p<.001) in BW and for elderly compared to the middle-aged group in FW. In BW the young also had a significantly (p<.03) narrower BOS than the middle-aged group. All groups walked significantly slower and with a significantly shorter stride length, lesser swing percent, greater stance and double support percent, and wider BOS during BW than FW (p<.001).
<table>
<thead>
<tr>
<th>Gait Measures</th>
<th>Young Mean Difference (SD)</th>
<th>Middle Aged Mean Difference (SD)</th>
<th>Elderly Mean Difference (SD)</th>
<th>Test Statistic for ANOVA Interaction Term (F statistic)</th>
<th>P-value for ANOVA Interaction Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity (m/s)</td>
<td>-.387 (.13)</td>
<td>-.458 (.15)</td>
<td>-.490* (.17)</td>
<td>F(2,127) = 5.00</td>
<td>0.008</td>
</tr>
<tr>
<td>Stride Length (cm)</td>
<td>31.43 (8.64)</td>
<td>37.94 (11.19)</td>
<td>46.49* (14.03)</td>
<td>F(2,127) = 7.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Base of Support (cm)</td>
<td>-4.53 (3.77)</td>
<td>-8.08† (3.67)</td>
<td>-6.81# (4.25)</td>
<td>F(2,127) = 15.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Swing Percent</td>
<td>1.13 (.57)</td>
<td>1.37 (2.08)</td>
<td>2.98# (3.01)</td>
<td>F(2,127) = 7.20</td>
<td>0.001</td>
</tr>
<tr>
<td>Stance Percent</td>
<td>-6.60 (4.95)</td>
<td>-1.34 (2.04)</td>
<td>-3.09# (2.80)</td>
<td>F(2,127) = 6.57</td>
<td>0.002</td>
</tr>
<tr>
<td>Double Support Percent</td>
<td>-2.62 (2.35)</td>
<td>-2.27 (3.27)</td>
<td>-6.44** (5.04)</td>
<td>F(2,127) = 7.17</td>
<td>0.001</td>
</tr>
<tr>
<td>CV Step Time</td>
<td>-1.22 (1.37)</td>
<td>-1.65 (2.80)</td>
<td>-5.20# (9.20)</td>
<td>F(2,125) = 6.67</td>
<td>0.002</td>
</tr>
<tr>
<td>CV Step Length</td>
<td>-3.77 (2.68)</td>
<td>-5.27 (3.86)</td>
<td>-12.75** (11.41)</td>
<td>F(2,125) = 24.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV Swing Time</td>
<td>-2.66 (1.82)</td>
<td>-4.39 (2.80)</td>
<td>-8.93** (7.13)</td>
<td>F(2,125) = 12.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV Double Support</td>
<td>-2.21 (1.69)</td>
<td>-2.76 (2.57)</td>
<td>-6.95* (7.94)</td>
<td>F(2,125) = 4.84</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Table 3.1 Interactions by age and direction of gait

Comparison of forward to backward walking interactions demonstrating that across most variables backward walking variables changed more dramatically and these changes were typically significant between the elderly and the young and middle aged. Elderly significantly different than: * young, p < .001; ** young and middle aged, p < .001; # young, p < .02; ∞ middle aged, p < .02 and † middle aged significantly different than young, p < .001. CV, coefficient of variation.
There were significant interaction effects among age and walking conditions indicating that as participants went from walking forward to backward, the changes in gait measures were significantly (p=.03 to p<.001) greater in the elderly compared to young and middle-aged, with the exception that differences were greater between only the young and elderly for velocity and stance percent (Table 3.1). In addition changes in BOS going from FW to BW were significantly larger in both middle aged and elderly compared to young.

3.3.2 Variability of Gait

The variability of gait was significantly greater for the elderly compared to young and middle-aged groups in both BW and FW (Table 3.2). There were no significant differences in CV values between young and middle-aged individuals. Increases in CVs across age were greater than changes in gait measures, ranging from an 83% increase in double support time CV between middle-aged and elderly to a 134% increase in stride length CV between young and elderly in BW. All groups had significantly greater CVs during BW than FW (p<.001). There were significant (p<.001) interaction effects among age and walking conditions (FW versus BW) across all CVs indicating that as participants went from FW to BW the changes in CVs were significantly greater in elderly compared to young and middle-aged individuals (Table 3.1).

3.3.3 Relationship of Gait Measures to Age

Correlational analysis revealed that age was more closely associated with BW than FW measures. Stronger correlations were observed between age and BW than FW in four of the five gait measures. This same pattern was not observed in the CV variables (Table 3.3).
<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Middle Aged</th>
<th>Elderly</th>
<th>Young</th>
<th>Middle Aged</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Velocity (m/s)</strong></td>
<td>1.49 ± .18</td>
<td>1.48 ± .22</td>
<td>1.07 ± .31</td>
<td>1.13 ± 2</td>
<td>1.03 ± 2</td>
<td>.52 ± 2</td>
</tr>
<tr>
<td></td>
<td>(1.08 - 1.86)</td>
<td>(1.1 - 1.9)</td>
<td>(.43 - 2.01)</td>
<td>(.67 - 1.61)</td>
<td>(.55 - 1.53)</td>
<td>(.2 - 1.05)</td>
</tr>
<tr>
<td><strong>Stride Length (cm)</strong></td>
<td>144.9 ± 12</td>
<td>141.1 ± 16.4</td>
<td>103.6 ± 23.3</td>
<td>112.9 ± 15.4</td>
<td>103.1 ± 17.4</td>
<td>52.8 ± 17.9</td>
</tr>
<tr>
<td></td>
<td>(115.1 - 166.3)</td>
<td>(113.2 - 191.8)</td>
<td>(44.6 - 151.6)</td>
<td>(69.2 - 139)</td>
<td>(67.2 - 151.5)</td>
<td>(21 - 106)</td>
</tr>
<tr>
<td><strong>Base of Support (cm)</strong></td>
<td>9.9 ± 2.0</td>
<td>8.5 ± 2.9</td>
<td>10.5 ± 4.1</td>
<td>14.5 ± 4.0</td>
<td>16.6 ± 3.7</td>
<td>17.2 ± 4.3</td>
</tr>
<tr>
<td></td>
<td>(6.45 - 13.7)</td>
<td>(3.3 - 14.1)</td>
<td>(1.37 - 20.4)</td>
<td>(2.1 - 21.8)</td>
<td>(6.8 - 25.3)</td>
<td>(7 - 25.9)</td>
</tr>
<tr>
<td><strong>Double Support Percent</strong></td>
<td>28.2 ± 4.0</td>
<td>28.2 ± 3.0</td>
<td>33.2 ± 6.5</td>
<td>29.4 ± 2.7</td>
<td>30.5 ± 5.0</td>
<td>40.2 ± 7.6</td>
</tr>
<tr>
<td></td>
<td>(21.5 - 37.5)</td>
<td>(18.7 - 32.5)</td>
<td>(22.6 - 54.3)</td>
<td>(28.6 - 30.3)</td>
<td>(28.7 - 32.3)</td>
<td>(38.3 - 42.2)</td>
</tr>
<tr>
<td><strong>Swing Percent</strong></td>
<td>36.7 ± 1.5</td>
<td>36.1 ± 1.9</td>
<td>33.5 ± 3.4</td>
<td>35.4 ± 1.7</td>
<td>34.7 ± 2.5</td>
<td>30.2 ± 3.3</td>
</tr>
<tr>
<td></td>
<td>(34.7 - 41.7)</td>
<td>(31.0 - 39.4)</td>
<td>(21.5 - 38.2)</td>
<td>(23.3 - 39.2)</td>
<td>(27.8 - 39.2)</td>
<td>(21.3 - 37.6)</td>
</tr>
<tr>
<td><strong>Stance Percent</strong></td>
<td>63.3 ± 1.5</td>
<td>63.9 ± 1.9</td>
<td>66.5 ± 3.4</td>
<td>64 ± 4.9</td>
<td>65.2 ± 2.5</td>
<td>69.8 ± 3.4</td>
</tr>
<tr>
<td></td>
<td>(58.2 - 65.3)</td>
<td>(60.6 - 69)</td>
<td>(61.8 - 78.5)</td>
<td>(60.8 - 72.2)</td>
<td>(60.8 - 72.2)</td>
<td>(62.4 - 78.7)</td>
</tr>
<tr>
<td><strong>Double Support Percent</strong></td>
<td>28.2 ± 4.0</td>
<td>28.2 ± 3.0</td>
<td>33.2 ± 6.5</td>
<td>29.4 ± 2.7</td>
<td>30.5 ± 5.0</td>
<td>40.2 ± 7.6</td>
</tr>
<tr>
<td></td>
<td>(21.5 - 37.5)</td>
<td>(18.7 - 32.5)</td>
<td>(22.6 - 54.3)</td>
<td>(28.6 - 30.3)</td>
<td>(28.7 - 32.3)</td>
<td>(38.3 - 42.2)</td>
</tr>
<tr>
<td><strong>CV of step time (%)</strong></td>
<td>3.1 ± 1.2</td>
<td>4.1 ± 1.4</td>
<td>6.4 ± 3.1</td>
<td>4.3 ± 1.1</td>
<td>6.9 ± 2.6</td>
<td>11.8 ± 9.6</td>
</tr>
<tr>
<td></td>
<td>(1.3 - 7.6)</td>
<td>(1.5 - 7.8)</td>
<td>(2.0 - 19.3)</td>
<td>(2.2 - 7)</td>
<td>(1.9 - 11.5)</td>
<td>(3.8 - 64.5)</td>
</tr>
<tr>
<td><strong>CV of stride length (%)</strong></td>
<td>2.1 ± .8</td>
<td>2.5 ± 1.1</td>
<td>13.7 ± 7.7</td>
<td>4.8 ± 1.9</td>
<td>6.9 ± 2.6</td>
<td>16.1 ± 6.7</td>
</tr>
<tr>
<td></td>
<td>(.7 - 4.5)</td>
<td>(.6 - 5.3)</td>
<td>(3.1 - 36.2)</td>
<td>(1.9 - 10.3)</td>
<td>(1.9 - 11.5)</td>
<td>(5.1 - 34.8)</td>
</tr>
<tr>
<td><strong>CV of swing time (%)</strong></td>
<td>2.9 ± 1.0</td>
<td>3.7 ± 1.6</td>
<td>14.8 ± 9.3</td>
<td>5.1 ± 1.7</td>
<td>6.4 ± 2.6</td>
<td>15.0 ± 8.5</td>
</tr>
<tr>
<td></td>
<td>(1.1 - 5.8)</td>
<td>(1.9 - 8.2)</td>
<td>(3.1 - 54.3)</td>
<td>(2.2 - 9.1)</td>
<td>(3.6 - 13.9)</td>
<td>(3.8 - 42.5)</td>
</tr>
<tr>
<td><strong>CV of double support time (%)</strong></td>
<td>5.8 ± 1.7</td>
<td>6.7 ± 2.6</td>
<td>9.8 ± 3.4</td>
<td>7.4 ± 2.5</td>
<td>9.0 ± 3.4</td>
<td>16.5 ± 12.8</td>
</tr>
<tr>
<td></td>
<td>(3.2 - 8.2)</td>
<td>(2.5 - 13.2)</td>
<td>(4.1 - 18.3)</td>
<td>(1.2 - 13.6)</td>
<td>(5.6 - 22.6)</td>
<td>(6.4 - 80.9)</td>
</tr>
</tbody>
</table>

Table 3.2 Spatiotemporal measures and CVs of forward and backward walking

All values are means ± SD (range); *significantly different than young at P < .001; †significantly different than middle-aged at P < .001; ‡Significant difference between forward walking and backward walking within group; CV, coefficient of variation.
<table>
<thead>
<tr>
<th>Measure</th>
<th>Forward</th>
<th>Backward</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity (m/s)</td>
<td>0.72*</td>
<td>0.79*</td>
</tr>
<tr>
<td>Stride Length (cm)</td>
<td>0.78*</td>
<td>0.84*</td>
</tr>
<tr>
<td>Base of Support (cm)</td>
<td>0.10</td>
<td>0.22*</td>
</tr>
<tr>
<td>Swing Percent</td>
<td>0.53*</td>
<td>0.53*</td>
</tr>
<tr>
<td>Double Support Percent</td>
<td>0.55*</td>
<td>0.59*</td>
</tr>
<tr>
<td>CV of step time (%)</td>
<td>0.55*</td>
<td>0.44*</td>
</tr>
<tr>
<td>CV of stride length (%)</td>
<td>0.62*</td>
<td>0.73*</td>
</tr>
<tr>
<td>CV of swing time (%)</td>
<td>0.66*</td>
<td>0.60*</td>
</tr>
<tr>
<td>CV of double support time (%)</td>
<td>0.57*</td>
<td>0.41*</td>
</tr>
</tbody>
</table>

Table 3.3 Relationship of gait and CV measures to age by walking direction: Pearson correlation coefficients

* significant at p < .001; coefficient of variation (CV)
3.3.4 Comparison Elderly Fallers and Non-fallers

Spatiotemporal measures for fallers and non-fallers were compared only for the elderly age group. Statistical differences were found in 5 out of 6 BW spatiotemporal measures, while only 2 out of 6 FW measures were significantly different (Table 3.4). Elderly fallers walked with a slower velocity and took significantly shorter strides than non-fallers in BW and FW. Fallers spent a larger percentage of the gait cycle in double support, single limb stance and had a wider BOS than non-fallers in BW ($p<.05$) but not in FW. In BW step time variability was higher in fallers than non-fallers. All other CVs were statistically equivalent in BW and FW.

<table>
<thead>
<tr>
<th>Gait Parameter</th>
<th>Forward Mean (SD)</th>
<th>Backward Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity (m/s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faller</td>
<td>.89* (.2)</td>
<td>.39* (.12)</td>
</tr>
<tr>
<td>Non - Faller</td>
<td>1.0 (.2)</td>
<td>.56 (.20)</td>
</tr>
<tr>
<td>Stride Length (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faller</td>
<td>84.5* (15.9)</td>
<td>37.1* (12.7)</td>
</tr>
<tr>
<td>Non - Faller</td>
<td>101.6 (18.7)</td>
<td>56.5 (17)</td>
</tr>
<tr>
<td>Base of Support (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faller</td>
<td>12.3 (2.8)</td>
<td>19.8* (3.8)</td>
</tr>
<tr>
<td>Non - Faller</td>
<td>10.2 (4.5)</td>
<td>16.6 (4.2)</td>
</tr>
<tr>
<td>Swing Percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faller</td>
<td>31.5 (3.6)</td>
<td>28.7 (2.1)</td>
</tr>
<tr>
<td>Non - Faller</td>
<td>33.4 (3.2)</td>
<td>30.6 (3.4)</td>
</tr>
<tr>
<td>Stance Percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faller</td>
<td>68.4 (3.7)</td>
<td>71.8* (2.4)</td>
</tr>
<tr>
<td>Non - Faller</td>
<td>66.6 (3.2)</td>
<td>69.4 (3.4)</td>
</tr>
<tr>
<td>Double Support Percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faller</td>
<td>37.1 (6.3)</td>
<td>44.7* (44.7)</td>
</tr>
<tr>
<td>Non - Faller</td>
<td>33.4 (6.0)</td>
<td>39.2 (39.2)</td>
</tr>
<tr>
<td>CV Step Time (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faller</td>
<td>7.3 (4.7)</td>
<td>12.8* (10.6)</td>
</tr>
<tr>
<td>Non - Faller</td>
<td>6.4 (2.5)</td>
<td>9.0 (2.5)</td>
</tr>
</tbody>
</table>

Table 3.4 Comparison of gait and mobility measures between elderly fallers and non-fallers

* - Significant $p < .05$; Fallers $n = 12$; non-fallers $n = 50$; 2 tailed, equal variances assumed; df = 60.
An interesting and unexpected finding was that all fallers had BW velocities of less than 0.6 m/s (Figure 3.1). Calculation of area under the curve demonstrated that BW velocity (AUC = .75) more accurately identified fallers than FW velocity (AUC = .70). A cut off score of 0.6 m/s BW velocity identified fallers with a sensitivity of 100% and a specificity of 33%. To optimize the specificity and positive likelihood ratio (+LR) value a cut off score of 0.4 m/s BW velocity identifies fallers with a sensitivity of 58%, specificity of 82%, and a +LR of 3.2.

![Figure 3.1: Backward walking velocity identifies fallers better than forward walking velocity in elderly. All self-reported elderly fallers had a backward walking velocity of less than 0.6 m/s.](image)

### 3.4 Discussion

This is the first study to examine spatiotemporal gait measures in BW across adulthood and to include middle-aged individuals and elderly individuals with impaired functional mobility.
and/or reported falls. Backward and forward walking performance declined significantly in elderly compared to young and middle-aged adults, with spatiotemporal measures of BW declining more precipitously than FW. Age was more strongly related to BW spatiotemporal measures than FW measures. In addition, we found that BW measures were significantly more impaired in fallers than in non-fallers. Taken together, our findings support that BW is a valuable addition to the examination of mobility.

Age-related changes in gait negatively impact function, as indicated by an increase in falls and use of assistive devices in old age. Our results show that gait measures in both BW and FW remained relatively stable in young and middle-aged but were significantly more impaired in the elderly group (Table 3.2). Our results concur with previous findings of greater deficits in gait measures in healthy elderly compared to young adults in FW and BW. These findings suggest that changes in gait measures emerge after middle-age. This is consistent with research showing that the cumulative effects of aging on muscle and neural tissue do not typically impact functional performance until age 65 or later.

Reversing from FW to BW led to a significant reduction in velocity, stride length, swing percent, and increased stance and double support percent and BOS for all age groups (Table 3.2). The magnitude of these changes was more pronounced in elderly than in young and middle-aged (Table 3.1), lending further support to the hypothesis that declines in gait measures may not emerge until after middle-age. For example, when compared to FW, elderly individuals decreased velocity by 51% (1.07m/s to 0.52m/s) in BW while young and middle-aged individuals decreased their velocity by 24% (1.49m/s to 1.13m/s) and 30% (1.48m/s to 1.03m/s), respectively. Similarly, Laufer (2003) reported that gait velocity decreased by 23% in young adults (20-31 years), while older adults (65-89 years) experienced a 45% decrease in velocity.
Possible reasons for these spatiotemporal changes in going from FW to BW are because BW places greater demands on postural control systems due to lack of visual information and because BW is not as habitually performed. Thus, decreased postural stability and/or fear of falling may induce changes such as lower gait velocity and shorter steps to avoid falls.

Gait variability was more pronounced in elderly compared to young and middle-aged individuals and was significantly increased by reversing from FW to BW in all age groups (Table 3.2). The magnitude of variability increase with direction reversal was significantly greater for elderly compared to other age groups (Table 3.1). Our finding that BW is more variable than FW concurs with previous findings in healthy elderly and individuals with Parkinson disease. Greater variability in BW than FW is clinically important since increased gait variability is associated with a greater fall risk in the elderly and some neurological populations. Our finding that step time CV in BW was significantly increased in fallers versus non-fallers (Table 3.4) would support the hypothesis that postural instability in BW may underlie the variability changes.

Four out of five BW spatiotemporal measures and stride length CV were more closely associated with age compared with the associations between age and FW measures (Table 3.3). Some studies suggest that the control networks for BW may be independent of those for FW. Our results raise the possibility that these networks may be differentially impacted by the aging process such that the BW system is more affected than the FW system. Further research is needed to determine whether clinicians can identify mobility deficits earlier by examining BW in addition to FW.

Backward walking measures were more sensitive than FW measures at differentiating elderly fallers from non-fallers. Significant differences were noted between fallers and non-
fallers in 5 out of 6 BW measures while only two out of 6 measures, velocity and stride length, were able to differentiate these groups in FW. Our finding that elderly fallers were on average significantly more impaired on the TMT than non-fallers raises the possibility that impaired BW performance may have contributed to lower TMT scores possibly due to difficulties with turning and backing up to a chair. Therefore, further investigations to examine the relationship between BW performance and functional mobility with aging seem warranted.

One of the most interesting and intriguing findings of our study was that BW velocity identified fallers more accurately than FW velocity. Walking backward at a speed less than 0.6 m/s identified 100% of fallers and those who walked backward at a speed less than 0.4 m/s had a 3.2 times greater likelihood of being a faller than those who walked faster. In comparison, FW velocity at a cut off of 1.0 m/s only identified 83% of fallers. In agreement with our findings, other studies have reported only a weak relationship between falling and forward gait velocity.\(^{21,22}\) Further investigations to determine the validity of BW velocity to identify individuals at risk of falls would be valuable.

This study has several limitations. Participants may not be representative as the sample was limited to individuals living in Ohio, included more females than males, and elderly subjects tended to be older and active. The cross-sectional design does not allow any conclusions to be made regarding individual changes in gait measures over time.

The findings of this study extend the available information on age-related differences in spatiotemporal measures of BW and highlight the importance of assessing BW as a component of gait assessment in the elderly. Gait measures in both BW and FW were mostly equivalent in the young and middle-aged groups but declined significantly in the elderly group. Velocity and stride length demonstrated a more rapid and robust decline in BW than FW that was more
closely associated with age than other gait measures. In addition, BW velocity was found to be significantly slower in elderly fallers than in non-fallers. All elderly fallers walked backward at a speed less than 0.6 m/s. Based on these findings, healthcare practitioners are encouraged to incorporate assessment of BW, in particular velocity, into their standard mobility evaluation. Additional studies to examine the relationship between BW performance and functional mobility and to determine the validity of BW velocity for the assessment of fall risk in different populations and disease states are recommended.
3.5 References


Chapter 4: Dual-Task Training for Balance and Mobility in a Person with Severe Traumatic Brain Injury: A Case Study

4.1 Introduction

Deficits in sustained and divided attention are common following traumatic brain injury (TBI). The frontal and temporal lobes, which are responsible for working memory and attention, are common contusion sites after motor vehicle accidents or blunt trauma because of their proximity to bony prominences in the skull. TBI frequently results in impairment of cognition and attention. Attention is a complex cognitive process contributing to arousal, alertness, cognitive speed, working memory, and shifting and dividing attention. Divided attention is the ability to respond to multiple stimuli simultaneously, and this ability is important for real-world function.

Dual-tasks are tasks that require divided attention; these tasks pair stimuli such as two motor tasks or a cognitive task paired with a motor task (e.g., walking while talking). Impairments in divided attention have specifically been linked with deficits in functional mobility in neurological populations including traumatic brain injury (TBI), acquired brain injury, multiple sclerosis, and in elderly and healthy adults. Indeed, when challenged with dual-tasks, individuals with Parkinson’s disease demonstrate slower walking speed, shorter strides, increased double-support time and increased stride-to-stride variability. Similarly,
environments that challenge the ability to perform combined locomotor and attentional tasks can identify residual deficits following a moderate to severe TBI.12

Automaticity indicates that a level of skill has been achieved in performance of a task such that it requires little to no attention from the performer, to the extent that a second task may be performed without degradation in skill of the primary task. Walking or standing balance, which are typically automatic prior to a brain injury, are more attention-demanding following a TBI. Recent evidence suggests that impaired executive function and attention negatively impact walking function in persons with neurologic disorders.11 Indeed, lower cognitive functioning at admission to inpatient rehabilitation has been associated with lower motor scores at discharge in individuals with TBI.13 However, even in the presence of cognitive dysfunction, tasks such as gait and balance can become skilled and more automatic with sufficient practice.7,14 The use of dual-task training (DTT) may promote recovery of automaticity with basic tasks so that attention can be focused on everyday activities such as navigating an environment or carrying on a conversation without thought to the primary task of walking or balancing.

Evidence from other populations, including elderly adults,15 chronic stroke,16 and Parkinson’s disease17 indicates that cognitive-motor DTT programs improve walking speed and ability to dual-task. Recently, a virtual reality program trained cognitive-motor dual-tasks in an individual following a concussion (mild TBI), and showed improvements in dynamic and static balance.18 Similarly, DTT improved balance during cognitive activities to a greater extent than mobility training alone in healthy individuals and those with concussion.10,19 Neuropsychological training programs in subacute and chronic severe TBI focusing either on cognitive dual-tasks20 or working memory21 resulted in improvements in reaction times on visual-auditory dual-tasks.
However, it is unknown if DTT in individuals with severe TBI has value for improving safe and functional mobility, or when might be the appropriate time to initiate such DTT.

The purpose of this case study was to determine the feasibility and potential value of incorporating cognitive-motor DTT into physical therapy interventions for an individual with a severe TBI. We speculated that DTT would be a useful addition to activity-dependent recovery and might contribute to both improved performance on dual-task measures and improved automaticity with locomotor tasks. To our knowledge, the case presented herein is the most severe case described in rehabilitation intervention literature and represents the first report of a cognitive-motor training program for severe TBI.

4.2 Case Description

The study was explained to both the subject of the case study and her family, and informed consent was obtained from her parents, who were her legally authorized representatives.

4.2.1 History

TK, a 26 year old female with no significant medical history, sustained a severe TBI following a high speed motor vehicle accident. She lost consciousness and was transported to the emergency department where imaging revealed areas of contusion in bilateral temporal fossae, a subarachnoid hemorrhage in right frontal and parietal lobes and a small right temporal fossa subdural hematoma. In addition, she presented with a left fixed pupil, and non-operative left-sided clavicle, sacral, and rib fractures. Prior to this accident, TK was a healthy, college graduate with no history of head injury or substance abuse. She was physically active and participated in regular exercise and jogging. TK spent 25 days in acute care (post-injury days 1-
where a PEG was placed and a tracheostomy performed to protect the airway; her stay was complicated by difficulty weaning from the ventilator (Table 4.1). She discharged to a long term acute care center for 21 days (post-injury days 25-46), where she was able to wean from the ventilator and tolerate trach capping.

<table>
<thead>
<tr>
<th>Post-Injury Day</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Sustained TBI</td>
</tr>
<tr>
<td>0-24</td>
<td>Acute care stay</td>
</tr>
<tr>
<td>25-45</td>
<td>Long term acute care stay</td>
</tr>
<tr>
<td>46</td>
<td>Initial PT evaluation at inpatient rehabilitation facility</td>
</tr>
<tr>
<td>46-57</td>
<td>Pre-baseline phase (Standard Physical Therapy)</td>
</tr>
<tr>
<td>51</td>
<td>• Attempted pre-baseline testing; TK was unable to complete dual-task activity</td>
</tr>
<tr>
<td>58-64</td>
<td>Phase A (Standard Physical Therapy)</td>
</tr>
<tr>
<td>60</td>
<td>• Cleared PTA</td>
</tr>
<tr>
<td>65-71</td>
<td>Phase B (Standard Physical Therapy + Dual-Task Training)</td>
</tr>
</tbody>
</table>

Table 4.1 Timeline of events

TK was treated with divalproex sodium (Depakote) for seizures initially, but was weaned due to abnormal liver lab values and subsequently placed on sertraline hydrochloride, quetiapine (Seroquel) and trazodone for behavioral stabilization and mood control. TK’s only other medications were for pain management of the non-operative fractures (fentanyl, oxycodone), DVT prophylaxis (enoxaparin [Lovenox]), and stool softeners (senna, docusate sodium). Unfortunately, both acute and long-term acute stays occurred outside our medical
system, so common prognostic variables (i.e., length of coma, Glasgow Coma Scale, intracranial pressure and pupillary size\textsuperscript{21}) were unknown. However, positive prognosis is associated with a number of other variables, including number of years of education,\textsuperscript{23,24} younger age,\textsuperscript{25} high socioeconomic status, and no prior history of head injury or substance abuse,\textsuperscript{24} all of which were true for TK.

4.2.2 Examination

TK presented to the inpatient rehabilitation center for intense physical, occupational, and speech therapy on post-injury day 46. Her cognitive function was categorized as Rancho IV on the Rancho Los Amigos Level of Cognitive Function scale with left cranial nerve III palsy and no weight bearing restrictions. The Rancho Los Amigos scale is used with the TBI population to assess overall level of cognition (see 4.11, Supplemental Content 1).\textsuperscript{26} During evaluation, TK’s agitation, restlessness, perseveration, and occasional aggression limited formal assessment of pain and strength. Strength was therefore assessed through functional activity; TK was able to toe walk, (but struggled to keep her left heel off the ground), squat and rise with assistance, march with decreased left hip flexion, side step with reduced left step lengths, achieve quadruped, perform single leg stance bilaterally, kneel with bilateral upper extremity support, and half-kneel (but unable to maintain right knee up position). In summary, TK presented with mild left-sided weakness and motor delays. TK’s sitting balance was rated as “fair”, she was able to safely maintain unsupported sitting for static but not dynamic activities. Her standing balance was “poor” and required both upper extremity and physical assistance for static and dynamic tasks. TK scored 9/56 on the Berg Balance Scale, indicating a high fall risk. Transfers from bed to wheelchair/tub/toilet required moderate assistance of two persons. Bed mobility required minimal assistance. TK required 100% assistance for wheelchair mobility. Walking
required moderate assistance of two persons for safety. Gait deviations included a left Trendelenburg, decreased left step length, and left leg dysmetria during swing phase. TK was able to ascend and descend 4 steps with a hand rail and moderate assistance of one person using a step-to pattern (Table 4.2). TK’s physical impairments were complicated by her level of cognition and poor short-term memory. While she was able to follow simple motor commands, she required minimal assistance for multi-step directions for ADLs and maximal cueing to provide verbal responses. Throughout the evaluation, she was impulsive, agitated, perseverative, and easily distracted.

Taken together, TK’s main impairments were left-sided weakness and incoordination, poor balance and reduced cognition and attention to task, which led to functional limitations in gait and mobility. Based on this examination, TK’s estimated length of stay was 2-3 weeks with a discharge plan of returning home with her family. Physical therapy goals were: 1) ambulatory transfers with stand-by assistance and no device to bed, toilet, car and on/off floor; 2) walk with no device and stand-by assistance of family on smooth and uneven surfaces 1000 feet, 3 times/day with no loss of balance; 3) ascend/descend one flight of stairs with 1 railing, no device, and contact-guard assistance of a family member. Accordingly, the physical therapy (PT) plan of care included family education as well as balance, gait, and stair training.
### Functional Independence Measure scores

<table>
<thead>
<tr>
<th>Skill</th>
<th>Evaluation Day 46</th>
<th>Begin Phase A Day 58</th>
<th>Begin Phase B Day 65</th>
<th>End Phase B Day 71</th>
<th>Discharge Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bed, Chair, Wheelchair Transfer</td>
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<td>4</td>
<td>5</td>
<td>5</td>
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<tr>
<td>Toilet Transfer</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Tub/Shower Transfer</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Walk Assistance Distance</td>
<td>1 Mod Assist x2 400’ x 2</td>
<td>4 CGA-HHA 300’</td>
<td>4 CGA &gt;1000’</td>
<td>5 SBA &gt;1500’</td>
<td>5 SBA of family 1000’, 3x/day</td>
</tr>
<tr>
<td>Wheelchair Mobility</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Stair Climbing</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 4.2 Functional Independence Measure scores

<table>
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<tr>
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<td>4</td>
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</tr>
</tbody>
</table>

4.3 Outcome Measures

The following outcome measures were used to identify functional deficits and monitor progress in mobility, balance, divided attention and dual-task ability.

4.3.1 Overall Function

The Functional Independence Measures (FIM) assesses level of assistance required for physical and cognitive independence in the areas of self-care, locomotion, mobility, sphincter control, communication and social cognition. The FIM is reliable in detecting changes in independence over time and valid for predicting burden of care in TBI. 
4.3.2 Mobility

Walking speed was assessed using the 10-meter walk test, which is reliable\textsuperscript{29} and valid\textsuperscript{30} in severe TBI. The time to ascend and descend 10 stairs was recorded as a measure of functional mobility.

4.3.3 Balance

The Berg Balance Scale is comprised of 14 items, each rated 0-4 for a maximal score of 56, which reliably measures static and dynamic balance during functional tasks in individuals with brain injury.\textsuperscript{31} A score of less than 45 predicts fallers with 85% sensitivity and specificity.\textsuperscript{32}

4.3.4 Divided Attention

The Walking While Talking Test (WWTT), a test of cognitive-motor dual-task ability, was administered as described by Verghese et al;\textsuperscript{33} the participant is timed while walking 40 feet with a 180 degree turn at the midpoint under three conditions: comfortable walking speed, comfortable walking speed while reciting the alphabet (WWT-simple) and comfortable walking speed while reciting every other letter of the alphabet (WWT-complex). A cut-off of 20 seconds for the WWT-simple, and 33 seconds for the WWT-complex, predicts elderly fallers with a specificity of 89% and 96%, respectively.\textsuperscript{33} While only 44% of individuals with acquired brain injury were able to accurately perform the WWT-complex in a small pilot study\textsuperscript{7} (vs. 87% for the WWT-simple), only the WWT-complex elicited a dual-task cost, suggesting that the rote tasks such as recital of the alphabet may not be sufficiently challenging for ambulatory individuals with brain injury.\textsuperscript{7} Reliability and validity of the WWTT have not been established in persons with TBI.

The Trail Making Test A & B measures cognitive divided attention and visual tracking;\textsuperscript{34} Part A requires the patient to connect 25 numbered circles, in order, as quickly as possible
without picking up their pencil. Part B requires the patient to connect the 25 circles, now labeled with numbers (1-13) and letters (A-L) in an alternating fashion (1-A, 2-B, 3-C, etc.)\textsuperscript{34} The Trail Making Test is one of the most commonly administered neuropsychological exams and is a sensitive measurement of divided attention in persons with TBI.\textsuperscript{35} Although disease-specific norms have not been identified, normative data for healthy females aged 25-34 years old with 12-19 years of education are 23.3±8.0 for Part A and 52.8±20.4 for Part B.\textsuperscript{36}

4.4 Prognosis

Recovery following TBI is highly variable. Despite the severity of TK’s injury, she had many positive prognostic indicators including age, education, and medical history. However, poorer prognosis is associated with increased severity of injury, which is determined by length of post-traumatic amnesia (PTA). PTA represents an interval of confusion during which the patient is likely to have behavioral disturbances as well as amnesia to ongoing events\textsuperscript{34} and serves as an acute predictor of TBI outcome. PTA duration of more than 24 hours is classified as severe TBI, while PTA duration of more than 4 weeks indicates a very severe TBI. Long term outcomes indicate that patients with more than 3 weeks of PTA generally experience residual cognitive deficits, in particular poor concentration and difficulty dividing attention at 1 year post injury.\textsuperscript{24} TK’s progress toward clearance of PTA was monitored in an orientation group setting using the orientation log (O-log), a 10-item scale that evaluates place, time, and situation domains.\textsuperscript{37} This setting and procedure reliably measures the duration of PTA.\textsuperscript{38,39} TK cleared PTA on post-injury day 60, indicating a very severe brain injury.\textsuperscript{24} Despite the severity of her injury, TK’s prognosis with intensive therapy was considered to be fair for achieving functional ambulation and self-care with supervision.
4.5 Assessment of Readiness to Initiate Dual-Task Training

TK received physical therapy services 60-90 minutes per day, 5-6 days per week for a total of 26 days. Pre-baseline treatment occurred over 12 days (post-injury days 46-58) and included standard PT (see 4.12, Supplemental Content II), which outlines examples of standard PT). There is a paucity of evidence indicating the ability of individuals with TBI to benefit from DTT while in PTA, or during the period that the Rancho level of cognitive function is categorized as “confused” (Rancho IV-VI). Therefore, we assessed TK performing a dual-task activity (i.e., walking while answering an orientation question) once a week to determine her ability to participate in training. With cognitive function classified as Rancho V on post-injury day 51, TK demonstrated inability to continue walking while talking and therefore we deemed that she was inappropriate for DTT. However, with cognitive function classified as Rancho V/evolving Rancho VI on post-injury day 57, TK was deemed ready for DTT because she was able to continue walking while answering orientation questions, although she was frequently incorrect, easily distracted, and required verbal cues to continue walking. Collection of baseline outcome measures occurred the following day (day 58) and baseline phase A began (Table 4.1), despite the fact that TK had not yet cleared PTA.

4.6 Intervention

This case study included two phases; a 7-day baseline period (phase A) and a 7-day dual-task intervention period (phase B) (Table 4.1). Outcome measures were assessed prior to phase A, between phases and following phase B. The 7-day duration of each phase was determined by the estimated length of stay for TK.
4.6.1 Phase A (post-injury days 58-64)

Phase A was a continuation of the standard PT care provided pre-baseline (see 4.12, Supplemental Content II) with progressions matching TK’s functional improvements. In terms of Gentile’s Taxonomy, the standard PT interventions represented closed environment body stability and transport activities with and without inter-trial variability, with no manipulation, while progression included open environments. Phase A served as a baseline period at a time when TK was able to participate in, and might receive benefit from, DTT. However, DTT was not utilized during the baseline period. TK cleared PTA on post-injury day 60, or day 2 of phase A.

4.6.2 Phase B (post-injury days 65-71)

Phase B included standard PT (see 4.12, Supplemental Content II) supplemented with a directed intervention of DTT for 7 days. DTT occurred for an average of 15 minutes out of each 30-minute session yielding at least 180 total minutes of DTT over 7 days. Interventions included motor-motor and cognitive-motor dual-tasks (see 4.13, Supplemental Content III) that represented an increase in complexity on Gentile’s Taxonomy by including manipulation to both open and closed environments during body stability and transport activities.

As independent mobility increased, TK demonstrated multiple gait abnormalities including step asymmetry, slow self-selected speed, poor arm swing, decreased push-off and reduced left knee extension during heel strike. These deviations did not improve with verbal cueing, and TK remained fearful of walking at a normal or near-normal pace. Thus, body-weight supported treadmill training was used to increase motor demands (i.e., higher velocity) without risking injury or falls. The goal of treadmill training was to attain long duration bouts of stepping without gait deviation and physical or verbal assistance. Four sessions of treadmill training occurred during phase B of the study. During each treadmill session, TK walked an average of 20
minutes with stepping bouts of approximately 4-5 minutes. We adjusted body weight support (BWS) until gait deviations for asymmetry were minimized, then increased treadmill speed to challenge locomotion. Speed was 3.0mph - 3.5mph for the first two sessions progressing to 4.0mph by session four. TK required BWS during the first two sessions and only the safety harness was in place for sessions 3 and 4. The BWS harness system at our facility (LiteGait, Mobility Research, Tempe, Arizona, USA) does not report percentage of BWS. During all sessions, TK’s heart rate and blood pressure were monitored and remained within an expected, safe range. In accordance with other phase B sessions, cognitive tasks (see 4.13, Supplemental Content III) such as addition, subtraction and synthesis of lists were paired with treadmill walking in the same manner as overground walking. However, these tasks were only added after TK was able to maintain a steady speed on the treadmill without assistance and comprised only 60-90 seconds of each stepping bout. Despite the greater demands of treadmill training, TK participated in dual-tasks during all sessions.

4.7 Outcomes

Performance on divided attention tests (WWTT and Trail Making Test) in phase B indicated modest improvement when compared to phase A (Table 4.3). TK required fewer cues, and had fewer errors and faster completion times for these tests.
TK showed clear improvements in functional tasks (Table 4.3 & Figure 4.1A). She had a 3-fold greater rate of change in walking speed during phase B than phase A (0.35 m/s vs. 0.1 m/s, respectively). TK’s time to descend stairs was markedly reduced after DTT (7.49 s) but only modestly reduced during the baseline phase (2.66 s) (Table 4.3 & Figure 4.1B).
Figure 4.1 Changes in gait speed (A) and time to descend stairs (B) by phase. Each phase was 1 week long. While there were improvements during the baseline phase, note an increase in the rate of change during the intervention phase.

*: represents a change that is greater than the MCID for gait speed in subacute post-stroke populations and reaches the threshold of 0.8m/s established for community ambulators.

Throughout her treatment (Day 46 – Day 71), TK demonstrated improvements on the FIM (Table 2) and Berg Balance Scale as expected with intensive multidisciplinary therapy. The majority of improvement in balance and FIM scores occurred prior to phase A (Table 3) and paralleled TK’s increased activity tolerance. Treadmill walking was a successful addition to TK’s locomotor training; after two sessions TK was able to achieve full arm swing and improved gait mechanics without cueing while walking at 3.5 mph. During the fourth and final treadmill walking session, TK was able to achieve symmetrical stride lengths.
4.8 Discussion

Cognitive-motor DTT programs may be effective in ameliorating attentional deficits during mobility in populations of mild TBI\textsuperscript{18} and other neurological populations.\textsuperscript{15-19} Longitudinal evidence indicates that individuals with severe TBI with greater than 3 weeks of PTA often have residual cognitive deficits in the areas of concentration and ability to divide attention;\textsuperscript{24} thus, we anticipated that TK may benefit from cognitive-motor DTT. Although the DTT intervention itself is not unique, its application to severe TBI is novel, and allowed us to target specific attentional deficits that may have been inhibiting safe mobility and to focus upon rehabilitation of both divided attention and mobility impairment with challenging customized tasks.

To our knowledge this case represents the only report of cognitive-motor DTT in a person with severe TBI. TK’s PTA of 60 days far exceeds that of previously reported cognitive-cognitive dual-task interventions in severe TBI (7-30 days\textsuperscript{20,21}). While prior work exploring DTT in TBI has targeted subjects in the outpatient arena; the DTT intervention described was successfully administered within an inpatient rehabilitation setting over a short, clinically feasible duration of 7 days. Other studies targeting cognitive improvements\textsuperscript{20,21} included 24 – 64 hours of DTT while our study and that of Rábago and Wilken,\textsuperscript{18} which also targeted mobility and balance in mild TBI, required markedly shorter durations (3 and 6 hours respectively) to achieve gains. This short duration may highlight the importance of task specificity in DTT.

TK’s overall improvements illustrate the feasibility of supplementing standard PT with DTT in persons with severe TBI. TK’s mobility continually improved through the baseline phase when no DTT was provided, which is consistent with expected recovery observed with intensive multidisciplinary therapy. However, the change in walking speed during the dual-task phase of 0.35 m/s was considerably larger than the minimal clinically important difference (MCID) of
0.16m/s established in subacute stroke populations. Of greater importance is the relationship of increased walking speed to community ambulation. Only after phase B did TK surpass 0.8 m/s to achieve speeds sufficient for community ambulation. TK demonstrated greater gains in time to descend stairs than to ascend stairs during the dual-task phase. This outcome is perhaps due to several factors including improved eccentric control, left-sided attention, and automaticity. Both walking and stair descent are considered automatic movements and objective improvement in these activities suggests a positive relationship between DTT and functional mobility. Interestingly, while many of KT’s FIM scores plateau after Day 58 (beginning of phase A), the acquisition of a walking speed sufficient for community ambulation occurs well beyond this point. Thus, program evaluation for dual-task training after TBI must be carefully considered. It appears that objective outcome measures such as walking speed and dual-task measures (WWTT) may prove to be more sensitive indicators of gains and treatment efficacy than measures focused on burden of care.

Previous studies reported difficulty with participation in the WWT-complex; however, we did not encounter this problem. All parts of the WWTT were easily and quickly administered, even during periods when PTA had not fully resolved. Unfortunately we did not record the time to complete the complex cognitive task in sitting, which would have allowed for the calculation of dual-task cost. However, based on our experience, WWTT could be applied clinically to gain objective measures of dual-task ability in individuals with severe TBI. While TK also demonstrated improvements on the Trail Making Test, it is important to note that this pen-and-paper test does not measure improvements in functional mobility or real-world dual-task situations.
The motor and cognitive tasks utilized throughout the progression of this program were dictated by TK’s functional gains and level of cognition. Her attention to task, memory and agitation all served as guides for treatment progression, particularly for the secondary cognitive tasks. As TK’s attention improved, we were able to introduce more cognitively challenging secondary tasks. If a task was introduced that caused frustration or severe detriment in the primary task, it was abandoned for an easier task. Increasing secondary task difficulty mirrored TK’s improvement in ability to dual-task throughout phase B.

4.8.1 Limitations

Several factors beyond the addition of DTT may have contributed to the positive outcomes seen in TK. Indeed, intensive multidisciplinary therapy alone may account for the improvements in walking speed and dual-task measures. Additionally, the use of treadmill training as a progression of gait training may be challenged; it has been used in TBI populations to improve both cardiorespiratory capacity and spatiotemporal characteristics of unsupported overground walking. In this case, it allowed us to modulate speed in a safe environment. All treadmill training occurred during phase B of the study and may have contributed to the observed gains in walking speed. Finally, TK was started on amantadine on post-injury day 65, the same day that phase B began. In TBI, amantadine can be used off-label to improve sustained and divided attention, increase arousal and reduce impulsivity. Whether this drug contributed to the observed functional improvements is unclear because other mood stabilizing drugs including quetiapine and sertraline were prescribed during phase A to reduce agitation and improve cognition and alertness.

The ability of individuals who have not cleared PTA to benefit from DTT is also an important consideration. With PTA, patients may be unable to retain training effects within or
between treatments. For TK, about 33% of phase A (2 days) occurred with PTA. Thus, the lower rate of recovery during this phase may be due in part to PTA. However, because TK’s impairments in attention to task were contributing to her mobility, we felt that a program of DTT may be beneficial. These limitations represent the true conditions encountered in the clinic and the best interests of the patient, without regard to the experimental design. Overall, these clinical modifications alone or in combination with the dual-task intervention, were associated with greater gains in phase B than were seen in phase A.

4.9 Summary

This case study provides support for the feasibility and possible benefits of DTT in addition to standard PT for an individual with severe TBI. Clinically meaningful improvements were found in functional mobility and ability to dual-task as measured by the WWTT. Specific improvements seen in the intervention phase cannot be solely attributed to DTT, but this training did not disrupt the progression of recovery. Indeed, gains in locomotion and attention with the addition of DTT outpaced those seen with standard physical therapy two- to three-fold. The results of this case study are encouraging and support the need for studies with larger sample sizes to identify the optimal time to initiate DTT following TBI, further examine whether gains in functional mobility and cognition can be enhanced with DTT in severe TBI, and explore the transfer of DTT to real-world dual-task demands.
4.10 References


### 4.11 Supplemental Content I: Rancho Los Amigos Levels of Cognitive Function Scale

<table>
<thead>
<tr>
<th>Rancho Los Amigos Level of Cognitive Function</th>
<th>Behavioral Descriptors Related to Attention: &quot;A person at this level may demonstrate:&quot;</th>
<th>Recommended Strategies for Family/Friends Related to Attention</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. No Response</td>
<td>Absence of observable change in behavior and response to stimuli.</td>
<td>Keep comments and questions short and simple. Keep the room calm and quiet. Care givers should explain what is about to be done in a normal tone of voice.</td>
</tr>
<tr>
<td>II. Generalized Response</td>
<td>Response to external stimuli with physiological changes, gross body movement and/or non-purposeful vocalization.</td>
<td>Same approach as Level I.</td>
</tr>
<tr>
<td>III. Localized Response</td>
<td>Periods of waking off and on during the day. Slow and inconsistent responses, but related to type of</td>
<td>Same approach as Levels I-II. Allow extra response time and rest.</td>
</tr>
<tr>
<td>IV. Confused-Agitated</td>
<td>Alertness and a heightened state of activity. Inability to pay attention or ability to concentrate for only a few seconds.</td>
<td>Same as for Levels I-III; orient and reassure patient. Allow as much activity as is safe.</td>
</tr>
<tr>
<td>V. Confused-Inappropriate-Non-Agitated</td>
<td>Alertness and ability to attend for a few minutes at a time. Restlessness when tired or over-stimulated. Difficulty starting and completing activities. Need for step by step help to finish tasks.</td>
<td>Repeat things as needed. Help organize and initiate familiar activities. Give frequent rest periods to allow refocusing of attention.</td>
</tr>
<tr>
<td>VI. Confused- Appropriate</td>
<td>Ability to attend to familiar tasks in quiet environment for 30 minutes with some help provided. Emerging awareness of how to care for own basic needs and respond to family and others.</td>
<td>Provide help in starting and continuing activities. Repeat activities and information to improve learning and recall.</td>
</tr>
<tr>
<td>VII. Automatic-Appropriate</td>
<td>Difficulty paying attention in distracting or stressful situations. Difficulty planning, starting and following thorough with activities. Delayed processing, especially in complex/stressful situations.</td>
<td>Approach for Levels VII and VIII are the same: Provide support and guidance for problem solving and decision making. Encourage continued therapy.</td>
</tr>
<tr>
<td>VIII. Purposeful and Appropriate</td>
<td>Ability to learn new things at a slower rate. Ability to use compensatory strategies. Delayed processing or problem solving difficulties in complex and stressful situations.</td>
<td>Encourage independence within appropriate safety guidelines (physical and cognitive). Encourage the use of compensatory strategies. Encourage participation in counseling and support groups to assist with adjustment issues.</td>
</tr>
</tbody>
</table>
4.12 Supplemental Content II: Examples of Standard Physical Therapy

<table>
<thead>
<tr>
<th>Activity</th>
<th>Initial Intervention</th>
<th>Progression of Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bed Mobility</td>
<td>Rolling, scooting, supine&lt;-&gt;sit</td>
<td>Reduced assistance provided</td>
</tr>
<tr>
<td>Transfers</td>
<td>Sit&lt;-&gt;stand</td>
<td>Reduced assistance provided; addition of floor&lt;-&gt;stand and stoop&lt;-&gt;stand</td>
</tr>
<tr>
<td></td>
<td>Bed/mat &lt;-&gt; wheelchair/chair</td>
<td></td>
</tr>
<tr>
<td>Gait Training</td>
<td>Level surfaces</td>
<td>Reduced assistance provided; addition of uneven surfaces (grass/gravel/inclines) and variable surfaces (tile to carpet)</td>
</tr>
<tr>
<td>Stair Climbing</td>
<td>Bilateral handrails, non-reciprocal</td>
<td>Reduced assistance, one handrail, reciprocal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balance</td>
<td>Static standing, narrowed base-of support and quick turning/ stopping</td>
<td>Obstacle courses to challenge dynamic balance, single-leg activities, backward walking</td>
</tr>
<tr>
<td>Orientation</td>
<td>Single-task during rest breaks or prior to start of therapy session; simple orientation questions</td>
<td>Single-task; more complex or challenging questions</td>
</tr>
</tbody>
</table>
4.13 Supplemental Content III: Description of Dual-Task Training Program

The following are examples of motor-motor and motor-cognitive pairings and progressions of pairings used in the Phase B. These pairings are by no means absolute; gross and fine motor tasks were paired with various cognitive tasks throughout Phase B to create unique pairings as appropriate.

**Examples of Paired Motor-Motor Tasks**

<table>
<thead>
<tr>
<th></th>
<th>Primary Motor Task</th>
<th>Secondary Motor Task</th>
<th>Secondary Cognitive Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tandem Walk</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Progression: Heel &amp; Toe Walk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Figure of 8 Backward Walk</td>
<td>Carrying bags of different sizes (groceries)</td>
<td>X</td>
</tr>
<tr>
<td>3</td>
<td>Forward Walk (smooth/uneven surfaces)</td>
<td>Carrying objects (laundry basket, plate)</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Progression: against resistance, fast walking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Balance on a Foam Surface (static and dynamic)</td>
<td>Folding laundry</td>
<td>X</td>
</tr>
<tr>
<td>5</td>
<td>Cone Walking (single leg balance)</td>
<td>Holding hand weights</td>
<td>X</td>
</tr>
<tr>
<td>6</td>
<td>Stair Climbing Progression: Step-ups</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>7</td>
<td>Stepping to Targets Obstacles (weaving, stepping over)</td>
<td>Object toss</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Progression: Side-stepping, side-step against resistance, object pick-up (stoop &amp; squat)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued
4.13 Supplemental Content III: Description of Dual-Task Training Program Continued

**Examples of Paired Motor-Cognitive Tasks**

<table>
<thead>
<tr>
<th></th>
<th>Primary Motor Task</th>
<th>Secondary Motor Task</th>
<th>Secondary Cognitive Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tandem Walk</td>
<td>X</td>
<td>Addition</td>
</tr>
<tr>
<td></td>
<td>Heel &amp; Toe Walk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Figure of 8</td>
<td>X</td>
<td>Subtraction</td>
</tr>
<tr>
<td></td>
<td>Backward Walk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Forward Walk</td>
<td>X</td>
<td>Spelling</td>
</tr>
<tr>
<td></td>
<td>(smooth/uneven surfaces) Progression: against resistance, fast walking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Balance on a Foam Surface (static and dynamic)</td>
<td>X</td>
<td>Puzzle or manual sorting/categorization of items</td>
</tr>
<tr>
<td>5</td>
<td>Cone Walking (single leg balance)</td>
<td>X</td>
<td>Remembering lists</td>
</tr>
<tr>
<td>6</td>
<td>Stair Climbing Progression: Step-ups</td>
<td>X</td>
<td>Synthesis of lists/categories</td>
</tr>
<tr>
<td>7</td>
<td>Stepping to Targets Obstacles (weaving, stepping over) Progression: Side-stepping, side-step against resistance, object pick-up (stoop &amp; squat)</td>
<td>X</td>
<td>Match footsteps to auditory or visual cue</td>
</tr>
</tbody>
</table>
Chapter 5: Dual-Task Walking Variability is Associated with Stroop and Dual-Task Questionnaire Performance in Multiple Sclerosis

5.1 Introduction

Multiple Sclerosis (MS) is the most common progressive neurological disease\textsuperscript{1} and the main cause of neurological disability\textsuperscript{2} in young adults. Within 15 years of onset of MS, up to 50% of individuals will require assistance with walking\textsuperscript{3} and 10% are restricted to a wheelchair.\textsuperscript{4} Fall risk in MS has been linked to impairments in both balance and quality of gait.\textsuperscript{5}

When compared to healthy controls, individuals with MS, even those with short disease duration, demonstrate decreased velocity, step length, cadence and step time, as well as a wider base of support\textsuperscript{6} and increased swing time variability.\textsuperscript{7} Variability in gait parameters has been correlated with fall risk in the elderly,\textsuperscript{8-10} Parkinson’s disease (PD),\textsuperscript{11} and Alzheimer’s disease.\textsuperscript{12}

In addition to mobility deficits, 45% of individuals\textsuperscript{13} with relapsing remitting MS (RRMS), including those in the early disease stages,\textsuperscript{2} demonstrate significant cognitive dysfunction in the areas of information processing speed, divided attention, and memory.\textsuperscript{14} Impairments in cognition and mobility can lead to difficulties with performing two tasks at once (i.e., dual-tasking) such as walking and talking. Indeed, individuals with MS devote greater cognitive reserve to walking than healthy controls, resulting in even greater variability in
spatiotemporal measures of gait (e.g., step length, velocity) when walking is paired with a cognitive task, even in the early disease stage when compared to single-task conditions. Not surprisingly, poor concentration and difficulty with divided attention necessary to perform dual-tasks have been linked with accidental falls in individuals with MS.

Backward walking is required for successful completion of many daily tasks including turning and maneuvering. Indeed, eight of ten independently ambulating individuals with MS have delayed postural reactions to backward translations in standing. This is explained in part by the fact that poor proprioception underlies imbalance and falls in MS and that backward walking and stepping requires increased proprioception when compared to forward walking because of the lack of visual cues. Backward walking is not regularly assessed clinically, but could be a useful assessment in individuals with neurologic conditions; indeed, individuals with PD have increased stance variability in backward walking when compared to forward walking, while controls had similar amounts of variability in both backward and forward walking. Furthermore, our lab has previously shown that backward walking speed is sensitive to age-related changes and that speeds less than 0.6 m/s can accurately discriminate between elderly fallers and non-fallers. This suggests that backward walking could represent an important rehabilitation target for fall reduction.

Although gait changes in forward walking have been well documented in MS, backward walking in MS has not been examined. The relationship between backward walking and attention has also been briefly explored in previous studies; individuals with PD with reduced attention capabilities demonstrated slower velocity, less swing and shorter stride lengths in both forward and backward walking and during dual-tasks than those with PD with better attention capabilities and healthy controls. Thus, poor attention can exacerbate gait
deficits in both forward and backward directions\textsuperscript{26} and raises a question of whether assessment of tasks that may amplify gait variability, such as backward walking and dual-task walking, are useful tools for identification of individuals with mobility deficits in the clinical setting. While the connection between cognition and quality of dual-task forward walking has been established in older adults,\textsuperscript{27-28} such a connection has not been established with backward walking. Thus, exploration of backward walking and dual-task walking spatiotemporal measures and their relationships with baseline measures of cognition in individuals with MS warrants investigation.

The objectives of this study were to:

1. Compare spatiotemporal measures in backward walking in individuals with RRMS and age and gender matched healthy adults.

2. Compare spatiotemporal measures during forward and backward dual-task walking in individuals with RRMS and age and gender matched healthy adults.

3. Examine the relationship between neuropsychological test performances and variability of spatiotemporal measures of backward and dual-task gait in individuals with RRMS.

4. Examine the usefulness of the Dual-Task Questionnaire (DTQ), a subjective measure of dual-task ability, by exploring its relationship with neuropsychological test performance and variability of dual-task gait measures in RRMS.

5. Explore the relationship between neuropsychological test performance and calculated dual-task cost for forward and backward walking in RRMS.

6. Explore the relationships between reported falls, neuropsychological test performance, and variability of backward and dual-task gait measures in individuals with RRMS.
We hypothesized that: 1) individuals with RRMS would demonstrate significantly greater variability and slower velocity during backward walking and dual-task walking compared to healthy control subjects; 2) variability of backward walking measured with coefficients of variation would correlate with neuropsychological test performance; 3) DTQ scores, calculated dual-task cost, and falls would negatively correlate with neuropsychological test performance; 4) falls would be positively correlated with variability of backward and dual-task gait.

5.2 Methods

This study uses preliminary baseline data from an ongoing randomized controlled trial examining the effects of Dance Dance Revolution on mobility, brain plasticity and cognition in individuals with Multiple Sclerosis. This trial was approved by the Institutional Review Board. All participants signed consent forms prior to participation.

5.2.1 Subjects

Eleven volunteers with RRMS and 11 age and gender-matched healthy adults participated in this study. Individuals attended a single hour-long session where they were assessed by a physical therapist. All participants ambulated across the GAITRite System (V3.9, MAP/CIR Inc.), a 4.88 meter electronic walkway that records spatiotemporal measures (e.g., velocity, step length, double support) of gait and is reliable and valid for use in individuals with MS. Individuals ambulated across the GAITRite for four trials each under four conditions: a) forward walking comfortable speed (FW); b) forward walking with a cognitive task of serial 3 subtraction starting at 97 (FWC); c) backward walking comfortable speed (BW); and d) backward walking with a cognitive task of serial 3 subtraction starting at 95 (BWC). Participants were instructed to walk 2 meters before and after the walkway to allow for acceleration and
deceleration. Participants completed all trials without an assistive device or bracing, wearing a gait belt and guarded by a physical therapist for safety. The final three trials for each condition were averaged and the spatiotemporal parameters of gait were exported for analysis and used to calculate coefficients of variation (CV). Dual-Task Cost (DTC) was calculated by comparing time to complete FW vs. FWC, and BW vs. BWC. The DTC for gait was calculated using the following formula (FW vs. FWC provided as an example):

\[
DTC = \left( \frac{\text{Gait Time FWC} - \text{Gait Time FW}}{\text{Gait Time FW}} \right) \times 100
\]

All participants completed a self-reported fall history (number of falls in the past week, 8 weeks, and past 6 months) as well as the DTQ, a 10 item subjective questionnaire of everyday tasks involving dual-tasking, to be rated for frequency of difficulty from 0-4 (4=highest frequency). Although reliability, validity and cut-off scores have not been established, the DTQ has been shown to be sensitive to the effects of brain injury and Alzheimer’s disease; it has not been utilized in individuals with MS.

Finally, all participants completed three neuropsychological tests: a) Symbol Digit Modality Test (SDMT); b) a word generation task; and the c) Stroop Task. The SDMT is a sensitive test of processing speed, visual tracking, and rapid decision making and has established validity and reliability in MS. During the SDMT, subjects are presented with nine symbol-digit pairings and asked to match as many symbols to their corresponding number as possible in 90 seconds. The number of responses was recorded. The phonemic fluency word generation task requires participants to generate as many words beginning with the letter “F” as possible in 60 seconds. This is followed by generating words with A and S. The total number of responses in three 60 second bouts was recorded. The word generation task is a test of working memory and executive function. During the Stroop task, participants are presented with three
different conditions: the congruent condition, where the color and the word match (e.g., the word RED printed in red ink); the neutral condition, where color words are written in black ink; and the incongruent condition, where the ink color will be incongruent with the meaning of the word (e.g., the word GREEN printed in blue ink). For each condition the accuracy of the stated word or color provided was recorded. The Stroop is a test of executive function, selective attention, processing speed, and response inhibition. Individuals with MS completed these tests on the computer in addition to a number of other neuropsychological tests, while healthy controls completed a pen and paper version of these tests. The computerized and paper versions of the Stroop task vary slightly. The computer version includes a defined set of prompts and responses are not time-dependent. The paper version requires participants to provide as many responses as they can in 45 seconds. In both cases, the accuracy of the given responses was recorded.

5.2.2 Data Analysis

An a priori sample size calculation based upon forward gait velocity values for individuals with MS and healthy controls obtained from Givon et al. indicated that with a conservative two-sample t-test, 7 pairs provided 80% power to detect differences in forward walking velocity between individuals with MS and healthy controls at p=0.01 with an effect size of 2.22. We set the family-wise error rate at 0.05 to control for type I error rate. Statistical analyses were performed using SPSS version 19.0. Individuals with MS and healthy controls were compared on:

a. spatiotemporal measures of gait (normalized velocity, stride length, double support %) and coefficients of variation (CV) for stride length and double support time) for FW (Hoetelling’s $T^2$), FWC, BW, and BWC (Wilcoxon-Signed Rank Test)

b. neuropsychological test performance (Wilcoxon Signed Rank Test)
Correlational analysis was performed to examine the relationship between:

a. neuropsychological test performance and variability of BW and dual-task walking (FWC, BWC) in RRMS

b. variability of BW and dual-task walking (FWC, BWC) and the DTQ to explore the utility of this subjective tool in ambulatory subjects with RRMS

c. DTQ and neuropsychological test performance in RRMS

d. DTC of forward and backward walking and neuropsychological test performance in RRMS

e. reported falls, neuropsychological test performance and variability of backward and dual-task gait (FWC, BWC) in RRMS

P-values were Bonferroni adjusted to account for multiple outcome variables. Pairwise comparisons were used to inform functions for canonical correlation analysis, with the more liberal p<0.05 utilized for identification of potentially important contributors. Canonical correlation analysis was used to further characterize the relationship between gait variability measures and neuropsychological test performance.

5.3 Results

Individuals with MS were included in the study if they were between 30-59 years of age, carried a diagnosis of RRMS, were physically inactive (<2 hours of exercise/week) and had an Expanded Disability Status Scale (EDSS) score between 1.0 and 5.5 (fully ambulatory without a device). The EDSS was assessed by a trained neurologist. Individuals with RRMS [mean age= 44.0 ± 9.4 SD (range 31-56), 11 females, EDSS mean= 2.8 ± 1.0 SD (range 1.5-4)], and age and gender matched healthy controls [mean age=43.7± 9.3 SD (range 31-55), 11 females] participated in this
study. One participant with MS was unable to complete the BWC condition due to fatigue, thus 10 pairs were assessed for BWC.

5.3.1 Comparison of Backward Walking between Individuals with MS and Healthy Controls

There were no significant differences in spatiotemporal measures of BW between MS and healthy control groups. Individuals with MS trended toward reduced stride length (p=0.05; significance achieved at 0.01 after Bonferroni correction) (Table 5.1).

5.3.2 Comparison of Dual-Task Walking between Individuals with MS and Healthy Controls

There were no significant differences in spatiotemporal measures of dual-task walking in either forward (FWC) or backward (BWC) directions (Table 5.1). Individuals with MS trended toward reduced velocity (p=0.05) and stride length (p=0.03) and increased double support time variability (p=0.05) in FWC. These findings were not seen in BWC; however, consistent with our previous work in BW,24 the switch from FWC to BWC resulted in greater change scores in MS for both velocity (0.41m/s vs. 0.38m/s) and CV double support time (-3.7% vs. -2.8%) than in healthy controls, though these were not significantly different. (Table 5.1). Similarly, there were no significant differences in the change from FW to FWC or BW to BWC between MS and healthy controls.

5.3.3 Comparison of Forward Walking between Individuals with MS and Healthy Controls

When compared to age and gender matched healthy adults, individuals with MS demonstrated significantly greater double support time variability (p=0.001) in FW (Table 5.1). When switching from FW to BW individuals with MS demonstrated significantly greater changes in velocity (change score 0.48m/s) compared to healthy controls (change score 0.29m/s); p=0.01. (Table 5.2) BW and dual-task walking (i.e., FWC, BWC) also amplified gait variability over forward
walking in MS to a greater degree than healthy controls (see Table 5.1 and 5.2 for values used for change scores). Although not statistically significant, the greatest discrepancy was seen in the switch from FW to BWC with an increase in variability for individuals with MS of 7-8% compared to 3-5% for healthy controls.

In summary, when compared to healthy controls, individuals with MS had significantly increased double support time CV in forward walking and switching from FW to BW resulted in significantly greater reduction in velocity in individuals with MS. Surprisingly, individuals with MS were not significantly different from healthy controls in any spatiotemporal measures of BW or dual-task walking.
Table 5.1. Spatiotemporal measures and CVs of forward and backward walking and forward and backward walking with a cognitive task. All values are mean (SD). P-value is significant at p≤0.01 after Bonferroni adjustment (paired t-test for each type of walking).

<table>
<thead>
<tr>
<th></th>
<th>Multiple Sclerosis</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FW N=11</td>
<td>FWC N=11</td>
</tr>
<tr>
<td>Velocity (m/s)</td>
<td>1.27 (0.32)</td>
<td>1.09 (0.27)</td>
</tr>
<tr>
<td>Stride Length (cm)</td>
<td>122.1 (17.6)</td>
<td>118.0 (17.3)</td>
</tr>
<tr>
<td>Double Support Percent</td>
<td>30.9 (6.3)</td>
<td>31.6 (6.3)</td>
</tr>
<tr>
<td>CV of Step Time (%)</td>
<td>4.97 (2.0)</td>
<td>7.76 (4.4)</td>
</tr>
<tr>
<td>CV of Double Support Time (%)</td>
<td>7.80 (2.0)*</td>
<td>11.1 (4.4)</td>
</tr>
</tbody>
</table>

* significantly different from control at p<0.01

CV: Coefficient of Variation; FW: forward walking; FWC: forward walking with cognitive task; BW: backward walking; BWC: backward walking with a cognitive task

Table 5.2. Change scores for forward – backward walking in MS and healthy controls. All values are mean (SD). P-value is significant at p≤0.01 after Bonferroni adjustment.

<table>
<thead>
<tr>
<th></th>
<th>Multiple Sclerosis Change Score FW – BW</th>
<th>Control Change Score FW – BW</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity (m/s)</td>
<td>0.48 (0.19)</td>
<td>0.29 (0.07)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Stride Length (cm)</td>
<td>33.8 (9.6)</td>
<td>27.2 (8.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>Double Support Percent</td>
<td>-6.3 (7.3)</td>
<td>-1.8 (2.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>CV of Step Time (%)</td>
<td>-3.8 (7.3)</td>
<td>-2.3 (1.8)</td>
<td>0.51</td>
</tr>
<tr>
<td>CV of Double Support Time (%)</td>
<td>-3.7 (5.9)</td>
<td>-5.5 (3.2)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

* significantly different from control

CV: Coefficient of Variation; FW: forward walking; BW: backward walking
5.3.4 Comparison of Neuropsychological Test Performance between Individuals with MS and Healthy Controls

Individuals with MS demonstrated significantly worse accuracy on the incongruent condition of the Stroop than healthy controls (p=0.001) (Table 5.3). There was a trend toward reduced performance on the SDMT and accuracy on the neutral and congruent conditions of the Stroop (p<0.03). Performance on the word generation task was not significantly different between groups.

<table>
<thead>
<tr>
<th></th>
<th>Multiple Sclerosis</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroop Accuracy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral</td>
<td>0.966 (0.040)</td>
<td>0.999 (0.004)</td>
<td>0.020</td>
</tr>
<tr>
<td>Congruent</td>
<td>0.971 (0.035)</td>
<td>1.0 (0.000)</td>
<td>0.021</td>
</tr>
<tr>
<td>Incongruent</td>
<td>0.960 (0.020)</td>
<td>0.996 (0.014)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Symbol Digit Modality Test</td>
<td>48.6 (15.6)</td>
<td>57.9 (7.6)</td>
<td>0.024</td>
</tr>
<tr>
<td>Word Generation</td>
<td>33.2 (12.2)</td>
<td>37.3 (10.2)</td>
<td>0.370</td>
</tr>
</tbody>
</table>

Table 5.3. Neuropsychological test performance in MS and healthy controls

All values are mean (SD). P-value is significant at p≤0.01 after Bonferroni adjustment.
* significantly different from control at p<0.01

5.3.5 Relationship of Variability of Backward and Dual-Task Walking to Neuropsychological Test Performance

In healthy adults, there were no significant correlations between backward or dual-task walking variability and neuropsychological test performance with one exception. Word generation was significantly positively correlated with FWC double support time CV (ρ=0.856; p=0.001).
In individuals with MS, performance on neuropsychological tests measuring processing speed and attention (i.e. SDMT and Stroop), was strongly negatively correlated with gait variability during dual-tasks (FWC and BWC) (Table 5.4). Similar to healthy controls, the word generation task was correlated only with double support time variability in FWC. The incongruent condition of the Stroop was not correlated with any of the gait variability measures (Table 5.3), despite it being the only measure that was significantly different between healthy controls and individuals with MS (Table 5.3). To better explore the relationship between dual-task gait variability and neuropsychological test performance in RRMS, we utilized canonical correlation analysis, which manages the association between sets of multiple dependent and independent variables. Based on trending and significance in the pairwise comparisons, we used a “set” of gait variables (BWC and FWC step length CV, BWC and FWC step time CV, FWC stride length CV, and BWC and FWC double support CV) and a “set” of neuropsychological test measures (SDMT and Stroop accuracy on congruent and neutral conditions). The analysis is achieved by developing a number of canonical functions that maximize the correlation between the sets of dependent and independent variables. Each canonical function is based on the correlation between two canonical variates, one each for the dependent and independent variables. The number of canonical functions created from the sets of variables is equivalent to the number of variables in the smallest data set (in this case, the three neuropsychological test variables). The first canonical function is derived to have the highest intercorrelation possible between the two sets of variables. Successive functions are based on the residual variance; thus the correlations become smaller with each additional function, and the functions are independent of each other. In this analysis, function one achieved significance (Table 5.5). Cross loadings show that while measures of processing speed do not appear to be associated...
with a common function, backward dual-task variability is most closely associated with function one. Indeed, 48% of the variance in BWC step length, 62% of the variance in BWC step time and 65% of the variance in BWC double support time are explained by the neuropsychological test measures. Similarly, 79% of the variance in the Stroop Neutral condition is explained by the dual-task gait variability measures. BWC gait variability measures carry a direct relationship with function one while the Stroop Neutral carries an inverse relationship. This can be interpreted similarly to the pairwise comparison; poor performance on the Stroop Neutral is associated with increased variability in BWC gait measures.
### Table 5.4. Pairwise comparisons of variability of backward and dual-task walking to neuropsychological test performance and falls in MS

Spearman’s Rho; all values are ρ (p-value). *p-value <0.013 significant after Bonferroni correction (Each neuropsychological test explored across CVs for each type of walking)

<table>
<thead>
<tr>
<th>Function</th>
<th>SDMT</th>
<th>Stroop</th>
<th>Stroop</th>
<th>Stroop</th>
<th>Word</th>
<th>Falls in Past 6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step length CV</td>
<td>-0.564 (0.071)</td>
<td>-0.449 (0.166)</td>
<td>-0.474 (0.140)</td>
<td>-0.498 (0.119)</td>
<td>-0.246 (0.466)</td>
<td>0.538 (0.088)</td>
</tr>
<tr>
<td>Step time CV</td>
<td>-0.345 (0.298)</td>
<td>-0.206 (0.544)</td>
<td>-0.545 (0.083)</td>
<td>-0.112 (0.744)</td>
<td>-0.597 (0.053)</td>
<td>0.478 (0.137)</td>
</tr>
<tr>
<td>Stride length CV</td>
<td>-0.464 (0.151)</td>
<td>-0.510 (0.109)</td>
<td>-0.315 (0.346)</td>
<td>-0.633 (0.037)</td>
<td>-0.269 (0.424)</td>
<td>0.239 (0.479)</td>
</tr>
<tr>
<td>Double Support CV</td>
<td>-0.718 (0.013)*</td>
<td>-0.416 (0.203)</td>
<td>-0.582 (0.060)</td>
<td>-0.228 (0.500)</td>
<td>-0.551 (0.079)</td>
<td>0.179 (0.598)</td>
</tr>
<tr>
<td>BWC</td>
<td></td>
<td></td>
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<td></td>
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<td>n=10</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Step length CV</td>
<td>-0.455 (0.187)</td>
<td>-0.722 (0.018)</td>
<td>-0.401 (0.250)</td>
<td>-0.729 (0.017)</td>
<td>-0.140 (0.700)</td>
<td>0.494 (0.147)</td>
</tr>
<tr>
<td>Step time CV</td>
<td>-0.612 (0.060)</td>
<td>-0.821 (0.004)*</td>
<td>-0.596 (0.069)</td>
<td>-0.642 (0.045)</td>
<td>-0.492 (0.148)</td>
<td>0.494 (0.147)</td>
</tr>
<tr>
<td>Stride length CV</td>
<td>-0.345 (0.328)</td>
<td>-0.525 (0.119)</td>
<td>-0.320 (0.367)</td>
<td>-0.430 (0.215)</td>
<td>-0.103 (0.776)</td>
<td>0.418 (0.230)</td>
</tr>
<tr>
<td>Double Support CV</td>
<td>-0.758 (0.011)*</td>
<td>-0.778 (0.008)*</td>
<td>-0.803 (0.005)*</td>
<td>-0.405 (0.245)</td>
<td>-0.456 (0.185)</td>
<td>0.570 (0.086)</td>
</tr>
<tr>
<td>FWC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step length CV</td>
<td>-0.609 (0.047)</td>
<td>-0.369 (0.264)</td>
<td>-0.197 (0.561)</td>
<td>-0.051 (0.881)</td>
<td>-0.232 (0.492)</td>
<td>-0.120 (0.726)</td>
</tr>
<tr>
<td>Step time CV</td>
<td>-0.682 (0.021)</td>
<td>-0.860 (0.001)*</td>
<td>-0.479 (0.136)</td>
<td>-0.428 (0.189)</td>
<td>-0.401 (0.222)</td>
<td>0.299 (0.372)</td>
</tr>
<tr>
<td>Stride length CV</td>
<td>-0.809 (0.003)*</td>
<td>-0.711 (0.014)</td>
<td>-0.446 (0.169)</td>
<td>-0.177 (0.603)</td>
<td>-0.478 (0.137)</td>
<td>0.000 (1.00)</td>
</tr>
<tr>
<td>Double Support CV</td>
<td>-0.764 (0.006)*</td>
<td>-0.767 (0.006)*</td>
<td>-0.789 (0.005)*</td>
<td>-0.079 (0.817)</td>
<td>-0.752 (0.008)*</td>
<td>0.359 (0.279)</td>
</tr>
</tbody>
</table>

### Table 5.5. Canonical correlations to examine the relationship between gait variability and neuropsychological test performance in MS

Sets used to create the functions: set 1=dual- task variability measures vs. set 2=neuropsychological test performance measures
5.3.6 Relationship between Dual-Task Questionnaire and Gait Variability and Neuropsychological Test Performance

There were no significant correlations between the DTQ and performance on any of the neuropsychological tests (p-value <0.01 required for significance after correction) or with any of the gait variability measures in BW, BWC or FWC in healthy adults (p-value <0.013 required for significance after correction). However, in individuals with MS, the DTQ was significantly inversely correlated with performance on the Stroop neutral condition (ρ=-0.803, p=0.003) and trended toward significance on the SDMT (ρ=-0.706, p=0.015). DTQ was also positively correlated with double support time variability in both BW and BWC in individuals with MS (ρ=0.843, p=0.001 and ρ=0.754, p=0.012 respectively). That is, higher scores on the DTQ (more subjective difficulty with dual-tasks) was associated with poorer performance on neuropsychological tests and higher gait variability in both BW and BWC.

5.3.7 Relationship of Dual-Task Cost and Neuropsychological Test Performance

There were no significant correlations between any of these DTCs and neuropsychological test performance in healthy adults or individuals with RRMS. Values for RRMS are reported in Table 5.6.

5.3.8 Relationship of Falls with Variability of Backward and Dual-Task Walking and Neuropsychological Test Performance

Individuals reported falls in the past week, 8 weeks and 6 months. None of the healthy controls reported falls. Only one subject with MS reported a fall in the past week, while two subjects reported falls in the past 8 weeks. We opted to assess the relationship of falls over the past 6 months with gait variability since four of eleven individuals with MS reported falls in the past 6 months. Individuals were dichotomized; those who reported 1 or more falls in the past 6
months were considered “fallers” while those with zero falls in the past 6 months were “non-fallers”. There was no significant relationship between falling in the past 6 months and gait variability. (Table 5.4). However, falls in the past 6 months were trending toward an inverse correlation with performance on the Stroop Neutral condition ($\rho=-0.679; p=0.021$) (Table 5.6), which was also significantly related to double support time gait variability in BWC and FWC (Table 5.4).

<table>
<thead>
<tr>
<th></th>
<th>Stroop Accuracy Neutral</th>
<th>Stroop Accuracy Congruent</th>
<th>Stroop Accuracy Incongruent</th>
<th>Symbol Digit Modality Test</th>
<th>Word Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls Past 6 Months</td>
<td>-0.679 (0.021)</td>
<td>-0.307 (0.358)</td>
<td>-0.122 (0.720)</td>
<td>-0.239 (0.479)</td>
<td>-0.479 (0.136)</td>
</tr>
<tr>
<td>DTC FW-FWC</td>
<td>-0.085 (0.805)</td>
<td>-0.280 (0.403)</td>
<td>-0.033 (0.924)</td>
<td>-0.145 (0.670)</td>
<td>-0.087 (0.800)</td>
</tr>
<tr>
<td>DTC BW-BWC</td>
<td>-0.082 (0.823)</td>
<td>0.191 (0.596)</td>
<td>-0.137 (0.706)</td>
<td>0.018 (0.960)</td>
<td>0.146 (0.688)</td>
</tr>
</tbody>
</table>

Table 5.6. Relationship of falls in the past 6 months and dual-task cost to neuropsychological test performance in RRMS

Spearman’s Rho; all values are $\rho$ (p-value). P-value <0.01 considered significant with Bonferroni adjustment.

**5.4 Discussion**

This is the first study to formally assess backward walking and backward dual-task walking in MS. Additionally, this study expands and strengthens the current knowledge base exploring baseline differences in walking and cognition in individuals with MS and healthy controls; rather than a convenience sample, a rigorous matching process was utilized to reduce variability and eliminate bias. Gait variability in ambulatory individuals with MS is associated
with performance on neuropsychological tests of attention and processing speed. Consistent with previous literature in MS, dual-task walking amplified variability of spatiotemporal measures of gait. BW also resulted in an increased amplification of gait variability in MS, which has been previously reported only in PD. This highlights the importance of cognitive function in mobility and suggests a potential role for cognitive training in exercise prescription.

We hypothesized that individuals with MS would demonstrate significantly greater variability and slower velocity during backward walking and backward walking with a cognitive task compared to healthy control subjects. We found a significant difference in the change score for FW – BW for velocity; individuals with MS demonstrated a significantly larger change in velocity than their healthy counterparts. Otherwise, there were no significant differences between groups for BW and BWC velocity or gait variability. To further explore gait variability, we examined change scores within group between FW and both BW and DT walking conditions (FWC and BWC). Both conditions of DT walking as well as BW amplified gait variability in MS to a greater degree than healthy controls; however, these values were not statistically significant. The lack of significance is perhaps due in part to large standard deviations in the MS group. Additionally, we were powered to detect differences in forward walking, but may be underpowered to detect differences in backward walking between groups. We only observed a significant difference in FW double support time variability between MS and healthy adults. This was especially interesting since our sample size calculation was based on FW gait speed for individuals with RRMS that had similar disability levels to those in our study and were measured in the same way (i.e., GAITRite). To examine the sample size required to achieve significance in dual-task and BW velocity, we performed a post-hoc power analysis. For velocity in all three conditions (BW,FWC, BWC), we were underpowered (power: 28.1%, 13.0%, 26.6%; effect size:
0.93, 0.67, 0.96 respectively) to detect changes between individuals with MS and healthy controls. To achieve 80% power, a sample size of 29, 54, and 28 per group would be required with a conservative two sample t-test and p=0.01 for BW, FWC and BWC respectively.

We further hypothesized that variability of backward walking measured with CV would correlate with neuropsychological test performance. The results confirmed our hypothesis; accuracy on the Stroop neutral and congruent conditions was strongly associated with BWC and FWC variability (Table 5.4). Performance on the SDMT was inversely correlated with gait variability in BW, BWC and FWC (Table 5.4). Our results suggest that measures of processing speed (i.e., SDMT, Stroop) are more closely associated with BW and dual-task gait variability in individuals with MS than other measures such as fluency. This finding is consistent with studies in older adults\(^\text{37}\) and individuals with Alzheimer’s disease\(^\text{38}\) demonstrating that gait variability was highly correlated with measures of processing speed.

This is the first study to apply the subjective DTQ to individuals with MS. We noted significant correlations with accuracy on the Stroop neutral condition as well as variability of BW and BWC. This suggests that individuals with MS may have insight into their deficits with dual-tasking and warrants further exploration of the utility of the DTQ as a clinical test of gait variability and dual-task deficits in individuals with MS.

Change scores reveal a larger change in velocity when switching from FW to FWC for MS (0.18 m/s) compared to healthy controls (0.01 m/s) while other spatiotemporal parameters remain relatively stable (Table 5.1). The switch from BW to BWC resulted in similar velocity declines (0.1m/s) in both groups; however, the switch did result in large increases in variability in the MS group while the variability remained stable in the healthy control group. The results for the FW to FWC switch are consistent with previous studies in MS, where gait speed was
shown to be the variable most affected by dual-task conditions.\textsuperscript{15} The degree of decrement resulting from dual-tasking in MS was not related to disease severity or duration, as might be expected, but rather to levels of fatigue and measures of general cognitive functioning.\textsuperscript{15} This is in contrast to individuals with PD,\textsuperscript{39} older adult fallers\textsuperscript{40} and individuals with Alzheimer’s disease,\textsuperscript{41} where the effect of dual-tasking on gait speed is similar to the decrement seen in healthy controls.

Poor performance on neuropsychological tests was significantly associated with increased gait variability during dual-task walking. Our work is supported by previous work in traumatic brain injury, which has suggested a role for cognition in dual-tasking.\textsuperscript{42} Indeed, individuals with TBI with greater deficits in psychosocial functioning performed worse on neuropsychological tests measuring dual-task ability than those with lesser deficits.\textsuperscript{42} In elderly adults, increasing the complexity of the cognitive task paired with gait resulted in decreasing gait speeds,\textsuperscript{28} and regression analysis indicated that underlying cognitive abilities contributed significantly as the complexity of the secondary task increased.\textsuperscript{28} Indeed, gait variability during dual-task walking has been significantly correlated with performance on neuropsychological tests of executive function, attention and processing speed in individuals with Alzheimer’s disease.\textsuperscript{38} Impairments in attention and executive function may prevent individuals with MS from allotting appropriate attentional resources to balance and gait, reduce their ability to confront and adapt to challenging environments, contribute to increased gait variability, and may be linked to increased fall risk, which is also seen in the elderly, PD\textsuperscript{39} and Alzheimer’s disease.\textsuperscript{41}

Despite our a priori sample size calculation, the present study appears to be limited by small sample size; however, we were still able to demonstrate robust relationships between gait
variability and neuropsychological test performance in RRMS. Indeed, canonical correlation analysis demonstrates that 79% of the variance in performance on the Stroop neutral condition is explained by dual-task gait variability, while up to 65% of the variance in gait variability measures is explained by performance on neuropsychological tests. This study only examined one type of cognitive dual-task (serial 3 subtraction); it is possible that a fluency dual-task would be more related with word generation test performance. Although we reported no relationship between falls in the past 6 months and gait variability, this is likely because the majority of our subjects were not frequent fallers. Indeed seven of eleven subjects reported no falls in the past 6 months. We anticipated that falls would be correlated with gait variability in BW and BWC as both our previous work and the work of others has suggested that BW velocity may be a sensitive indicator of falls in elderly adults\textsuperscript{24,44} and that BW and dual-tasks increase gait variability in individuals with neurologic conditions.\textsuperscript{23,45-46} It appears that more research is necessary to determine if tasks that amplify gait variability may be useful in identifying deficits and assessing fall risk in individuals with MS.

This study highlights the importance of examining gait variability in MS; clinically useful activities such as BW or dual-task walking that amplify gait variability may identify early deficits in mobility or cognition that could contribute to fall risk. Gait variability can be challenging to objectively examine clinically without expensive equipment such as 3D motion capture or GAITRite. Strong correlations between gait variability, neuropsychological test performance and the DTQ suggest that increased gait variability may be related to cognitive deficits and perceived dual-task ability in MS. This is the first study to provide evidence for several clinically useful tests that correlate with gait variability for examining deficits in individuals with MS.
This study further clarifies the important contribution of baseline cognition to gait
deficits and the potential for therapy utilizing cognitive training in addition to mobility training.
While there has been limited research to suggest benefits from dual-task training in individuals
with neurologic diseases,\textsuperscript{29,47-49} there have been, to date, no intervention studies exploring dual-
task training in MS. Future research should further elucidate the role of early cognitive deficits in
MS as potential contributor to mobility deficits. This should include larger sample sizes and the
examination of additional cognitive tasks, such as fluency, during gait. However, at present, we
endorse that the clinical evaluation of gait should go beyond forward walking assessment to
include functional locomotor tasks that challenge dynamic balance and amplify gait variability,
such as dual-task walking and backward walking.
5.5 References


Chapter 6: SMA Connectivity May Be Associated With Dual-Task Walking in Multiple Sclerosis

6.1 Introduction

Multiple Sclerosis (MS) is a chronic, autoimmune disease of the central nervous system affecting over 400,000 Americans with an annual health care cost in the billions. MS is the most common progressive neurological disease in young adults. Individuals with MS often experience declines in walking ability and cognitive dysfunction, particularly with attention, processing speed, and memory. Indeed, 22-25% of individuals with MS report specific attentional problems. The simplest form of attention, attention span, is generally intact, while the more complex aspects, such as selective, divided, or alternating attention, are most often impaired. Divided attention is the ability to respond to multiple stimuli simultaneously and can encompass both motor-motor and motor-cognitive tasks. Individuals with MS have difficulty with divided attention during gait; not surprisingly, cognitive dysfunction has been identified as a risk factor for accidental falls in MS.

Magnetic resonance imaging (MRI) is the most commonly used paraclinical assessment tool, both for investigation of underlying pathology and evaluation of disease progression in MS. Diffusion tensor imaging (DTI) is a technique that quantifies the amount of non-random water diffusion within tissues to provide an \textit{in vivo} model of white matter integrity and
microstructural damage. The diffusion of molecular water in grey matter is highly isotropic (i.e., the same in all directions), while in white matter, diffusion is often restricted to a particular direction. This anisotropy is dictated by axonal cell membranes, myelin sheaths, neurofilaments, and other structures with the direction of highest diffusivity coinciding with the tissue’s fiber tract axis. Diffusion tensors are often visualized as ellipsoids with the size and shape reflecting the degree of diffusion along each principle axis. The principle axes correspond to the eigenvectors of the tensor (e1, e2 and e3) and the relative size of each axis is determined by the eigenvalues of the tensor (λ1, λ2 and λ3). (Figure 6.1).

Figure 6.1. Elliptical representation of a diffusion tensor; the principle axes correspond to the eigenvectors of the tensor (e1, e2 and e3) and the relative size of each axis determined by the eigenvalues of the tensor (λ1, λ2 and λ3).

Anisotropy is highest in compact white matter pathways where the fiber bundles are oriented in parallel, such as the corpus callosum or pyramidal tracts. Higher fractional anisotropy (FA) value and lower mean diffusivity (MD) value indicates a greater degree of white matter integrity. FA is the most commonly used anisotropy index in the literature and the FA
index is normalized to values of 0 (isotropic) to 1 (anisotropic). Compared to healthy controls, individuals with relapsing remitting MS (RRMS) have significantly lower FA values in the corticospinal tracts,\textsuperscript{16-17} and corpus callosum\textsuperscript{18} and these FA values correlate well with both motor\textsuperscript{17} and cognitive\textsuperscript{18-19} impairment. In addition, the mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) provide useful information about the tract or white matter region of interest. The AD is equivalent to the primary eigenvalue ($\lambda_1$), indicates the direction of highest diffusivity and coincides with the fiber tract axis.\textsuperscript{20-21} The RD is calculated by averaging the mean of the other two eigenvalues ($\lambda_2$ and $\lambda_3$). Animal work suggests that the AD may be specific to axonal degeneration while the RD may be modulated by myelin.\textsuperscript{20} The MD is the average of all three eigenvalues, and is therefore not indicative of direction. The MD is inversely related to the FA. DTI studies in MS have demonstrated decreased FA and increased MD in regions that appear normal on conventional MRI\textsuperscript{21-28} suggesting damage beyond the resolution of conventional MRI.\textsuperscript{10}

Diffusion images can also be used to perform tractography, the only available tool for identifying and measuring white matter pathways non-invasively and \textit{in vivo}.\textsuperscript{29} Tractography identifies the path along which diffusion is least hindered and thus allows for the exploration of connectivity and for the measurement of diffusivity along a tract of interest. MS lesions can result in a loss of connectivity, a term that describes the physical connections linking brain regions\textsuperscript{29} but no studies have examined the relationship between clinical tests of dual-task and neural connectivity. The supplemental motor area (SMA) is active during complex motor tasks,\textsuperscript{30} cognitive dual-tasks,\textsuperscript{31} and tasks requiring interlimb coordination,\textsuperscript{32} but its relationship to clinical measures of motor-cognitive dual-task has not been explored. The \textit{objective} of this study was to examine the relationship between clinical measures of dual-task performance (Walking While
Talking Test, TUG Cognitive, walking with a subtraction task) and measures of diffusivity (FA, MD, RD, AD) in the interhemispheric SMA tract. Although this has not been previously explored, we hypothesized that SMA interhemispheric connectivity would correlate with a clinical measure of dual-task ability. This is the first study to explore lower extremity motor-cognitive dual-tasks in relationship to imaging metrics in MS and the first to examine the relationship between the SMA interhemispheric tract and clinically useful motor measures in individuals with MS.

6.2. Methods

This study uses preliminary baseline data from an ongoing randomized controlled trial examining the effects of Dance Dance Revolution on mobility, brain plasticity and cognition in individuals with Multiple Sclerosis. This trial was approved by the Institutional Review Board. All participants signed consent forms prior to participation.

6.2.1 Participants

Eleven volunteers with RRMS participated in this study. All subjects were screened for any contraindications for MRI participation. All eligible subjects participated in a mobility assessment and a multi-modal 3T MRI. This study was approved by the Institutional Review Board. All participants signed consent forms prior to participation.

6.2.2 Mobility Measures

Mobility measures included walking (forward and backward dual-task walking (walk with subtraction)), the Walking While Talking Test, and the TUG Cognitive. All participants ambulated across the GAITRite System (V3.9, MAP/CIR Inc.), which records spatiotemporal measures (e.g., velocity, step length, double support) of gait and is reliable and valid for use in
individuals with MS. Individuals ambulated across the GAITRite for four trials of each of four conditions: a) forward walking comfortable speed (FW); b) forward walking with a cognitive task of serial 3 subtraction starting at 97 (FWC); c) backward walking comfortable speed (BW); and d) backward walking with a cognitive task of serial 3 subtraction starting at 95 (BWC). Participants were instructed to walk 2 meters before and after the walkway to allow for acceleration and deceleration. Participants completed all trials without an assistive device or bracing, wearing a gait belt and guarded by a physical therapist. The final three trials for each condition were averaged and the spatiotemporal parameters of gait were exported for analysis and used to calculate coefficients of variation (CV).

The Walking While Talking Test (WWTT) is a reliable and valid test to identify older individuals at high risk for falls. The test is performed and timed under three conditions: 1) walk 40 feet with a 180° turn at the midpoint; 2) condition 1 + recite the alphabet aloud (WWT-simple); 3) condition 1 + recite alternate letters of the alphabet aloud (WWT-complex). Poor performance on the WWT-simple and complex was strongly predictive of falls; a cut-off of 33 seconds for the WWT-complex predicted elderly fallers with a specificity and sensitivity of 95.6% and 38.5% respectively.

The Timed Up and Go (TUG) is a common test to examine mobility in elderly. Time to complete the TUG, which requires standing from a chair, walking 10 feet, turning, walking back and sitting down, is correlated with level of mobility in elderly adults. The TUG has been utilized in MS populations and correlates with longer walking tests. The TUG Cognitive is the TUG while performing a subtraction task; this modification of the TUG measures dual-task performance and is sensitive and specific for identifying fall risk in elderly. A time of >15
seconds to complete the TUG Cognitive accurately identifies elderly fallers with an 86.7% prediction rate. The TUG Cognitive accurately predicts fallers in MS with a sensitivity of 73%.

6.2.3 MRI Acquisition

Participants were scanned in a Siemens 3T Magnetom Trio scanner. High resolution structural images were collected using a 3D magnetization prepared rapid gradient echo imaging (MPRAGE) protocol with 160 contiguous axial slices (TE/TR/TI 4.68/2000/950 ms), with 256mm FOV and a 1.0x1.0mm² in-plane resolution. To identify white matter lesions, we acquired 60 T2-weighted fluid attenuated inversion recovery (FLAIR) axial slices (TE/TR 7.3/14000ms) with a 256mm FOV and 0.8x0.8mm² in-plane resolution.

Diffusion tensor images were acquired in the axial plane (TE/TR 85/8300ms) with diffusion gradients in 64 directions. The field of view was 288mm resulting in voxel sizes of 2.0x2.0mm². The b values were 0 and 800s/mm².

6.2.4. Imaging Analysis

Lesion Load Analysis

T2 FLAIR images were processed using Jim 6.0 (Xinapse Systems, www.xinapse.com), a semi-automated segmentation tool that localizes white matter hyperintensities. Lesions were identified manually and used to create a region of interest mask that was applied to a fuzzy connectivity algorithm, thus creating a 3D representation of the identified lesions using the fuzzy affinity between neighboring voxels. Fuzzy connectedness compares each manually identified region of interest’s size and location to an MS lesion template, while the probability weighting takes into account the similarities in intensity values and the degree of adjacency among voxels. We used pre-determined values suggested by the Jim software to set the fuzzy connectedness threshold at 0.62 and the associated probability weighting at 0.25.
Diffusion Tractography Reconstruction

The diffusion-weighted images were preprocessed using FMRIB’s Diffusion Toolbox (FDT). The raw data were corrected for head movement and eddy current distortion. The tensor model was then fitted to the preprocessed diffusion images to generate FA and eigenvector 1-3 images. The Harvard-Oxford Cortical Probability Atlas for tractography was used to identify the SMA ROI. Masks were created to standardize tractography across subjects. Seed and target masks were created in the sagittal plane to track from the left SMA to the right SMA. Eighty-eight voxel seed and target masks were placed 8mm from the midline in the juxtapositional lobule cortex (Harvard-Oxford Cortical Probability Atlas). Both a 119-voxel mask corresponding to the middle one-third of the corpus callosum and the subject’s individual white matter mask were used as waypoint masks. An axial/frontal exclusion mask was applied below the level of the corpus callosum to improve the sensitivity of the tractography. Finally, a termination mask was applied 2mm lateral to the target mask, and probabilistic tractography was used to model the SMA interhemispheric tract.

To determine specificity of the SMA tract’s relationship to dual-task walking, we chose a control interhemispheric tract that would be unlikely to be involved in dual-tasking but crosses at the corpus callosum. The Harvard-Oxford Cortical Probability Atlas was used to localize V4. Forty voxel seed and target masks were created in the sagittal plane in the occipital fusiform gyrus to track from left V4 to right V4. A 120 voxel mask corresponding to the posterior one-third of the corpus callosum and the subject’s individual white matter mask were used as waypoints. An axial exclusion mask placed below the supratentorium at the level of the superior cerebellum was applied. Finally, a termination mask was applied 2mm lateral to the target mask, and probabilistic tractography was used to model the V4 interhemispheric tract.
6.2.5 Statistical Analysis

Statistical analyses were performed using SPSS version 19.0. We set the family-wise error rate at 0.05 to control for type I error rate. Bivariate correlations were performed to determine if a relationship was present between lesion volume, area or number and measures of dual-task ability (FWC, BWC, WWTT, TUG Cognitive) or the EDSS. Correlational analysis was used to examine the relationship between:

a) Spatiotemporal measures forward and backward dual-task walking velocity and SMA interhemispheric tract diffusion parameters (fractional anisotropy (FA) and axial, radial and mean diffusivity (AD, RD and MD respectively)

b) Clinical measures of dual-task ability (WWTT, TUG Cognitive) and SMA interhemispheric tract diffusion parameters

c) Both spatiotemporal measures of dual-task walking and clinical measures of dual-task ability and V4 interhemispheric tract diffusion parameters to determine the specificity of the SMA tract.

P-values were Bonferroni adjusted to account for multiple outcome variables. Linear regression was used to identify the predictive value of the variables with the strongest relationship identified in the correlation analysis described in (a) and (b) above.

6.3 Results

Individuals with MS were included in the study if they were between 30-59 years of age, had a diagnosis of RRMS, were physically inactive (<2 hours of exercise/week) and had an Expanded Disability Status Scale (EDSS) score between 1.0 and 5.5 (fully ambulatory without a
device). The EDSS was assessed by a trained neurologist. Eleven females with RRMS [mean age=44.0 ± 9.4 SD (range 31-56) EDSS mean= 2.8 ± 1.0 SD (range 1.5-4)] participated in this study.

6.3.1 Clinical dual-task measures

Clinical measures of dual-task ability assessed were walking velocity during forward (FWC) and backward walking (BWC) when paired with a secondary cognitive task (serial 3 subtraction), the Walking While Talking Test (WWTT) and the TUG Cognitive (Timed Up and Go Cognitive). Velocity in FWC was on average 1.09 ± 0.27m/s while BWC velocity was 0.68 ± 0.26m/s. One individual was unable to complete the BWC trials secondary to fatigue, so only 10 individuals were analyzed for this measure. Average time to complete the WWTT was 14.98 ± 3.80s and average time on the TUG Cognitive was 10.24 ± 3.20s.

6.2.2 Lesion Load Analysis

The total lesion volume for all regions: mean ± SD (range) was 7685.4 ± 4905.3 (22.2 – 16365.7)mm³. The total number of lesions per patient in all regions: mean± SD (range) was 19 ± 13 (1 - 43). The lesions were found predominantly in juxtacortical regions 11 ± 11 (0 –33) and periventricular regions 8 ± 3 (1 –14). Only two participants had evidence of infratentorial lesions. Total lesion area, volume, and number did not correlate with clinical measures of dual-task (FWC velocity, BWC velocity, TUG Cognitive, WWTT) (p<0.2 in all cases) nor were they related to EDSS score (p>0.2 in all cases). A lesion probability map was created by registering the T2 FLAIR images to standard space. Lesions were manually drawn in FSLview, and all lesion masks were binarized. The registered, binarized, lesion masks from all participants were then added using FSLmaths to create a single probability map with values ranging from 0 to 8, indicating the number of participants with overlapping lesions in the tract of interest (Figure 6.2). There is some overlap of lesions with the tract of interest; however, the majority of overlapping voxels
were in 10-20% of subjects. We were able to track the SMA on all participants; thus, a lesion in part of this tract is included in the measurements obtained, and contributes to the relationship seen with clinical measures of dual-task. Axial and sagittal slices from the map indicate that the bulk of MS lesions in the participants were not near the SMA interhemispheric tract of interest, and overlap of the tract is minimal (Figure 6.3).
Figure 6.2. Lesion probability map showing the interhemispheric SMA tract (blue) of a representative subject overlaid with lesions from all MS participants (scaled red to yellow to indicate the number of subjects with lesions overlapping in this area, see color bar) in MNI152 coordinate space (slices identified by Y coordinate). All images are in radiological convention.
Figure 6.3. Sagittal and axial slices through the interhemispheric SMA tract (blue) of a representative subject demonstrate that the bulk of MS lesions are not near the tract of interest, and overlap of the tract is minimal. Lesion overlap is indicated by the color bar, with the color indicating the number of subjects with lesions in this area. All images are in radiological convention and displayed in MNI152 coordinate space.
6.3.3 Diffusion Tractography

There were moderately strong correlations identified between interhemispheric SMA (Figure 6.4a) tract-specific diffusivity measures and forward dual-task walking velocity, a clinical measure of dual-task. In particular, axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD) demonstrated moderately strong correlations with forward dual-task walking velocity (Table 6.1). Since AD, RD and MD are highly correlated, resulting in multicollinearity and precluding multiple regression analysis, we chose to explore the strongest correlation (i.e., FWC velocity vs. AD) with linear regression to determine the predictive value of AD. Linear regression demonstrates a strong, significant relationship between forward dual-task walking velocity and AD of the SMA interhemispheric tract ($R^2 = 0.436$, $p=0.014$), indicating that AD explains 43.6% of the variance in forward dual-task walking velocity (Figure 6.5). Further exploration of non-linear relationships and the residual plot confirms that non-linear relationships do not explain these data and normality is present in the residual plots. Given the small sample size, this result shows promise and merits further exploration.
To examine the specificity of the interhemispheric SMA tract diffusion measures, we explored a control interhemispheric tract that we would not expect to be involved in clinical measures of dual-task. We modeled the V4 interhemispheric tract (Figure 6.4b), which crosses in the splenium, and found no significant or trending correlations between any of the tract-specific diffusivity measures and the clinical measures of dual-task.

Figure 6.4. Tractography models in representative subjects demonstrating successful modeling of the (a) interhemispheric SMA (coronal view) and (b) interhemispheric V4 (axial view) connectivity.
### Table 6.1. Relationship between clinical dual-task measures and interhemispheric SMA tract-specific parameters

<table>
<thead>
<tr>
<th>Measure</th>
<th>AD (λ1)</th>
<th>RD (λ2 + λ3)/2</th>
<th>MD (λ1 + λ2 + λ3)/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forward Dual-Task Velocity (m/s)</td>
<td>-0.660</td>
<td>-0.595</td>
<td>-0.552</td>
</tr>
<tr>
<td>Backward Dual-Task Velocity (m/s)</td>
<td>-0.565</td>
<td>-0.432</td>
<td>-0.482</td>
</tr>
<tr>
<td>WWTT-complex (s)</td>
<td>0.277</td>
<td>0.189</td>
<td>0.237</td>
</tr>
<tr>
<td>TUG Cognitive (s)</td>
<td>0.328</td>
<td>0.047</td>
<td>0.124</td>
</tr>
</tbody>
</table>

Pearson’s correlation R values.

![Graph](image)

**Figure 6.5** The relationship between interhemispheric SMA axial diffusivity and forward dual-task walking velocity.
6.4 Discussion

This is the first study to examine the relationship between the SMA interhemispheric tract and clinically useful motor measures in individuals with MS, and the first to explore lower extremity motor-cognitive dual-tasks in relationship to imaging metrics in MS.

The results of the DTI data revealed that individuals with RRMS who demonstrated faster forward dual-task walking speeds (i.e., higher velocities) tended to have lower interhemispheric SMA AD, RD and MD values (Table 6.1). Linear regression showed a significant relationship between FWC velocity and interhemispheric AD, suggesting that dual-task performance in forward walking may depend on the integrity of the SMA interhemispheric tract. This relationship was not observed in the V4 interhemispheric tract, further supporting that the SMA tract may be related to dual-task walking in individuals with MS. Although we cannot definitively implicate the interhemispheric SMA tract in dual-task, it points toward great potential for white matter tractography to predict functional performance and provide important information about recovery patterns in MS.

DTI can be challenging to interpret in MS due to the unpredictable combination of axon loss, gliosis, inflammation and demyelination, which may result in competing influences on the diffusion tensor. Our results showed no correlation between FWC velocity and FA, but moderate correlations between FWC velocity and AD, MD and RD values. Although FA is the most commonly reported diffusivity measure, it is considered a non-specific marker of pathology. Indeed, FA has been shown to correlate poorly with actual fiber anisotropy, compared to MD which correlates well with individual fiber MD. FA is problematic as it is influenced by the number of dominant fiber directions within each voxel, the anisotropy of each fiber, and partial volume effects from neighboring grey matter. Indeed, our tract of interest
passes through the corpus callosum, which is known to have a crossing fiber structure within a single voxel, that could skew FA values. Thus, FA may be suboptimal for use in disease processes that affect myelination. Our work supports newer work suggesting that both MD and FA metrics should be estimated to maximize the findings from DTI.

Only one other study has explored the interhemispheric SMA pathway in MS. They reported that the nine hole peg test, a functional measure of hand coordination and dexterity, was significantly correlated with transverse diffusivity ($\lambda_2$) ($p<0.02$). The authors concluded that diffusivity along the primary axis ($\lambda_1$) appears to be less affected by MS disease activity than transverse diffusivity. To examine transverse diffusivity in our dataset, we correlated $\lambda_2$ with FWC velocity and found similar results ($R=-0.574$ $p=0.065$) to the analysis of FWC velocity with AD, RD and MD reported in Table 6.1.

6.4.1 Limitations

This study is limited by small sample size. In addition, lesion load analysis demonstrated a high variability between the number and size of lesions across participants that was unrelated to functional performance. While this may be related to the inherent variability of MS lesions, it is also likely that many of our participants had lesions in their spinal cord, which were not evaluated in this study. As shown in Figure 6.3, the bulk of MS lesions did not overlap with our tract of interest, but it is likely that these lesions contribute to overall atrophy and could explain changes in the SMA tract of individuals with MS.

A focused approach for examining relationships between white matter connectivity must be interpreted with caution as it describes only one potential tract related to dual-task ability. Further, the interhemispheric SMA tract has not been examined in healthy adults to characterize its variability. The variability of SMA diffusion measures for individuals with MS (42-
56%) is much higher than the 10% coefficients of variation found by Heiervang et al.\textsuperscript{45} in healthy adults using similar tracts. It is possible that this is due to the inherent variability in MS lesions and may be reduced with an increased sample size. Indeed it has been suggested that a sample size of >106 or >72 is needed to detect between subject changes in FA and MD, respectively with a 1% effect size for the corpus callosum.\textsuperscript{45} The interhemispheric SMA tract passes through a small portion of the corpus callosum, so it is likely that a larger sample size is necessary to demonstrate between subject differences.

6.4.2 Clinical Implications

This study correlated DTI with clinical outcome measures to gain a better understanding of the neural connectivity that underlies dual-task performance in individuals with RRMS. Our results suggest that the SMA interhemispheric tract may play a role in dual-task performance. DTI may be a useful adjunct to clinical measures to predict dual-task performance and provide important information about recovery patterns in MS. In neurodegenerative diseases like MS, functional recovery can be challenging to objectively report, and use of DTI could show microstructural improvements and suggest improved connectivity. As always, it is important to note that a direct relationship to axon or myelin structure should not be assumed from DTI, which is an indirect measure of \textit{in vivo} brain structure.

6.4.3 Future Directions

Future work in this area should include a larger sample size and matched healthy controls to further identify underlying changes in individuals with MS and to define the variability of these interhemispheric tracts in healthy adults. Our future work aims to explore changes in the SMA interhemispheric tract following an exercise training program targeting
dual-task. We plan to explore the ability of imaging measures to predict which individuals with MS can benefit from rehabilitation training programs.
6.5 References


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Chapter 7: Research Findings and Future Directions

The objective of this research was to investigate the interaction between motor and cognitive factors contributing to gait variability and falls and to explore the underlying neural connectivity related to dual-task ability in persons with neurologic disabilities. It was hypothesized that motor and cognitive factors contribute to the increased gait variability and could increase fall risk in individuals with both minimal and severe baseline deficits. It was further hypothesized that the neural connectivity would be related to functional measures of dual-task, which could improve clinical prediction and rehabilitation of such deficits.

7.1 Summary of Findings

In chapter 2, the available literature on motor-cognitive dual-task training (DTT) in individuals with neurologic conditions was reviewed. We found that although the evidence was inconclusive, it appeared that DTT was not detrimental to rehabilitation and may be beneficial. Indeed, the double-blinded study with the largest sample size\(^1\) reported significant improvements in both dual-task cost velocity and stride length. This review highlighted several important gaps which directed our research program. The gaps identified were: 1) all studies had utilized minimally-moderately impaired individuals only; 2) there was no evidence that DTT could be successful in individuals with severe injury; 3) although it is known that dual-tasking increases gait variability, this was not utilized as an outcome in any of the studies; 4)
none of these studies measured backward walking, which has also been shown to increase gait variability in Parkinson’s disease (PD),\textsuperscript{2,3} 5) few studied cognitive outcomes, making it difficult to ascertain the degree to which the interaction between motor and cognitive domains plays a role in dual-task ability; and finally 6) although many neurologic populations were represented in these works, there were no studies exploring DTT in multiple sclerosis (MS), despite deficits in dual-task being well documented in this population. Figure 7.1 demonstrates how the gaps identified in this systematic review directed our research aims.

Thus, we undertook a study exploring gait variability and backward walking in a minimally impaired population to understand whether it might be an important contributor to fall risk (chapter 3). We tested young, middle-aged and both healthy and frail elderly adults and explored the difference in variability and other spatiotemporal measures of gait in both forward and backward walking. In chapter 3, we showed that while all subjects demonstrated an increase in gait variability when switching from forward to backward walking, young and middle aged adults had similar changes, while elderly individuals demonstrated significantly larger increases in gait variability than young and middle-aged adults. Elderly fallers all walked with a BW velocity of less than 0.6m/s and after further analysis, 0.6m/s backward walking velocity accurately identified elderly fallers with a sensitivity of 100% and a specificity of 33%.\textsuperscript{4} This demonstrated that backward walking could be a useful tool in individuals with minimal to mild impairment (elderly fallers), and could hold potential for use in individuals with more severe impairment.

To explore the feasibility and acceptability of DTT in individuals with severe impairments, we undertook a case study in an individual with a severe traumatic brain injury (TBI) (chapter 4). Despite marked baseline impairments in attention and global left-sided
weakness, this individual demonstrated improvements in both previously automatic movements (e.g., gait speed, descending stairs) as well as the ability to dual-task on the Walking While Talking Test at a greater rate following DTT than standard physical therapy alone. Although we are unable to draw conclusions about effectiveness from a single subject, we can once again say that the addition of DTT to standard physical therapy was feasible, was not detrimental to the subject, and appears to be related to benefits in motor function. To our knowledge, this was the first study to explore motor-cognitive DTT in an individual with severe TBI. These findings suggested that DTT could be an important tool for rehabilitation in individuals with other conditions across the impairment spectrum.
Figure 7.1 Schema exploring how a review of the literature identified several gaps in knowledge (orange box) that directed the research aims (purple box) of this document.
The results of both chapters 5 and 6 are part of a large randomized controlled trial examining the effect of dual-task training using the video game Dance Dance Revolution on mobility, cognition and brain plasticity in individuals with MS. Baseline data is presented in chapters 5 and 6 as the trial is ongoing and unblinding has yet to occur.

Only descriptive studies exist to outline the dual-task deficits seen in MS. It is well known that individuals with MS experience impairments in both motor and cognitive function. These impairments can often occur early in the disease process, although the heterogeneity of MS presentation makes this challenging to generalize. In chapter 5, we explored the relationship between mobility (gait variability in backward and dual-task walking) and cognition (neuropsychological test performance) and demonstrated the influence of dual-task on gait variability in a small sample of individuals with RRMS. Gait variability measures in both conditions of dual-task (FWC, BWC) correlate strongly with performance on the SDMT and Stroop congruent and neutral conditions, suggesting the role of cognitive dysfunction in dual-task ability. Furthermore, performance on neuropsychological tests of processing speed explained between 48 and 65% of the variance in dual-task gait variability measures. Our results are supported by a recent study exploring the contribution of cognition to dual-task cost of velocity that showed cognitive impairment was an independent predictor of dual-task cost in MS. Although we were unable to show a relationship between variability of dual-task walking and fall risk or indeed backward walking velocity and fall risk in this MS sample, as we did in elderly fallers, this is likely due to small sample size, a group of infrequent fallers and large standard deviations in BW measures among participants. Despite these limitations, this study is encouraging and supports further work to explore dual-task in MS and potential rehabilitation strategies that incorporate both motor and cognitive measures.
Psychologists have explored dual-task ability, in the context of two cognitive tasks (cognitive-cognitive dual-task) in healthy adults using functional neuroimaging. However, the exploration of motor-cognitive dual-task using DTI diffusivity measures and probabilistic tractography represents a novel analysis. In chapter 6, we showed a moderate relationship between velocity of forward dual-task walking and measures of axial, radial and mean diffusivity (AD, RD, MD) in the interhemispheric supplemental motor area (SMA) tract. Individuals who walked at slower speeds during dual-tasks had higher values of AD, RD and MD. When the strongest of these relationships was further examined with linear regression, we found that interhemispheric SMA AD explained 43.6% of the variance in forward dual-task walking velocity. This work was done in the same individuals as in chapter 5; thus, given the small sample size, the relationship between dual-task walking velocity and diffusion tensor imaging (DTI) measures shows promise.

There was no relationship between dual-task walking and tract-specific diffusion measures in another interhemispheric tract, suggesting that the SMA tract may be specifically related to dual-task ability. Indeed the SMA has been implicated in complex tasks and interlimb coordination in other studies. To this investigator’s knowledge, there are no DTI studies examining the relationship with dual-task walking; however, studies in other neurologic populations have demonstrated an association between DTI measures and motor function. In MS, the RD of the transcallosal hand motor fibers predicted decline on a coordination task over 12 months, while fractional anisotropy (FA) of the corticospinal tract predicted gait function in chronic stroke and chronic idiopathic hydrocephalus, as well as balance function in children with TBI. Similarly, FA of the corpus callosum predicted motor function in community-dwelling elderly adults and adolescents with TBI. Recent studies are exploring the predictive value of
DTI measures for future walking, motor, and ADL functional deficits in both children\textsuperscript{16} and adults\textsuperscript{17-19} with stroke. Our results support the literature from other neurologic conditions; DTI measures have the potential to predict motor function in MS. This is the first study to explore the association of DTI to dual-task function.

7.2 Limitations

This work has many limitations. The results in chapters 5 and 6 are limited primarily by sample size. We analyzed eleven individuals with relapsing remitting MS. Our analysis priori sample size calculation in chapter 5 indicated that 10 matched pairs of healthy adults and individuals with MS would be sufficient to demonstrate differences in forward walking velocity. Despite that calculation, we noted no significant differences in forward walking velocity, but did note robust relationships between gait variability and neuropsychological test performance. Additionally, this study examined only one type of cognitive dual-task (arithmetic task); it may be beneficial to explore additional secondary cognitive tasks such as fluency or working memory.

Aside from small sample size, chapter 6 was limited by the exploration of only one tract (interhemispheric SMA) with a potential relationship to dual-task ability; such a focused approach must be interpreted with caution. Additionally, the interhemispheric SMA tract has not been examined in healthy adults to characterize its variability. However, the variability of the SMA diffusion measures for individuals with MS was much higher than the 10% coefficients of variation found by Heiervang et al., 2006\textsuperscript{20} in healthy adults using similar tracts. While this may be due in part to the inherent variability of MS lesion location and size, it may also be limited by a small sample size.
7.3 Future Research

7.3.1 Contribution of Cognition and Gait Variability to Dual-Task Ability

Our work reinforces the important link between gait variability and the interplay of cognition and mobility. Work in the elderly suggests that increased gait variability noted in backward walking may be associated with increased fall risk.221 A prospective study exploring this phenomenon would be useful for treatment planning and wellness programs in individuals with MS. Work is also needed to further elucidate the role of early cognitive deficits as potential contributor to mobility deficits in MS. Future work should include a wider range of neuropsychological tests as well as dual-tasks that span multiple cognitive domains (e.g., fluency, working memory). While the interaction of cognition and mobility seems to be particularly relevant in MS, it is possible that such a relationship also exists in other neurological populations. Future work involving dual-task in other neurological conditions should include the assessment of both cognitive domains and mobility outcomes.

7.3.2 Dual-Task Training in General

The variety of activities that may be performed for each type of dual-task (i.e., motor-motor, motor-cognitive, cognitive-cognitive) during training studies clouds study design and can make reproducibility and generalizability of findings challenging. Our review suggests that motor-cognitive DTT may be useful for improving dual-task gait, but the necessary dose of training required for such outcomes is unknown. Furthermore, such training has been largely unsuccessful at generalizing to novel dual-task situations. That is to say, individuals improve only on the dual-task on which they were trained; however, many studies do not include an outcome measure of a novel dual-task. Future studies should include a dual-task assessment in pre and post-testing that is not part of the training session to assess carryover of dual-task skills to novel
dual-task situations. Indeed, a recent pilot study\textsuperscript{22} suggests that carryover is possible if functional tasks are the focus of training. Thus, it appears that a DTT program focusing on functional skills may be beneficial in the transition to novel dual-tasks.

Our review also highlighted a surprising lack of research in the area of DTT for individuals with neurological disorders resulting in severe impairments. Our work suggests that functional mobility can be enhanced with DTT, even in individuals with severe injury. Future studies should include a larger sample size of individuals with severe injury as well as explore DTT in neurological conditions other than TBI.

7.3.3 Dual-Task Training in MS

Our ongoing work is exploring the effect of a dual-task training program on individuals with MS. Based on the gaps identified in the literature review, we have incorporated both fall assessment and a novel dual-task assessment in the outcome measures of this randomized controlled trial.

7.3.4 Validation of Dual-Task Tools in MS

Although there have been several measurement tools utilized to assess dual-task ability, none of them have been validated in MS. Future work will validate the Walking While Talking Test, the Dual-Task Questionnaire, and the TUG Cognitive in individuals with MS.

7.3.5 Examine Variability in Healthy Controls for MRI Measures

Interpretation of our data in chapter 6 was limited not only by small sample size, but also by the lack of information on SMA tract variability in healthy controls. While we anticipated that our MS sample would have higher variability in measures of diffusivity, they were significantly higher than those seen in other tracts in healthy adults.\textsuperscript{20} To my knowledge, the interhemispheric SMA tract has not been explored in healthy adults, so comparison of our
values in this study was not possible. Future work should include MRI measures for the healthy control subjects in addition to mobility testing. An exploration of connectivity of other tracts that may be related to dual-tasks as well as relationships with clinical tests of dual-task ability in individuals with MS would contribute to our understanding of the neural connectivity associated with dual-task ability.

7.3.6 Examine Responders vs. Non-Responders to Rehabilitation Training Programs and Explore the Predictive Potential of MRI Measures.

In addition to exploring mobility and neuropsychological test performance outcomes following the dual-task training program in MS, we will also examine the effect of a DTT program on connectivity in the interhemispheric SMA tract. We also plan to explore the relationship between measures of diffusivity and success or improvement following the DTT program in individuals who were randomized to the intervention group. Prediction of individuals with MS who can benefit from rehab training programs indicates that this work has the potential to be a valuable tool in the prescription of exercise programming and rehabilitation in MS.

7.4 Conclusion

Deficits in dual-task that amplify gait variability and increase fall risk are a significant concern for individuals with MS and other neurological disorders. The studies completed in this research support the hypothesis that motor and cognitive factors contribute to gait variability that could increase fall risk in individuals with both minimal and severe baseline deficits. These studies also demonstrate the relationship between connectivity and functional measures of dual-task, which could be useful in improving clinical prediction and rehabilitation.
Although continued research is necessary to refine the interaction between mobility and cognition in MS and other neurologic populations, this work certainly contributes to the knowledge base and is a step toward better understanding of the many factors contributing to gait variability and fall risk. Physical therapist interest in the area of dual-task has increased over the last several years. While the number of descriptive studies has greatly increased, knowledge about rehabilitation of dual-task deficits with training programs is still in its infancy. Indeed, the success of such programs and the type of training tasks that should be utilized for different populations or different severities of injury are unknown. Our ongoing and future work will aim to better define appropriate training, assessment, and predictive tools for each neurologic population.
7.5 References


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