

MULTI-TASKING, EXECUTIVE FUNCTION, AND FUNCTIONAL ABILITIES IN OLDER  
ADULTS WITH TYPE 2 DIABETES MELLITUS

BY

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## **Abstract**

There is growing evidence that older adults with type 2 diabetes exhibit deficits in executive function, the set of processes responsible for planning, organizing, sequencing, and monitoring goal-oriented behavior. However, the specific nature of these executive impairments and their functional consequences in this population remain poorly understood. The primary purpose of this work was to determine whether older adults with type 2 diabetes demonstrated impairments in the executive process of multi-tasking when compared to their peers without diabetes, and to examine how multi-tasking abilities contributed to gait and other functional abilities in these individuals. We also sought to examine the integrity of other executive functions in those with diabetes, including the processes responsible for updating information, shifting between different tasks, inhibiting predominant responses, and organizing and recalling visuospatial and verbal data, and to explore their relationships to gait and functional ability.

Chapter 2 describes the results of our pilot investigation, in which we administered a measure of multi-tasking, the Cognitive Timed Up and Go (cTUG), and a battery of 7 common executive function tests to 20 adults (age 40-65 years) with diabetes and diabetic peripheral neuropathy (DPN) and 20 individuals of similar age without diabetes. We found that those with DPN performed worse on the cTUG test, and also demonstrated poorer performance on executive function measures assessing visuospatial and verbal processing. Moreover, we observed that overall cognitive performance and symptoms of depression were significantly related to each other and to a measure of functional ability, whereas signs and symptoms of DPN were not associated with this functional measure. Although preliminary, this study illustrated the

potential relationships between neuropsychological and physical function, and highlighted that functional impairments, fall risk, and disability in those with DPN is likely the result of a complex and multi-factorial process that extends beyond somatosensory and proprioceptive impairment.

Building upon the data and experience we obtained from this pilot project, we next selected two instruments, the Walking and Remembering and Pursuit Rotor tests, in an effort to describe multi-tasking in much greater detail than was possible with the cTUG alone. As described in Chapter 3, these multi-tasking assessments, along with measures of single-task gait and self-reported functional ability and limitation, were administered to a group of 40 older adults (age 60 years and older) with type 2 diabetes and a group of 40 individuals without diabetes, pair-matched according to age, sex, education, and the presence or absence of hypertension. Our analysis of this data revealed that those with diabetes performed worse than comparison subjects when asked to multi-task while walking, appearing to preserve less critical task demands at the expense of gait stability. Interestingly, we observed little association between multi-tasking ability and our gait and functional measures. However, we did note rather striking relationships between these measures and symptoms of depression, physical activity level, and sleep quality. Overall, this data suggested that older adults with type 2 diabetes did exhibit disturbances that could impair safety when required to multi-task while walking. Furthermore, although these changes did not appear to substantially influence single-task gait mechanics or self-reported functional ability, we also found that commonly overlooked variables such as depression, physical activity, and sleep

quality may make important contributions to everyday gait and function in this population.

Examining these relationships in further detail, we next performed a series of regression analyses investigating the contributions of multi-tasking ability, depression, physical activity, and sleep quality to single-task gait speed and variability, and self-reported physical function and disability in our group with diabetes. Described in Chapter 4, this data demonstrated that there was little association between multi-tasking ability and single-task gait parameters or self-reported physical function and disability. However, our secondary analyses revealed significant adverse relationships between depression and gait variability and disability, between physical activity levels and walking speed and physical function, and between sleep quality and gait variability. Although often overlooked, factors such as depression, physical inactivity, and poor sleep quality are widespread in those with diabetes. Our analysis emphasizes the importance of appropriately identifying and treating such modifiable comorbidities, as well as the need for further research examining their relationships to different aspects of physical function and disability.

Having completed our examination of multi-tasking, we turned our attention to exploring the integrity of other executive functions in those with diabetes. Alongside of our multi-tasking measures, we administered a battery of executive function tests assessing the processes of information updating, task shifting, response inhibition, and visuospatial and verbal processing and memory. Analysis of this data revealed that those with diabetes appeared to perform more poorly than comparison subjects on a specific measure of updating and a measure of visuospatial processing. However, we

did not observe deficits on a second updating measure, or on any other executive test. Interestingly, although there was little relationship between executive performance and gait or functional abilities in the diabetes group, we observed a number of significant correlations between updating, shifting, and visuospatial memory and gait and function in the comparison group. These findings clearly emphasize the need for further research examining executive function in those with diabetes, and investigating how these processes contribute to physical deficits, falls, and/or disability in health and disease.

In summary, the results of this body of work suggest that older adults with type 2 diabetes demonstrate significant changes in gait stability when required to walk while multi-tasking, and may also exhibit deficits in areas of executive function related to the ability to update information and process visuospatial stimuli. The influence of these and other executive functions on gait and functional ability remains unclear, but may differ between those with and without diabetes. Certainly, it appears that factors such as depression, physical activity, and sleep quality make important contributions to everyday function. Overall, our findings emphasize the need for further research investigating the physiological, psychological, and functional consequences of type 2 diabetes in older adults, and the diverse factors that may contribute to the higher incidence of falls, functional deficits, or disability in this high risk patient population.

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## Chapter 1

### Introduction

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## **1.1 Abstract**

The devastating impact of type 2 diabetes mellitus (DM) on vascular, renal, retinal, and peripheral nerve function is well documented. However, there is also evidence that older adults with this disease exhibit impairments in the planning, coordinating, sequencing, and monitoring of cognitive operations, collectively known as executive function. Although poorly understood, it is possible that disturbances in executive function, particularly those involved in the ability to multi-task, contribute to the gait abnormalities and increased risk for falls, functional impairments, and disabilities associated with type 2 DM. Despite this, the relationships between executive function and functional abilities remain poorly understood in this population.

This introductory chapter presents current neuropsychological research regarding the concept of executive function as a framework upon which to examine this highly functional cognitive entity in adults with type 2 DM. The pathophysiological mechanisms thought to underlie diabetes-related executive dysfunction are also explored, as are the potential contributions of executive deficits to impairments in gait and function observed in the older population with type 2 DM. The chapter concludes with a brief discussion of dual-task assessment and intervention strategies which may facilitate the care and rehabilitation of this growing patient population.

## 1.2 Overview

The public health threat posed by diabetes is unequivocal. It is currently estimated that one out of every ten health care dollars spent in the United States is attributable to this disease (American Diabetes Association, 2008), and the incidence of type 2 DM, already among the most common major diseases in older adults, is projected to continue to rise due to an aging population, urbanization, and the increasing prevalence of obesity and physical inactivity (Wild, Roglic, Green, Sicree, & King, 2004).

Characterized by the improper utilization of insulin and resulting dysregulation of blood glucose levels, type 2 DM is associated with an array of debilitating clinical sequelae, including visual loss, renal dysfunction, wound formation, limb amputation, neuropathy, and cardio- and cerebrovascular disease (Nathan, 1993). Alongside of these traditional complications, type 2 DM has also been identified as a significant risk factor for falls and disability (Gregg, Beckles, et al., 2000); as well as for cognitive impairment and dementia (Arvanitakis, Wilson, & Bennett, 2006).

While still poorly recognized, the impact of type 2 DM on cognition appears to extend across a broad range of functions (Kodl & Seaquist, 2008). Of particular concern are deficits that have been observed in the set of high-level central processes responsible for planning, sequencing, organizing, and monitoring cognitive operations (Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001; Okereke et al., 2008; Qiu et al., 2006; Yeung, Fischer, & Dixon, 2009). Collectively known as executive function, this cognitive entity has substantial functional implications. As explained by Jurado and Rosselli (2007):

In a constantly changing environment, executive abilities allow us to shift our mind set quickly and adapt to diverse situations while at the same time inhibiting inappropriate behaviors. They enable us to create a plan, initiate its execution, and persevere at the task at hand until its completion. Executive functions mediate the ability to organize our thoughts in a goal-directed way and are therefore essential for success in school and work situations, as well as everyday living. (p. 214)

Consistent with this, executive dysfunction has been linked to impairments in gait (Persad, Jones, Ashton-Miller, Alexander, & Giordani, 2008) and functional abilities (Pereira, Yassuda, Oliveira, & Forlenza, 2008); deficits which are more broadly implicated in falls (Anstey, von Sanden, & Luszcz, 2006), the loss of independence (Royall, Palmer, Chiodo, & Polk, 2004) and, ultimately, to institutionalization and mortality (Cesari et al., 2005).

Although growing evidence suggests that older adults with type 2 DM suffer from executive dysfunction, the complexities of both executive function and the diabetic disease process make interpretation of these deficits and their functional consequences difficult. This has important implications for rehabilitation, as physical therapists and other rehabilitation providers are ideally positioned to identify and address such impairments before they can result in catastrophic functional loss.

### **1.3 Executive Function: Concept and Processes**

Despite extensive neuropsychological study, executive function remains notoriously resistant to formal definition. Effectively first identified by Baddeley and

Hitch (1974) as the “central executive” responsible for overseeing working memory, executive function has evolved to more broadly describe a loosely defined set of control processes responsible for planning, coordinating, sequencing, and monitoring other cognitive operations (Hull, Martin, Beier, Lane, & Hamilton, 2008). These processes enable the performance of goal-directed and future-oriented behavior (Suchy, 2009), with various authors placing highly functional cognitive activities ranging from attention and visuospatial processing to reasoning and planning under the auspices of executive function (Miyake, Friedman, et al., 2000).

Traditionally, the assessment and interpretation of executive abilities has been based on an assumption that performance on one or two measures reflects overall executive functioning (Miyake, Emerson, & Friedman, 2000). However, the fact that executive functions must, by definition, express themselves through non-executive processes such as language, vision, or memory has brought such methodology into doubt, leading some neuropsychologists to caution that “a low score on a single executive test does not necessarily mean inefficient or impaired executive functioning” (Miyake, Emerson, et al., 2000). Rather, they suggest that executive function may be more accurately described in terms of a number of related but dissociable processes. Table 1.1 illustrates these processes, and how they may relate to more complex cognitive activities, neuroanatomical areas, and clinical behaviors. The processes relevant to our investigation, multi-tasking, updating, shifting, inhibition, and visuospatial function, are described in detail in the following sections.

**Table 1.1: Executive Processes and Their Relationships to Cognitive Abilities, Anatomical Structures, and Clinical Behaviors**

<b>Executive Processes</b>	<b>Cognitive Ability</b>	<b>Anatomical Correlate</b>	<b>Clinical Presentation</b>
<ul style="list-style-type: none"> <li>• <b>Multi-tasking</b></li> <li>• <b>Updating</b></li> <li>• <b>Sequencing</b></li> </ul>	<ul style="list-style-type: none"> <li>• Planning</li> <li>• Reasoning</li> </ul>	<ul style="list-style-type: none"> <li>• Dorsolateral pre-frontal cortex</li> </ul>	<ul style="list-style-type: none"> <li>• Disorganization</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Sequencing</b></li> <li>• <b>Updating</b></li> <li>• <b>Shifting</b></li> <li>• <b>Initiation</b></li> <li>• <b>Multi-tasking</b></li> <li>• <b>Visuospatial Function</b></li> </ul>	<ul style="list-style-type: none"> <li>• Organization</li> </ul>	<ul style="list-style-type: none"> <li>• Superomedial pre-frontal cortex</li> </ul>	<ul style="list-style-type: none"> <li>• Apathy</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Updating</b></li> <li>• <b>Inhibition</b></li> </ul>	<ul style="list-style-type: none"> <li>• Judgment</li> </ul>	<ul style="list-style-type: none"> <li>• Ventromedial and orbitofrontal cortex</li> </ul>	<ul style="list-style-type: none"> <li>• Disinhibition</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Multi-tasking</b></li> <li>• <b>Shifting</b></li> <li>• <b>Updating</b></li> <li>• <b>Visuospatial Function</b></li> </ul>	<ul style="list-style-type: none"> <li>• Problem Solving</li> </ul>	<ul style="list-style-type: none"> <li>• Dorsolateral pre-frontal cortex</li> </ul>	<ul style="list-style-type: none"> <li>• Perseveration</li> </ul>

*Adapted from Suchy (2009)*

### 1.3.1 Dividing Attention (“Multi-tasking”)

Associated with prefrontal cortical activity (D'Esposito et al., 1995; Wagner & Smith, 2003), the ability to time share or “multi-task” in order to perform simultaneous activities is traditionally identified as an executive function due to Baddeley and Hitch's (1974) widely influential model of working memory, which consists of a central executive mechanism responsible for the supervision of subordinate “slave” systems. According to this model, the concurrent performance of a primary cognitive task and a secondary task tapping a slave system will disrupt performance of the primary task from its baseline, or single-task level, presumably due to an insufficient executive capacity to share attention between the competing demands of the two tasks (Hegarty, Shah, & Miyake, 2000). These “dual-task costs” can be easily calculated via the following formula:

$$|\text{Dual-task Cost}| = \frac{(\text{Dual-task Performance} - \text{Single-task Performance})}{\text{Single-task Performance}} \times 100$$

This value represents a percent difference between single- and dual-task conditions (for example, a 5% decline in walking speed) and allows for comparison across individuals, groups, or time (K. McCulloch, 2007). It is important to note that dual-task costs can be either positive or negative. Conventionally, a decline in task performance under dual-task conditions is denoted as a positive dual-task cost, while an improvement in performance under dual-task conditions is represented by a negative dual-task cost.

Several factors figure in the interpretation of such dual-task costs as reflections of executive function. First, the type and difficulty of the tasks must be carefully



considered. For example, if a participant is asked to simultaneously perform two tasks which require visual input, such as a visual discrimination task and a walking task which involves visually locating obstacles, interference will likely occur within the visual system and performance on one or both tasks will deteriorate. Similarly, very simple or familiar tasks may be well within the participant's attentional capacity and thus fail to elicit dual-task costs; whereas tasks involving mathematical computation or complex language skills may be more difficult for those with limited education (K. McCulloch, 2007), and thus distort the degree to which executive abilities are represented.

Additionally, researchers have observed that subjects will typically allocate more attention to the task perceived to be the most challenging, regardless of whether it is designated as primary or secondary (Hegarty et al., 2000). This "strategic tradeoff" may result in a small dual-task cost for the primary task at the expense of secondary task performance. Task prioritization can be influenced by task demands, instructions, and participant goals, and is particularly relevant to assessments involving gait and balance activities, as these tasks may be prioritized as a means of maintaining safety (Hegarty et al., 2000; K. McCulloch, 2007). In order to account for these strategic tradeoffs, both the primary and secondary tasks must be monitored for dual-task costs (Hegarty et al., 2000) and many researchers have found it advantageous to abandon the designation of primary and secondary tasks altogether (K. McCulloch, 2007). Table 1.2 provides several examples of clinical measures that are commonly used to assess multi-tasking ability, including the Walking and Remembering Test, which is employed in our investigation.

**Table 1.2: Sample Clinical Assessments of Multi-tasking**

Measure	Description	Outcome Measure*	Reference
<b>Walking and Remembering</b>	<p><b>Motor:</b> Ambulate 20' along 19 cm wide path</p> <p><b>Concurrent:</b> Forward digit span (e.g. recall of the longest series of random numbers subject can correctly recall under single-task conditions)</p>	<ul style="list-style-type: none"> <li>• Time to walk path</li> <li>• Steps off path</li> <li>• Number of correctly recalled digits</li> </ul>	McCulloch et al. (2004)
<b>Timed Up and Go</b>	<p><b>Motor:</b> Stand from chair, ambulate 3m, turn 180°, return to chair and sit down</p> <p><b>Concurrent:</b></p> <ul style="list-style-type: none"> <li>- Serial subtraction by 3 from a random number between 20 and 100</li> <li>- Carry cup of water, or tray of water-filled cups</li> </ul>	<ul style="list-style-type: none"> <li>• Time to complete test</li> <li>• Number of correct calculations</li> <li>• Amount of water spilled</li> </ul>	Shumway Cook et al. (2000) Lundin-Olsson et al. (1998)
<ul style="list-style-type: none"> <li>- <b>Cognitive</b></li> <li>- <b>Manual</b></li> </ul>			
<b>Walking While Talking</b>	<p><b>Motor:</b> Ambulate 20', turn 180° and return</p> <p><b>Concurrent:</b></p> <ul style="list-style-type: none"> <li>- Recite letters of the alphabet</li> <li>- Recite alternating letters of the alphabet</li> <li>- Recite as many animals/vegetables/etc. as possible</li> </ul>	<ul style="list-style-type: none"> <li>• Time to complete test</li> <li>• Number of correct letters/items</li> </ul>	Verghese et al. (2002)

\*Outcome measures are expressed as the percent change in performance from single- to dual-task conditions, or dual-task cost.

This is calculated as: (Dual-task performance – Single-task performance) / Single-task performance, X 100

### *1.3.2 Updating and Monitoring Information (“Updating”)*

Closely related to working memory, the executive function described as “updating” provides a means by which external information can be utilized to update internal representations in order to effectively respond to changing environmental demands (Salthouse, Atkinson, & Berish, 2003). To accomplish this, incoming information is monitored and processed for relevance to an active task, and then employed to update older, irrelevant information held in the working memory with newer, more relevant information (Miyake, Friedman, et al., 2000).

The crucial distinction between updating and working memory is that updating involves the active manipulation of data within the working memory, as opposed to the passive storage of task-relevant information (Miyake, Friedman, et al., 2000). This distinction has been supported by neuroimaging studies indicating that the passive storage and maintenance of working memory are linked to activity in the premotor frontal cortex and parietal lobes, whereas active updating is associated with the dorsolateral prefrontal cortex (Jonides & Smith, 1997; Stuss et al., 2002).

### *1.3.3 Mental Set and Task Shifting (“Shifting”)*

Alternatively referred to as attention switching or cognitive flexibility, the executive function known as “shifting” is considered to be responsible for the ability to transfer attention back and forth between multiple operations, tasks, or mental sets (Monsell, 1996). Extending beyond the spatial switching of visual attention via voluntary eye movement, the process of shifting involves disengagement from an irrelevant task set with the subsequent engagement of a more relevant task set (Miyake, Friedman, et

al., 2000). Recent evidence indicates that the shifting function may also, or perhaps instead, reflect the ability to override the interference or negative priming generated by a previously performed task in order to perform a different cognitive operation (Allport & Wylie, 2000).

A prominent feature of frontal lobe damage, repeated perseveration on an inappropriate response is commonly interpreted as a deficit in the ability to shift mental sets, and neuropsychological and neurophysiological studies have implicated frontal, as well as occipital and parietal areas, in this process (Miyake, Friedman, et al., 2000; Stuss et al., 2002).

#### *1.3.4 Response Inhibition*

The executive function known as “inhibition” represents a process described by Logan (1994) as an “internally generated act of control” which enables the deliberate suppression of a prepotent, or automatic, response when desired (Miyake, Friedman, et al., 2000; Salthouse et al., 2003). This provides an important and highly adaptive means by which dependence on habit and familiarity may be overcome; as well as a mechanism by which responses already in preparation may be suppressed (Salthouse et al., 2003).

Conceptually distinct from the involuntary decrease in activation levels often used to describe neural networks, this controlled and deliberate executive process has been closely linked to activation of the prefrontal cortex (Stuss et al., 2002), and deficits in inhibition are frequently associated with frontal lobe damage or dysfunction (Jahanshahi et al., 1998; Kiefer, Marzinzik, Weisbrod, Scherg, & Spitzer, 1998).

### *1.3.5 Visuospatial Function*

Responsible for perception of the surrounding world in two and three dimensional space, visuospatial functions encompass the encoding of visual information, maintenance of visual imagery, and manipulation of this data within memory. Broadly, these abilities are mediated by separate pathways responsible for perception and action (Goodale & Milner, 1992). The ventral stream, traveling through the occipitotemporal cortex to the ventrolateral prefrontal cortex, is traditionally characterized as the “What” pathway. The dorsal stream, traversing the occipitoparietal cortex to the dorsolateral prefrontal cortex, appears to mediate spatial perception (“Where”) and visually guided action (“How”) pathways (Tankus & Fried, 2012).

The unconscious translation of this information from a retinal image into an internal construction of the perceived world is fundamentally cognitive, described by Hoffman (1998) as an intelligent process in which retinal images are used to develop internal representations that are tested and updated as the perceiver scans and interacts with the environment. In particular, neuropsychological evidence indicates that visuospatial problems requiring complex, multi-step solutions heavily involve executive function (Kuo et al., 2005). Table 1.3 provides examples of measures commonly used to assess visuospatial function and the other executive functions described above.

**Table 1.3: Sample Measures of Executive Functions**

<b>Process</b>	<b>Sample Measure</b>	<b>Task Description</b>	<b>Reference</b>
<i>Updating</i>	• N-back	• Participant views a continuous string of letters and identifies those that are repeated after an intervening letter (e.g. 2-back).	• Hull et al. (2008); see also Kirchner (1958)
	• Keep-Track	• Participant views 10 words from 6 semantic categories and identifies the last word viewed in each of 2 randomly selected categories.	• Miyake et al. (2000); see also Yntema (1963)
<i>Shifting</i>	• Trail Making	• Participant connects numbered or lettered circles in order (part A) and alternating between numbers and letters (part B).	• Homack et al. (2005)
	• Local-Global	• Participant views a series of large figures composed of smaller figures (e.g. an "A" made up of small "E's") and identifies "local" or "global" features based on figure color.	• Miyake et al. (2000); see also Navon (1977)
<i>Inhibition</i>	• Stroop Word Color	• Participant identifies the color of a series of colored "X's" (condition A), followed by a series of incongruously colored words (e.g. the word "blue" printed in green ink; condition B).	• Miyake et al. (2000); see also Stroop (1935)
	• Hayling Sentence Completion	• Participant is asked to complete 15 simple sentences with a word that logically completes the sentence (condition A), and with a word that is nonsensical (condition B).	• Burgess and Shallice (1996)
<i>Visuospatial Function</i>	• Rey-Osterrieth Complex Figure	• Participant draws an asymmetrical geometric figure as accurately as possible. Recall after 15-60 minutes may also be tested.	• Lezak et al. (2004); see also Rey and Osterrieth (1993)

## **1.4 Executive Function and Type 2 Diabetes Mellitus**

Although there is no clear consensus as to the impact of type 2 DM on executive function in older individuals, there does appear to be good cause for concern. Indeed, impaired performance on a variety of executive tasks has been reported in older adults with type 2 DM (de Wet, Levitt, & Tipping, 2007; Munshi et al., 2006; Qiu et al., 2006; Thabit et al., 2009; van den Berg et al.; Yeung et al., 2009), while a significantly greater risk of executive decline has also been observed in longitudinal investigations of type 2 DM and cognition (Fontbonne et al., 2001; Kuo et al., 2005; Okereke et al., 2008; van den Berg et al.).

Perhaps the strongest evidence of diabetes-related executive dysfunction stems from Yeung et al.'s (2009) analysis of a multi-dimensional executive battery administered to 465 older adult subjects, of whom 41 suffered from type 2 DM. Those with diabetes scored approximately 12% and 14% worse than their non-diabetic peers on executive measures of inhibition and shifting, respectively. This detrimental effect of diabetes on executive function remained significant even after the sample was divided into young-old (53-70 years) and old-old (71-90 years) groups, suggesting that these impairments were more likely mediated by diabetic status than by age.

Others have also reported indications of executive dysfunction in samples of older adults with type 2 DM. One group, for instance, examined the cognitive profiles of 291 homebound individuals over the age of 60, finding that those with type 2 DM (n=115) demonstrated significant deficits of approximately 7%, 17%, and 21% on executive measures of updating/working memory, visuospatial function, and shifting, respectively (Qiu et al., 2006). These findings are broadly consistent with longitudinal

data describing small but significant baseline deficits of up to 10% on measures of attention and shifting in older adults with type 2 DM (Fontbonne et al., 2001; Gregg, Yaffe, et al., 2000). These individuals also suffered nearly a two-fold greater risk of decline on these measures over 4- and 6-year periods.

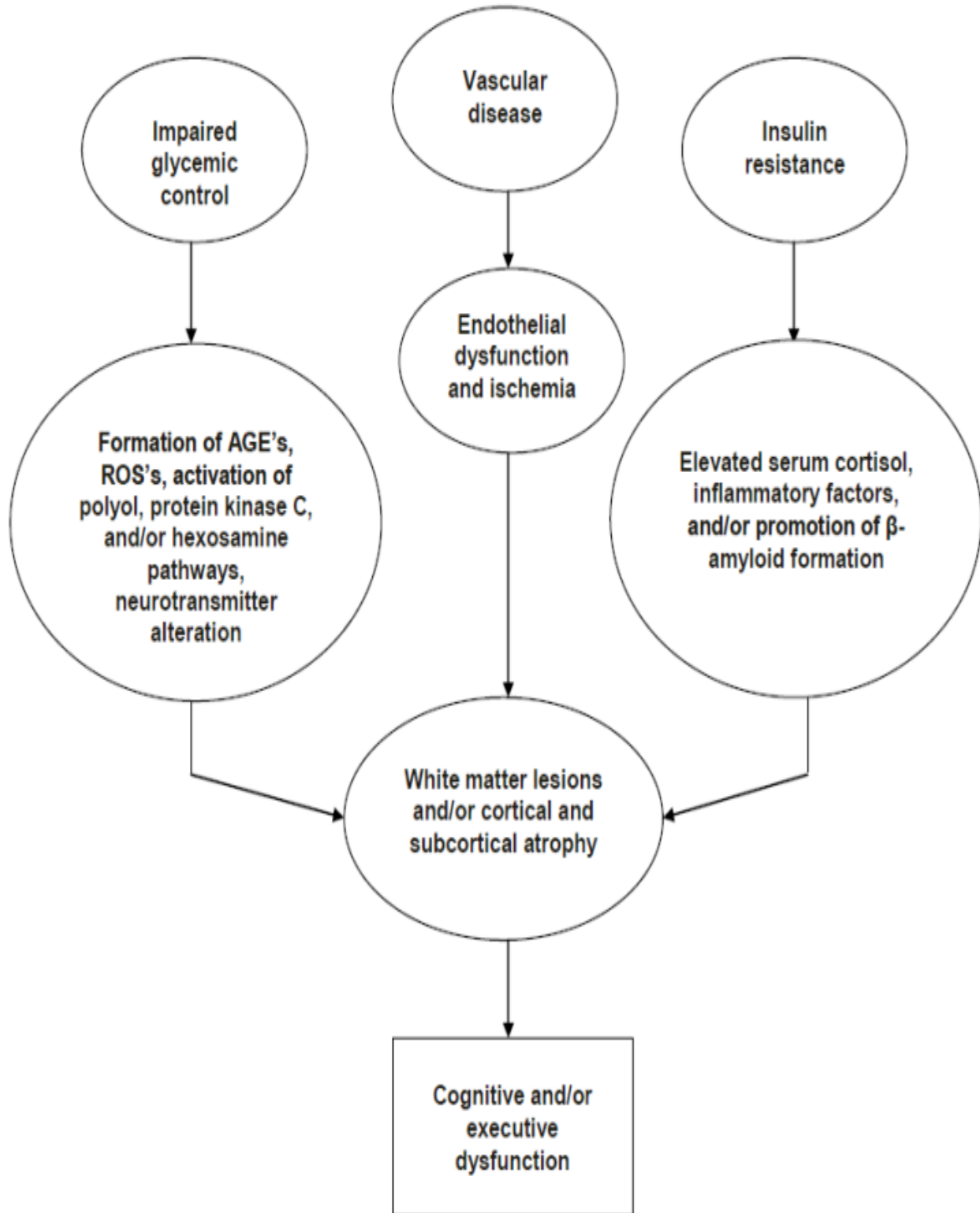
It is important to note, however, that associations between type 2 DM and executive dysfunction have not been uniformly demonstrated. For example, a sample of 1,917 elderly individuals (n=218 with type 2 DM) revealed no significant executive impairments on a composite measure of updating and inhibition tasks (Saczynski et al., 2008). Likewise, Ruis et al. (2009) noted no impairments on a series of unspecified executive tasks in a sample of 183 older subjects with recently diagnosed type 2 DM. These results corroborate literature reviews describing only inconsistent relationships between type 2 DM and executive dysfunction (Awad, Gagnon, & Messier, 2004; Messier, 2005).

### **1.5 Pathophysiological Mechanisms of Executive Dysfunction in Diabetes**

Despite somewhat conflicting clinical evidence, physiological data appears to reinforce the likelihood of executive dysfunction in older adults with type 2 DM; potentially due to neuroanatomical changes resulting from impaired glycemic control, vascular disease, and insulin resistance (Figure 1.1). While there is empirical support for each of these mechanisms, the etiological pathways underlying diabetes-related cognitive and executive impairments likely result from a multi-factorial process including these and other factors (Kodl & Seaquist, 2008).



**Figure 1.1: Potential Mechanisms of Executive Dysfunction in Diabetes**



*Adapted from Kodl and Seaquist (2006)*

### *1.5.1 Neuroanatomical Changes*

Among the notable findings of structural abnormalities associated with diabetes are magnetic resonance imaging observations of diffuse brain atrophy and white matter lesions in individuals with type 2 DM (Manschot et al., 2006; Schmidt et al., 2004). For example, Manshot et al.'s (2006) study of 164 older adults revealed that those with type 2 DM (n=113) exhibited as much as 23% more cortical atrophy, 12% more subcortical atrophy, and significantly more deep white matter lesions and infarcts than control subjects. Interestingly, this study also observed small to moderate (effect size=0.2-0.4), statistically significant deficits in attention, processing speed, and memory in these individuals.

Other MRI investigations have also demonstrated that those with type 2 DM exhibit periventricular, amygdalar, and hippocampal atrophy similar to that observed in Alzheimer's disease (den Heijer et al., 2003). Moreover, a recent functional magnetic resonance imaging (fMRI) study conducted by Zhou et al. (2010) revealed reduced functional connectivity between the hippocampus and frontal and temporal cortical structures in a sample of elderly adults with type 2 DM when compared to a group without diabetes. While these findings were not directly associated with deficits in executive performance, subjects with diabetes were noted to perform significantly worse on a measure of executive function than their counterparts without diabetes.

### *1.5.2 Role of Glycemic Control*

The hallmark feature of diabetes, impaired glycemic control has long been suspected to contribute to the development of diabetes-related cognitive dysfunction

(Kodl & Seaquist, 2008). Supporting this are studies describing significant inverse relationships between glycosylated hemoglobin (HbA1c) and measures of working memory ( $r=-0.37$ ) and visuospatial function ( $r=-0.38$ ) (Munshi et al., 2006). However, other studies have contradicted these findings, demonstrating no association between hyperglycemia and cognitive function; as well as between repeated episodes of hypoglycemia and cognitive function (Lindeman et al., 2001; Scott, Kritz-Silverstein, Barrett-Connor, & Wiederholt, 1998).

Theories as to how hyperglycemia may mediate cognitive dysfunction are largely centered around observations that, in animal models of diabetes, hyperglycemia results in the formation of advanced glycation end products (AGEs) and reactive oxygen species (ROSs), activation of polyol and protein kinase C pathways, increased glucose shunting in the hexosamine pathway, and alterations in neurotransmitter function (Biessels, van der Heide, Kamal, Bleys, & Gispen, 2002; Klein & Waxman, 2003). Such changes may ultimately lead to neuronal damage; however further research is necessary to determine which, if any, of these mechanisms contribute to cognitive impairments and/or executive dysfunction in humans with diabetes (Kodl & Seaquist, 2008).

### *1.5.3 Role of Vascular Disease*

Diabetes is known to be associated with a greater risk of cardio- and cerebrovascular disease (Nathan, 1993), and it has been suggested that vascular dysfunction may contribute to executive disturbance (Kodl & Seaquist, 2008). This is consistent with findings that the interaction of diabetes and hypertension is related to

cortical brain atrophy (Schmidt et al., 2004) and may confer as much as a two-fold greater risk of dementia (Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). In addition, neuro- and angiopathic changes have been observed in the cranial nerves and spinal cord of the diabetic nervous system (Kodl & Seaquist, 2008).

While the mechanisms through which vascular dysfunction may mediate neurological abnormalities in diabetes remain unknown, there is speculation that reduced cerebral blood flow combined with the activation of the thromboxane A2 receptor, which has also been noted in diabetes (Biessels et al., 2002), may result in inadequate vasodilation of the cerebral vasculature and an increased likelihood of ischemia (Kodl & Seaquist, 2008).

There is also evidence that the coupling of ischemia and hyperglycemia may provide an environment in which agents such as lactate (McCall, 1992) and/or glutamate (Li et al., 2000), can accumulate in the brain and exacerbate neurological injury. Despite some preliminary data supporting this theory, the extent to which vascular mechanisms may contribute to diabetes-related executive dysfunction or to broader cognitive impairments remains unclear.

#### *1.5.4 Role of Insulin Resistance*

Originally thought to be insulin-independent, it is now known that insulin plays an important neurotrophic role within the brain (Craft & Watson, 2004), easily crossing the blood-brain barrier (Banks, Jaspan, Huang, & Kastin, 1997; Banks, Jaspan, & Kastin, 1997) and interacting with widely distributed receptors in many brain regions (Craft & Watson, 2004). These regions include areas that are critical to cognitive and behavioral

function, such as the cerebral and frontal cortices, hippocampus, basal ganglia, substantia nigra, hypothalamus, septum, and amygdala (Marks, Porte, Stahl, & Baskin, 1990; Unger et al., 1989).

The relationship between insulin resistance and cognitive dysfunction is particularly interesting in light of findings suggesting that the incidence of Alzheimer's disease is elevated in individuals with type 2 DM and insulin resistance (Cukierman-Yaffe et al., 2009; Kuusisto et al., 1997; Luchsinger et al., 2007; Ott et al., 1999), and vice versa (Janson et al., 2004). It is unclear whether this relationship arises directly from the effects of insulin or insulin resistance on neural tissues, or from the impact of poor metabolic control. However, there is some evidence that those with Alzheimer's disease and normal glycemic levels secrete a greater amount of insulin than control subjects when provided with oral glucose, indicating an increased degree of insulin resistance (Bucht, Adolfsson, Lithner, & Winblad, 1983; Fujisawa, Sasaki, & Akiyama, 1991).

The means by which insulin resistance may contribute to executive and cognitive dysfunction remain a matter of much speculation. Some researchers, noting correlations between inflammatory markers and both type 2 DM and Alzheimer's disease, have proposed the existence of as-yet-unknown common pathophysiological pathways between insulin resistance, inflammation, and Alzheimer's disease (Hak et al., 2001; Yaffe, Blackwell, Whitmer, Krueger, & Barrett Connor, 2006). Others (Lee et al., 1999; Tojo et al., 1996) have observed upregulation of the hypothalamic-pituitary-adrenal axis, and it has been speculated that disruption of this neurological pathway may result in elevated serum cortisol levels that have been linked to impairments in

cognitive processes such as attention, reasoning, concept formation and memory (Forget, Lacroix, Somma, & Cohen, 2000; Lupien et al., 1994).

Although still controversial, it has also been suggested that insulin resistance may promote development of the amyloid beta plaques characteristic of Alzheimer's disease; possibly by increasing the deposition and/or inhibiting the degradation of this protein (Kodl & Seaquist, 2008). Similarities have been noted between the deposition of islet amyloid in the pancreatic islets of individuals with type 2 DM and the deposition of amyloid beta in Alzheimer's disease, suggested that a common pathological mechanism may underlie these findings (Craig, Weissman, & Horwich, 1994). Interestingly, the association between type 2 DM and Alzheimer's disease may hinge, in part, on the presence or absence of the apolipoprotein (APOE) allele  $\epsilon 4$ . Although there is evidence suggesting that insulin-resistance poses a significant risk factor for Alzheimer's disease only in those individuals without this allele (Kuusisto et al., 1997), some research has contradicted this finding (Peila, Rodriguez, & Launer, 2002).

## **1.6 Executive Function, Diabetes, and Gait**

Ambulation is one of the most complex human functions, involving the integration of input from numerous sensory and motor sources with carefully controlled, repetitive motor movements. When intact, this system produces the highly efficient and consistent pattern that is a characteristic of stable gait. When disrupted, however, whether through the process of normal aging or through pathology, the resulting loss of stability results in fluctuations in both temporal and spatial parameters (Hausdorff, 2007). These changes are of considerable concern due to their association with falls, a

major source of mortality, injury, and mobility restriction among older adults (Tinetti & Williams, 1997). Such concerns are magnified within the diabetic population, as these individuals have been shown to be at a higher risk for falls (Gregg, Beckles, et al., 2000) and report a higher incidence of fall-related injuries (Miller, Lui, Perry, Kaiser, & Morley, 1999; Wallace et al., 2002) than those without diabetes.

Among the gait parameters most strongly linked to negative outcomes such as falls are alterations in gait velocity and variability (Cesari et al., 2005; Hausdorff, 2007). More commonly utilized, gait velocity provides a quick, reliable, and easily administered clinical assessment, and a well-established means of predicting major health-related outcomes (Cesari et al., 2005). Specifically, slower self-selected gait velocities, particularly below the level of 1 m/s, have been linked to falls, persistent lower extremity limitation, hospitalization, and death (Cesari et al., 2005; Harada et al., 1995).

Even more powerfully related to fall risk, however, are stride to stride fluctuations in gait across time, commonly referred to as gait variability (Hausdorff, 2005). When conceptualized as inconsistencies in the neuromuscular ability to maintain and regulate a steady gait sequence, it is not surprising that increasing variability in features such as stride length, width, and/or time are associated with increasing instability and a risk for falls (Hausdorff, 2005). Consistent with this, increased gait variability is associated with increased fall risk, with one group observing that an increase in stride length variability of as little as 0.017 m doubled the risk for falls over the following 6-months in community-dwelling older adults (Maki, 1997).

Although cognitive function was once thought to exert little influence on walking ability; however, the neuropsychological factors underlying gait are now increasingly

recognized. This is likely due to a growing appreciation for the fact that locomotion requires not only the generation and control of motor commands, but also an awareness of purpose and ability to process multiple incoming stimuli in order to adapt to dynamic environments (Yogev-Seligmann, Hausdorff, & Giladi, 2008). The integration, sequencing, and monitoring of these various cognitive, motor, and behavioral demands is often attributed to executive function (Lord, Rochester, Hetherington, Allcock, & Burn, 2009). Indeed, a number of studies have indicated that individuals with executive deficits walk slower (Ble et al., 2005; Pettersson, Olsson, & Wahlund, 2007; Sheridan, Solomont, Kowall, & Hausdorff, 2003), demonstrate increased stride variability (Hausdorff, Yogev, Springer, Simon, & Giladi, 2005; Sheridan et al., 2003), and fall more frequently than those with intact executive abilities (Shumway-Cook et al., 2000; Shumway-Cook, Woollacott, Kerns, & Baldwin, 1997).

As with individuals suffering from executive dysfunction, those with diabetes have been shown to exhibit abnormal gait characteristics (Mueller, Minor, Sahrman, Schaaf, & Strube, 1994; Petrofsky, Lee, & Bweir, 2005), likely contributing to the higher risk of falls experienced by this population (Gregg, Beckles, et al., 2000). Highlighting these findings in a recent review of 28 high to moderate quality studies encompassing 772 individuals with diabetes, Allet et al. (2008) identified broad agreement that individuals with diabetes walked more slowly, with greater stride variability, and increased plantar pressures than those without diabetes. This review also described evidence suggesting the existence of abnormalities in kinematic, kinetic, and muscle activation parameters in these individuals.



While the gait deviations observed in older adults with diabetes resemble those associated with executive dysfunction, these abnormalities are most frequently attributed to diabetic peripheral neuropathy. However, there is evidence that individuals with diabetes but no evidence of neuropathy walk at speeds as much as 48% slower than of non-diabetic individuals, with a significantly wider stance, and with increased lower extremity flexion/extension and lateral joint movements, or “errors”. These joint errors appear to be due, in part, to tremors occurring at frequencies implicating a central neurological origin (Petrofsky et al., 2005). Moreover, Brach et al. (2008) found that those with diabetes (n=119) ambulated at speeds 8% slower than non-diabetics, with an 8% shorter step length, 14% wider and 4% longer stance, and 6% longer double support time. Each of these differences was statistically significant, as was the amount (approximately 6%) of the association between diabetes and walking speed explained by executive tasks assessing attention and shifting. When combined with a global cognitive task and a measure of depression, these measures attenuated the relationship between diabetes and gait speed by over 50% after controlling for age, sex, and race.

Furthermore, it appears that the gait abnormalities associated with diabetes could be exacerbated in situations requiring higher levels of executive involvement, such as those involving multi-tasking between simultaneous tasks. For example, Paul et al. (2009) found that performing a serial mental subtraction task or carrying a tray of water-filled cups while walking significantly slowed gait speed by up to 27% in 15 older adults with diabetes and no signs of peripheral neuropathy. In addition, these tasks decreased step length by up to 20% and increased double support time by as much as

17%. That these changes were not significantly different from those elicited in a similar group with diabetic peripheral neuropathy would seem to emphasize a central limitation in the executive ability needed to divide attention between the tasks, rather than a peripheral limitation in the somatosensory pathways affected by diabetic neuropathy.

### **1.7 Executive Function, Diabetes, and Functional Abilities**

It is clear that severe damage to brain areas implicated in executive functioning can produce impairments across a wide spectrum of functional abilities. However, even subtle disturbances that occur in the absence of overt neurological damage are of significant concern, as they are powerful predictors of functional loss (Cahn-Weiner, Malloy, Boyle, Marran, & Salloway, 2000). Although very few studies have investigated whether executive dysfunction may contribute to the disproportionately large degree of physical impairment and disability known to exist within the elderly diabetic population, there is some evidence that this may be the case.

For example, Kuo et al. (2007) analyzed measures of cognition, physical function, and activity of daily living (ADL) status in 2,802 community-dwelling older adults (n=358 with diabetes), revealing a significantly greater rate of decline in performance on an executive measure of attention in subjects with diabetes. This was matched by a significantly increased rate of decline in performance on the physical function component of the Short-Form-36 Health Survey and a measure of ADL function assessing meal preparation, housework, financial and health care management, phone use, shopping, and traveling.

These findings appear to be largely consistent with those reported in a sample of homebound individuals aged 60 and older (Qiu et al., 2006). Indeed, this study noted that subjects with type 2 DM exhibited significant impairments of up to 21% in executive tasks of shifting, working memory, and visuospatial function; as well as a 10% reduction in ADL function on a measure assessing walking, eating, dressing, bathing, toileting, and food preparation. While the authors reported that these poorer ADL scores were related to the observed executive deficits, this was not elaborated upon.

### **1.8 Clinical Implications**

As keen observers of both cognitive and physical functioning, rehabilitation providers are ideally positioned to recognize and address cognitive-motor impairments such as those that appear to be associated with type 2 DM. Given the enormous prevalence of this disease in the elderly population and the known consequences of executive dysfunction in terms of falls and functional limitations, this may have critical implications – especially as multi-disciplinary input from neuropsychology, speech-language pathology, and other such disciplines is not always readily available.

While a number of instruments are available for assessing executive function and its component processes, it seems that the most clinically relevant of these, from a physical therapy and rehabilitation standpoint, are dual-task assessments of multi-tasking ability (Table 1.3). Although such dual-task assessments have yet to achieve widespread use in diabetic populations, the bulk of evidence appears to suggest that these measures can provide valuable objective data regarding an individual's executive ability to safely coordinate and perform simultaneous tasks. In particular, the Walking

and Remembering Test described by McCulloch et al. (2009) addresses many of the limitations generally associated with dual-task assessment (K. McCulloch, 2007). Further research and collaboration with the neuropsychological community will be necessary to establish the validity and reliability of such tasks for older adults with diabetes. However, it seems likely that the use of these tools will enhance recognition of cognitive-motor deficits in this population, and may help identify patients at risk for falls and other functional impairments.

In addition to facilitating clinical assessment, the executive process of multi-tasking appears to be an attractive target for intervention strategies aimed at improving functional and/or cognitive ability. Indeed, preliminary evidence indicates that dual-task training interventions may beneficially impact function. Silsupadol et al. (2009), for example, found that a randomized and controlled 4-week training intervention combining balance activities with number recall and animal naming tasks improved dual-task gait speed by as much 0.18 m/s (effect size 0.46-0.57) in older adults with balance impairments. Similar results have also been reported in randomized, controlled studies examining dual-task interventions in older adults with dementia (Schwenk, Zieschang, Oster, & Hauer, 2010). Notably, the lack of significant improvements in dual-task abilities observed in the control groups of these studies indicate that single-task training alone may not improve dual-task ability. As dual-task activities often more closely mimic normal function than do single-task activities, therapists may be well advised to consider incorporating such activities into their treatment plans.

## **1.9 Conclusions**

While it is difficult to fully elucidate their impact, it seems likely that disease-related changes in executive function adversely affect functional abilities in older adults with type 2 DM. Physical therapists and other rehabilitation providers should be prepared to recognize possible impairments in executive function in older patients with diabetes, and understand that these changes may directly or indirectly influence even the most basic daily activities.

Although not commonly applied in populations with DM, executive assessments involving dual-task performance appear to represent a promising means of both assessment and treatment. Through close collaboration with the neuropsychological community, future research should establish the validity, predictive ability, efficacy, and generalizability of such strategies. Ultimately this will allow a clearer picture of diabetes-related executive and cognitive impairment to emerge, facilitating the development of clinical tools that may be employed to detect and address the devastating consequences of this disease.

## **1.10 Specific Aims and Hypotheses of this Work**

As illustrated in this chapter, the integrity and influence of multi-tasking and other executive functions in older adults with type 2 diabetes remains poorly understood. *The purpose of this body of work is to determine whether executive processes, particularly those involved in multi-tasking, are impaired in older adults with type 2 DM, and to examine how these processes may contribute to functional abilities.*

Specific Aim 1: To determine whether the executive domain of multi-tasking is impaired in older adults with type 2 DM. Impairments in the ability to multi-task have been observed in older adults, as well as in individuals suffering from a broad range of disorders associated with executive dysfunction. Although some evidence suggests that individuals with type 2 DM also exhibit deficits in the multi-tasking, much of this research suffers from substantial methodological limitations. *We hypothesize that older adults with type 2 DM will demonstrate impaired multi-tasking, as evidenced by increased dual-task costs associated with the performance of the Walking and Remembering Test (Hypothesis 1) and a Pursuit Rotor test (Hypothesis 2), when compared to those without diabetes.*

Specific Aim 2: To examine the relationship between the executive domain of multi-tasking and measures of functional ability in older adults with type 2 DM. Despite apparent links between multi-tasking and the ability to perform functional activities, such as gait and activities of daily living, the extent to which multi-tasking contributes to these functional abilities in individuals with type 2 DM remains largely unknown. *We hypothesize that a measure of multi-tasking, the grand dual-task cost associated with the Walking and Remembering Test and Pursuit Rotor test, will serve as a significant predictor of criterion measures of gait velocity (Hypothesis 3), stride time variability (Hypothesis 4), physical functioning (Hypothesis 5) and disability (Hypothesis 6), obtained from quantitative gait analysis and the Late Life Function and Disability Index, in older adults with type 2 DM.*

Specific Aim 3: To explore whether other domains of executive function and cognition are impaired in older adults with type 2 DM, and how these domains may relate to functional ability in this population. In addition to multi-tasking, there are indications that older adults with type 2 DM may also exhibit impairments in domains of executive function such as updating, shifting, and inhibition; as well as in executive and cognitive operations such as perceptual and visuospatial organization and memory and logical memory. Due to limitations in the measures used to assess this population, however, the nature of diabetes-related dysfunction with regard to these processes remains unclear, as do their potential contributions to functional abilities. *In this exploratory aim we will collect data on these executive and cognitive domains in order to examine their integrity in older adults with type 2 DM, as well as their associations with physical function and disability.*

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## **Chapter 2 Preface**

As described in Chapter 1, individuals with diabetes appear to be susceptible to disturbances in executive function that may adversely affect functional abilities. Chapter 2 details our first attempt to examine multi-tasking and executive function in this population, and explore its relationship to physical function. Through collaboration with a larger study of fall risk in people with diabetic peripheral neuropathy, led by Stephen Jernigan PT, PhD, we administered a measure of multi-tasking, the Cognitive Timed Up and Go test, and a small battery of common tests of executive function to a total of 20 subjects.

The initial comparison of these results to normative values reported in the literature proved very interesting; our subjects appeared to perform poorly on the Cognitive Timed Up and Go and in areas of verbal and visuospatial function. Armed with this data, we received institutional approval to administer our multi-tasking and executive assessment battery to a group of 20 non-diabetic individuals of similar age. The comparison of this group to our sample of individuals with diabetic peripheral neuropathy comprises Chapter 2.

## Chapter 2

### Pilot Study of Multi-tasking and Executive Function in Adults with Diabetic Peripheral Neuropathy

Rucker JL, Jernigan, SD, McDowd JM, and Kluding PM. Adults with Diabetic Peripheral Neuropathy Exhibit Deficits in Multi-tasking and Other Executive Functions. *Journal of Neurologic Physical Therapy*. 2014; (38)2: xx-xx (in press).

## 2.1 Abstract

**BACKGROUND AND PURPOSE:** Diabetic peripheral neuropathy (DPN) contributes to functional impairment, and there is growing evidence that neuropsychological factors also influence physical function. We compared cognitive and executive function in adults with DPN to an age-matched comparison group, and examined the relationships between DPN, executive function, and physical function. **METHODS:** Twenty subjects with DPN and 20 comparison subjects were assessed. DPN was quantified via the Michigan Neuropathy Screening Instrument and nerve conduction velocity testing. Subjects were administered Beck's Depression Inventory, the Mini Mental Status Examination, and the Timed Up and Go test (TUG). Each subject also completed a battery of 7 executive function tasks, including the Cognitive Timed Up and Go test (cTUG), in which a concurrent mental subtraction task was added to the standard TUG test. **RESULTS:** The DPN group had poorer global cognitive scores and reported more symptoms of depression. This group also performed worse on executive measures of verbal fluency and visuospatial function, and took longer to complete both the TUG and cTUG. Poorer global cognitive performance and greater depression symptoms were significantly related to each other and to slower TUG times. **DISCUSSION AND CONCLUSIONS:** Verbal, visuospatial, and multi-tasking measures of executive function may be impaired in adults with DPN. Future research should examine how these and other cognitive and psychological factors, such as depression, affect physical function in this population.

## 2.2 Introduction

Current estimates suggest that diabetes affects at least 25.8 million individuals in the United States and, with aging, will likely affect over one-quarter of the adult population (Centers for Disease Control and Prevention [CDC], 2011). Of the many complications related to diabetes, diabetic peripheral neuropathy (DPN) is among the most common, occurring in up to 60% of adult patients (CDC, 2011). Resulting from peripheral nerve degeneration and impaired neural regeneration, DPN typically manifests as symmetrical pain and/or loss of sensation in the distal extremities (Sinnreich, Taylor, & Dyck, 2005). This is of substantial concern, as DPN is associated with impaired balance, gait abnormalities, and an increased risk for lower extremity amputation (Mueller, Minor, Sahrman, Schaaf, & Strube, 1994; Thurman, Stevens, & Rao, 2008).

While its destructive effects on peripheral nerve function are well established, there is also evidence that diabetes damages central nervous system structures underlying important cognitive functions (Kodl & Seaquist, 2008). In particular, adults with diabetes appear to demonstrate deficits in executive function; the broadly defined set of processes responsible for planning, coordinating, sequencing, and monitoring cognitive operations (de Wet, Levitt, & Tipping, 2007; Manschot et al., 2006; Qiu et al., 2006; Yeung, Fischer, & Dixon, 2009). Such diabetes-related executive impairments are especially interesting in light of studies highlighting the complex interplay between cognitive processes and functional motor skills.

Much of the research related to the association between cognitive and motor functions centers on the ability to multi-task in order to perform simultaneous activities. However, other executive processes, such as attention, task shifting, working memory,

verbal fluency and organization, and visuospatial organization, may also link cognitive and physical function. Several investigations have found that executive function contributes to gait in individuals with diabetes. Brach et al. (2008) examined walking speed in a sample of 558 older adults, finding it to be significantly slower in those with diabetes. Interestingly, scores on the Trail Making Test, a common measure of executive function, explained a greater portion of this relationship than lower extremity vibratory perception, a measure of DPN. Likewise, executive measures involving dual-task performance (e.g. walking while performing serial mental subtraction) have been shown to impair gait in individuals with diabetes, both with and without DPN (Paul, Ellis, Leese, McFadyen, & McMurray, 2009; Roman de Mettelinge et al., 2013).

Although it is clear that DPN contributes to the elevated fall risk and functional impairments experienced by those with diabetes, almost nothing is known about executive abilities in those with DPN and how these factors interact to influence physical function. The purpose of this study was to examine whether adults with DPN exhibited changes suggestive of executive dysfunction, and to explore the relationships between measures of neuropsychological function, peripheral neuropathy, and functional ability.

## **2.3 Methods**

### *2.3.1 Study Design and Sample*

This cross-sectional study was conducted in collaboration with a larger investigation of fall risk assessment in individuals with DPN. Institutional approval for both studies was granted by the human subjects committee of the University of Kansas Medical Center.

A total of 20 individuals with DPN and 20 individuals without diabetes (ages 40-65 years) were recruited for the study. Diagnosis of DPN was confirmed via administration of the Michigan Neuropathy Screening Instrument (MNSI) and nerve conduction studies of the tibial and peroneal nerves. If screening and/or nerve conduction testing raised questions about the presence of DPN, a collaborating neurologist was consulted to determine the presence or absence of the condition. Exclusion criteria included the following: 1) major medical depression, 2) musculoskeletal problems limiting ambulation, 3) open wounds on the feet, 4) inability to ambulate independently, 5) uncorrectable visual deficits, 6) central nervous system pathology or dementia, and 7) untreated vestibular disorder and/or postural hypotension.

### *2.3.2 Procedures*

After signing an institutionally-approved consent form, data regarding age, height, and weight were recorded for each subject. Those with DPN were then administered the MNSI, and glycosylated hemoglobin (HbA1c) and nerve conduction testing were completed. Finally, all subjects completed measures assessing depression symptoms and global cognitive function, followed by the TUG, cTUG, and a battery of executive function tests administered in a standardized order. All cognitive testing was conducted by the same investigator in a quiet laboratory setting to minimize distraction. Nerve conduction assessment was conducted by a research technician in the Department of Neurology at the University of Kansas Medical Center.

### 2.3.3 Measures

The following assessments were obtained from subjects with DPN:

- 1) The Michigan Neuropathy Screening Instrument (MNSI) symptom questionnaire was used to assess self-reported symptoms of DPN via yes/no response to 15 items, reflecting the frequency and severity of neuropathic symptoms. A higher score on a scale of 0-13 indicated greater neuropathic symptoms ().
- 2) The MNSI physical exam score was used to assess foot appearance, vibration sense, reflexes, and monofilament sensation. A score of 2 or more on a scale of 0-10 suggested the presence of peripheral neuropathy (Feldman, Russell, Sullivan, & Golovoy, 1999).
- 3) Nerve conduction studies were used to assess nerve conduction velocity, amplitude, and latency of the right lower extremity peroneal and tibial nerves.

The following assessments were obtained from all subjects in both the DPN and comparison groups:

- 1) Beck's Depression Inventory-II was used to quantify self-reported symptoms of depression. This measure is scored on a 21-item, 63-point scale, with scores of 19 or less indicating minimal symptoms of depression, 20-28 moderate symptoms, and  $\geq 29$  severe symptoms (Beck, Steer, & Brown, 1996).
- 2) The Mini-Mental Status Examination (MMSE) was used to assess global cognitive function. This 30-point instrument broadly reflected orientation, memory, concentration, and praxis, with scores of  $< 24$  indicating severe cognitive impairment (Folstein, Folstein, & McHugh, 1975).

- 3) The Timed Up and Go test (TUG) was used to assess functional mobility (Shumway-Cook, Brauer, & Woollacott, 2000). Subjects stood from a chair and walked 3 m, turned, returned to the chair, and sat down. The TUG was performed twice, and the average time in seconds recorded. This value also represented single-task walking time for analyses of multi-tasking ability.
- 4) The Cognitive Timed Up and Go Test (cTUG) was used to assess multi-tasking during functional mobility (Shumway-Cook et al., 2000). Subjects performed the standard TUG with a simultaneous cognitive task in which they serially subtracted 3's from a random number between 80 and 100. The cTUG was performed twice, and the average time to complete the walking task and the rate of correctly reported digits per second of walking time were recorded. A single-task trial of the cognitive task was then performed while the subject was seated. The time allowed for this single-task cognitive trial was equivalent to the subject's average cTUG time.
- 5) The Rey Osterrieth Complex Figure was used to assess visuospatial organization. Subjects were given a copy of an asymmetrical geometric figure and asked to draw the figure as accurately as possible without the use of a straight edge. Each drawing was scored by the same examiner on a standardized 36-point scale, with higher scores indicating greater accuracy (Lezak, Howieson, Loring, Hannay, & Fischer, 2004).
- 6) Letter and Category Fluency were used to assess verbal fluency and organization (Lezak et al., 2004). Subjects were given a letter of the alphabet (F, A, S) or category (animals, vegetables, articles of clothing) and allowed 1 minute



to verbally provide as many words as possible (excluding proper nouns) beginning with that letter or falling within that category. The total number of words provided for the 3 letters and 3 categories represented letter fluency and category fluency, respectively.

- 7) Forward and reverse digit span were used to assess attention and working memory, respectively (Lezak et al., 2004). Subjects were read a series of digits and asked to immediately repeat the digits back in the same order, or in reverse order. The number of correctly reported digits, ranging from 0-8 (forward) and 0-7 (reverse), was recorded.
- 8) The Trail Making Test was used to assess task shifting ability (Homack, Lee, & Riccio, 2005). In part A of the test, subjects drew a line connecting series of letters or numbers in order as quickly as possible (e.g. A-B-C; 1-2-3 etc). In part B of the test subjects drew a line connecting numbers and letters in an alternating fashion (e.g. 1-A-2-B etc.). A percent difference score between the two conditions was calculated by taking the difference between the times required to complete parts A and B, divided by the time required to complete part A.

#### *2.3.4 Statistical Analysis*

Data analysis was conducted using SPSS 16.0 for Windows (Chicago, IL). In order to examine multi-tasking performance on the cTUG a percent change, or dual-task cost, from the single-task condition to the dual-task condition was calculated for both walking time and rate of cognitive task performance via the following formula:

$$|\text{Dual-task Cost}| = \frac{(\text{Dual-task performance} - \text{Single-task performance})}{\text{Single-task performance}} \times 100$$

Data distribution was examined via scatterplot, and descriptive statistics calculated for each measure. Between-group mean differences were assessed with 2-tailed independent t-tests, and within-group changes from single- to dual-task conditions assessed with 2-tailed paired t-tests. Pearson-product-moment correlations examined the relationships between variables. An alpha level of 0.05 was used to assess the significance of all findings.

## **2.4 Results**

### *2.4.1 Sample Characteristics*

General characteristics of the two groups are illustrated in Table 2.1. Twenty people with DPN (8 female; age 58.4±6.2 years) and 20 people without diabetes (14 female; age 54.9±6.1 years) participated in the study. Differences in age between the two groups were not significant (p=0.08). Glycemic control in those with DPN was impaired (HbA1c 7.2±1.4%; range 5.6-11.0). Subjects with DPN demonstrated greater BMI (37.0±8.4 vs. 24.8±4.1 kg/m<sup>2</sup>, p<0.001); as well as higher levels of depression (Beck's Depression Inventory 11.3±6.5 vs. 1.6±1.8, p<0.001) and lower global cognitive scores (MMSE 27.8±2.0 vs. 29.5±0.8, p=0.001).

**Table 2.1: Subject Characteristics**

	DPN (n=20)	Comparison (n=20)	P-value
Age	58.4 ± 6.2	54.9 ± 6.1	0.080
Sex	8 female	14 female	NA
BMI	37.0 ± 8.4*	24.8 ± 4.1	< 0.001
BDI	11.3 ± 6.5*	1.6 ± 1.8	< 0.001
MMSE	27.8 ± 2.0*	29.5 ± 0.8	0.001
HbA1c	7.2 ± 1.4	NA	NA

**Table 2.1:** Data are presented as mean ± SD. Abbreviations: DPN, diabetic peripheral neuropathy; BMI, body mass index; BDI, Beck's Depression Inventory; MMSE, Mini-Mental Status Examination; NA, not applicable. \*Significant between-group difference at p<0.05.

#### 2.4.2 Peripheral Neuropathy Measures

The results of DPN screening and tibial and peroneal nerve conduction testing are provided in Table 2.2. One subject declined to undergo nerve conduction testing. In the remaining sample of 19 subjects, MNSI-subjective (mean score 3.1±2.0), MNSI-physical (mean score 5.9±2.6), and nerve conduction measures (peroneal nerve conduction velocity 40.9±5.1 m/s; tibial nerve conduction velocity 38.9±4.3 m/s) were consistent with the presence of neuropathy.

**Table 2.2: Results of Peripheral Neuropathy and Executive Assessments**

	DPN	Comparison	P-value
<b>MNSI – subjective (score out of 13)</b>	3.1 ± 2.0	NA	NA
<b>MNSI – physical (score out of 10)</b>	5.9 ± 2.6	NA	NA
<b>Peroneal nerve conduction velocity (m/s)</b>	40.9 ± 5.1	NA	NA
<b>Tibial nerve conduction velocity (m/s)</b>	38.9 ± 4.3	NA	NA
<b>Rey-Osterrieth Complex Figure (score out of 36)</b>	25.9 ± 4.3*	31.7 ± 2.4	< 0.001
<b>Letter fluency (words)</b>	34.2 ± 11.6*	46.2 ± 12.2	0.003
<b>Category fluency (words)</b>	47.0 ± 8.1*	56.3 ± 8.5	0.001
<b>Forward digit span (digits)</b>	10.1 ± 1.9	10.5 ± 2.6	0.535
<b>Reverse digit span (digits)</b>	6.3 ± 2.3	6.0 ± 1.9	0.655
<b>Trail Making Test Change (% difference)</b>	32.1 ± 43.0	12.7 ± 21.0	0.077

**Table 2.2:** Data are presented as mean ± SD. Peroneal and tibial nerve conduction velocity was assessed in 19 subjects. Abbreviations: DPN, diabetic peripheral neuropathy; MNSI, Michigan Neuropathy Screening Instrument; NA, not applicable. \*Significant between-group difference at p<0.05.

#### *2.4.3 Timed Up and Go Performance*

The results of the TUG are illustrated in Figure 2.1. On average, the DPN group required more time to complete the TUG than the comparison group (10.3±2.8 vs. 5.9±1.0 seconds, p<0.001).

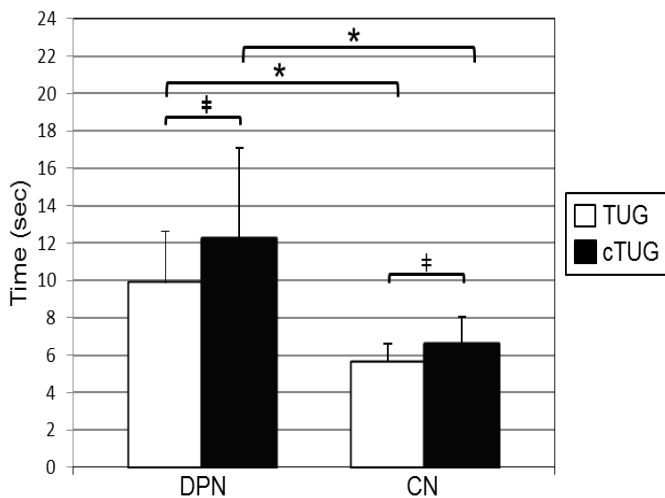
#### *2.4.4 Cognitive Timed Up and Go Performance*

The results of the cTUG are illustrated in Figures 2.1 and 2.2. Those with DPN required more time to complete the cTUG than comparison subjects (13.0±5.8 vs.

6.9±1.6 seconds,  $p<0.001$ ). The added cognitive task slowed walking time in both the DPN (+2.7±3.4 seconds,  $p=0.002$ ) and comparison groups (+1.0±0.9 seconds,  $p<0.001$ ). However, percent changes from single- to dual-task conditions (e.g. dual-task cost) for walking speed were not different between the groups ( $p=0.45$ ).

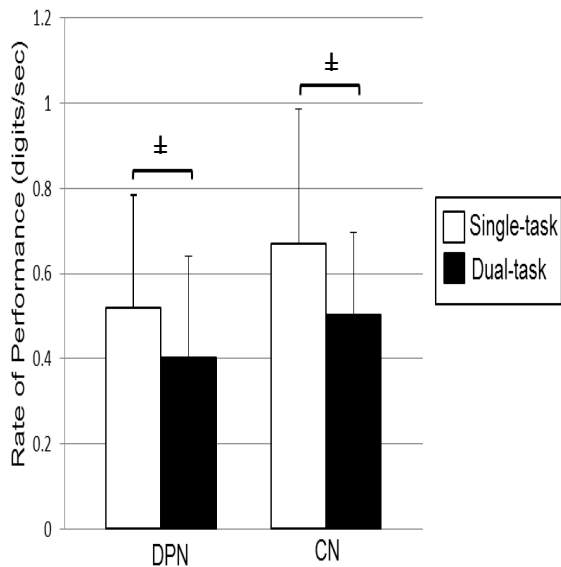
The rate at which subjects performed the cognitive task also declined under dual-task conditions in both groups (DPN:  $-0.12\pm0.12$  digits/second,  $p<0.001$ ; CN:  $-0.17\pm0.22$  digits/second,  $p=0.003$ ). However, there were no between-group differences in either single- or dual-task cognitive performance ( $p=0.11$  and  $0.14$ , respectively) or in the dual-task cost for the cognitive task ( $p=0.53$ ).

**Figure 2.1: Timed Up and Go and Cognitive Timed Up and Go Walking Speed**



**Figure 2.1:** Timed Up and Go (TUG; white bars) and Cognitive Timed Up and Go tests (cTUG; black bars) walking speed. The cTUG test involved the addition of a simultaneous cognitive task to the standard TUG test. \*Significant between-group difference at  $p<0.05$ . #Significant within-group difference at  $p<0.05$ .

## **Figure 2.2: Single- and Dual-task Cognitive Performance**

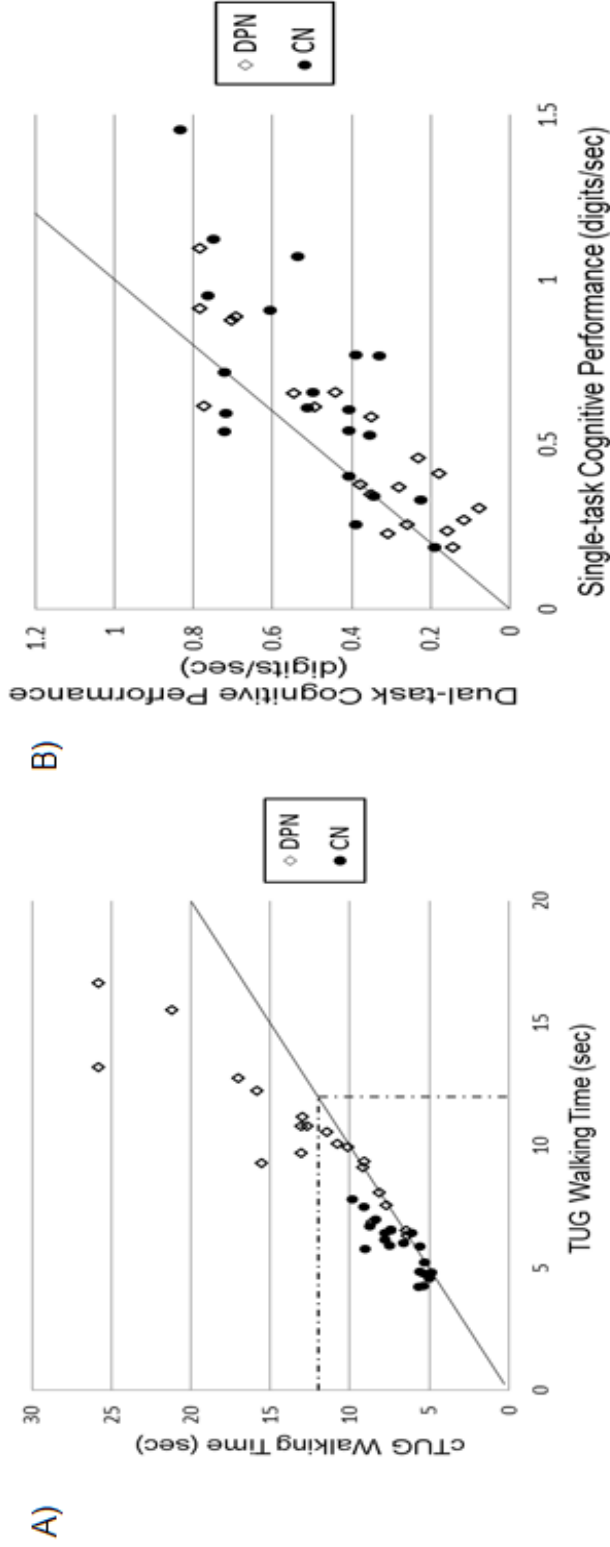


**Figure 2.2:** Cognitive task performance under single- (white bars) and dual-task conditions (black bars). Under single-task conditions, subjects serially subtracted 3's from a random number between 80 and 100 while seated. Under dual-task conditions, subjects completed the same cognitive task while simultaneously performing the TUG test (e.g. the cTUG). The time allowed for the cognitive task under single- and dual-task conditions was equivalent. ±Significant within-group difference at  $p < 0.05$ .

In order to explore whether subjects with DPN prioritized the two cTUG tasks differently than comparison subjects, we examined the patterns of individual dual-task costs for the walking and cognitive tasks (Figure 2.3). This was done by plotting each subject's single-task performance against their dual-task performance for both walking speed (A) and rate of cognitive task performance (B). The distance the point fell from a line representing no change in performance from single- to dual-task conditions (e.g. a dual-task cost of 0%) reflected the dual-task cost for that particular task.

This analysis revealed that comparison subjects exhibited an average dual-task cost in walking speed of  $17.0 \pm 14.6\%$ , with a similar but more variable cost to the cognitive task of  $17.5 \pm 28.5\%$ . In contrast, subjects with DPN exhibited large and highly variable dual-task costs in both walking speed and cognitive task performance ( $22.1 \pm 26.1$  and  $23.0 \pm 26.7\%$ , respectively).

**Figure 2.3: Dual-task Effect on Walking (A) and Cognitive (B) Performance**



**Figure 2.3:** Effect of dual-task performance on walking speed (A) and cognitive task (B) performance. Solid diagonal line represents identical task performance in single- and dual-task conditions (e.g. no change in performance, or dual-task cost, from single- to dual-task conditions). In A, the dual-task conditions of the cTUG generally increased walking time from the single-task TUG. Thus points falling above the diagonal line reflect poorer walking performance under dual-task conditions (e.g. a greater dual-task cost); whereas points below the line reflect improved walking performance under dual-task conditions. Dashed lines indicate proposed TUG fall-risk cut-off of 12 seconds for adults 65-85 years (Bischoff et al., 2003). In B, dual-task conditions generally decreased the rate of performance of the cognitive task. Thus points falling below the diagonal line reflect poorer cognitive task performance under dual-task conditions; whereas points falling above the line reflect improved cognitive performance under dual-task conditions.

#### *2.4.5 Executive Function Measures*

The results of the remaining executive function measures are provided in Table 2.2. The DPN group performed worse on the Rey Osterrieth Complex Figure ( $25.9 \pm 4.3$  vs.  $31.7 \pm 2.4$  points,  $p < 0.001$ ) and measures of letter ( $34.2 \pm 11.6$  vs.  $46.2 \pm 12.2$  words,  $p = 0.003$ ) and category fluency ( $47.0 \pm 8.1$  vs.  $56.3 \pm 8.5$  words,  $p = 0.001$ ). No between-group differences were observed on forward digit span ( $p = 0.535$ ), reverse digit span ( $p = 0.655$ ), or Trail Making Test ( $p = 0.077$ ).

#### *2.4.6 Relationships between Neuropsychological Function, DPN Measures, and TUG Performance*

For 19 subjects with DPN, relationships between age, BMI, HbA1c, depression, signs and symptoms of DPN, and neuropsychological function were examined using Pearson-product moment correlation coefficients. Selected correlations from this data are presented in Table 2.3. Surprisingly, older age was associated with a lower MNSI physical score ( $r = -0.57$ ,  $p = 0.009$ ), and higher scores on this instrument (e.g. more signs of DPN) were associated with better category fluency scores ( $r = 0.45$ ,  $p = 0.05$ ).

No other measure of DPN was significantly related to any neuropsychological test or to the TUG. Of the remaining variables only depression, BMI, and MMSE scores were associated with cognitive function or TUG performance. Greater symptoms of depression were related to poorer performance on the MMSE ( $r = -0.46$ ,  $p = 0.04$ ) and TUG ( $r = 0.54$ ,  $p = 0.02$ ), while poorer MMSE score was related to slower TUG time ( $r = -0.53$ ,  $p = 0.02$ ). Paradoxically, higher BMI was associated with a better score on the Rey Osterrieth Complex Figure test ( $r = 0.47$ ,  $p = 0.04$ ).



**Table 2.3: Correlations between Measures of Neuropsychological Function, Nerve Function, and the TUG Test in Subjects with DPN**

	MMSE	ROCF	LF	CF	TUG
BDI	-0.46*	-0.03	0.12	0.20	0.54*
MNSI-S	-0.25	-0.03	-0.25	0.22	0.19
MNSI-P	0.14	0.30	0.06	0.45	-0.07
PNCV	-0.09	-0.25	0.03	-0.02	0.04
TNCV	0.17	-0.15	-0.04	0.03	-0.25
TUG	-0.53*	-0.19	-0.28	-0.08	--

**Table 2.3:** Abbreviations: BMI, body mass index; BDI, Beck's Depression Inventory; MNSI-S, Michigan Neuropathy Screening Instrument – subjective; MNSI-P, Michigan Neuropathy Screening Instrument – physical; PNCV, peroneal nerve conduction velocity; TNCV, tibial nerve conduction velocity; TUG, Timed Up and Go; MMSE, Mini-Mental Status Examination; ROCF, Rey-Osterrieth Complex Figure; LF, Letter fluency; CF, Category fluency. \*Significant at  $p < 0.05$ .

## 2.5 Discussion

Our study provides preliminary evidence suggesting that individuals with DPN exhibit disturbances in aspects of executive function. Other researchers have reported similar findings of neuropsychological dysfunction in those with diabetes. For example, Yeung et al. (2009) reported that older adults with type 2 diabetes performed significantly worse on several executive measures than those without diabetes.

Notably, these differences persisted after dividing the subjects into young-old (53-70 years) and old-old (71-90 years) sub-groups, suggesting that the deficits were due to diabetic status rather than age. Likewise, Thabit et al. (2009) found that nearly half of their sample of 50 older adults with type 2 diabetes demonstrated significant executive

impairments, particularly in verbal fluency, on a standardized measure of executive function.

While our data are broadly consistent with such studies, it is important to note that we did not establish the educational level of our subjects. It is possible that some of the deficits we observed, particularly with regard to verbal fluency, reflect differences in education between the groups. However, we also observed differences on a measure less likely to be influenced by educational level. Specifically, we found that those with DPN performed significantly worse on the Rey Osterrieth Complex Figure, an untimed test of visuospatial organization in which the subject simply copies an asymmetrical geometric figure and is scored according to the accuracy of their reproduction.

Although our neuropsychological findings are interesting, their impact on everyday function remains unclear. We did not observe relationships between measures of executive function and the TUG; however others have reported that poor performance on executive measures containing visuospatial and verbal executive components negatively influences diabetes care (Munshi et al., 2006) and disease self-management (Thabit et al., 2009). Further research is clearly needed to examine whether visuospatial, verbal, and/or other measures of executive function can be specifically linked to functional outcomes such as gait or ADL performance in this and other populations.

Our analysis of TUG performance revealed that the DPN group walked significantly slower than the comparison group. They also took longer to complete the walking portion of the cTUG, with the added cognitive task slowing walking speed by

22%. This is consistent with reported declines of 25% and 22% under similar dual-task walking conditions in subjects with diabetes with and without DPN, respectively (Paul et al., 2009); although the “dual-task cost” in walking speed for our subjects with DPN was not statistically greater than the 17% decline we observed in comparison subjects.

In comparison to published literature, the average cTUG time for our comparison group (6.9 seconds) was well below the average TUG time reported by Bohannon (2006) for individuals aged 60-69 years (8.1 seconds). In contrast, the average cTUG time for those in the DPN group (13.0 seconds) was comparable to the reported average TUG time of individuals aged 80-99 years (Bohannon, 2006). The average cTUG time for those in the DPN group also exceeded the fall risk cut-off score of 12 seconds proposed for community-dwelling adults aged 65-85 years (Bischoff et al., 2003). The fact that the mean age of our DPN sample was only 58 appears to highlight the potential functional implications of multi-tasking in this population.

One possible explanation for the decline in cTUG walking performance is that subjects focused their attention on the cognitive task at the expense of walking speed. This does not appear to have been the case in our study, as cognitive task performance also declined significantly in both groups; although the 26% decline in cognitive performance exhibited by the DPN group was not statistically different than the 19% decline observed in the comparison group.

The fact that we did not observe differences in the dual-task costs of walking or cognitive performance between the groups may result from the large degree of variability elicited by these tasks. This may have occurred because, while we instructed subjects to “walk as quickly and safely as possible,” we did not explicitly instruct them to

prioritize either the walking or cognitive task during the cTUG. The substantially greater degree of variability in cognitive versus walking task performance exhibited by comparison subjects suggests that this group more often opted to sacrifice cognitive task performance in order to protect walking speed. This was in rather stark contrast to those in the DPN group, who seemed unable to consistently protect either task. We observed that subjects who performed worst on the TUG appeared least likely to protect walking performance under the dual-task conditions of the cTUG. This was particularly notable in the DPN group and is alarming, as it indicates that individuals already at risk for falling may fail to self-protect walking and/or balance when multi-tasking – potentially placing them at even greater fall risk.

In order to more clearly characterize multi-tasking performance, future research may benefit from dual-task measures that do not require mathematical ability and account for both gait speed and stability, such as the Walking and Remembering Test (McCulloch & Marshall, 2004). Likewise, studies that directly influence and/or manipulate task priority may improve understanding of how attention is allocated under dual-task conditions and help explain whether and/or why different populations fail to protect function and safety while multi-tasking.

Because little research has explored the relationships between central and peripheral nervous system function in those with DPN, and it is unclear how these measures may be associated with functional ability in this population, we explored the correlations among measures of neuropsychological function, DPN, and the TUG. Interestingly this analysis indicated that depression and cognitive function were associated with each other, and were the only variables significantly related to slower

TUG performance. This is consistent with other studies that have linked depression to cognitive dysfunction in those with diabetes (Bruce, Casey, & Grange, 2003) and associated both factors with gait (Brach et al., 2008) and functional deficits (Ciechanowski, Katon, & Russo, 2000).

Despite the fact that the prevalence of depression in those with diabetes is nearly twice as high as the non-diabetic population (Ali, Stone, Peters, Davies, & Khunti, 2006) these relationships remain largely unrecognized. This is perhaps because conventional wisdom suggests that somatosensory and proprioceptive deficits resulting from DPN are the primary mediators of functional impairments. Although exploratory, our findings suggest that the factors underlying fall risk and disability in those with DPN are much more numerous, diverse, and subtle than traditionally thought.

Our analysis also indicated an association between higher BMI and better visuospatial performance on the Rey Osterrieth Complex Figure. Although counter-intuitive, there is a large body of recent evidence supporting a so-called “obesity paradox,” in which obesity and/or higher BMI provide some degree of protective benefit in terms of cognitive functions, including attention and visuospatial function (Gunstad, Lhotsky, Wendell, Ferrucci, & Zonderman, 2010), and lower the risk of mortality in those with diabetes (Carnethon, Chavez, & Biggs, 2012; Kokkinos et al., 2012; Doehner, Erdmann, & Cairns, 2012). Clearly, no conclusions on such matters can be drawn from our small sample. However, our findings join those of others in cautioning that the factors positively and/or negatively influencing cognitive function in complex diseases such as diabetes may not be as straightforward as conventional wisdom would suggest.

We acknowledge that there are a number of factors limiting interpretation of our data. In addition to the small sample size, first and foremost is the fact that we did not establish the education level of our subjects. This factor undoubtedly may have influenced performance on some cognitive measures, particularly those involving verbal fluency and/or mathematical ability. However, we also observed deficits in measures, such as the Rey Osterrieth Complex Figure, that would not seem to be heavily influenced by education, and the fact that the groups did not perform differently on the mathematical component of the cTUG suggests that education level may not have substantially influenced this measure. Differences in variables such as sex, duration of diabetes, and the presence and number of other comorbidities may have also influenced our results.

Another limitation, inherent to our study, is the difficulty in assessing complex cognitive abilities such as executive function. This is a topic of much debate within the neuropsychological community, and a standardized approach has yet to be determined (Miyake, Emerson, & Friedman, 2000). Our assessment battery is consistent with current recommendations that executive function be analyzed via multiple measures assessing specific aspects of the executive construct; as opposed to simply relying on one or two measures to globally represent executive function.

Finally, we performed multiple correlations to explore the relationships between demographic factors, measures of neuropsychological function and DPN, and the TUG. Due to the small size and novel nature of our investigation, we did not correct for these multiple analyses. While this unquestionably limits our interpretation, the significant correlation coefficients we observed were relatively strong and provide interesting

avenues for further research. The findings of our study should be regarded with caution, and certainly causal relationships cannot be inferred between any of the variables we examined. It is not clear that differences in cognitive function resulted directly from diabetes or depression. Nor can it be said that cognitive deficits, depression, or any other variable caused gait dysfunction. However, we feel that our data do emphasize the complex and multi-factorial relationships between neuropsychological and physiological factors and physical function in those with diabetes and DPN.

## **2.6 Conclusions**

Our investigation suggests that adults with DPN exhibit disturbances in visuospatial and verbal aspects of executive function. Further, our data support the view that gait dysfunction, fall risk, and disability in those with diabetes may not be solely a consequence of DPN and/or musculoskeletal impairment. It is critical that clinicians recognize the potential influence of cognitive and psychological function on physical abilities in patients with DPN so that gait dysfunction, fall risk, and disability can be effectively identified and treated in this high risk patient population.

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### **Chapter 3 Preface**

Our preliminary investigation of executive function in individuals with diabetes revealed possible executive deficits in multi-tasking, verbal fluency, and visuospatial organization. Although these findings were quite interesting, our ability to interpret this data was hampered by a number of substantial methodological limitations. In order to address these limitations, we first turned our attention to conducting a more detailed analysis of what we felt was likely the most functionally relevant of these executive processes – the ability to multi-task. We also chose to shift our focus to the segment of the diabetic population commonly identified as being at highest risk for both cognitive and functional decline – older adults with type 2 diabetes.

We first identified two instruments, the Walking and Remembering and Pursuit Rotor Tests, that would allow us to describe multi-tasking much more robustly than the Cognitive Timed Up and Go alone. These assessments, in addition to spatiotemporal measures of single-task gait and self-reported functional ability and limitation, were administered to 40 individuals with diabetes aged 60 and older, as well as a comparison group of 40 non-diabetic individuals paired according to age, sex, educational level, and the presence or absence of hypertension. The analysis of multi-tasking performance between these two groups, and our exploration of the relationships between these abilities and measures of gait and function, comprises Chapter 3.

## Chapter 3

### Multi-tasking in Older Adults with Type 2 Diabetes Mellitus

A version of this chapter is in preparation for submission to *Physical Therapy: the Journal of the American Physical Therapy Association* (2014)

### **3.1 Abstract**

**BACKGROUND AND PURPOSE:** Deficits in the ability to multi-task contribute to gait abnormalities and falls in many at-risk populations. However, it is unclear whether older adults with type 2 diabetes mellitus (DM) also demonstrate impairments in multi-tasking. We examined multi-tasking performance in older adults with DM and explored its relationship to measures of gait and functional ability. **METHODS:** Forty individuals with type 2 DM were compared to a matched group of 40 individuals without diabetes. Multi-tasking was examined during ambulation via the Walking and Remembering Test (WART), and while seated via the Pursuit Rotor Test (PRT). Self-selected normal and fast walking speed and stride length variability were measured using a GaitMat II System, and self-reported functional ability assessed via the Late Life Function and Disability Index (LLFDI). **RESULTS:** Subjects with DM were slower and more unstable when multi-tasking while walking, and performed worse overall on the WART than comparison subjects. This group was also walked more slowly under normal and fast conditions, demonstrated greater variability under fast conditions, and reported lower levels of physical function on the LLFDI. Measures of multi-tasking demonstrated little correlation with gait and functional ability in either group; however symptoms of depression, physical activity level, and sleep quality were significantly associated with these measures in both groups. **DISCUSSION AND CONCLUSIONS:** Older adults with DM appear to exhibit disturbances that may impair safety when required to multi-task while walking. Further research should explore whether these and other neuropsychological and health factors influence safety, falls, and function in this high risk patient population.

### 3.2 Introduction

The ability to divide attention between simultaneous activities in order to multi-task is among the most essential behaviors for human function. This intricate balancing of attentional resources is often attributed to executive function (Miyake, Emerson, & Friedman, 2000) and is best elicited via dual-task paradigms that examine disruptions in performance that typically occur when multiple tasks are undertaken simultaneously (McCulloch, 2007). Such dual-task studies suggest that an impaired ability to multi-task may influence gait and function in a number of high risk groups (Haggard, Cockburn, Cock, Fordham, & Wade, 2000; Sheridan, Solomont, Kowall, & Hausdorff, 2003; Yogev et al., 2005), including one of the fastest growing segments of the American population – the older adult with diabetes (Paul, Ellis, Leese, McFadyen, & McMurray, 2009; Roman de Mettelinge et al., 2013)

Characterized by impairments in insulin production and utilization and the resulting dysregulation of glucose levels, diabetes currently affects an estimated 25.8 million individuals, including fully one-quarter of all older adults (Centers for Disease Control and Prevention [CDC], 2011). Type 2 diabetes accounts for up to 95% of this number (CDC, 2011) and, frighteningly, is projected to afflict 1 in every 3 Americans by the year 2050 (Boyle et al., 2001).

There is no question that type 2 diabetes can devastate the peripheral nervous system (Sinnreich, Taylor, & Dyck, 2005). However, it also appears to have important consequences for the central nervous system, including neuroanatomical changes in cortical areas linked to aspects of neuropsychiatric and executive functions (Kodl & Seaquist, 2008). At present the degree to which neuropsychological disturbances



influence gait and physical function in older individuals with diabetes remains largely unknown. In many cases, these functional deficits are attributed nearly exclusively to diabetic peripheral neuropathy. However, gait abnormalities have been observed in individuals with diabetes but no evidence of neuropathy (Petrofsky, Lee, & Bweir, 2005; Yavuzer, Yetkin, Toruner, Koca, & Bolukbasi, 2006), and several groups have reported that depression and cognitive function may be as much related to gait and function as signs and symptoms of neuropathy (Brach, Talkowski, Strotmeyer, & Newman, 2008; Rucker, Jernigan, McDowd, & Kluding, in press)

Also of substantive interest is evidence that walking while performing a cognitive task significantly disrupts gait speed and kinematics in individuals with diabetes, both with and without peripheral neuropathy, when compared to those without diabetes. That these changes do not appear to differ greatly between those with and without neuropathy seems to suggest a primary limitation in the executive ability required to divide attention between the tasks, rather than in peripheral somatosensory function (Paul et al., 2009; Roman de Mettelinge et al., 2013)

Despite this preliminary evidence, few studies have examined multi-tasking in older adults with diabetes, or explored whether this contributes to the widespread incidence of falls and functional deficits observed in this population. We hypothesized that subjects with type 2 diabetes would demonstrate impaired performance on two measures of multi-tasking, the Walking and Remembering and Pursuit Rotor Tests, when compared to a group of non-diabetic subjects matched for age, sex, education, and hypertension status. Our secondary hypothesis was that multi-tasking performance in subjects with diabetes would be significantly correlated with quantitative measures of

gait speed and variability, and with self-reported measures of physical function and disability.

### **3.3 METHODS**

#### *3.3.1 Study Design and Sample*

Institutional approval for this cross-sectional study was granted by the Human Subjects Committee of the University of Kansas Medical Center.

A total of 40 individuals aged 60 years and older with a medical diagnosis of type 2 diabetes and 40 similarly aged individuals without diabetes were recruited. Each subject with diabetes (DM) was matched to a comparison subject (CN) in terms of age ( $\pm 5$  years), sex, highest level of education completed (high school vs. college), and the presence or absence of hypertension. This yielded a total sample of 40 matched pairs. Subjects were provided with a \$50 stipend upon completing the study. Exclusion criteria included the following: 1) known history of central nervous system pathology, 2) musculoskeletal or orthopedic conditions significantly affecting gait and/or balance, 3) inability to ambulate without an assistive device, 4) self-reported body mass index of  $> 45 \text{ kg/m}^2$ , 5) uncorrectable visual/auditory deficits or color blindness, 6) wounds on the weight bearing surfaces of the feet, 7) less than a high school level of education, and/or 8) cognitive impairment as evidenced by a score of  $\geq 2$  on the AD8 Dementia Screening Interview or a score of  $< 26$  on the Mini-Mental Status Examination.

### 3.3.2 Procedures

Following telephone screening and the signature of an institutionally-approved informed consent form, data regarding age, height, weight, medical comorbidities, current medications, and number of falls in the past 6 months were gathered. A fasting blood glucose measurement was then obtained from each subject (Contour Blood Glucose Monitoring System, Bayer, Tarrytown, NY), and glycosylated hemoglobin (HbA1c) levels measured for each subject with diabetes via disposable finger-stick kits (Metrika A1CNow+, Bayer, Tarrytown, NY). Potential comparison subjects exhibiting fasting blood glucose levels  $\geq 126$  mg/dL were excluded from participation and referred to a physician for further metabolic evaluation. A small snack was made available to each subject once fasting blood glucose level was established. All study participants were tested in a normoglycemic state, defined as a blood glucose level of between 80 and 250 mg/dL.

After glycemic testing, each subject was administered a series of questionnaires assessing symptoms of depression, physical activity level, sleep quality, and functional ability. This was followed by two randomly ordered measures of multi-tasking, the Walking and Remembering and Pursuit Rotor Tests, and quantitative analysis of gait speed and variability. All testing was conducted by the same research personnel in a quiet laboratory setting to minimize distraction.

### 3.3.3 Measures

#### *Multi-tasking Assessments*

- 1) The Walking and Remembering Test (WART, Figure 3.1A) is a clinical measure of multi-tasking ability involving the individual (e.g. single-task) and simultaneous (e.g. multi-task) performance of ambulatory and cognitive tasks (McCulloch & Marshall, 2004). Subjects first performed single-task ambulation, in which they were asked to walk as quickly and safely as possible along a marked 6.1m long, 19cm wide path. An appropriate cognitive challenge (e.g. the longest random number sequence the individual could correctly recall) was then determined via administration of a seated forward digit span test.

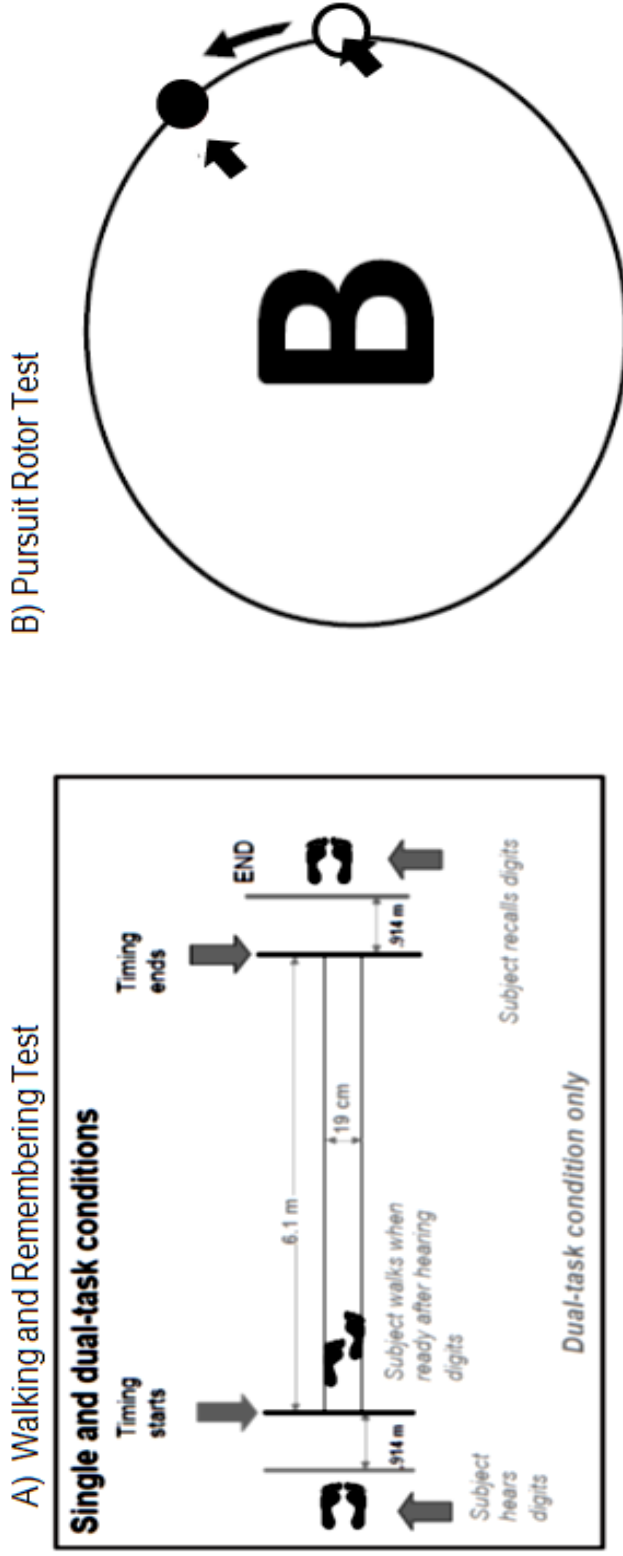
For the multi-task condition, subjects were read a random number sequence equivalent in length to their forward digit span performance. Immediately after the sequence was read, subjects performed the walking component of the test described previously. Upon reaching the end of the path, they attempted to recall as many numbers as possible in the correct sequence. Subjects wore their normal footwear and were not allowed to utilize an assistive device while walking. The number of correctly recalled digits, walking speed, and number of steps off of the path under both single- and multi-task conditions were averaged over 4 trials and recorded for analysis.

- 2) The Pursuit Rotor Test (PRT, Figure 3.1B) is an internally developed version of a computerized measure of multi-tasking (Digital Electronics and Engineering Core, Biobehavioral Neurosciences and Communication Disorders Center, University of Kansas, Lawrence, KS) in which subjects used a trackball mouse

(Kensington Technology Group, Redwood Shores, CA) to pursue a target around an elliptical track while performing a verbal fluency task (Kemper, Schmalzried, Hoffman, & Herman, 2010). The speed of the target was adjustable and could be varied from 0.2 to 2 rotations per minute. The location of the mouse cursor was sampled every 100 ms, determining whether the cross-hairs were on- or off-target and, if off-target, the distance off-target. This data was averaged over 3 successive 100 ms periods, generating a moving average of time on target and distance of error.

Prior to testing, subjects practiced the computer task and target speed was adjusted until the average time on target plateaued and oscillated around 80% accuracy. A 1-minute tracking trial was then administered to determine single-task tracking performance. Next, 2 trials of a single-task verbal fluency test were conducted, in which subjects were given a letter of the alphabet (F and M) and asked to say as many words as possible (excluding proper nouns) beginning with that letter in 1-minute. The average number of words reported during these two trials reflected single-task verbal fluency. Two trials of the multi-tasking condition of the test followed, in which the participant tracked the target for 1-minute while simultaneously completing the verbal fluency task using different letters (B and L). A final 1-minute single-task tracking trial completed the test, and the average time on target, error score, and number of words obtained under single- and dual-task conditions were recorded.

**Figure 3.1: Multi-tasking Assessments**



*McCulloch et al (2009)*

**Figure 3.1:** For the Walking and Remembering Test (A) subjects attempted to recall a list of random digits after ambulating along a 6.1m long, 19cm wide path. For the Pursuit Rotor Test (B) subjects attempted to say as many words beginning with a specified letter while using a trackball mouse to perform a 1 minute computerized target tracking task.

### *Gait and Functional Assessments*

- 1) Quantitative analysis of gait was performed using a GaitMat II gait analysis system (E.Q., Inc., Chalfont, PA). This system consists of a 4 meter long walkway housing 38 rows of 256 pressure sensitive switches connected to a computer analysis system via a USB interface. Subjects began walking approximately 2 meters prior to stepping onto the GaitMat, and were instructed to continue walking to a point approximately 2 meters beyond the GaitMat. Three trials were conducted at each participant's self-selected "normal" walking speed, followed by three trials in which they were instructed to walk "as quickly and safely as possible". Subjects wore their normal footwear, and were not allowed to utilize an assistive device during gait analysis. Gait velocity (in m/s) and stride length variability (expressed as the coefficient of variation:  $[SD/mean]*100$ ) for both normal and fast walking conditions were collected and averaged across the 3 trials.
- 2) The Late Life Function and Disability Instrument (LLFDI) is a comprehensive measure of physical function and disability specifically designed for older adult populations (Dubuc, Haley, Ni, Kooyoomjian, & Jette, 2004) The physical function component of the measure consists of 32 items evaluating self-reported difficulty in physical activities involving upper extremity function, lower extremity function, and advanced lower extremity function (e.g. running, etc.). Subjects were asked "How much difficulty do you have doing [a particular activity] without the help of someone else and without the use of an assistive device?" and responded "none", "a little", "some", "quite a lot", or "cannot do." Overall physical functioning was scored on a scale of 0-100, with higher scores reflecting higher levels of function.

A further 16 items assessed the frequency of participation in and ability to perform major life tasks. Subjects were asked how often they performed a particular task, and rated the extent to which they felt limited in that task with responses of “not at all,” “a little,” “somewhat,” “a lot,” and “completely”. Frequency and disability indices were also scored on scales of 0-100, with higher scores reflecting a higher frequency of participation and a lower degree of disability.

### *General Assessments*

- 1) The Mini-Mental Status Examination (MMSE) was used to assess global cognitive function. This 30-point instrument broadly reflects orientation, memory, concentration, and praxis, and is sensitive to moderate to severe cognitive impairment (Folstein, Folstein, & McHugh, 1975). As it seemed unlikely that severe cognitive deficits would be due exclusively to diabetes, any individual scoring < 26 on this measure was excluded from study participation.
- 2) Beck’s Depression Inventory-II (BDI) was used to assess self-reported symptoms of depression. This measure is scored on a 21-item, 63-point scale, with scores of 19 or less indicating minimal symptoms of depression, 20-28 moderate symptoms, and  $\geq 29$  severe symptoms (Beck, Steer, & Brown, 1996)
- 3) The Rapid Assessment of Physical Activity (RAPA) was used to assess physical activity level (Topolski et al., 2006). Subjects responded “yes or no” to 7 questions describing their participation in physical activity. Scores categorized subjects into one of 5 levels of activity: 1=sedentary, 2=underactive, 3=regular underactive (light activity), 4-5=regular underactive, and 6-7=regular active.



- 4) The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality and disturbance (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). This questionnaire consists of 19 self-rated questions comprising 7 component scores, each rated on a Likert scale of 0 (no difficulty) to 3 (severe difficulty). Addition of the 7 component scores generated a global score of 0-21. A global score of 5 or greater indicated poor sleep quality.

### 3.3.4 Statistical Analysis

Data analysis was conducted using SPSS 16.0 for Windows (Chicago, IL). Normally distributed data are presented as mean  $\pm$  standard deviation, and non-normal data as median (range). Sample size was determined via an analysis of cognitive-motor multi-tasking data from our pilot sample of individuals with diabetic peripheral neuropathy (Rucker et al., in press) and studies of cognitive-motor multi-tasking in healthy older adults (Shumway-Cook, Brauer, & Woollacott, 2000). Based on an estimated effect size of 0.44, this analysis indicated that a sample of 40 subjects would yield a power of between 74 and 86%, depending upon the balance of discrete and overlapping information provided by the two measures of multi-tasking.

Multi-tasking test components were analyzed, in part, as the percent change in performance, or dual-task cost, from single- to dual-task conditions. This was calculated via the following formula:

$$|\text{Dual-task Cost}| = \frac{(\text{Dual-task performance} - \text{Single-task performance})}{\text{Single-task performance}} \times 100$$

By convention, a positive dual-task cost reflected a decline in task performance from single- to dual-task conditions (e.g. a 5% decline in walking speed), whereas a negative dual-task cost represented an improvement in performance under dual-task conditions. In addition to the individual dual-task costs for each component of the two multi-taking measures, a total dual-task cost for each measure was calculated by averaging component costs. For example, the total dual-task cost for the WART reflected the average of the dual-task costs elicited for digit span recall, walking speed, and steps off of the path.

Data distribution and variance was examined via scatter and Q-Q plots, assessed with Kolmogorov-Smirnov and Shapiro-Wilk tests, and descriptive statistics were calculated for all variables. One outlying data point was identified in steps off path on the WART; however analyses conducted with and without the data point were not statistically different and it was not removed from the final analysis. As subjects in the diabetes and comparison groups were paired, mean between- and within-group differences and 95% confidence intervals were examined via 2-tailed, 1 sample paired t-tests. The Wilcoxon signed rank test assessed differences in non-normally distributed data. Pearson product moment and Spearman's rank sum correlations explored the relationships between variables for normal and non-normally distributed data, respectively. Type I error rate was set at 0.05.

## **3.4 Results**

### *3.4.1 Sample Characteristics*

Table 3.1 provides the general characteristics of the groups. Forty individuals with type 2 diabetes (65% female) and 40 paired individuals without diabetes (65% female) consented and participated in this study. Seventy-eight percent of the individuals in both groups were college educated, with the same percentage reporting a diagnosis of hypertension.

Those with diabetes exhibited higher fasting blood glucose ( $p < 0.001$ ), were more obese ( $p < 0.001$ ), and had more symptoms of depression ( $p = 0.04$ ) than comparison subjects. Longer term glycemic control in the diabetes group was also impaired (mean HbA1c  $7.0 \pm 1.3\%$ , range 5.4 – 11.2). Eight subjects (20%) in this group reported a diagnosis of peripheral neuropathy, 2 (5%) mild retinopathy, and 1 (2.5%) nephropathy. A total of 6 subjects (15%) in the diabetes group and 2 in the comparison group (5%) reported having 2 or more falls in the preceding six months. No significant between-group differences were observed in age, global cognitive function, and self-reported physical activity level or sleep quality.

### *3.4.2 Multi-tasking Performance*

Results of the Walking and Remembering Test are provided in Table 3.1 and illustrated in Figures 3.2 and 3.3. Pursuit Rotor Test results are reported in Table 3.1 and illustrated in Figure 3.4. Consistent with our primary hypothesis, the diabetes group demonstrated poorer overall performance on the WART ( $p = 0.005$ ); however we did not observe significant between-group differences in overall PRT performance ( $p = 0.14$ ).

**Table 3.1: Sample Characteristics and Testing Results**

	Diabetes (n=40)	Comparison (n=40)	P-value	95% CI
Age (years)	72.9 ± 8.3	72.9 ± 7.7	0.90	-1.1 – 1.2
BMI (kg/m <sup>2</sup> )	31.1 ± 4.7	26.6 ± 4.4	< 0.001	2.6 – 6.4
FBG (mg/dL)	134.3 ± 45.9	92.3 ± 14.1	< 0.001	25.0 – 51.3
MMSE (score out of 30)	28.7 ± 1.2	29.2 ± 1.0	0.07	-1.0 – 0.04
BDI (score out of 63)	4.5 (0 – 28)	3.0 (0 – 31)	0.04 <sup>a</sup>	-0.4 – 5.2
RAPA (score out of 10)	4.9 ± 1.3	4.8 ± 1.5	0.63	-0.6 – 0.9
PSQI (score out of 21)	5.0 (1 – 12)	4.0 (1 – 18)	0.34 <sup>a</sup>	-1.2 – 2.0
WART Total Cost (% Change)	34.7 (-29.7 – 186.3)	12.3 (-24.1 – 171.3)	0.005 <sup>a</sup>	0.01 – 0.40
PRT Total Cost (% Change)	1.1 ± 12.8	4.7 ± 10.1	0.14	-0.1 – 0.01
LLFDI – Frequency (score out of 100)	56.3 ± 6.5	58.6 ± 9.7	0.42	-4.5 – 1.9
LLFDI – Disability (score out of 100)	79.7 ± 14.2	85.3 ± 13.8	0.05	-11.3 – 0.1
LLFDI – Physical Function (score out of 100)	60.6 ± 9.6	67.5 ± 8.2	< 0.001	-10.1 – -3.7

**Table 3.1:** Data are presented as mean ± SD or median (range). <sup>a</sup> Wilcoxon signed rank test.

Abbreviations: CI, Confidence Interval; BMI, body mass index; FBG, fasting blood glucose; MMSE, Mini-Mental Status Examination; BDI, Beck's Depression Inventory-II; RAPA, Rapid Assessment of Physical Activity; PSQI, Pittsburgh Sleep Quality Index; WART, Walking and Remembering Test; PRT, Pursuit Rotor Test; LLFDI, Late Life Function and Disability Index.

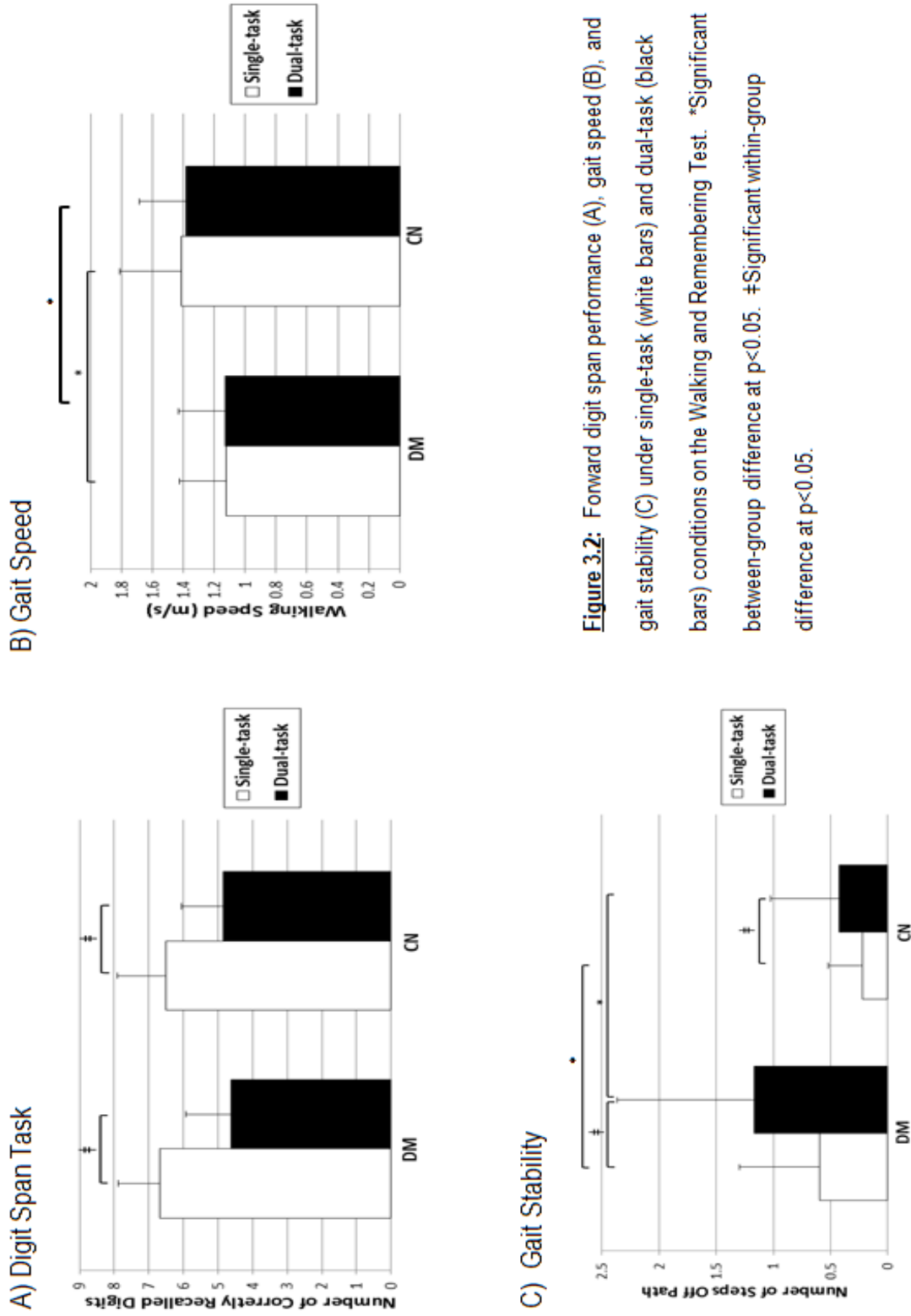
### *Walking and Remembering Test*

Analysis of WART components (Fig. 2 and 3) revealed that both groups demonstrated similar cognitive performance under single-task conditions ( $p=0.54$ ); however those with diabetes ambulated more slowly ( $p<0.001$ ) and took more steps off path ( $p<0.001$ ). Multi-tasking resulted in within-group declines in cognitive task performance (DM:  $p<0.001$ , CN:  $p<0.001$ ) and gait stability (DM:  $p<0.001$ , CN:  $p=0.004$ ) in both groups. No significant changes in gait speed were observed in either group while multi-tasking (DM:  $p=0.79$ , CN:  $p=0.06$ ). Although the percent changes, or dual-task costs, for cognitive task performance and gait speed were not different between the two groups ( $p=0.47$  and  $0.11$ , respectively), those with diabetes exhibited a greater decline in gait stability from single- to dual-task conditions ( $p=0.008$ ).

### *Pursuit Rotor Test*

Analysis of PRT components (Fig. 4) revealed that both groups exhibited a similar amount of time on target ( $p=0.21$ ) and distance of error ( $p=0.11$ ) under single-task conditions; however those with diabetes performed worse on the verbal fluency task ( $p=0.03$ ). Multi-tasking resulted in a decline in the amount of time on target in both groups (DM:  $p=0.002$ , CN:  $p<0.001$ ), but did not significantly alter either verbal fluency performance (DM:  $p=0.42$ , CN:  $p=0.29$ ) or the distance of error (DM:  $p=0.39$ , CN:  $p=0.55$ ). No between-group differences were noted in the dual-task costs for verbal fluency performance ( $p=0.05$ ), time on target during tracking ( $p=0.49$ ), or the distance of tracking error ( $p=0.80$ ) (Fig. 4).

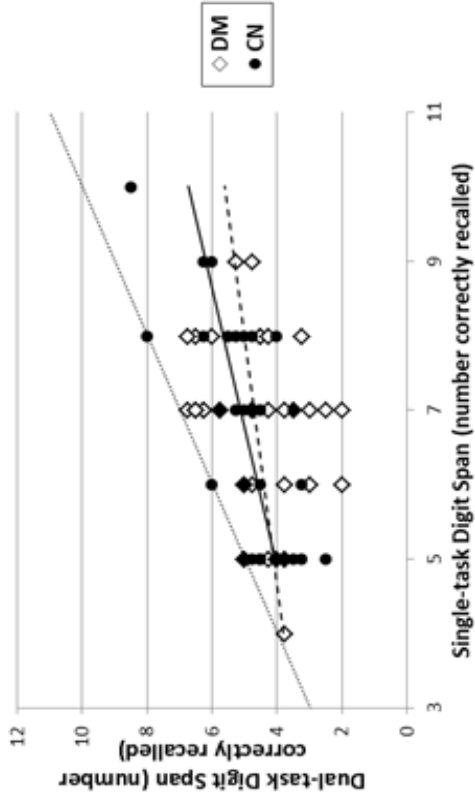
**Figure 3.2: Performance on the Walking and Remembering Test**



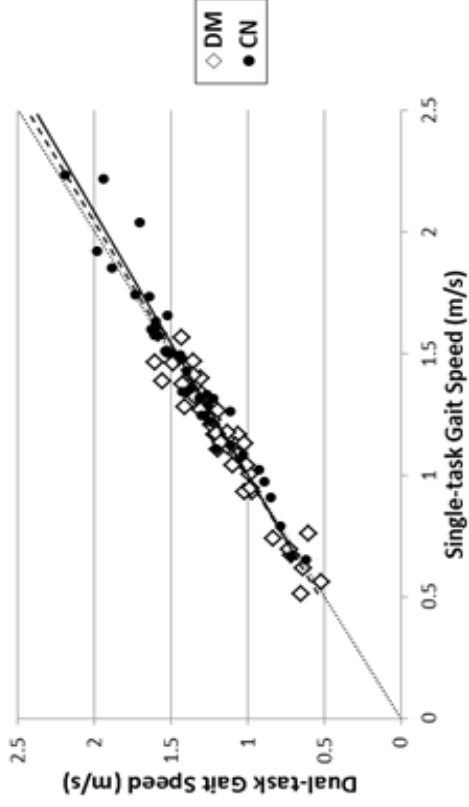
**Figure 3.2:** Forward digit span performance (A), gait speed (B), and gait stability (C) under single-task (white bars) and dual-task (black bars) conditions on the Walking and Remembering Test. \*Significant between-group difference at  $p < 0.05$ . #Significant within-group difference at  $p < 0.05$ .

**Figure 3.3: Dual-task Effects on the Walking and Remembering Test**

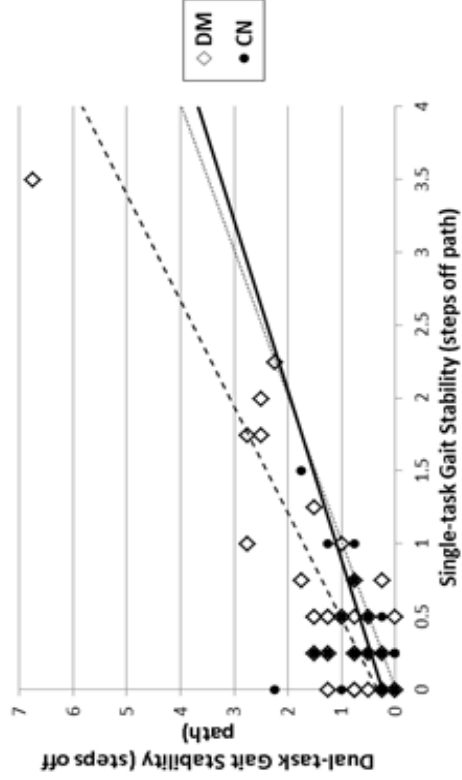
A) Dual-task Effect on Digit Span Performance



B) Dual-task Effect on Gait Speed

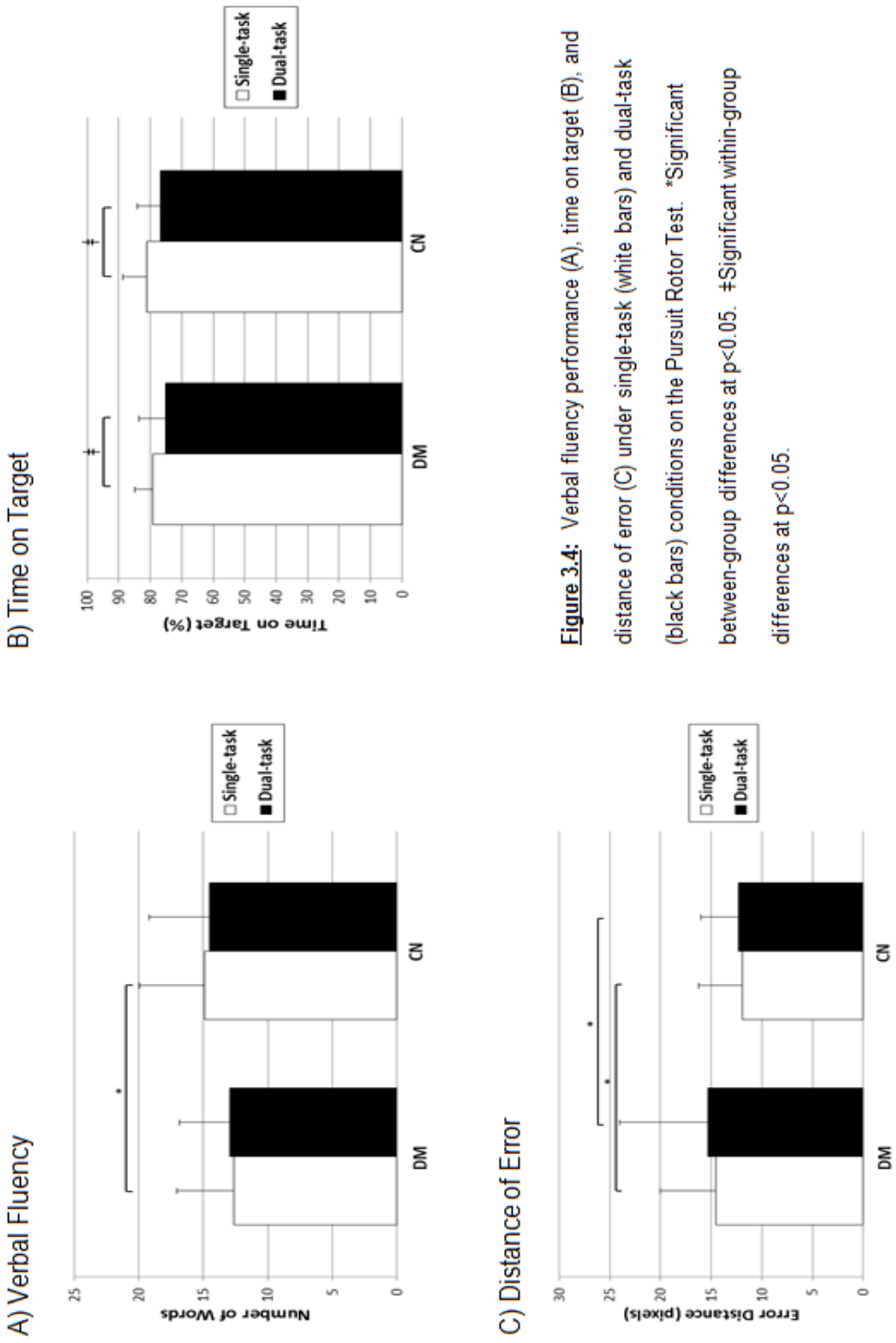


C) Dual-task Effect on Gait Stability



**Figure 3.3:** Dual-task Effect on digit span performance (A), gait speed (B), and gait stability (C) on the WART. Lightly dotted lines represent no change in performance (dual-task cost) from single- to dual-task conditions. Dashed and solid lines reflect trend lines for the diabetes and comparison groups, respectively. In A and B, points falling below the dotted line reflect poorer cognitive performance and slower walking speed under dual-task conditions. In C, points falling above the dotted line reflect greater instability under dual-task conditions.

**Figure 3.4: Performance on the Pursuit Rotor Test**



**Figure 3.4:** Verbal fluency performance (A), time on target (B), and distance of error (C) under single-task (white bars) and dual-task (black bars) conditions on the Pursuit Rotor Test. \*Significant between-group differences at  $p < 0.05$ . #Significant within-group differences at  $p < 0.05$ .



### *3.4.3 Quantitative Gait Analysis*

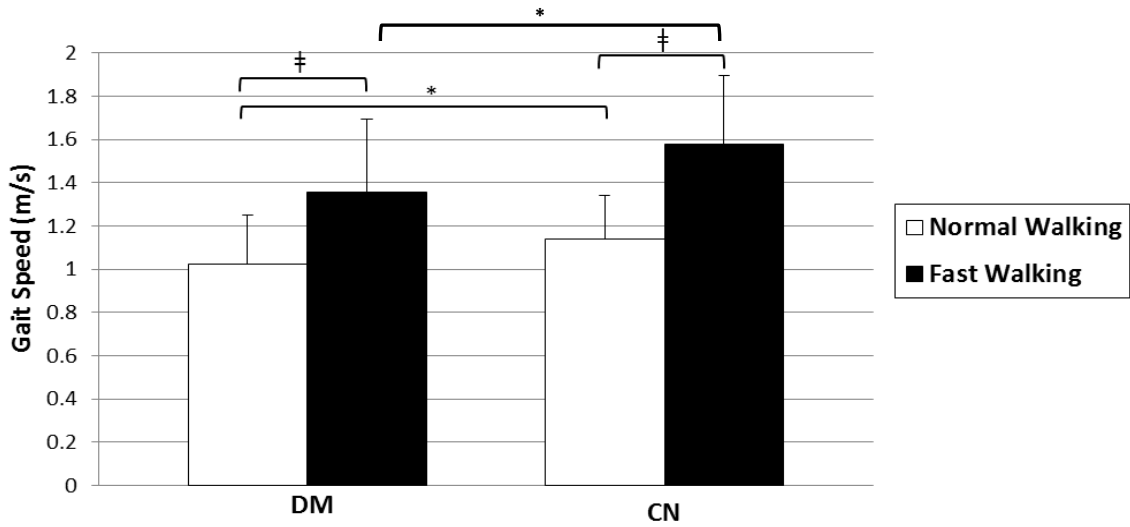
Due to equipment malfunction, quantitative gait data could not be obtained for 3 individuals, and data for the corresponding pair-matched subjects were also removed from the analysis. Results from the 37 remaining pairs are illustrated in Figure 3.5. Individuals with diabetes ambulated more slowly than comparison subjects at a self-selected “normal” walking pace ( $p=0.03$ ), but with a similar degree of stride length variability ( $p=0.77$ ). When instructed to walk “as quickly and safely as possible”, those with diabetes demonstrated both slower speeds ( $p=0.001$ ) and greater stride variability than comparison subjects ( $p=0.02$ ).

### *3.4.4 Late Life Function and Disability Index*

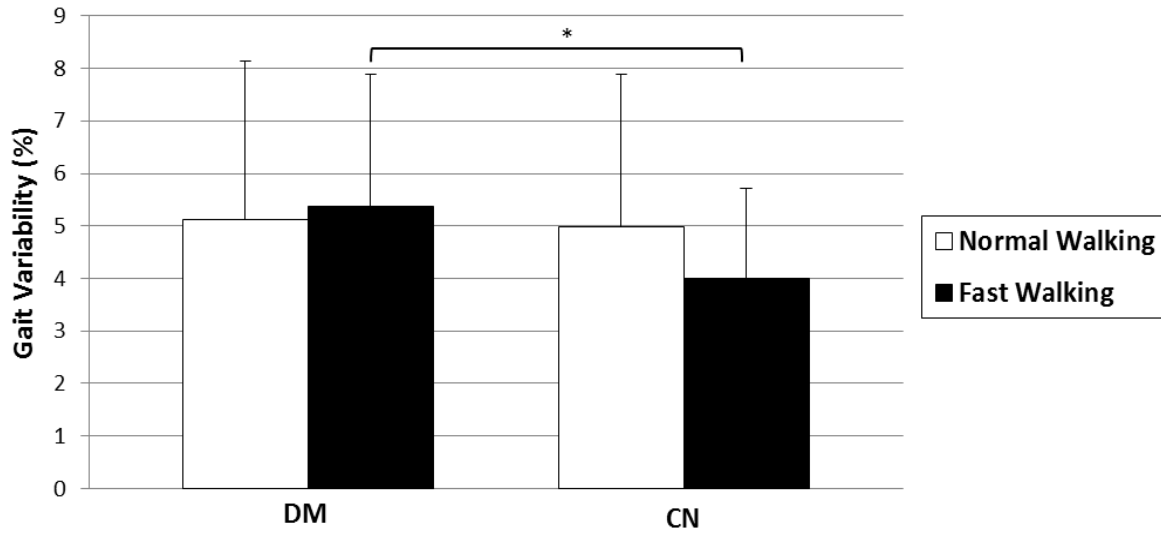
Results of the Late Life Function and Disability Index are reported in Table 3.1. The groups scored similarly on the frequency ( $p=0.42$ ) and disability ( $p=0.06$ ) scales of the LLFDI; however those with diabetes scored significantly lower on the physical function component ( $p<0.001$ ).

**Figure 3.5: Quantitative Gait Analysis During Normal and Fast Walking**

A) Gait Speed



B) Gait Variability



**Figure 3.5:** Gait speed and variability assessed in 36 subject pairs while normal walking (white bars) and fast walking (black bars). \*Significant between group difference at  $p < 0.05$ . #Significant within-group difference at  $p < 0.05$ .

### *3.4.5 Relationships between Multi-tasking Performance and Gait and Functional Ability*

Our secondary hypothesis was that multi-tasking performance would be significantly correlated with quantitative measures of gait and self-reported functional ability. We used bivariate correlations to explore these relationships separately in the diabetes and comparison groups. Table 3.2 provides the results of this analysis. Overall, the data did not support our hypothesis, revealing only small, non-significant relationships between total WART and PRT costs and gait speed, variability, and LLFDI scores in both groups.

### *3.4.6 Other Relationships*

Post-hoc analysis revealed that self-reported symptoms of depression, physical activity level, and sleep quality were significantly related to gait and function in both groups. Specifically, we observed that more symptoms of depression were associated with a slower normal walking gait speed ( $r_s = -0.32$ ,  $p = 0.04$ ) and poorer scores on all aspects of the LLFDI (frequency:  $r =$ physical function:  $r_s = -0.56$ ,  $p < 0.001$ ; disability:  $r_s = -0.44$ ,  $p = 0.005$ ; physical function:  $r_s = -0.35$ ,  $p = 0.03$ ) in the diabetes group, and with a poorer LLFDI disability score in the comparison group ( $r_s = -0.40$ ,  $p = 0.01$ ). Likewise, a higher physical activity level was correlated with less normal walking gait variability ( $r_s = -0.34$ ,  $p = 0.04$ ), and higher scores on all LLFDI components (frequency:  $r = 0.34$ ,  $p = 0.03$ ; disability:  $r = 0.35$ ,  $p = 0.03$ ; physical function:  $r = 0.39$ ,  $p = 0.01$ ) in those with diabetes, and with an increased LLFDI frequency score ( $r = 0.45$ ,  $p = 0.003$ ) in comparison subjects. Poor sleep quality was related to poorer LLFDI disability ( $r_s = -0.32$ ,  $p = 0.04$ ) and physical function ( $r_s = -0.37$ ,  $p = 0.02$ ) scores in subjects with diabetes.

**Table 3.2: Multi-tasking and Other Correlates of Gait and Functional Ability**

A) Diabetes Group

	Normal Gait		Fast Gait		Late Life Function and Disability Index		
	Speed	Variability	Speed	Variability	Frequency	Disability	Function
<b>Age</b>	-0.31	0.20 <sup>a</sup>	-0.38*	0.27	-0.25	-0.25	-0.35*
<b>BMI</b>	-0.05	-0.15 <sup>a</sup>	0.07	-0.26	-0.19	-0.16	-0.27
<b>FBG</b>	-0.20	0.28 <sup>a</sup>	-0.14	0.06	-0.29	-0.46**	-0.22
<b>BDI</b>	-0.32 <sup>a*</sup>	0.19 <sup>a</sup>	-0.06 <sup>a</sup>	0.16 <sup>a</sup>	-0.56 <sup>a**</sup>	-0.44 <sup>a*</sup>	-0.35 <sup>a*</sup>
<b>RAPA</b>	0.31	-0.34 <sup>a*</sup>	0.32*	-0.32	0.34*	0.35*	0.39*
<b>PSQI</b>	-0.10 <sup>a</sup>	0.08 <sup>a</sup>	0.31 <sup>a</sup>	-0.12 <sup>a</sup>	-0.25 <sup>a</sup>	-0.32 <sup>a*</sup>	-0.37 <sup>a*</sup>
<b>WART</b>	-0.07 <sup>a</sup>	0.22 <sup>a</sup>	-0.14 <sup>a</sup>	0.29 <sup>a</sup>	-0.03 <sup>a</sup>	-0.03 <sup>a</sup>	0.05 <sup>a</sup>
<b>PRT</b>	0.09 <sup>a</sup>	-0.07 <sup>a</sup>	0.11	-0.15 <sup>a</sup>	0.33 <sup>a</sup>	-0.03 <sup>a</sup>	-0.01 <sup>a</sup>

B) Comparison Group

	Normal Gait		Fast Gait		Late Life Function and Disability Index		
	Speed	Variability	Speed	Variability	Frequency	Disability	Function
<b>Age</b>	-0.35*	0.29 <sup>a</sup>	-0.49**	-0.01	-0.08	-0.08	-0.29
<b>BMI</b>	-0.45*	0.17 <sup>a</sup>	-0.14	0.44**	-0.02	-0.14	-0.27
<b>FBG</b>	-0.25	0.16 <sup>a</sup>	-0.12	0.13	0.10	-0.15	-0.27
<b>BDI</b>	0.02 <sup>a</sup>	-0.19 <sup>a</sup>	0.25 <sup>a</sup>	-0.24 <sup>a</sup>	-0.23 <sup>a</sup>	-0.40 <sup>a**</sup>	-0.07 <sup>a</sup>
<b>RAPA</b>	-0.12	-0.14 <sup>a</sup>	-0.11	-0.19	0.46**	0.17	0.05
<b>PSQI</b>	-0.04 <sup>a</sup>	-0.01 <sup>a</sup>	0.18 <sup>a</sup>	-0.02 <sup>a</sup>	-0.18 <sup>a</sup>	-0.22 <sup>a</sup>	0.07 <sup>a</sup>
<b>WART</b>	-0.06 <sup>a</sup>	0.09 <sup>a</sup>	0.12 <sup>a</sup>	-0.14 <sup>a</sup>	0.11 <sup>a</sup>	-0.06 <sup>a</sup>	0.22 <sup>a</sup>
<b>PRT</b>	-0.17 <sup>a</sup>	0.19 <sup>a</sup>	-0.15 <sup>a</sup>	-0.06 <sup>a</sup>	0.24 <sup>a</sup>	0.08 <sup>a</sup>	-0.05 <sup>a</sup>

**Table 3.2:** Abbreviations: BMI, body mass index; FBG, fasting blood glucose; BDI, Beck's Depression

Inventory-II; RAPA, Rapid Assessment of Physical Activity Questionnaire; PSQI, Pittsburgh Sleep Quality

Instrument; WART, Walking and Remembering Test; PRT, Pursuit Rotor Test. <sup>a</sup>Spearman rank sum

correlation coefficient. \*Significant at p<0.05. \*\*Significant at p≤0.01.

### 3.5 Discussion

This study is among the most detailed examinations of multi-tasking yet conducted in older adults with type 2 diabetes and, to our knowledge, is the first to explicitly characterize multi-tasking abilities in this population. Specifically, we observed that older adults with diabetes performed worse than their non-diabetic counterparts on an ambulatory measure of multi-tasking. Of even greater concern, however, was the fact that they appeared to self-prioritize competing task demands such that gait stability was sacrificed in order to preserve cognitive performance and walking speed.

To date we are aware of only one other investigation comparing multi-tasking abilities in older adults with and without diabetes. Roman de Mettelinge et al. (2013) administered dual-task measures of walking while performing serial subtraction by 3 and walking while reciting animal names to 28 older individuals with diabetes and peripheral neuropathy, 28 individuals with diabetes but no neuropathy, and 45 age- and sex-matched comparison subjects. They found that both tasks negatively influenced gait speed, stride length, and stride time variability in both groups with diabetes. These changes were not different between individuals with and without neuropathy; however they did appear to be magnified in those exhibiting poorer cognitive and executive function.

Although we did not examine differences in multi-tasking between individuals with and without neuropathy, our results expand upon this study in a number of important ways. Like this group, we found that subjects with diabetes walked slower and with less stability than comparison subjects under both single- and dual-task conditions. However, we did not observe a change in walking speed while multi-

tasking. Rather, our subjects maintained their speed, but at a substantial cost to gait stability. While a corresponding decline in gait stability also occurred in the comparison group, the magnitude of this change (e.g. the dual-task cost) was significantly greater in those with diabetes.

One possible explanation for this difference is that the cognitive tasks employed in the previous study were more difficult for those with diabetes; possibly due to differences in educational level. Consequently, these subjects may have been required to allocate resources to the cognitive task that comparison subjects were instead able to delegate to maintaining gait. These tasks may have also been more difficult than our memory task, thereby explaining why we observed a decrease in stability but not in speed. Such task difficulty problems are a common limitation of research employing dual-task methodology, particularly when data regarding educational level and cognitive task performance are not reported. Our study addresses this limitation through the use of an individually prescribed cognitive task in subjects pair-matched for educational level. Furthermore, our analysis of digit span performance revealed no significant between-group differences under either single- or dual-task conditions, indicating that our cognitive task was similarly challenging for both groups.

Another possible source of difference lays in the fact that these authors instructed their subjects to “concentrate equally on walking and the cognitive task”. We did not provide subjects with explicit instructions for task prioritization. Rather, we provided only implicit instruction to perform the WART “as quickly and safely as possible”, as this seemed more reflective of a real-world environment in which task priorities are rarely explicit or pre-established.

Regardless, our WART results demonstrate that, in addition to being slower and more unstable both at baseline and while multi-tasking, this sample of older adults with diabetes performed worse on the WART as a whole, and largely failed to self-prioritize stability while walking in order to preserve other task demands. All the more alarming, we observed this phenomenon in subjects both with and without peripheral neuropathy, and note that it appears to be more prominent in those who demonstrated the greatest degree of instability at baseline.

In an interesting counterpoint to our WART findings, however, we observed few differences between diabetes and comparison subjects in our non-ambulatory measure of multi-tasking, the PRT. In this case, both groups appeared to minimize losses in verbal fluency and tracking error at the expense of target accuracy (e.g. time on target), and no between-group dual-task cost differences were elicited for any of the task components. Taken together, our WART and PRT results seem to suggest that older adults with diabetes do not necessarily demonstrate global, gross impairments in multi-tasking. Rather more insidiously, these individuals may fail to adopt compensatory strategies that maximize safety during “high risk” situations in which simultaneous task demands outstrip attentional and/or functional resources.

Given these implications, we were somewhat surprised to find little correlation between our multi-tasking assessments and measures of gait and functional ability. This may reflect the fact that our sample consisted of relatively high-functioning older adults, and the multi-tasking disturbances we observed were subtle. As such changes may be largely sub-clinical, they may not strongly influence gait under normal conditions or self-reported measures of function and disability such as the LLFDI. It is possible

that more pervasive deficits in multi-tasking would demonstrate more substantial relationships with these variables or, likewise, that more complex, challenging gait or functional scenarios would be more strongly associated with multi-tasking abilities.

Our analyses did, however, reveal a number of striking relationships between symptoms of depression, physical activity level, and sleep quality and gait and physical function in both groups. These findings contribute to an important but largely overlooked body of evidence linking such modifiable factors to gait (Brach et al., 2008; Rucker et al., in press) and functional deficits (Huang et al., 2012), and are especially critical for older adults with diabetes – a population known to exhibit a disproportionate prevalence of depression (Corriere, Rooparinesingh, & Kalyani, 2013), physical inactivity (Zhao, Ford, Li, & Balluz, 2011), and poor sleep quality (Resnick et al., 2003).

Certainly there are a number of factors that limit our interpretation of this data. First, our sample was of modest size and consisted primarily of Caucasian subjects of middle to upper socioeconomic status. Although we accounted for the potentially confounding effect of educational level, future research will be necessary to determine whether our results can be generalized outside of this population. In addition, it is important to note that we did not correct for the multiple correlations that explored the variables associated with gait and function in our study. This limits the conclusions that can be drawn from this data; however our results clearly highlight interesting avenues for future research.

Another significant limitation is that we examined individuals both with and without diabetic peripheral neuropathy. There is no question that somatosensory loss can significantly impact gait and function; however neuropathy is notoriously difficult to



diagnose and quantify. In order to obtain an adequate sample of individuals with diabetes, as many as half of whom could potentially be expected to exhibit some symptoms of neuropathy (CDC, 2011), we opted to record whether individuals had been diagnosed with the condition but did not exclude them from the study.

Although the inclusion of these subjects undoubtedly complicates interpretation of the data, it also raises a very interesting question: Why did these individuals, who would seem to have the highest fall risk and the smallest pool of functional resources from which to draw, fail to slow down in order to focus their attention on walking safely? In fact, the 8 subjects diagnosed with neuropathy actually increased their walking speed an average of 1% when required to multi-task, but at a cost of more than double the number of steps off path. Further research will clearly be needed to explore how somatosensation and task demands interact to influence task prioritization and multi-tasking during ambulation in this sub-population.

Certainly, it does not seem unreasonable to suspect that the multi-tasking phenomena observed in this study could contribute to falls in a population already at relatively high risk. As yet, however, there are no established links between the changes we observed on the WART and falls or functional deficits, nor have fall risk cut-offs been established for this instrument. Future research should address these issues, and specifically explore the effect of manipulating and/or influencing task priorities and task demands, in order to more clearly examine whether function and safety can be better balanced during ambulatory multi-tasking activities.

### 3.6 Conclusions

This investigation provides evidence that older adults with type 2 diabetes exhibit deficits in the ability to multi-task while walking. Although these changes do not appear to exert an undue influence on gait mechanics or function under normal circumstances, they may impair safety in more challenging situations. Our data also suggest that modifiable but commonly overlooked factors, such as symptoms of depression, physical activity level, and sleep quality, may play an important role everyday gait and function. As such, clinicians should recognize that widely varying factors contribute to gait and physical dysfunction in older adults with type 2 diabetes, and be prepared to assess and intervene appropriately.

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## Chapter 4 Preface

In Chapter 3 we demonstrated significant changes in gait stability when our sample of older adults with type 2 diabetes was asked to multi-task while walking. The next step in our planned analysis involved a more detailed exploration of the influence of multi-tasking ability on spatiotemporal parameters of single-task gait and self-reported levels of physical function and limitation in everyday activities in this population. Somewhat to our surprise, the preliminary analysis of these relationships revealed very little correlation between multi-tasking and either gait or functional ability. However, we did observe rather striking associations between these variables and symptoms of depression, physical activity level, and sleep quality – all factors known to disproportionately affect those with diabetes.

In the context of these findings, we first completed our planned series of regression models, in which Walking and Remembering and Pursuit Rotor Test outcomes were used to predict criterion measures of gait velocity, stride length variability, physical function, and disability in subjects with diabetes. We then constructed an additional series of models exploring the effects of depression, physical activity level, and sleep quality on the same set of criterion variables. Together, these analyses comprise Chapter 4.

## Chapter 4

### The Contribution of Multi-tasking to Gait and Functional Ability in Older Adults with Type 2 Diabetes

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## 4.1 Abstract

**BACKGROUND AND PURPOSE:** It is unclear whether the ability to multi-task contributes to the disproportionate risk of functional impairment and disability in older adults with type 2 diabetes. We examined the relationships between multi-tasking ability and spatiotemporal gait parameters and self-reported physical function and disability in this population. **METHODS:** Forty individuals with type 2 DM were examined. Multi-tasking was assessed during ambulation via the Walking and Remembering Test (WART), and while seated via the Pursuit Rotor Test (PRT). Self-selected normal and fast walking speed and stride length variability were measured using a GaitMat II System, and self-reported functional ability assessed via the Late Life Function and Disability Index (LLFDI). Symptoms of depression, physical activity level, and sleep quality were also assessed. **RESULTS:** Multi-tasking ability was not significantly associated with gait speed or variability under either normal or fast walking conditions, or with self-reported physical function or disability. Secondary analyses revealed significant adverse relationships between higher depression levels and fast walking variability and disability, lower physical activity levels and both normal and fast walking speed and physical function, and poorer sleep quality and normal walking variability. **CONCLUSIONS:** Multi-tasking ability has relatively little influence on single-task gait parameters or self-reported levels physical function and disability in older adults with type 2 diabetes. However, potentially modifiable factors such as depression, physical activity level, and sleep quality may significantly affect these variables. Future research should explore how neuropsychological function, physical activity, and sleep interact with different aspects of physical function in older adults with diabetes.

## 4.2 Introduction

Diabetes can profoundly interfere with everyday function, and current estimates suggest that as many as half of all individuals with diabetes suffer from some form of disability – a rate 2-3 times greater than that observed in the non-diabetic population (Gregg et al., 2000). These disabilities often arise from impairments in physical function, mobility, and the ability to perform routine functional activities, and have a direct impact on employability, socio-economic status, and health care access. This, in turn, has far-reaching social, economic, political, and public health implications (Centers for Disease Control and Prevention [CDC], 2011).

Commonly, this increased risk for functional impairment and disability is attributed to the major vascular and neuropathic sequelae of diabetes. While these factors undoubtedly contribute to functional loss, it is increasingly acknowledged that less commonly recognized comorbidities, such as cognitive and neuropsychiatric dysfunction, may also be of substantial importance (Volpato, Maraldi, & Fellin, 2009). In particular, deficits in executive function – the ability to plan, organize, sequence, and monitor the processes underlying goal-oriented behavior – appear to be strong predictors of functional deterioration (Cahn-Weiner, Malloy, Boyle, Marran, & Salloway, 2000).

Executive dysfunction has been observed in older individuals with diabetes (Kodl & Seaquist, 2008), and several studies have indicated that even relatively insidious executive deficits can produce impairments in gait (Brach, Talkowski, Strotmeyer, & Newman, 2008; Kuo, Leveille, Yu, & Milberg, 2007) and activities of daily living in this population (Kuo et al., 2007; McGuire, Ford, & Ajani, 2006). Of specific interest in

relation to these findings is the executive ability responsible for dividing attention between simultaneous activities, or multi-tasking. Deficits in multi-tasking have been linked to both gait and functional impairments in many high risk populations (Dubost et al., 2006; Hausdorff, Balash, & Giladi, 2003; Hyndman & Ashburn, 2003; Sheridan, Solomont, Kowall, & Hausdorff, 2003), including those with diabetes (Paul, Ellis, Leese, McFadyen, & McMurray, 2009; Roman de Mettelinge et al., 2013), and may play a role in mediating the association between executive dysfunction and physical function and disability.

This study is among the first to examine the specific contributions of multi-tasking to gait and every day physical function and disability in older adults with diabetes, and to explore how other under-recognized comorbidities may influence these variables. Our primary hypothesis was that multi-tasking ability would significantly predict quantitative gait speed and variability during single-task walking, as well as self-reported levels of physical function and disability. A secondary aim was to explore the influence of depression, physical activity level, and sleep quality on the same criterion variables of gait and function.

## **4.3 Methods**

### *4.3.1 Study Design and Sample*

Institutional approval for this cross-sectional study was granted by the Human Subjects Committee of the University of Kansas Medical Center. Data was gathered from a total of 40 individuals aged 60 years and older with a medical diagnosis of type 2 diabetes. Each subject received a \$50 stipend upon completing the study. Exclusion

criteria included the following: 1) known history of central nervous system pathology, 2) musculoskeletal or orthopedic conditions significantly affecting gait and/or balance, 3) inability to ambulate without an assistive device, 4) self-reported body mass index of  $> 45 \text{ kg/m}^2$ , 5) uncorrectable visual/auditory deficits or color blindness, 6) wounds on the weight bearing surfaces of the feet, 7) less than a high school level of education, and/or 8) cognitive impairment as evidenced by a score of  $\geq 2$  on the AD8 Dementia Screening Interview or a score of  $< 26$  on the Mini-Mental Status Examination.

#### *4.3.2 Procedures*

Following telephone screening and the signature of an institutionally-approved informed consent form, data regarding age, height, weight, medical and diabetic comorbidities, and current medications were gathered. Fasting blood glucose measurements (Contour Blood Glucose Monitoring System, Bayer, Tarrytown, NY) and glycosylated hemoglobin levels (HbA1c; Metrika A1CNow+, Bayer, Tarrytown, NY) were then obtained from each subject. A small snack was made available once fasting blood glucose level was established. All subjects were tested in a normoglycemic state, defined as a blood glucose level of between 80 and 250 mg/dL.

After glycemic testing, each subject was administered a series of questionnaires assessing symptoms of depression, physical activity level, sleep quality, and functional ability. This was followed by two randomly ordered measures of multi-tasking, the Walking and Remembering and Pursuit Rotor Tests, and quantitative analysis of gait speed and variability. All testing was conducted by the same research personnel in a quiet laboratory setting to minimize distraction.

### 4.3.3 Measures

#### *Multi-tasking Assessments*

- 1) The Walking and Remembering Test (WART; Chapter 3, Figure 3.1A) was used to assess multi-tasking ability during gait (McCulloch & Marshall, 2004). As described in Chapter 3, subjects first performed single-task ambulation, in which they were asked to walk as quickly and safely as possible along a marked 6.1m long, 19cm wide path. An appropriate cognitive challenge (e.g. the longest random number sequence the individual could correctly recall) was then determined via administration of a seated forward digit span test.

For the multi-task condition, subjects were read a random number sequence equivalent in length to their forward digit span performance. Immediately after the sequence was read, subjects performed the walking component of the test described previously. Upon reaching the end of the path, they attempted to recall as many numbers as possible in the correct sequence. Subjects wore their normal footwear and were not allowed to utilize an assistive device while walking. The number of correctly recalled digits, walking speed, and number of steps off of the path under both single- and multi-task conditions were averaged over 4 trials and recorded for analysis.

- 2) The Pursuit Rotor Test (PRT; Chapter 3, Figure 3.1B) was used to assess multi-tasking in a non-gait situation (Kemper, Schmalzried, Herman, Leedahl, & Mohankumar, 2009). As described in Chapter 3, subjects used a trackball mouse (Kensington Technology Group, Redwood Shores, CA) to pursue a target around an elliptical track while performing a verbal task. The speed of the target was

adjustable and could be varied from 0.2 to 2 rotations per minute. The location of the mouse cursor was sampled every 100 ms, determining whether the cross-hairs were on- or off-target and, if off-target, the distance off-target. This data was averaged over 3 successive 100 ms periods, generating a moving average of time on target and distance of error.

Prior to testing, subjects practiced the computer task and target speed was adjusted until the average time on target plateaued and oscillated around 80% accuracy. A 1-minute tracking trial was then administered to determine single-task tracking performance. Next, two trials of a single-task verbal fluency test were conducted, in which subjects were given a letter of the alphabet (F and M) and asked to say as many words as possible (excluding proper nouns) beginning with that letter in 1-minute. The average number of words reported during these two trials reflected single-task verbal fluency. Two trials of the multi-tasking condition of the test followed, in which the participant tracked the target for 1-minute while simultaneously completing the verbal fluency task using different letters (B and L). A final 1-minute single-task tracking trial completed the test, and the average time on target, error score, and number of words obtained under single- and dual-task conditions were recorded.

### *Gait and Functional Assessments*

- 1) Quantitative analysis of gait was performed using a GaitMat II gait analysis system (E.Q., Inc., Chalfont, PA). This system consists of a 4 meter long walkway housing 38 rows of 256 pressure sensitive switches connected to a computer analysis

system via a USB interface. Subjects began walking approximately 2 meters prior to stepping onto the GaitMat, and were instructed to walk to a point approximately 2 meters beyond the GaitMat. Three trials were conducted at each participant's self-selected usual walking speed (e.g. normal walking), followed by three trials in which they were instructed to walk "as quickly and safely as possible" (e.g. fast walking). Subjects wore their normal footwear, and were not allowed to utilize an assistive device during gait analysis. Gait velocity (in m/s) and stride length variability (expressed as the coefficient of variation:  $[\text{standard deviation}/\text{mean}] * 100$ ) for both normal and fast walking conditions were collected and averaged across the 3 trials.

- 2) The Late Life Function and Disability Instrument (LLFDI) is a comprehensive measure of physical function and disability specifically designed for older adult populations (Dubuc, Haley, Ni, Kooyoomjian, & Jette, 2004). The physical function component of the measure consists of 32 items evaluating self-reported difficulty in physical activities involving upper extremity function, lower extremity function, and advanced lower extremity function (e.g. running, etc.). Subjects were asked "How much difficulty do you have doing [a particular activity] without the help of someone else and without the use of an assistive device?" and responded "none", "a little", "some", "quite a lot", or "cannot do." Overall physical functioning was scored on a scale of 0-100, with higher scores reflecting higher levels of function.

A further 16 items assessed the ability to perform major life tasks. Subjects rated the extent to which they felt limited in various tasks with responses of "not at all," "a little," "somewhat," "a lot," and "completely". The disability index was also scored on scales of 0-100, with higher scores reflecting a lower degree of disability.

### *Other Assessments*

- 1) Beck's Depression Inventory-II (BDI) was used to assess self-reported symptoms of depression. This measure is scored on a 21-item, 63-point scale, with scores of 19 or less indicating minimal symptoms of depression, 20-28 moderate symptoms, and  $\geq 29$  severe symptoms (Beck, Steer, & Brown, 1996).
- 2) The Rapid Assessment of Physical Activity (RAPA) was used to assess physical activity level (Topolski et al., 2006). Subjects responded "yes or no" to 7 questions describing their usual level of participation in physical activity. Scores categorized subjects into one of 5 levels of activity: 1=sedentary, 2=under-active, 3=regular under-active (light activity), 4-5=regular under-active, and 6-7=regular active.
- 1) The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). This questionnaire consists of 19 self-rated questions comprising 7 component scores, each rated on a Likert scale of 0 (no difficulty) to 3 (severe difficulty). Addition of the 7 component scores generated a global score of 0-21, with a score of 5 or indicating poor sleep quality.

#### *4.3.4 Statistical Analysis*

Data analysis was conducted using SPSS 16.0 for Windows (Chicago, IL). Normally distributed data are described as mean  $\pm$  standard deviation, and non-normal data as median (range).

Multi-tasking abilities were described as the percent change in performance, or dual-task cost, from single- to dual-task conditions. This was calculated via the following formula:



$$|\text{Dual-task Cost}| = \frac{(\text{Dual-task performance} - \text{Single-task performance})}{\text{Single-task performance}} \times 100$$

By convention, positive dual-task costs reflect a decline in performance from single- to dual-task conditions (e.g. a 5% decline in walking speed), whereas negative dual-task costs represent an improvement in performance under dual-task conditions. Dual-task costs were calculated for each component of the two multi-tasking measures, and a total dual-task cost for each measure was calculated by averaging the component costs. For example, the total dual-task cost for the WART reflected the average of the dual-task costs elicited for digit span recall, walking speed, and steps off of the path. Total dual-task costs for the WART and PRT were then averaged to generate a single predictor variable of multi-tasking ability: overall dual-task cost.

Next, a backward model building procedure was used to construct a series of multiple linear regression models, and the squared multiple correlation ( $R^2$ ), unstandardized (B), and standardized ( $\beta$ ) regression coefficients utilized to examine the collective and individual effects of overall multi-tasking cost, along with covariates of age and glycemic control (HbA1c), on quantitative measures of gait velocity and stride length variability. This procedure, with an additional covariate of BDI score of depression symptoms, also examined the effect of overall multi-tasking ability and self-reported physical function and disability (Table 4.1A). Finally, the backwards model building procedure was repeated in a post-hoc secondary analysis exploring the effects of symptoms of depression, physical activity level, and sleep quality on the same criterion measures (Table 4.1B). An alpha level of 0.05 assessed the significance of all relationships.

**Table 4.1A: Primary Regression Models**

<b>Model 1a: Normal Gait Velocity</b>	$a + b_1 (\text{age}) + b_2 (\text{glycemic control}) + b_3 (\text{overall dual-task cost}) + e$
<b>Model 1b: Fast Gait Velocity</b>	
<b>Model 2a: Normal Stride Variability</b>	
<b>Model 2b: Fast Stride Variability</b>	
<b>Model 3: Physical Function</b>	$a + b_1 (\text{age}) + b_2 (\text{glycemic control}) + b_3 (\text{depression}) + b_4 (\text{overall dual-task cost}) + e$
<b>Model 4: Disability</b>	

**Table 4.1B: Secondary Regression Models**

<b>Model 5a: Normal Gait Velocity</b>	$a + b_1 (\text{depression}) + b_2 (\text{physical activity level}) + b_3 (\text{sleep quality}) + e$
<b>Model 5b: Fast Gait Velocity</b>	
<b>Model 6a: Normal Stride Variability</b>	
<b>Model 6b: Fast Stride Variability</b>	
<b>Model 7: Physical Function</b>	
<b>Model 8: Disability</b>	

## 4.4 RESULTS

### 4.4.1 Sample Characteristics

The general characteristics of this group of 40 community dwelling individuals aged 60 and older with type 2 diabetes are provided in Table 4.2. Briefly, the group consisted of 26 females (65%) and 14 males (35%), with an overall group mean age of  $72.9 \pm 8.3$  years. Thirty-one (78%) were college educated. As expected, glycemic control was impaired to both short-term (mean fasting blood glucose  $134.3 \pm 45.9$  mg/dL) and long-term (median HbA1c 6.8%, range 5.4 – 11.2) measures. The median time since diagnosis with diabetes was 10 years (range 1- 40), with 8 subjects (20%) reporting disease-related complications of peripheral neuropathy, 2 (5%) mild retinopathy, and 1 (2.5%) nephropathy.

### 4.4.2 Multi-tasking Performance

As described and illustrated in Chapter 3, multi-tasking demands during the WART resulted in significant within-group declines in both cognitive task performance ( $p < 0.001$ ) and gait stability ( $p < 0.001$ ). No significant dual-task changes were observed in gait speed ( $p = 0.79$ ). Multi-tasking during the PRT resulted in a decline in the amount of time on target while tracking ( $p = 0.002$ ), but did not significantly alter either verbal fluency ( $p = 0.42$ ) or distance of tracking error ( $p = 0.39$ ). Total dual-task costs for the WART and PRT were 44.4% and 1.1%, respectively, yielding an overall dual-task cost of 22.6%.<sup>1</sup>

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<sup>1</sup> Due to the large difference in the dual-task costs elicited on the WART and PRT, a parallel regression analysis was conducted using total WART task cost in lieu of the overall task cost. These results did not differ substantially from the planned analysis reported here.

**Table 4.2: Sample Characteristics**

<b>Age (years)</b>	72.9 ± 8.3
<b>Body Mass Index (kg/m<sup>2</sup>)</b>	31.1 ± 4.7
<b>Time Since Diagnosis (years)</b>	10 (1-40)
<b>Fasting Blood Glucose (mg/dL)</b>	134.3 ± 45.9
<b>Glycosylated Hemoglobin (%)</b>	6.8 (5.4-11.2)
<b>Mini-Mental Status Examination (score out of 30)</b>	28.7 ± 1.2
<b>Beck's Depression Inventory-II (score out of 63)</b>	4.5 (0 – 28)
<b>Rapid Assessment of Physical Activity (score out of 10)</b>	4.9 ± 1.3
<b>Pittsburgh Sleep Quality Index (score out of 21)</b>	5.0 (1 – 12)

**Table 4.2:** Data are mean ± SD or median (range). Abbreviations: BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; MMSE, Mini-Mental Status Examination; BDI, Beck's Depression Inventory-II; RAPA, Rapid Assessment of Physical Activity; PSQI, Pittsburgh Sleep Quality Index.

#### 4.4.3 Quantitative Gait Analysis

Due to equipment malfunction, quantitative gait data could not be obtained for 3 subjects. At their self-selected “normal” walking speed the remaining 37 subjects ambulated at an average rate of 1.0 ± 0.2 m/s, with a stride length variability of 5.2 ±

2.9%. When asked to ambulate “as quickly and safely as possible” for fast walking trials, subjects ambulated at an average rate of  $1.4 \pm 0.4$  m/s, with a stride variability of  $5.2 \pm 2.5\%$ .

#### *4.4.4 Late Life Function and Disability Index*

Physical function and disability scales of the LLFDI yielded mean scores of  $60.6 \pm 9.6$  and  $79.7 \pm 14.2$ , respectively. Both reflect “slight limitations” according to classifications described by Lapier and Mizner (2009).

#### *4.4.5 Additional Measures*

On average, subjects reported minimal symptoms of depression (BDI score  $6.6 \pm 6.1$ ), a regular but under-active level of physical activity (RAPA score  $4.9 \pm 1.3$ ), and poor sleep quality (PSQI score  $5.7 \pm 3.0$ ).

#### *4.4.6 Effect of Multi-tasking on Spatiotemporal Measures of Gait*

Results of regression models 1 and 2 are provided in Table 4.3. Contrary to our primary hypotheses, the overall dual-task cost elicited by our multi-tasking measures was not associated with either gait velocity ( $\beta=-0.05$ ,  $p=0.76$ ) or variability ( $\beta=-0.12$ ,  $p=0.50$ ) at self-selected “normal” speed, when controlled for age and glycemic control. Together, these 3 factors accounted for only a very small portions of the variation in gait speed ( $R^2=0.017$ ,  $p=0.89$ ) during normal walking, with backwards elimination resulting in the respective removal of age (model  $R^2=0.015$ ,  $p=0.75$ ), multi-tasking cost (model  $R^2=0.013$ ,  $p=0.48$ ), and HbA1c (all variables removed from model).

Similarly, these factors explained only a small portion of the variation in normal stride length variability during normal walking ( $R^2=-0.035$ ,  $p=0.75$ ), with subsequent models removing HbA1c (model  $R^2=0.033$ ,  $p=0.57$ ), multi-tasking cost (model  $R^2=0.019$ ,  $p=0.42$ ), and age (all variables removed from model).

There was also little relationship between overall multi-tasking cost and gait velocity ( $\beta=0.004$ ,  $p=0.98$ ) or stride variability ( $\beta=-0.18$ ,  $p=0.29$ ) under fast walking conditions, and multi-tasking cost, age, and HbA1c together predicted only small amounts of the variation in these variables (gait velocity:  $R^2=0.033$ ,  $p=0.75$ ; stride length variability:  $R^2=-0.064$ ,  $p=0.53$ ). For fast walking speed, backwards elimination resulted in the respective removal of multi-tasking cost (model  $R^2=0.032$ ,  $p=0.54$ ), age (model  $R^2=0.030$ ,  $p=0.29$ ), and HbA1c (all variables removed from model). For fast walking stride length variability, backwards elimination resulted in the respective removal of HbA1c (model  $R^2=0.048$ ,  $p=0.43$ ), age (model  $R^2=0.027$ ,  $p=0.33$ ), and multi-tasking cost (all variables removed from model). No significant interactions were observed in any of the models.

**Table 4.3: Effect of Age, Glycemic Control, and Multi-tasking Ability on Gait Velocity and Stride Length Variability**

Variable	Model 1a: Normal Walking Gait Velocity			Model 1b: Fast Walking Gait Velocity			Model 2a: Normal Walking Gait Variability			Model 2b: Fast Walking Gait Variability		
	B	SEB	$\beta$	B	SEB	$\beta$	B	SEB	$\beta$	B	SEB	$\beta$
<b>Age</b>	0.001	0.005	0.039	0.002	0.008	0.049	0.069	0.073	0.167	0.045	0.046	0.172
<b>Glycosylated Hemoglobin</b>	-0.020	0.030	-0.112	-0.056	0.052	-0.175	-0.163	0.526	-0.054	-0.247	0.332	-0.128
<b>Overall Multi-tasking Cost</b>	-0.050	0.161	-0.052	0.006	0.278	0.004	-1.582	2.341	-0.117	-1.575	1.475	-0.183
<b>R<sup>2</sup></b>	0.017			0.033			0.035			0.064		
<b>F Statistic</b>	0.203			0.403			0.404			0.749		

**Table 4.3:** Results from the full model (e.g. all variables included) are shown. Abbreviations: B, Unstandardized coefficients; SEB, Standard error of unstandardized coefficients;  $\beta$ , Standardized coefficients.

#### 4.4.7 Effect of Multi-tasking on Self-reported Physical Function and Disability

Results of regression models 3 and 4 are provided in Table 4.4. Again, contrary to our primary hypotheses, we found little association between multi-tasking cost and self-reported physical function ( $\beta=0.057$ ,  $p=0.71$ ) on the LLFDI, when controlled for age, glycemic control, and symptoms of depression. Together, this combination of factors predicted small but statistically significant portions of the variation in physical function ( $R^2=0.236$ ,  $p=0.04$ ). Backwards elimination resulted in the respective removal of multi-tasking cost (model  $R^2=0.233$ ,  $p=0.02$ ), age (model  $R^2=0.221$ ,  $p=0.01$ ), and

HbA1c (model  $R^2=0.207$ ,  $p=0.003$ ). Symptoms of depression remained significantly associated with physical function in the final model ( $\beta=-0.455$ ,  $p=0.003$ ).

Although the combination of multi-tasking cost, age, glycemic control, and symptoms of depression also predicted significant portions of the variation in disability ( $R^2=0.278$ ,  $p=0.02$ ), there was little association between multi-tasking cost and disability ( $\beta=0.035$ ,  $p=0.81$ ). Backward elimination resulted in the respective removal of HbA1c (model  $R^2=0.277$ ,  $p=0.008$ ), multi-tasking cost (model  $R^2=0.276$ ,  $p=0.003$ ), and age (model  $R^2=0.255$ ,  $p=0.001$ ). Symptoms of depression remained significantly associated with disability in the final model ( $\beta=-0.505$ ,  $p=0.001$ ). No significant interactions were observed in either model.

**Table 4.4: Effect of Age, Glycemic Control, and Multi-tasking Ability on LLFDI Physical Function and Disability Scores**

Variable	Model 3: Physical Function			Model 4: Disability		
	B	SE B	$\beta$	B	SE B	$\beta$
Age	0.130	0.194	0.100	-0.249	0.240	-0.151
Glycosylated Hemoglobin	-1.072	1.271	-0.127	-0.234	1.569	-0.022
Depression	-0.949	0.304	-0.472*	-1.268	0.375	-0.497*
Overall Multi-tasking Cost	2.546	6.756	0.057	2.000	8.342	0.035
$R^2$	0.236*			0.278*		
F Statistic	2.702			3.363		

**Table 4.4:** Results from the full model (e.g. all variables included) are shown. Abbreviations: B, Unstandardized coefficients; SE B, standard error of unstandardized coefficients;  $\beta$ , Standardized coefficients. \*Significant at  $p<0.05$ .



#### *4.4.8 Effects of Depression, Physical Activity Level, and Sleep Quality on Gait*

Results of regression models 5 and 6 are provided in Table 4.5. This exploratory analysis of the effects of depression symptoms, physical activity level, and sleep quality on gait velocity and variability revealed moderately strong and statistically significant relationships between physical activity level and normal walking gait speed ( $\beta=0.357$ ,  $p=0.03$ ), with all 3 variables combined accounting for a statistically significant 21% of the variation in gait speed ( $R^2=0.210$ ,  $p=0.04$ ). Backwards elimination resulted in the respective removal of sleep quality (model  $R^2=0.209$ ,  $p=0.01$ ) and symptoms of depression (model  $R^2=0.163$ ,  $p=0.01$ ), while physical activity level remained significantly associated with gait speed in the final model ( $\beta=0.403$ ,  $p=0.01$ ). In contrast, sleep quality was significantly associated with stride length variability under normal walking conditions ( $\beta=0.194$ ,  $p=0.02$ ), with the combination of all 3 factors predicting a non-significant 18% of the variation in this criterion ( $R^2=0.178$ ,  $p=0.09$ ). Backwards elimination resulted in the respective removal of symptoms of depression (model  $R^2=0.174$ ,  $p=0.04$ ) and physical activity level (model  $R^2=0.166$ ,  $p=0.01$ ), while sleep quality remained significantly associated with stride length variability in the final model ( $\beta=0.408$ ,  $p=0.01$ ).

Physical activity level continued to demonstrate a moderate association with gait speed under fast walking conditions ( $\beta=0.385$ ,  $p=0.02$ ), and the combination of all 3 factors accounted for a significant proportion of the variation in fast walking gait speed ( $R^2=0.209$ ,  $p=0.04$ ). Backwards elimination resulted in the removal of symptoms of depression (model  $R^2=0.204$ ,  $p=0.02$ ) and sleep quality (model  $R^2=0.158$ ,  $p=0.01$ ) respectively, while physical activity level remained significantly associated with fast

walking gait speed in the final model ( $\beta=0.397$ ,  $p=0.01$ ). Finally, symptoms of depression were moderately associated with stride length variability under fast walking conditions ( $\beta=0.498$ ,  $p=0.005$ ), and together with physical activity level and sleep quality accounted for significant proportions of the variance in this criterion variable ( $R^2=0.317$ ,  $p=0.005$ ). Backwards elimination resulted in the removal of sleep quality (model  $R^2=0.301$ ,  $p=0.002$ ), leaving both symptoms of depression ( $\beta=0.432$ ,  $p=0.006$ ) and physical activity level ( $\beta=-0.253$ ,  $p=0.09$ ) in the final model. No significant interactions were observed in any of the models.

**Table 4.5: Effect of Depression, Physical Activity Level, and Sleep Quality on Gait Speed and Stride Variability**

Variable	Model 5a: Normal Walking Gait Velocity			Model 5b: Fast Walking Gait Velocity			Model 6a: Normal Walking Gait Variability			Model 6b: Fast Walking Gait Variability		
	B	SEB	$\beta$	B	SEB	$\beta$	B	SEB	$\beta$	B	SEB	$\beta$
<b>Depression</b>	-0.009	0.007	-0.201	-0.006	0.013	-0.081	-0.044	0.111	-0.073	0.193	0.065	0.498**
<b>Physical Activity Level</b>	0.035	0.015	0.357*	0.065	0.026	0.385**	-0.151	0.236	-0.106	-0.209	0.137	-0.229
<b>Sleep Quality</b>	-0.003	0.013	-0.044	-0.024	0.022	-0.180	0.485	0.194	0.446*	-0.097	0.113	-0.140
<b>R<sup>2</sup></b>	0.210*			0.209**			0.178			0.317**		
<b>F Statistic</b>	3.197			3.166			2.375			5.099		

**Table 4.5:** Results from the full model (e.g. all variables included) are shown. Abbreviations: B, Unstandardized coefficients; SE B, standard error of unstandardized coefficients;  $\beta$ , Standardized coefficients. \*Significant at  $p<0.05$ , \*\*Significant at  $p<0.01$ .

#### *4.4.9 Effects of Depression, Physical Activity Level, and Sleep Quality on Function*

Results of regression models 7 and 8 are provided in Table 4.6. Physical activity level demonstrated a significant and moderately strong relationship to self-reported physical function on the LLFDI (beta=0.371, p=0.01), and this variable, together with depression and sleep quality, predicted a significant portion of the variation in this criterion variable ( $R^2=0.378$ , p=0.001). Backwards elimination removed symptoms of depression (model  $R^2=0.331$ , p=0.001), leaving both physical activity level (beta=0.434, p=0.003) and sleep quality (beta=-0.394, p=0.006) in the final model.

Similarly, depression symptoms demonstrated a moderately strong and statistically significant association with LLFDI disability score (beta=-0.409, p=0.01) and, together, the 3 variables explained a statistically significant 31% of the variation in disability scores ( $R^2=0.311$ , p=0.004). Backwards elimination removed sleep quality (model  $R^2=0.304$ , p=0.001) and physical activity level (model  $R^2=0.255$ , p=0.001), respectively, leaving only symptoms of depression (beta=-0.505, p=0.001) in the final model. No significant interactions were observed in either model.

## **4.5 DISCUSSION**

This study is among the first to examine the specific contributions of multi-tasking to single-task gait and functional outcomes in older adults with type 2 diabetes. Our findings suggest that multi-tasking disrupts gait stability when performed while walking. However, the ability to multi-task itself appears to play only a small role in ambulation under single-task conditions and, likewise, appears to exert little influence on self-reported levels of physical function and disability in this population.

**Table 4.6: Effect of Depression, Physical Activity Level, and Sleep Quality on LLFDI Physical Function and Disability Scores**

Variable	Model 7: Physical Function			Model 8: Disability		
	B	SE B	$\beta$	B	SE B	$\beta$
Depression	-0.498	0.301	-0.248	-1.043	0.403	-0.409*
Physical Activity Level	1.680	0.621	0.371*	1.389	0.829	0.241
Sleep Quality	-1.030	0.517	-0.290	-0.424	0.691	-0.094
$R^2$	0.378**			0.311**		
F Statistic	7.290			5.412		

**Table 4.6:** Results from the full model (e.g. all variables included) are shown. Abbreviations: B, Unstandardized coefficients; SE B, standard error of unstandardized coefficients;  $\beta$ , Standardized coefficients. \*Significant at  $p < 0.05$ , \*\*Significant at  $p < 0.01$ .

As described in Chapter 3, the results of this investigation are consistent with others in demonstrating that multi-tasking while walking can impair spatiotemporal gait characteristics in older adults with diabetes (Paul et al., 2009; Roman de Mettelinge et al., 2013). However, we are unaware of any previous attempts to examine whether multi-tasking abilities influence single-task gait in this population. Our study found little association between these variables, supporting current neuropsychological models describing executive function as active “only when the novelty and/or complexity of a given situation precludes an automatic, routine response” (Suchy, 2009, p. 106). That multi-tasking was not significantly associated with either normal or fast walking gait parameters in our sample of relatively high-functioning older adults with diabetes may

indicate that even fast walking remained a relatively automatic process in this group, requiring minimal attention and/or executive input.

In much the same way, we observed little association between overall multi-tasking ability and physical function or disability. This may also be partly attributable to the high-functioning nature of our sample, which generally reported only “slight” levels of physical impairment and disability. As a result, the relatively subtle changes we observed in multi-tasking abilities may have exerted little influence on these variables. It would seem worthwhile for future research to examine whether multi-tasking exhibits a stronger association with gait under more complex conditions than those employed in our study or, conversely, whether multi-tasking deficits can eventually become pervasive enough to influence single-task gait parameters, physical function, and/or disability in this and other populations.

The results of our investigation may also provide some context for studies of dual-task training interventions, which have been shown to improve gait and balance under dual-task conditions in elderly adults (Silsupadol, Lugade, et al., 2009; Silsupadol, Shumway-Cook, et al., 2009; You et al., 2009) and those with dementia (Schwenk, Zieschang, Oster, & Hauer, 2010), but have little effect on single-task performance, and vice versa. This training specificity may arise because the resources necessary to maintain gait and balance under single-task conditions are somewhat distinct from those required during multi-tasking, particularly in terms of the need for executive input. Our study did not address this issue directly; however the lack of association we observed between multi-tasking ability and single-task gait parameters is broadly consistent with such hypotheses.

Also of considerable interest are our secondary findings that depression, physical activity level, and sleep quality each contributed significantly to at least one gait or functional measure. In particular, the beneficial effect of physical activity on gait velocity and self-reported physical function further emphasizes the critical role of physical activity in the management of type 2 diabetes. Likewise, the negative effects of depression and poor sleep quality on gait variability and disability suggest that the identification and treatment of these common comorbidities may have important functional implications for this population, and should not be trivialized.

Although these findings are very interesting, it is important to acknowledge that several factors limit interpretation of the data. First among these is the relatively small size of our sample, which clearly limits the power of our regression analysis. Further, this sample consisted largely of high functioning older individuals with impaired but generally well-maintained glycemic control. It is currently unclear whether our findings can be extrapolated to other individuals with diabetes, and how variables such as multi-tasking ability, depression, physical activity, and sleep quality might relate to gait and/or functional abilities in subjects with fewer cognitive or physical resources, or in those with more poorly controlled diabetes.

It is also somewhat difficult to determine the clinical significance of our findings, particularly with regard to gait velocity and variability. Previous research has indicated that an increase of as little as 3% in stride length variability may nearly double fall risk (Maki, 1997), while self-selected normal gait speeds below 1 m/s have been linked to an increased risk for hospitalization and death (Cesari et al., 2005). We did not observe a substantial increase in stride length variability from normal to fast gait conditions in our

subjects; however their normal gait speed averaged only  $1.0\pm 0.3$  m/s, with well over a third of the group (40.5%, n=15) ambulating below this cut-off rate. Further research will be needed to determine the effects of depression, physical activity level, and sleep quality on gait and physical function in those with diabetes, and elucidate the mechanisms that may underlie these relationships in those with diabetes and other populations at high risk for functional impairments and disability.

#### **4.6 Conclusions**

Overall, the results of our investigation indicate that multi-tasking while walking negatively affects gait stability in community dwelling older adults with type 2 diabetes. However, multi-tasking ability itself has relatively little influence on gait velocity or variability under single-task conditions, or on self-reported levels of physical function or disability in these individuals. Our data do suggest that potentially treatable and/or modifiable factors such as depression, physical activity level, and sleep quality may exert substantial influence on important aspects of both quantifiable and self-perceived physical function in this population. This emphasizes the importance of appropriately identifying and treating such common comorbidities, and highlights the need for further research exploring how executive and neuropsychiatric function, physical activity, and sleep influence different aspects of physical function in those with diabetes.

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## **Chapter 5 Preface**

Previous chapters have demonstrated that multi-tasking while walking can adversely affect gait stability in older adults with type 2 diabetes, although multi-tasking ability itself appears to have relatively little influence on single-task gait measures or self-reported levels of physical function and disability. However, multi-tasking is generally considered to be only one of a variety of executive functions, and the integrity and functional contributions of other executive abilities remain largely unknown in this population.

Therefore, alongside our multi-tasking tests, we also administered a battery of 10 executive measures assessing attention shifting, information updating, response inhibition, visuospatial organization, and verbal logical memory to each subject in both the diabetes and comparison groups. Our analyses of the results obtained from this executive testing battery, and our exploration of the relationships between these abilities and measures of gait and function, comprise Chapter 5.

## Chapter 5

The Integrity of Other Executive Functions in Older Adults with Type 2 Diabetes

A version of this chapter is in preparation for submission to *Neuropsychological*

*Rehabilitation (2014)*

## 5.1 Abstract

**BACKGROUND AND PURPOSE:** It is unclear whether older adults with type 2 diabetes (DM) exhibit impairments in executive function, the set of processes responsible for goal-oriented behavior. We examined executive function in older adults with DM, and explored its relationships to gait and functional ability. **METHODS:** Forty individuals with type 2 diabetes were compared to a matched group of 40 individuals without diabetes. Each subject completed a battery of 10 executive function tests assessing the processes of information updating, task shifting, response inhibition, and visuospatial and verbal processing and memory. Self-selected normal and fast walking speed and stride length variability were measured using a GaitMat II System, and self-reported functional ability assessed via the Late Life Function and Disability Index (LLFDI). **RESULTS:** Subjects with DM performed more poorly on a measure of updating and visuospatial function. No significant differences were observed on measures of shifting, inhibition, visuospatial memory, and verbal processing or memory. Visuospatial memory was the only variable associated with gait or functional ability in those with DM. However, measures of updating, shifting, inhibition, and visuospatial memory were associated with gait and/or functional abilities in the comparison group. **DISCUSSION AND CONCLUSIONS:** Older adults with DM may exhibit deficits in the executive processes responsible for updating and visuospatial processing. It also appears that executive functions may contribute differently to gait and functional ability in those with and without diabetes. Further research should more clearly examine executive function in those with DM, and determine whether executive dysfunction contributes to physical deficits, falls, and disability in this high risk patient population.

## 5.2 Introduction

A central component of human behavior, executive function refers to the collective set of cognitive processes responsible for planning, coordinating, sequencing, and monitoring goal-oriented activities (Hull, Martin, Beier, Lane, & Hamilton, 2008). Representing a critical link between cognitive and physical function, executive abilities are thought to provide an awareness of purpose and ability to process and integrate the myriad cognitive, motor, and behavioral demands required to function in a complex and dynamic environment (Yogev-Seligmann, Hausdorff, & Giladi, 2008). Broadly, these processes are operationalized in tasks that require, among others, the monitoring and updating of incoming information, the division and shifting of attention between tasks, the inhibition of automatic responses, and the organization of visuospatial and verbal information (Hull et al., 2008; Miyake, Friedman, et al., 2000; Miyake, Friedman, Rettinger, Shah, & Hegarty, 2001).

Such abilities clearly have important implications for rehabilitation and, indeed, there are indications that even subtle executive disturbances are powerful predictors of functional loss (Cahn-Weiner, Malloy, Boyle, Marran, & Salloway, 2000). Consistent with this, a substantial amount of research has linked executive dysfunction to spatiotemporal gait abnormalities (Ble et al., 2005; Hausdorff, Yogev, Springer, Simon, & Giladi, 2005; Pettersson, Olsson, & Wahlund, 2007; Sheridan, Solomont, Kowall, & Hausdorff, 2003), falls (Shumway-Cook, Brauer, & Woollacott, 2000; Shumway-Cook, Woollacott, Kerns, & Baldwin, 1997), and other functional impairments (Kuo, Leveille, Yu, & Milberg, 2007; Qiu et al., 2006).



Although deficits in executive function are most commonly associated with Alzheimer's disease, Parkinson's disease, multiple sclerosis, traumatic brain injury, and other overtly neurological disorders, there is also increasing evidence of executive dysfunction in older adults with type 2 diabetes. For example, Yeung et al. (2009) reported that both "young-old" (ages 53-70) and "old-old" (ages 71-90) members of this population performed significantly worse on measures of attention shifting and response inhibition than their peers without diabetes. Likewise, Qui et al. (2006) observed that elderly homebound individuals with diabetes exhibited significant deficits on measures of updating, visuospatial function, and attention shifting when compared to a similar group without diabetes. This cross-sectional data appears to be corroborated by several longitudinal studies describing small but significant baseline deficits in attention and attention shifting in this population, with a nearly two-fold risk of decline in these areas at 4- and 6-year follow-ups (Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001; Gregg et al., 2000).

In contrast to these findings, however, some researchers have reported no significant impairments on composite measures of executive function in older adults with type 2 diabetes (Ruis et al., 2009; Saczynski et al., 2008). This raises the possibility that, if existent, the executive deficits observed in this population may be confined to relatively specific processes, and are thus sensitive to the heterogeneous methods currently used to assess executive function. Likewise, although a small amount of evidence has linked executive dysfunction to gait abnormalities (Brach, Talkowski, Strotmeyer, & Newman, 2008; Paul, Ellis, Leese, McFadyen, & McMurray, 2009; Roman de Mettelinge et al., 2013) and functional impairments (Kuo et al., 2007;

Qiu et al., 2006) in those with diabetes, very little is known about the influence of executive function on gait and/or functional ability in this population.

In chapter 3, we demonstrated that older adults with type 2 diabetes exhibited changes in a specific executive ability, multi-tasking, that may have important clinical implications. However, it remains unclear whether these individuals also suffer from deficits in other important dimensions of executive function. The purpose of this investigation was to examine the integrity of the executive processes involved in information updating, attention shifting, response inhibition, and visuospatial and verbal processing and memory in older adults with type 2 diabetes when compared to their peers without diabetes. A secondary aim was to explore the relationships between these executive processes and quantitative gait parameters and self-reported physical function and disability in this population. Our exploratory hypotheses were that subjects with diabetes would demonstrate significant impairments in these areas of executive function, and that poorer executive performance would be associated with poorer gait and functional abilities in these individuals.

## **5.3 Methods**

### *5.3.1 Study Design and Sample*

Institutional approval for this cross-sectional study was granted by the Human Subjects Committee of the University of Kansas Medical Center.

A total of 40 individuals aged 60 years and older with a medical diagnosis of type 2 diabetes and 40 similarly aged individuals without diabetes were recruited. Each subject with diabetes (DM) was matched to a comparison subject (CN) in terms of age

(± 5 years), sex, highest level of education completed (high school vs. college), and the presence or absence of hypertension. This yielded a total sample of 40 matched pairs. Subjects were provided with a \$50 stipend upon completing the study. Exclusion criteria included the following: 1) known history of central nervous system pathology, 2) musculoskeletal or orthopedic conditions significantly affecting gait and/or balance, 3) inability to ambulate without an assistive device, 4) self-reported body mass index of > 45 kg/m<sup>2</sup>, 5) uncorrectable visual/auditory deficits or color blindness, 6) wounds on the weight bearing surfaces of the feet, 7) less than a high school level of education, and/or 8) cognitive impairment as evidenced by a score of ≥ 2 on the AD8 Dementia Screening Interview or a score of < 26 on the Mini-Mental Status Examination.

### *5.3.2 Procedures*

Following telephone screening and the signature of an institutionally-approved informed consent form, data regarding age, height, weight, medical comorbidities, current medications, and number of falls in the past six months were gathered. Fasting blood glucose measurements were then obtained from each subject (Contour Blood Glucose Monitoring System, Bayer, Tarrytown, NY), and glycosylated hemoglobin (HbA1c) levels measured for each subject with diabetes via disposable finger-stick kits (Metrika A1CNow+, Bayer, Tarrytown, NY). Potential comparison group subjects exhibiting fasting blood glucose levels ≥ 126 mg/dL were excluded from participation and referred to a physician for further metabolic evaluation. A small snack was made available to each subject once fasting blood glucose level was established. All study

subjects were tested in a normoglycemic state, defined as a blood glucose level of between 80 and 250 mg/dL.

After glycemic testing, each subject was administered a series of questionnaires assessing symptoms of depression, physical activity level, sleep quality, and functional ability. This was followed by a pseudo-randomized battery of executive measures and quantitative analyses of gait speed and variability (measures such as the Rey-Osterrieth and Wechsler Logical Memory Tests included immediate and delayed recall components, and could not be truly randomized). All testing was conducted by the same research personnel in a quiet laboratory setting to minimize distraction.

### *5.3.3 Measures*

#### *Executive Function Assessments*

Each subject was administered a battery of executive function assessments selected on the basis of neuropsychological research and recommendations (Hull et al., 2008; Miyake, Emerson, & Friedman, 2000) and expert consultation (J. McDowd). This battery included measures specifically selected to assess each of the following executive domains:

#### *Monitoring and Updating of Information (Updating)*

- 1) The Keep-track Verbal Test was used to assess the ability to update internal representations in response to changing external stimuli (Miyake, Friedman, et al., 2000; Yntema, 1963). Subjects were first familiarized with a series of 6 index cards, each of which contained the title of a semantic category (relatives, metals, distances,

countries, colors, and animals), as well as with a series of cards containing 10 words from each category. Before each trial, the subject randomly selected 2 of the 6 category cards, which remained visible throughout the trial. They were then shown 10 randomly ordered cards containing words from each of the 6 categories. After viewing all 10 cards, the subject attempted to recall the last word presented in each of the 2 relevant target categories. Subjects completed 2 practice trials, followed by 4 blocks of 10 target trials. The number of correct responses on the 40 target trials was recorded for data analysis.

- 2) The N-back test was also used to assess the executive ability of updating (Hull et al., 2008; Kirchner, 1958). Subjects were asked to monitor a continuous series of 5 letters (C, K, N, R, and V) projected onto a 15" computer monitor, and to provide a yes or no response indicating whether each letter was repeated after an intervening letter (e.g. C-K-C = yes, C-K-R = no). Each viewed letter represented one trial, and was displayed for a period of 2.5 seconds before advancing to the next trial. Subjects completed 1 practice run of 20 trials, followed by 1 test run of 60 trials, of which 15 trials consisted of a repeated letter. The number of correct responses on the 60 target trials was recorded for data analysis.

### *Mental Set and Task Shifting (Shifting)*

- 1) The Trail Making Test was used to assess the ability to shift attention between different task requirements (Homack, Lee, & Riccio, 2005). In part A of the test subjects drew a line connecting series of letters or numbers in order as quickly as possible (e.g. A-B-C; 1-2-3 etc.). In part B of the test subjects drew a line

connecting numbers and letters in an alternating fashion (e.g. 1-A-2-B-3-C etc.).

The percent change in the time required to complete the two conditions was calculated, with a higher percent change reflected poorer shifting ability.

- 2) The Local-Global Test was also used to assess shifting ability (Miyake et al., 2000; Navon, 1977). Subjects were first familiarized with a series of Navon figures, in which a “global” figure (e.g. a large letter H) is comprised of smaller “local” figures (e.g. many small letter S’s), and instructed to verbally identify the local letters if the figure was red, and the global letter if the figure was blue. A block of 15 practice trials was provided, followed by the random administration of 2 blocks of 30 test trials in which the figure colors remained constant across successive trials (e.g. non-switching trials) and 2 blocks of 30 test trials in which figure colors changed (e.g. switching trials). Incorrect responses were immediately pointed out by the examiner, so that error-correction influenced the total time required to complete the trial. The average times required to complete the switching and non-switching trials were used to calculate the percent change between the two conditions. As with the TMT, a higher percent change reflected poorer shifting ability.

### *Response Inhibition (Inhibition)*

- 1) The Stroop Word Color Test was used to assess the ability to inhibit automatic, predominant responses (Miyake, Friedman, et al., 2000; Stroop, 1935). In the color naming condition of the test, subjects were provided with an 8”x11” card containing 120 blue, red, and green colored X’s arranged in a 20 row by 6 column configuration. Upon beginning the test, subjects moved horizontally across each

row, stating aloud the color of as many of the X's as possible within a 45-second period. In the second, inhibition condition, subjects were presented with an 8"x11" card containing an identical 20 by 6 configuration of the words "blue," "red," and "green" printed in incongruous colors (e.g. the word "green" printed in blue ink). Subjects were asked to state aloud the color of as many of the words as quickly as possible in a 45-second period. The percent change in the number of correct responses obtained from each condition was calculated, with a higher percent change reflecting poorer inhibition ability.

- 2) The Hayling Sentence Completion Test was also used to assess inhibition ability (Burgess & Shallice, 1996). In part A of the test, subjects were read a series of 15 simple sentences with the last word missing, and asked to verbally provide a word that would logically complete the sentence as quickly as possible. For example, the sentence "The old house will be torn..." might be completed with the word "down." In part B of the test, subjects were read a second set of 15 similar sentences and asked to verbally complete each sentence as quickly as possible with a word that did not fit the context of the sentence. For example, the sentence "The old house will be torn..." might be completed with a word such as "peanut." Inappropriate responses were immediately pointed out by the examiner, so that error-correction influenced the total time required to complete the trial, and the amount of time required to complete parts A and B were used to calculate a percent change score between the two conditions. As with the Stroop test, a higher percent change reflected poor inhibition ability.

## *Visuospatial and Verbal Processing and Memory*

- 1) The Rey-Osterrieth Complex Figure Test was used to assess visuospatial organization and memory (Lezak, Howieson, Loring, Hannay, & Fischer, 2004; Rey & Osterrieth, 1993). Subjects were given a copy of an asymmetrical geometric figure and asked to draw the figure as accurately as possible on a blank sheet of paper without the use of a straight edge. Immediately following this copy trial, both the figure and the subject's drawing were removed. After a delay of 40-60 minutes, the subject was provided with a second blank sheet of paper and asked to reproduce the figure from memory as accurately as possible. Both figures were scored on a standardized 36-point scoring system according to the accuracy and relative position of 18 specified components of the drawing, with a score of 36 reflecting a nearly identical reproduction of each component.
- 2) The Wechsler Logical Memory Test was used to assess the ability to organize and recall ideas expressed in story form (Lezak et al., 2004; Wechsler, 1997). Subjects were read a standardized thematic story and asked to immediately recall the story using as many of the same words as possible. After a delay of 40-60 minutes, subjects were asked to recall the story again in as much detail as possible. Both the immediate and delayed recall tests were scored according to a standardized system based on the correct recall of 25 specified story units, in which a score of 25 points indicated nearly perfect recall.



### *Gait and Functional Assessments*

- 1) Quantitative analysis of gait was performed using a GaitMat II gait analysis system (E.Q., Inc., Chalfont, PA). This system consists of a 4 meter long walkway housing 38 rows of 256 pressure sensitive switches connected to a computer analysis system via a USB interface. Subjects began walking approximately 2 meters prior to stepping onto the GaitMat, and were instructed to continue walking to a point approximately 2 meters beyond the GaitMat. Three trials were conducted at each subject's self-selected "normal" walking speed, followed by three trials in which they were instructed to walk "as quickly and safely as possible". Subjects wore their normal footwear, and were not allowed to utilize an assistive device during gait analysis. Gait velocity (in m/s) and stride length variability (expressed as the coefficient of variation:  $[SD/mean]*100$ ) for both normal and fast walking conditions were collected and averaged across the 3 trials.
- 2) The Late Life Function and Disability Instrument (LLFDI) is a comprehensive measure of physical function and disability specifically designed for older adult populations (Dubuc, Haley, Ni, Kooyoomjian, & Jette, 2004). The physical function component of the measure consists of 32 items evaluating self-reported difficulty in physical activities involving upper extremity function, lower extremity function, and advanced lower extremity function (e.g. running, etc.). Subjects were asked "How much difficulty do you have doing [a particular activity] without the help of someone else and without the use of an assistive device?" and responded "none", "a little", "some", "quite a lot", or "cannot do." Overall physical functioning was scored on a scale of 0-100, with higher scores reflecting higher levels of function.

A further 16 items assessed the frequency of participation in and ability to perform major life tasks. Subjects were asked how often they performed a particular task, and rated the extent to which they felt limited in that task with responses of “not at all,” “a little,” “somewhat,” “a lot,” and “completely”. Frequency and disability indices were also scored on scales of 0-100, with higher scores reflecting a higher frequency of participation and a lower degree of disability.

### *General Assessments*

- 1) The Mini-Mental Status Examination (MMSE) was used to assess global cognitive function (Folstein, Folstein, & McHugh, 1975). This 30-point instrument broadly reflects orientation, memory, concentration, and praxis, and is sensitive to moderate to severe cognitive impairment. As it seemed unlikely that severe cognitive deficits would be due exclusively to diabetes, any individual scoring < 26 on this measure was excluded from study participation.
- 2) Beck’s Depression Inventory-II (BDI) was used to assess self-reported symptoms of depression (Beck, Steer, & Brown, 1996). This measure is scored on a 21-item, 63-point scale, with scores of 19 or less indicating minimal symptoms of depression, 20-28 moderate symptoms, and  $\geq 29$  severe symptoms.
- 3) The Rapid Assessment of Physical Activity (RAPA) was used to assess physical activity level (Topolski et al., 2006). Subjects responded “yes or no” to 7 questions describing their usual level of participation in physical activity. Scores categorized subjects into one of 5 levels of activity: 1=sedentary, 2=under-active, 3=regular under-active (light activity), 4-5=regular under-active, and 6-7=regular active.

4) The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality and disturbance (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). This questionnaire consists of 19 self-rated questions comprising 7 component scores, each rated on a Likert scale of 0 (no difficulty) to 3 (severe difficulty). Addition of the 7 component scores generated a global score of 0-21. A global score of 5 or greater indicated poor sleep quality.

#### *5.3.4 Statistical Analysis*

Data analysis was conducted using SPSS 16.0 for Windows (Chicago, IL). Normally distributed data are presented as mean  $\pm$  standard deviation, and non-normal data as median (range). In many cases, test results were analyzed as the percent change in performance between a baseline condition and a more challenging experimental condition. This was calculated via the following formula:

$$|\text{Percent Change}| = \frac{(\text{Baseline performance} - \text{Experimental performance})}{\text{Baseline performance}} \times 100$$

By convention, a positive percent change reflected a decline in task performance from baseline, whereas a negative percent change represented an improvement in performance from baseline.

Data distribution and variance was examined via scatter and Q-Q plots, assessed with Kolmogorov-Smirnov and Shapiro-Wilk tests, and descriptive statistics were calculated for all variables. As subjects in the diabetes and comparison groups were paired, mean between- and within-group differences and 95% confidence intervals were examined via 2-tailed, 1 sample paired t-tests. The Wilcoxon signed rank test

assessed differences in non-normal data. Pearson-product-moment and Spearman's rank sum correlations explored the relationships between variables for normally and non-normally distributed data, respectively. Type I error rate was set at 0.05.

## **5.4 Results**

### *5.4.1 Sample Characteristics*

Table 5.1 provides the general characteristics of the groups. Forty individuals with type 2 diabetes (65% female) and 40 paired individuals without diabetes (65% female) consented and participated in this study. Seventy-eight percent of the individuals in both groups were college educated, with the same percentage reporting a diagnosis of hypertension.

Those with diabetes exhibited higher fasting blood glucose ( $p < 0.001$ ), were more obese ( $p < 0.001$ ), and had more symptoms of depression ( $p = 0.04$ ) than comparison subjects. Longer term glycemic control in the diabetes group was also impaired (median HbA1c 6.8%, range 5.4 – 11.2). Eight subjects (20%) in this group reported a diagnosis of peripheral neuropathy, 2 (5%) mild retinopathy, and 1 (2.5%) nephropathy. A total of 6 subjects (15%) in the diabetes group and 2 in the comparison group (5%) reported having 2 or more falls in the preceding six months. No significant between-group differences were observed in age, global cognitive function, and self-reported physical activity level or sleep quality.

**Table 5.1: Sample Characteristics**

	Diabetes (n=40)	Comparison (n=40)	P-value	95% CI
Age (years)	72.9 ± 8.3	72.9 ± 7.7	0.90	-1.1 – 1.2
BMI (kg/m <sup>2</sup> )	31.1 ± 4.7	26.6 ± 4.4	< 0.001	2.6 – 6.4
FBG (mg/dL)	134.3 ± 45.9	92.3 ± 14.1	< 0.001	25.0 – 51.3
MMSE (score out of 30)	28.7 ± 1.2	29.2 ± 1.0	0.07	-1.0 – 0.04
BDI (score out of 63)	4.5 ( 0 – 28)	3.0 (0 – 31)	0.04 <sup>a</sup>	-0.4 – 5.2
RAPA (score out of 10)	4.9 ± 1.3	4.8 ± 1.5	0.63	-0.6 – 0.9
PSQI (score out of 21)	5.0 (1 – 12)	4.0 (1 – 18)	0.34 <sup>a</sup>	-1.2 – 2.0

**Table 5.1:** Abbreviations: BMI, body mass index; FBG, fasting blood glucose; MMSE, Mini-Mental Status Examination; BDI, Beck’s Depression Inventory-II; RAPA, Rapid Assessment of Physical Activity; PSQI, Pittsburgh Sleep Quality Index. <sup>a</sup>Wilcoxon Signed Rank Test.

#### 5.4.2 Executive Assessments

Table 5.2 provides the results of the executive function testing battery. Broadly, the data provides limited support for our exploratory hypothesis of executive dysfunction in older adults with type 2 diabetes. Specifically, subjects with diabetes performed worse on one measure of updating, the Keep Track Test (p=0.014), but not on the second, the N-back Test (p=0.80). Those with diabetes also performed more poorly on the copy trial of the Rey Osterrieth Complex Figure Test of visuospatial processing

( $p=0.007$ ), but not on the recall trial of visuospatial memory ( $p=0.16$ ). No significant differences were observed on either measure of shifting (Trail Making,  $p=0.96$ ; Local Global,  $p=0.32$ ) or inhibition (Stroop,  $p=0.97$ ; Hayling,  $p=0.38$ ). Likewise, no differences were observed on either the immediate ( $p=0.177$ ) or delayed recall ( $p=0.123$ ) trials of the Wechsler Logical Memory Test.

#### *5.4.3 Quantitative Gait Analysis*

Due to equipment malfunction, quantitative gait data could not be obtained for 3 individuals, and data for the corresponding pair-matched subjects were also removed from the analysis. Results from the 37 remaining pairs are provided in Table 5.3 and illustrated in Chapter 3, Figures 3.5 A and B. Individuals with diabetes ambulated more slowly than comparison subjects at a self-selected “normal” walking pace ( $p=0.03$ ), but with a similar degree of stride length variability ( $p=0.77$ ). When instructed to walk “as quickly and safely as possible”, those with diabetes demonstrated both slower speeds ( $p=0.001$ ) and greater stride variability than comparison subjects ( $p=0.02$ ).

#### *5.4.4 Late Life Function and Disability Index*

Results of the Late Life Function and Disability Index are also reported in Table 5.3. The groups scored similarly on the frequency ( $p=0.42$ ) and disability ( $p=0.06$ ) scales of the LLFDI; however those with diabetes scored significantly lower on the physical function component ( $p<0.001$ ).

**Table 5.2: Executive Assessments**

	<b>Diabetes (n=40)</b>	<b>Comparison (n=40)</b>	<b>P- value</b>	<b>95% CI</b>
<b>Updating</b>				
<b>Keep Track (score out of 40)</b>	36 (20-40)	38 (27-40)	0.01 <sup>a</sup>	-4.2 – -0.6
<b>N-Back (score out of 60)</b>	43.8 ± 9.6	43.2 ± 9.3	0.80	-4.1 – 5.2
<b>Shifting</b>				
<b>Trail Making (% change)</b>	19.9 ± 36.9	19.5 ± 35.7	0.96	-16.3 – -17.1
<b>Local-Global (% change)</b>	37.8 (8.5 – 62.8)	38.8 (12.8 – 133.8)	0.59 <sup>a</sup>	-13.6 – 4.5
<b>Inhibition</b>				
<b>Stroop Word Color (% change)</b>	42.8 ± 15.0	42.9 ± 11.3	0.97	-7.1 – 6.8
<b>Hayling Sentence Completion (% change)</b>	146.8 ± 83.3	129.8 ± 73.7	0.38	-21.6 – 55.7
<b>Visuospatial Organization</b>				
<b>Rey Osterrieth, Copy (score out of 36)</b>	28.5 ± 4.2	30.8 ± 2.6	0.007	-3.9 – -0.7
<b>Rey Osterrieth, Recall (score out of 36)</b>	10.4 ± 5.1	12.4 ± 5.9	0.16	-4.9 – 0.8
<b>Verbal Logical Memory</b>				
<b>Wechsler Logical Memory, Immediate (score out of 25)</b>	13 (3 – 19)	14 (3 – 25)	0.18 <sup>a</sup>	-2.9 – 0.7
<b>Wechsler Logical Memory, Delayed (score out of 25)</b>	10.1 ± 4.2	11.8 ± 5.2	0.12	-3.8 – 0.5

**Table 5.3:** Data are presented as mean ± SD or median (range). <sup>a</sup>Wilcoxon Signed Rank Test

**Table 5.3: Gait and Functional Assessments**

	Diabetes (n=37)	Comparison (n=37)	P-value	95% CI
<b>Gait Velocity</b>				
Normal Walking (m/s)	1.0 ± 0.2	1.1 ± 0.2	0.03	-0.2 – -0.01
Fast Walking (m/s)	1.4 ± 0.4	1.6 ± 0.3	0.001	-0.3 – -0.1
<b>Gait Variability</b>				
Normal Walking (%)	4.3 (0.1 – 16.1)	4.6 (2.4 – 15.9)	0.77 <sup>a</sup>	-1.1 – 1.9
Fast Walking (%)	5.4 ± 2.5	4.0 ± 1.7	0.02	0.3 – 2.5
<b>Late Life Function and Disability</b>				
Frequency (score out of 100)	56.3 ± 6.5	58.6 ± 9.7	0.42	-4.5 – 1.9
Disability (score out of 100)	79.7 ± 14.2	85.3 ± 13.8	0.06	-11.3 – 0.1
Physical Function (score out of 100)	60.6 ± 9.6	67.5 ± 8.2	< 0.001	-10.1 – -3.7

**Table 5.3:** Data are presented as mean ± SD or median (range). <sup>a</sup>Wilcoxon Signed Rank Test

#### 5.4.5 Relationships between Executive Functions and Gait and Functional Ability

Bivariate correlations explored the relationships between executive function assessments and quantitative measures of gait and self-reported functional ability separately in the diabetes and comparison groups. Tables 5.4 A and B provide the results of these analyses. Largely in contrast to our secondary hypothesis, the Rey Osterrieth Complex Figure recall was the only executive factor significantly related to any gait or functional measure in subjects with diabetes. Specifically, poorer



performance on this measure was associated with a lower reported frequency of participation on the LLFDI ( $r=0.32$ ,  $p=0.04$ ).

In comparison subjects, however, we observed a number of significant relationships between executive function and gait and functional ability. In this group, poorer performance on both of our updating measures, the Keep Track and N-back tests, was associated with slower walking speed under both normal ( $r=0.34$ ,  $p=0.03$  and  $r=0.34$ ,  $p=0.03$ , respectively) and fast walking conditions ( $r=0.37$ ,  $p=0.02$  and  $r=0.43$ ,  $p=0.006$ , respectively). Moreover, poorer performance on shifting (Trail Making;  $r=-0.33$ ,  $p=0.04$ ) and inhibition measures (Stroop;  $p=-0.35$ ,  $r=0.03$ ) were also related to slower normal walking speed, whereas poorer visuospatial memory was associated with a greater walking speed under fast walking conditions (Rey Osterrieth recall;  $r=-0.53$ ,  $p=0.001$ ). Finally, poorer performance on an inhibition measure, the Hayling Sentence Completion Test, was associated with a lower frequency of participation on the LLFDI ( $r=-0.32$ ,  $p=0.04$ ) in this group.

## **5.5 Discussion**

Although exploratory, the results of this investigation provide insight into the integrity of executive functions in older adults with type 2 diabetes, and their possible contributions, or lack thereof, to gait and functional abilities. Specifically, we observed that these individuals performed worse on some measures of updating and visuospatial organization. Further, our data appear to suggest that executive functions may contribute differentially to gait in those with and without diabetes.

**Table 5.4A: Executive Function Correlates of Gait and Functional Ability in Subjects with Diabetes**

Executive Measure	Normal Gait		Fast Gait		Late Life Function and Disability Index		
	Speed	Variability	Speed	Variability	Frequency	Disability	Function
<b>Keep Track</b>	0.15	-0.16 <sup>a</sup>	0.24	-0.12	-0.01	0.23	-0.03
<b>N-back</b>	0.15	-0.26 <sup>a</sup>	0.24	-0.11	-0.31	-0.10	-0.11
<b>Trail Making</b>	-0.22	0.22	-0.32	0.26	-0.01	-0.02	-0.13
<b>Local-Global</b>	-0.03 <sup>a</sup>	0.27 <sup>a</sup>	0.21 <sup>a</sup>	0.04 <sup>a</sup>	-0.04 <sup>a</sup>	-0.02 <sup>a</sup>	-0.15 <sup>a</sup>
<b>Stroop</b>	-0.01	-0.02 <sup>a</sup>	-0.07	-0.04	0.31	0.24	0.13
<b>Hayling</b>	-0.17	0.01 <sup>a</sup>	-0.28	0.17	-0.26	-0.04	-0.08
<b>Rey Osterrieth Copy</b>	0.06	0.01 <sup>a</sup>	-0.16	-0.15	0.14	0.02	0.01
<b>Rey Osterrieth Recall</b>	0.14	-0.01 <sup>a</sup>	0.07	0.01	0.32*	0.06	0.06
<b>Wechsler Immediate</b>	0.09	-0.14 <sup>a</sup>	0.02	0.01	0.15	0.27	0.20
<b>Wechsler Delayed</b>	0.23	-0.16 <sup>a</sup>	0.18	0.06	0.22	0.22	0.21

Table 5.4A: <sup>a</sup>Spearman rank sum correlation coefficient. \*Significant at p<0.05. \*\*Significant at p<0.01.

**Table 5.4B: Executive Function Correlates of Gait and Functional Ability in Subjects with Diabetes**

	Normal Gait			Fast Gait			Late Life Function and Disability Index		
	Speed	Variability		Speed	Variability		Frequency	Disability	Function
<b>Keep Track</b>	0.34*	-0.07 <sup>a</sup>		0.37*	-0.04		0.03	0.21	0.05
<b>N-back</b>	0.34*	-0.11 <sup>a</sup>		0.43**	-0.10		-0.06	0.07	0.23
<b>Trail Making</b>	-0.33*	0.04 <sup>a</sup>		-0.28	-0.06		-0.13	-0.19	-0.17
<b>Local-Global</b>	-0.08 <sup>a</sup>	0.10 <sup>a</sup>		-0.13 <sup>a</sup>	0.15 <sup>a</sup>		0.20 <sup>a</sup>	-0.10 <sup>a</sup>	-0.05 <sup>a</sup>
<b>Stroop</b>	-0.35*	0.25 <sup>a</sup>		-0.23	-0.01		0.12	-0.21	-0.21
<b>Hayling</b>	-0.31	0.06 <sup>a</sup>		-0.14	-0.03		-0.32*	-0.07	-0.07
<b>Rey Osterrieth Copy</b>	-0.14	0.19 <sup>a</sup>		0.05	0.15		0.09	-0.13	0.02
<b>Rey Osterrieth Recall</b>	0.26	-0.02 <sup>a</sup>		-0.53**	0.01		-0.21	0.04	0.11
<b>Wechsler Immediate</b>	0.14	0.02 <sup>a</sup>		0.11	0.09		-0.14	-0.04	-0.07
<b>Wechsler Delayed</b>	0.19	-0.06 <sup>a</sup>		0.13	0.13		-0.01	0.07	-0.10

Table 5.4B: <sup>a</sup>Spearman rank sum correlation coefficient. \* Significant at p<0.05. \*\*Significant at p<0.01.

Broadly, the results of our executive assessment are consistent with those of Yeung et al. (2009), Qui et al. (2006), and others (Fontbonne et al., 2001; Gregg et al., 2000) in describing features of executive dysfunction in older adults with diabetes. However, the widely varied testing methods used to assess executive function in these studies provide limited context by which to interpret our results. Perhaps most analogous to our investigation, Yeung and colleagues (2009) administered a cognitive battery including a total of 4 executive measures, 3 of which, the Hayling, Stroop, and Trail Making Tests<sup>1</sup>, were also administered in our study. This group reported that subjects with diabetes exhibited significant impairments of 14% and 12% on the Hayling and Trail Making Tests, respectively, with non-significant decrements of 16% on the Stroop Test and 13% on a measure of visuospatial processing, the Brixton Spatial Anticipation Test. In contrast, we observed a significant deficit of 7% on visuospatial processing measure, the copy trial of the Rey Osterrieth Complex Figure, a similar but non-significant decrement of 12% on the Hayling Test, and virtually no differences ( $\leq 2\%$ ) on the Stroop and Trail Making Tests. In addition, we noted a significant deficit of 7% on the Keep Track Test, a measure of updating not represented in Yeung et al.'s testing battery.

Although a common problem in research examining executive function, the factors that underlie these discrepancies are not entirely clear. It is certainly plausible that sample characteristics such as age, sex, education, and other demographic and/or comorbid factors could account for these conflicting results. Equally relevant is the fact

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<sup>1</sup> These authors administered a slightly different version of the Trail Making Test, the Colored Trails Test, in which subjects were asked to shift between numbers and colors, rather than numbers and letters. This may reduce the influence of verbal function and/or language on the test.

that executive function itself currently lacks a clear definition and conceptual framework upon which to develop and standardize tests and measures. As a result, executive measures are often posited to measure ambiguous and poorly operationalized qualities such as “planning” or “reasoning,” and many are highly sensitive to task impurity – a phenomenon in which deficits in non-executive processes such as language or vision impair test performance despite intact executive function (Miyake, Emerson, et al., 2000).

In addition to the fact that our diabetes and comparison groups were pair-matched in terms of age, sex, education, and the presence or absence of hypertension, a major strength of the present study is the use of a battery of relatively well-defined executive measures supported by current neuropsychological research (Hull et al., 2008; Miyake, Emerson, et al., 2000). Further, our use of multiple measures to assess each executive process provides additional context by which to interpret our results. For example, we observed that subjects with diabetes performed more poorly on one measure of updating, the Keep Track Test. However, there were no significant differences on a second updating measure, the N-back Test. It is possible that this reflects a difference in the difficulty of the two tasks, as many subjects found the Keep Track Test to be relatively simple, while most reported that the N-back was extremely challenging. This may have resulted in a floor effect on the N-back Test, and thus masked potential executive differences. It may also, or instead, suggest that those with diabetes did not demonstrate gross impairments in updating ability but, rather, exhibited deficits in a task specific aspect of the Keep Track Test. Unfortunately, it is unclear

whether this deficit involves features of the executive process of updating or a separate, non-executive process.

It is also difficult to interpret the results of our correlational analyses, which revealed few relationships between executive performance and gait or functional ability in those with diabetes, but a number of significant associations between these factors in comparison subjects. Particularly notable was the fact that both of our measures of updating, the Keep Track and N-back Tests, were significantly associated with self-selected normal walking speed in this group, and these relationships strengthened during fast walking. This may indicate that some executive functions, and particularly the ability to process incoming information from the environment, normally play a role in mediating gait speed. The lack of such relationships in subjects with diabetes could reflect a pathological dissociation of executive function and gait, and it is possible that this contributed to the significantly slower normal and fast walking speeds we observed in these individuals.

Although consistent with our data, this speculation is hypothetical and must be considered in the context of several factors that limit interpretation of our findings. First among these is the relatively small size of our sample, which does not fully power our multiple comparisons. Due to the exploratory nature of this investigation, we did not correct for the multiple comparisons and correlations we performed. This limits the conclusions that can be drawn from this data; however our findings clearly provide interesting directions for future research. Another limitation is the possibility that some subjects included in our study may have suffered from undiagnosed mild cognitive impairment or early Alzheimer's disease. This is of particular concern because type 2

diabetes is associated with an increased risk for these conditions (Kuusisto et al., 1997; Luchsinger et al., 2007; Ott et al., 1999). We attempted to control for this confounding factor by screening all potential subjects with the AD8 Dementia Screening Interview (Galvin et al., 2005) prior to inclusion in the study, and excluding any individual scoring less than 26 on the Mini-Mental Status Examination. However, it is certainly possible that these measures may have failed to identify some individuals with these conditions.

Finally, our data do not establish a direct link between executive function and the gait impairments, functional deficits, and disability commonly observed in older adults with type 2 diabetes. However, our findings are broadly consistent with those of other researchers who have identified links between executive function and self-care, disease management, and physical function in these individuals. Future efforts should be directed towards identifying the anatomical and physiological mechanisms underlying diabetes-related cognitive changes, and more closely examining the characteristics and functional consequences of cognitive and executive dysfunction in this highly vulnerable and dramatically expanding population.

## **5.6 Conclusions**

This investigation provides evidence that older adults with type 2 diabetes may exhibit changes in the executive abilities required to update and monitor incoming information and process visuospatial information. Our data also suggest that these and other executive functions may contribute differently to gait and functional ability in those with and without diabetes. Further research should attempt to more clearly examine cognitive and executive function in those with diabetes, and determine the extent to

which cognitive impairments contribute to physical deficits, falls, and disability in this high risk population.

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## Chapter 6

### Multi-tasking, Executive Function, and Functional Abilities in Older Adults with Type 2 Diabetes Mellitus

## 6.1 Summary of Findings

Collectively, the data presented here represent one of the most detailed cross-sectional examinations of multi-tasking and executive function conducted in older adults with type 2 diabetes. Our results indicate that these individuals demonstrate significant changes in gait stability when required to multi-task while walking. In addition, they may exhibit changes in the executive abilities responsible for updating and processing incoming stimuli and visuospatial information. The influence of these and other executive processes on gait and functional abilities remains unclear, but appears to differ between those with and without diabetes. This chapter summarizes the findings of our investigations and describes our preliminary exploration of possible mechanisms underlying diabetes-related executive impairments. The chapter concludes with the potential clinical implications, limitations, and future directions that can be drawn from this body of work.

### *Chapter 2: Pilot Study of Multi-tasking and Executive Function in Adults with Diabetic Peripheral Neuropathy*

Laying the groundwork for our primary investigation, this pilot study employed a small battery of common measures of executive function to compare executive performance between a convenience sample of individuals with diabetic peripheral neuropathy (DPN) and a similar group of individuals without diabetes or neuropathy. We also explored the relationships between executive and neuropsychological function, signs and symptoms of peripheral neuropathy, and a measure of functional ability in those with DPN.



We found that this relatively young sample of adults with DPN performed poorly on verbal and visuospatial measures of executive function, as well as a measure of multi-tasking, the Cognitive Timed Up and Go Test. In addition, we observed significant relationships between overall cognitive function and depression, and found that both factors were associated with performance on the traditional, single-task Timed Up and Go Test.

### *Chapter 3: Multi-tasking in Older Adults with Type 2 Diabetes*

Despite previous research demonstrating that multi-tasking while walking impairs gait speed and kinematics in individuals with diabetes irrespective of the presence of peripheral neuropathy, we were unable to identify a comprehensive assessment of multi-tasking abilities in older adults with diabetes. The purpose of this portion of our investigation, and the primary overall aim of this body of work, was to provide such an assessment.

Our results indicated that older adults with type 2 diabetes did not exhibit broad, global impairments in multi-tasking abilities. However, they did perform more poorly than their peers without diabetes when required to multi-task while walking and, alarmingly, appeared to sacrifice gait stability in order to preserve other task demands. Interestingly, although multi-tasking ability demonstrated little relationship with measures of gait, physical function, or disability in either group, factors such as depression, physical activity, and sleep quality were significantly associated with these measures in both groups – most notably in those with diabetes.

*Chapter 4: The Contribution of Multi-tasking to Gait and Functional Ability in Older Adults with Type 2 Diabetes*

The secondary aim of our investigation was to more closely examine the contribution of multi-tasking abilities to single-task gait and physical function and disability in those with diabetes. In order to do this, we constructed a series of regression equations in which multi-tasking, along with variables such as age, glycemic control, and depression, were used to predict gait velocity and variability during normal and fast walking, as well as self-reported levels of physical function and disability. In addition, based on the unexpected strength of the correlations we had observed between these criterion variables and depression, physical activity, and sleep quality, we also developed a series of post-hoc regression models specifically assessing these relationships.

This analysis revealed that multi-tasking ability exerted little influence on our measures of single-task gait, physical function, or disability. In contrast, we did observe a number of significant relationships between these criterion variables and depression, physical activity, and sleep quality. Overall, our findings suggest that multi-tasking abilities may play a limited role in the performance of routine, every day activities in higher functioning older adults with diabetes. However, they also highlight the importance of appropriately identifying and treating other modifiable but easily overlooked comorbidities common in this population.

*Chapter 5: The Integrity of Other Executive Functions in Older Adults with Type 2 Diabetes*

The final aim of our investigation was to examine whether older adults with type 2 diabetes exhibited impairments in the executive functions responsible for *updating* incoming information from the environment, *shifting* attention between different tasks, *inhibiting* predominant responses, and *visuospatial* and *verbal* processing and organization. Additionally, because few previous studies had attempted to examine how such executive functions might relate to gait and/or functional abilities, we explored the relationships between our executive assessments and measures of gait speed and variability and self-reported physical function and disability.

We found that subjects with diabetes demonstrated poorer performance on specific measures of updating and visuospatial function when compared to a non-diabetic group of individuals pair-matched for age, sex, education, and hypertensive status. Interestingly, we observed few relationships between executive and gait or functional measures in those with diabetes, but a number of significant associations between these variables in those without diabetes. Although difficult to interpret, our findings appear to suggest that older adults with diabetes demonstrate features of executive dysfunction, and may provide the first evidence that executive functions contribute differently to gait and function in those with and without diabetes.

## **6.2 Possible Mechanisms of Executive Dysfunction in Diabetes**

As discussed in Chapter 1, there is now a good deal of evidence that the diabetic disease process can result in neuroanatomical changes in brain areas associated with

executive function (Kodl & Seaquist, 2008). The mechanisms by which these changes occur remain a matter of considerable speculation; however there is growing interest in the relationships between type 2 diabetes and Alzheimer's disease, and the role that insulin resistance may play in the cognitive deficits associated with both. In particular, several investigations have indicated that insulin is associated with one of the key pathological markers of Alzheimer's disease, amyloid beta (A $\beta$ ) (De Felice et al., 2009; Kulstad et al., 2006; Zhao et al., 2008). This relationship may occur directly, as insulin itself appears to promote A $\beta$  transport and deposition (Gasparini et al., 2001), and/or indirectly via increased cortisol production, which has also been linked to both A $\beta$  deposition and cognitive dysfunction (Toledo et al., 2012).

In order to establish a framework for future studies investigating the pathological mechanisms that may link type 2 diabetes and Alzheimer's disease, we analyzed fasting plasma levels of insulin, cortisol, and A $\beta$  in a subset of individuals from both our diabetes and comparison groups. The preliminary results of this exploratory investigation are described below.

### *6.2.1 Sample and Methods*

A total of 20 subjects from the diabetes group and 20 subjects from the comparison group volunteered to submit a blood sample for analysis. As this study component was optional, we did not attempt to pair-match diabetes and comparison group subjects. Each subject completed the primary study measures of executive function, gait, and functional ability, as detailed in Chapters 3 and 5. After signing a separate institutionally approved informed consent form, those who volunteered for the

optional study component fasted for a minimum of 8 hours before presenting to the University of Kansas Medical Center's Clinical and Translational Science Unit, where a peripheral venous blood draw was conducted.

Following collection, blood specimens were centrifuged at 1000G, flash frozen, and stored at -80 degrees C. On the day of testing, all samples were thawed simultaneously at room temperature and 300µL of plasma aliquoted from each sample for analysis of insulin, cortisol, and the amyloid peptide Aβ-42. Enzyme-linked immunosorbent assays (ELISAs) for each analyte were performed by the Disease Model and Assessment Core at the University of Kansas Medical Center. A single average value of each analyte was calculated from each specimen via duplicate determination, and quality controlled through examination of internally referenced control values, standard curve graphs, and replicate variability.

Fasting insulin and blood glucose levels for each subject were used to determine insulin resistance via the Homeostatic Model of Assessment – Insulin Resistance (HOMA-IR). This was calculated as described by Matthews et al. (1985):

$$\frac{\text{Fasting Glucose Level (mg/dL)} \times \text{Fasting Insulin Level (}\mu\text{IU/mL)}}{405^1}$$

### 6.2.2 Statistical Analysis

Non-parametric methods were employed for all analyses due to the exploratory nature of the investigation. Mann-Whitney U Tests assessed between-group

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<sup>1</sup> This conversion factor applies to samples measured in mg/dL (glucose) and µIU/mL (insulin). A conversion factor of 22.5 is used for samples measured in mmol/L (glucose) and mU/L (insulin).

differences, while Spearman's rank sum correlations assessed relationships between variables. Type I error rate was set at 0.05.

### *6.2.3. Results*

#### *Sample Characteristics and General Assessments*

Table 6.1 provides the general characteristics of the groups. Twenty subjects with diabetes (60% female) and 20 subjects without diabetes (60% female) consented to this sub-study. No significant differences in age were observed between the two groups ( $p=0.27$ ). Those with diabetes were more obese ( $p=0.001$ ) and demonstrated impaired fasting blood glucose levels ( $p<0.001$ ) when compared to those without diabetes. No between-group differences were observed on the Mini-Mental Status Examination (MMSE;  $p=0.13$ ), Beck's Depression Inventory (BDI;  $p=0.11$ ), Rapid Assessment of Physical Activity (RAPA;  $p=0.12$ ), or Pittsburgh Sleep Quality Index (PSQI;  $p=0.32$ ).

#### *Insulin Resistance, Cortisol, and Amyloid Beta-42 Assessments*

Table 6.2 provides the results of ELISA analyses of insulin resistance, cortisol, and A $\beta$ -42 levels. Subjects with diabetes exhibited a higher level of insulin resistance when compared to those without (median HOMA-IR 2.7 vs. 1.5 units,  $p=0.02$ ). No significant differences were observed in either cortisol ( $p=0.14$ ) or A $\beta$ -42 levels ( $p=0.26$ ).

**Table 6.1: Sample Characteristics**

	<b>Diabetes (n=20)</b>	<b>Control (n=20)</b>	<b>P-value</b>
<b>Age (years)</b>	70 (60 – 85)	68 (61 – 83)	0.27
<b>BMI (kg/m<sup>2</sup>)</b>	33.3 (23.7 – 39.5)	26.85 (20.2 – 40.6)	0.001
<b>FBG (mg/dL)</b>	113.5 (89.0 – 282.0)	90.5 (68.0 – 119.0)	< 0.001
<b>MMSE (score out of 30)</b>	29.0 (27.0 – 30.0)	29.0 (28.0 – 30.0)	0.13
<b>BDI (score out of 63)</b>	4.0 ( 1.0 – 17.0)	3.0 (0 – 31)	0.11
<b>RAPA (score out of 10)</b>	5.5 (3.0 – 7.0)	6.0 (3.0 – 7.0)	0.63
<b>PSQI (score out of 21)</b>	5.5 (2 – 12)	4.0 (1 – 18)	0.34

**Table 6.2:** Data are median (range). Abbreviations: BMI: body mass index; FBG: fasting blood glucose; MMSE: Mini-mental Status Examination; BDI: Beck's Depression Inventory - II; RAPA: Rapid Assessment of Physical Activity; PSQI: Pittsburgh Sleep Quality Instrument

**Table 6.2: Insulin Resistance, Cortisol, and Amyloid Beta-42 Levels**

	<b>Diabetes (n=20)</b>	<b>Comparison (n=20)</b>	<b>P-value</b>
<b>Insulin Resistance (HOMA-IR)</b>	2.7 (0.6 – 7.3)	1.5 (0.5 – 3.0)	0.02
<b>Cortisol (ng/mL)</b>	66.7 (31.3 – 413.3)	56.5 (18.2 – 104.3)	0.14
<b>Amyloid Beta-42 (pg/mL)</b>	27.3 (2.5 – 171.5)	18.7 (3.6 – 145.4)	0.26

**Table 6.2:** Data are median (range). HOMA-IR: Homeostatic Model of Assessment – Insulin Resistance

### *Executive Assessments*

Results of the executive testing battery are not presented, as between-group comparisons of executive performance were not a primary focus of the investigation.

Those with diabetes performed more poorly on the copy version of the Rey Osterrieth Complex Figure Test (median score 28.5 vs. 31.5 points,  $p=0.01$ ), a measure of visuospatial function. No significant differences were observed in measures of multi-tasking ( $p=0.11$ ), updating ( $p=0.23$  and  $0.24$ ), task shifting ( $p=0.40$  and  $0.73$ ), inhibition ( $p=0.42$  and  $0.75$ ), or verbal logical memory ( $p=0.07$ ).

### *Relationships between Insulin Resistance, Cortisol, Amyloid Beta-42, and Executive Function*

Correlations between insulin resistance, cortisol, A $\beta$ -42, and executive function measures are provided in Table 6.3. Higher cortisol levels were associated with higher A $\beta$ -42 levels in the diabetes group ( $r=0.45$ ,  $p=0.04$ ); however this relationship was not observed in the comparison group (Fig.1). Insulin resistance was not significantly associated with cortisol or A $\beta$ -42 levels in either group.

In subjects with diabetes, higher cortisol levels were associated with poorer performance on a measure of updating (N-back;  $r=-0.58$ ,  $p=0.008$ ) and task shifting (Trail Making;  $r=0.49$ ,  $p=0.03$ ), while higher A $\beta$ -42 levels were associated with poorer performance on an updating measure (Keep Track;  $r=-0.45$ ,  $p=0.04$ ) and two measures of task shifting (Trail Making;  $r=0.59$ ,  $p=0.006$  and Local-Global;  $r=0.59$ ,  $p=0.01$ ). Insulin resistance was not significantly correlated with any measure of executive function in either group, and cortisol and A $\beta$ -42 were not correlated with any executive measures in the comparison group.



**Table 6.3: Relationships between Insulin Resistance, Cortisol, Amyloid Beta-42, and Executive Function**

A) Diabetes Group

	HOMA-IR	Cortisol	A $\beta$ -42
HOMA-IR	1	-0.21	0.14
Cortisol	-0.21	1	0.45*
A $\beta$ -42	0.14	0.45*	1
KPTK	-0.10	-0.27	-0.45*
NBCK	-0.06	-0.58*	-0.28
TMT	0.05	0.49*	0.59*
LCL-GBL	-0.36	0.19	0.56*

B) Comparison Group

	HOMA-IR	Cortisol	A $\beta$ -42
HOMA-IR	1	-0.22	-0.29
Cortisol	-0.22	1	-0.17
A $\beta$ -42	-0.29	-0.17	1
KPTK	-0.02	-0.04	0.04
NBCK	-0.42	0.26	0.07
TMT	0.43	0.10	0.04
LCL-GBL	0.16	-0.27	-0.39

Table 6.3: Abbreviations: HOMA-IR, Homeostatic Model of Assessment – Insulin Resistance; A $\beta$ -42, amyloid beta-42; KPTK, Keep Track Test; NBCK, N-back Test; TMT, Trail Making Test; LCL-GBL, Local Global Test. \*Significant at  $p < 0.05$ .

#### 6.2.4. Discussion

The results of this exploratory investigation appear to indicate a relationship between plasma cortisol and A $\beta$ -42 levels in older adults with type 2 diabetes, and suggest that these factors may be associated with aspects of executive function in this population. Although the role of A $\beta$  in cognitive dysfunction is notoriously controversial, our results are consistent with studies linking elevated A $\beta$  (Dore et al., 2013) and cortisol levels to cognitive deficits (Lupien et al., 1999).

In addition, our findings are broadly in line with a recent study by Toledo et al. (2012), which found a significant association between elevated plasma cortisol levels and increased brain amyloid deposition in a group comprised of 22 cognitively normal individuals, 21 individuals with Alzheimer's disease, and 56 individuals with mild cognitive impairment.

While the specific mechanisms underlying the interaction of cortisol and amyloid are unresolved, and their impact on cognitive function remains unclear, there is evidence that both type 2 diabetes and Alzheimer's disease are associated with upregulation of the hypothalamic-pituitary-adrenal axis (Csernansky et al., 2006; Lee et al., 1999; Tojo et al., 1996). The resulting hypercortisolemia may initiate a damaging cascade that increases amyloid and tau production and causes structural injury (Kodl & Seaquist, 2008; Tortosa-Martinez & Clow, 2012). However, it is also possible that these neuropathological features precede the elevation of cortisol levels, and that hypercortisolemia is instead a consequence of this neurological damage (Tortosa-Martinez & Clow, 2012).

Also unclear is the role of insulin and insulin resistance, which were not correlated to cortisol, amyloid, or executive function in either of our groups. These findings are somewhat in contrast to investigations that have observed a differential role for insulin in mediating A $\beta$  metabolism and cognitive function in those with and without Alzheimer's disease (Burns et al., 2012), and found that insulin resistance was associated with cognitive impairment and an increased risk of cognitive decline in non-demented individuals (Yaffe et al., 2004).

One factor that may help explain these conflicting results is the use of oral anti-glycemic medications and/or exogenous insulin agents by subjects in our diabetes group, which may have altered or masked relationships between insulin and the other variables we examined. A second factor is the possible role of apolipoprotein E (APOE) genotype, which we were unable to assess. The  $\epsilon 4$  allele of APOE is a known risk factor for Alzheimer's disease (Saunders et al., 1993), and the presence or absence of the  $\epsilon 4$  allele may mediate relationships between insulin,  $A\beta$ , and cognitive function (Morris & Burns, 2012).

#### *6.2.5. Preliminary Conclusions*

This exploratory investigation provides interesting evidence that peripheral levels of cortisol and  $A\beta$ -42 are differentially related to each other and to aspects of executive function in older adults with type 2 diabetes when compared to those without diabetes. Future studies will be needed to clarify the mechanisms by which these factors interact in health and disease, and to more clearly determine their effects on cognitive and executive function. Further research will also be necessary to determine the role of inflammatory factors, reactive oxygen species, advanced glycation end products, endothelial dysfunction, and other factors not examined in the current study. Described in detail in Chapter 1, these variables may also contribute to the pathophysiology of cognitive dysfunction in both diabetes and Alzheimer's disease.

### **6.3 Clinical Implications**

Type 2 diabetes is projected to affect a staggering 592 million individuals by the year 2035 – fully 10% of the world’s population (International Diabetes Federation [IDF], 2013). In the United States alone, the disease is expected to affect nearly 30 million individuals and cost well in excess of \$336 billion (Huang, Basu, O’Grady, & Capretta, 2009). Among the most common diseases of aging, diabetes is associated with a devastating array of neurological complications affecting both the peripheral and central nervous systems.

With one in every three older adults in the United States expected to suffer from diabetes by the year 2050 (Centers for Disease Control and Prevention [CDC], 2011), there is an increasingly urgent need to understand its physiological and functional consequences so that effective preventive and treatment strategies can be established and administered. From a rehabilitation standpoint, this includes interventions aimed at reducing falls, functional and disability, improving gait and functional ability, and increasing physical activity and fitness. The body of work presented here has a number of clinical implications related to such rehabilitation strategies.

A major factor implicit in the development of this project is the disproportionately high prevalence, risk, and severity of falls experienced by older adults with diabetes (Crews, Yalla, Fleischer, & Wu, 2013). One of the primary findings of our investigation is that these individuals exhibit deficits in the ability to multi-task while walking, such that gait stability is sacrificed in favor of less critical task demands. Although further research will be necessary to establish whether this does indeed contribute to falls and functional deficits in this population, it does not seem unreasonable to suspect that this

may be the case. If so, our results are encouraging in that the deficits we observed appeared to reflect poor task prioritization, as opposed to gross or global impairments in the ability to multi-task per se. This may suggest that relatively simple educational and multi-task training interventions could reorient at-risk individuals to more appropriate task prioritization strategies that minimize risk and maximize safety.

Although not directly addressed in our investigation, our findings also have implications for the clinical application of single- and multi-task training interventions. It is not uncommon for rehabilitation service providers to administer gait and functional training under controlled, single-task conditions with the assumption that improvements will carry over to more complex, environmentally realistic conditions. Likewise, it is often assumed that training conducted under dual-task conditions should translate to improvements in the single-task performance of either or both tasks. In fact, this may not be the case. Our results indicate that the resources required to multi-task are relatively distinct from those required for ambulation under single-task conditions, and emphasize that clinicians should carefully consider task and context specificity when designing and implementing rehabilitation interventions.

Finally, our results challenge the commonly held belief that gait abnormalities, falls, and functional deficits in those with diabetes are primarily the result of neuropathic and/or musculoskeletal impairments. This body of work argues, instead, that these deficits are multi-factorial and influenced by a diverse array of variables. In particular, we found that some aspects of executive function appeared to be differentially related to gait and physical function in older adults with and without diabetes, and observed surprisingly strong relationships between depression, physical activity, sleep quality,

and gait and function. These findings stress the importance of appropriately managing common and modifiable but easily overlooked comorbidities in older adults with diabetes, and emphasize that clinicians must be prepared to identify and address both physical and neuropsychological dysfunction in these individuals.

## **6.4. Limitations**

### *Subject Characteristics and Sample Size*

We attempted to control for several important confounding variables by pair-matching each subject with diabetes to a comparison subject in terms of age ( $\pm 5$  years), sex, level of education, and the presence or absence of diagnosed hypertension. However, it is inherently difficult to perfectly match non-discrete variables such as education and blood pressure, and we acknowledge that this may have affected our sample. Likewise, we did not control for intelligence (e.g. IQ), race/ethnicity, or socioeconomic status, and these factors may also have influenced our results. Despite these limitations, the characteristics of our groups were largely homogenous and do not appear to have differed greatly from those of other investigations.

An additional limitation of our sample was its relatively modest size of 40 subjects per group. This sample size adequately powers the primary aim of our investigation, the comparison of multi-tasking abilities described in Chapter 3. However, it does limit the conclusions that can be drawn from the regression analyses undertaken in Chapter 4 and the multiple comparisons of executive function conducted in Chapter 5. As such, caution should be exercised in interpreting these results until they can be validated by future research.

### *Comorbidities and Medications*

Although we collected data on the comorbid conditions and medication usage of each subject, we did not exclude participants on the basis this information unless it was deemed to result in significant cognitive or physical impairment. As a result, our sample included individuals with osteoarthritis, joint arthroplasty, mild visual impairments, peripheral neuropathy, and other such conditions. Moreover, our subjects took a variety of medication for many different purposes, including the use of anti-diabetic agents and exogenous insulin by many subjects in our diabetes group. Given the widespread prevalence of diabetic complications (CDC, 2011) and the fact that the population of interest in our investigation was individuals 60 years old and older, it would likely be impossible to recruit a sample that controlled for all of these variables.

In order to limit the influence of confounding variables, each subject completed a telephone screening interview designed to elicit information about their current cognitive and functional status, as well as any impairments in vision, gait, and/or balance. However, we did not formally assess visual acuity, somatosensory or proprioceptive function, or other such factors. Nor is it possible to say with certainty that our cognitive screening procedures successfully excluded all individuals with mild cognitive impairment or pre-clinical Alzheimer's disease. Clearly, it is important that our findings be interpreted in the context of such potential limitations.

### *Executive Assessments*

As described in Chapter 1, executive function is notoriously difficult to define and assess. This is especially true because executive function is dependent upon and

expressed by non-executive processes such as language, vision, and/or memory, and broadly considered to be responsible for complex and poorly operationalized abilities such as planning, reasoning, and organization. At present there is no standardized methodology for assessing executive function; however neuropsychological researchers have recommended that 1) executive terms and processes be clearly defined, 2) assessment measures carefully selected to target these executive functions, and 3) multiple, simple measures used to assess each executive function (Miyake, Emerson, & Friedman, 2000; Suchy, 2009).

Perhaps more than any previous examination of executive function in individuals with diabetes, our executive assessment battery reflects these guidelines. Chapter 1 provides a detailed explanation of the executive processes we selected, as well as research underlying the measures we employed to assess these processes. Despite this, it is possible that differences in task difficulty or other characteristics may have influenced our results, or that they may have been affected by differences in non-executive processes. Further research will be needed in order to fully characterize executive abilities in older adults with diabetes.

## **6.5 Future Directions**

This body of work addresses several key areas of interest with regard to multi-tasking and executive function in older adults with type 2 diabetes, and the relationships between these variables to gait and functional ability in this population. However, a number of questions remain unanswered. For example, although we speculate that the changes in Walking and Remembering Task performance we observed in our subjects



with diabetes could contribute to the elevated fall risk known to occur in this population, there are currently no established links between such changes and fall risk. Future research will be needed to determine fall risk cut-offs on this measure, as well as whether specific task prioritization strategies may be associated with differing levels of fall risk.

In much the same way, it will be important to examine how different populations utilize task difficulty and contextual information to assign task priority during multi-tasking. For example, one might expect that individuals suffering from somatosensory and proprioceptive deficits due to peripheral neuropathy would adopt compensatory strategies that maximize safety when required to multi-task while walking. However, we observed that subjects with peripheral neuropathy, like their counterparts without neuropathy, actually sacrificed gait stability in order to preserve less important task demands. Future research should use task combinations of varying type, complexity, and environmental validity to better understand how attention is allocated during multi-tasking, and explain why and under what circumstances safety may be sacrificed.

Equally important will be research examining the effectiveness of intervention strategies designed to improve multi-tasking function and/or task prioritization strategies during multi-tasking. Consistent with our findings suggesting little relationship between multi-tasking ability and single-task gait speed and stability, other investigations have reported that dual-task training interventions have little effect on single-task function, and vice versa (Schwenk, Zieschang, Oster, & Hauer, 2010; Silsupadol, Lugade, et al., 2009; Silsupadol, Shumway-Cook, et al., 2009; You et al., 2009). Future studies should continue to more clearly define the respective roles of single- and dual-task training so

that rehabilitation intervention strategies can be more effectively designed and administered.

In addition to the issues related to multi-tasking discussed above, a number of questions remain regarding the relationship between diabetes and executive and cognitive functions. This investigation elicited evidence of potential impairment in several executive processes, specifically those related to updating and visuospatial function. However, it is possible that these impairments arose due to specific task characteristics and/or task impurity, rather than true executive dysfunction. Moreover, it remains unclear why we observed such substantial differences in the contributions of executive functions to gait and function in those with and without diabetes. Future research using similarly designed executive testing batteries will be needed to more clearly characterize executive function in those with diabetes, as well as to determine how it contributes to gait and functional ability in older adults both with and without diabetes.

Finally, as discussed previously in this chapter, there is a great deal of interest in the mechanisms that may underlie cognitive dysfunction in type 2 diabetes, and their relationships to the pathology of Alzheimer's disease. Consistent with many other investigations, the exploratory data presented here appear to suggest shared pathological mechanisms between the two diseases. However, further research will be necessary to specifically determine how insulin and insulin resistance, dysglycemia, cortisol, vascular disease, genetics, and other factors interact and relate to neurocognitive impairments in diabetes and Alzheimer's disease.

## **6.6 Conclusions**

This body of work provides evidence that older adults with type 2 diabetes exhibit deficits in the ability to multi-task while walking that result in decreased gait stability. In addition, these individuals may demonstrate impairments in other areas of executive function, particularly those responsible for updating incoming information and processing visuospatial stimuli. There seems to be little relationship between multi-tasking or other executive functions and single-task gait or self-reported physical function and disability in individuals with diabetes; however these factors and others such as depression, physical activity, and sleep quality appear to influence gait and function differently in those with and without diabetes. Overall, our findings emphasize the diverse factors that may contribute to functional abilities in this high-risk population, and highlight the need for further research investigating the physiological, psychological, and functional consequences of type 2 diabetes.

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