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Specific Cognitive Domains Associated with Gait Performance in Mild Cognitive Impairment

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Kinesiology

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SPECIFIC COGNITIVE DOMAINS ASSOCIATED WITH GAIT PERFORMANCE IN MILD
COGNITIVE IMPAIRMENT

(Thesis format: Monograph)

by

Elyse Michele Gordon

Graduate Program in Kinesiology

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

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ABSTRACT

The study aim was to identify associations between deficits in specific cognitive domains and gait performance in Mild Cognitive Impairment (MCI). Sixty-eight participants with MCI underwent cognitive function testing in executive function (EF), attention, working memory, episodic memory and language domains. Gait was assessed using an electronic walkway (GaitRITE®). The means and co-efficient of variation of five gait parameters were evaluated: velocity, stride time, stride length, step width and double support time during single (SG) and dual-task (DT) test conditions. Multivariable linear regression analysis demonstrated deficits in EF, working memory and episodic memory were significantly associated with increased gait variability (GV) under both walking test conditions. DT gait revealed additional significant associations between deficits in attention and language domains and increased GV. Deficits in multiple cognitive domains such a language, working and episodic memory are associated with increases in GV. The associations also suggest gait control shares similar neural networks as memory and language.

Keywords: *gait, gait variability, aging, dual-task, cognitive function, mild cognitive impairment*

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“When you have exhausted all possibilities, remember this: you haven’t.” Thomas Edison

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LIST OF ABBREVIATIONS

AD: Alzheimer's disease
ADL: Activities of daily living
ANOVA: Analysis of variance
aMCI: Amnesic mild cognitive impairment
BMI: Body Mass Index
BNT: Boston Naming Test
CoV: Co-efficient of variation
CPG: Central Pattern Generators
DST-F: Digit Span Test Forward
DST-B: Digit Span Test Backward
 Δ DST: Difference between digit span test forwards and digit span test backward
DT: Dual Task
EF: Executive function
GDS: General depression scale
IADL: Instrumented activities of daily living
ICC: Intraclass correlation co-efficient
LNS: Letter Number Sequencing Test
MCI: Mild cognitive impairment
MLR: Midbrain locomotor region
MMSE: Mini Mental State Examination
MoCA: Montreal Cognitive Assessment
MRI: Magnetic resonance imaging
naMCI: Non-amnesic MCI
PAC: Primary auditory cortex
PD: Parkinson's disease
PET: Proton emission tomography
PPN: Pedunculopontine nucleus
RAVLT: Rey Auditory Verbal Learning Test
SD: Standard deviation
SMA: Supplementary Motor Area

STV: Stride time variability

TMT: Trail Making Test

Δ TMT: Difference between Trail Making Test A and Trail Making Test B

Chapter 1: LITERATURE REVIEW

1.1 Introduction

Within Canada's aging population, recent estimates suggest an overwhelmingly rapid increase in the proportion of people aged 65 and older (Fries, 2002). This steady increase will be accompanied by considerable amounts of disability and dependency impacting quality of life and everyday functioning of older adults (van Iersel, Kessels, Bloem, Verbeek & Rikkert, 2008). Cognitive and gait impairments are common geriatric syndromes which often coincide in an older adult. Gait impairments have been associated with an increased risk for falls and functional decline (Callisaya, Blizzard, McGinley, Schmidt & Srikanth, 2010; Hausdorff, Rios & Edelberg, 2001; Maki, 1997; Sudarsky, 2001; Tinetti, Speechley & Ginter, 1988). In addition, gait impairments have also been found to be a risk factor for the development of mild cognitive impairment (MCI) and further progressive cognitive decline (Buracchio, Dodge, Howieson, Wasserman & Kaye, 2010; Mielke et al., 2013; Verghese, Wang, Lipton, Holtzer & Xue, 2007; Verghese et al., 2002). A decline in cognitive abilities, specifically executive function (EF), has been recognized as another independent risk factor for falls and serious fall-related injuries in the elderly (Herman, Mierlman, Giladi, Schweiger & Hausdorff, 2010; Holtzer et al., 2007; Muir, Gopaul & Montero-Odasso, 2012; Springer et al, 2006; van Iersel et al., 2008; Yogev-Seligmann, Hausdorff & Giladi, 2008). In fact, those with moderate to severe cognitive impairments are twice as likely to experience a fall compared to cognitively intact older adults (Montero-Odasso, Muir & Speechley, 2012; Sheridan & Hausdorff, 2007; Tinetti et al., 1988). Given the evidence supporting these associations and the demographic change in the proportion of adults over age 65, it is not surprising that the relationship between cognitive impairment and gait dysfunction has received increasing attention over the past decade.

Gait and balance have traditionally been perceived as automatic, biomechanical processes and falls were considered an outcome due to the failure of these motor control mechanisms (Segev- Jacobovski et al., 2011). Age- related declines in physiological

systems such as cardiovascular, musculoskeletal, visual, vestibular and proprioception are viewed as key elements related to detrimental changes in gait and balance. With advancing age, the control of gait becomes more difficult because it is less automatic and requires more attention (Woollacott & Shumway-Cook, 2002). In the past, cognitive and mobility impairments have been treated as separate geriatric syndromes which may have led to gaps in the literature preventing our understanding of cognitive and motor interactions (Montero-Odasso, Verghese, Beauchet & Hausdorff, 2012). However, over the past decade evidence has emerged for a pathophysiological interaction between gait and cognitive function, suggesting decreases in attentional capacity that can accompany aging highlights the cortical and sub-cortical involvement of gait control (Alexander, 1996; Hausdorff, Yogev-Seligmann, Springer, Simon & Giladi, 2005; Sheridan & Hausdorff, 2007; Woollacott & Shumway-Cook, 2002). Despite recent developments, the mechanisms by which cognitive impairment affects gait performance or the temporal relationship between the two are not fully understood (Amboni, Barone & Hausdorff, 2013; Montero-Odasso et al., 2012). Observing an individual while walking and performing a secondary task is used as the method to evaluate the cortical control regulating gait (Woollacott & Shumway-Cook, 2002). This method of testing is referred to as the dual-task (DT) paradigm and is of particular interest because of strong associations found between DT gait changes and increased fall risk (Dubost et al., 2006; Lundin-Olsson et al., 1997). It has been well established under these test conditions that deficits in EF are associated with gait performance, but very few studies have evaluated other key cognitive domains such as memory and language or examined the independent contribution of each cognitive domains from each other (Martin et al., 2012).

There is a growing interest in defining early gait abnormalities and neuropsychological features that will help identify people who will develop dementia (Ambrose et al., 2010; Montero-Odasso et al. 2012). Recently, there has been an expanding area of research investigating gait variability, (measured by the standard deviation (SD) or the co-efficient of variation (CoV)) as a measure of cognitive control in gait, as well as a marker of cognitive decline and falls in older adults (Dubost et al., 2006; Montero-Odasso et al., 2011; Verghese et al., 2007). Gait impairments, defined by

increased variability, rarely play a role in early clinical diagnosis of ‘pre-dementia’ (such as MCI) subtypes despite evidence to suggest its use as a clinical entity (Scherder et al., 2007). Studying the relationship between gait and cognition will provide further insight to the neural substrates, or structures of the brain underlying gait control in aging and help provide targets for therapeutic interventions that have the potential to prevent both mobility and cognitive decline (Brach, Perera, Studenski & Newman, 2008; Martin et al., 2012; Montero-Odasso et al., 2012).

The goal of this study was to: 1) evaluate the association between gait and cognition using gait analysis that allows the for analysis of a wide range of gait parameters and 2) to demonstrate that the evaluation of specific cognitive domains and gait in the earliest stages of pre-dementia can reveal relationships between gait impairments and cognitive decline.

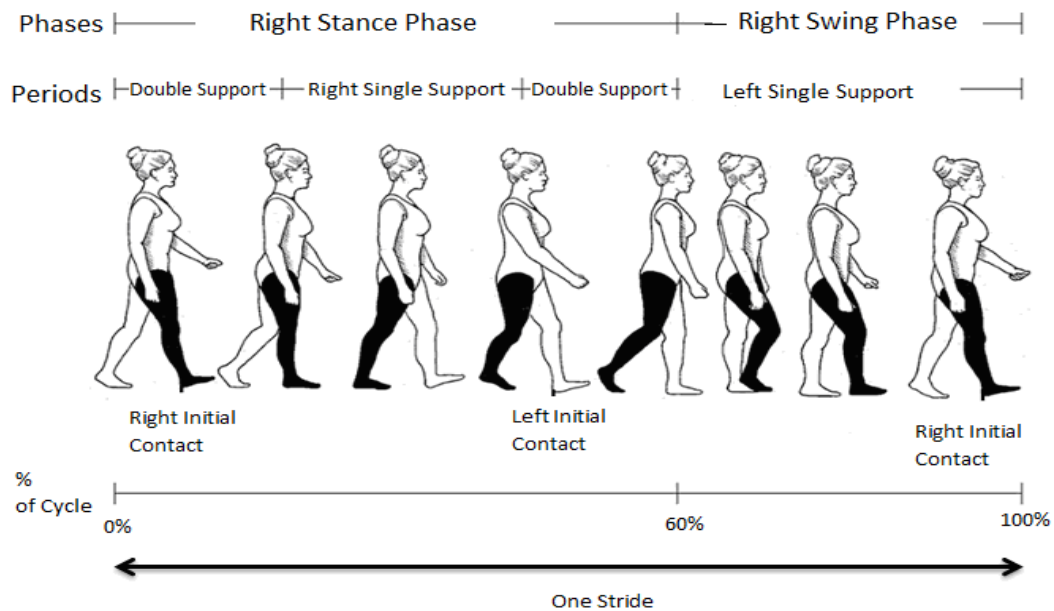
1.2 Gait and Mobility

The term gait is widely used within the rehabilitation field to describe human ambulation. Gait requires two functional abilities of equilibrium and locomotion. Equilibrium is the ability to maintain upright posture and balance, whereas locomotion is the ability to initiate and maintain dynamic rhythmic stepping (Nutt, Marsdon & Thompson, 1993). Gait is considered the most important expression of mobility capability (Hausdorff & Alexander, 2005). Mobility, defined as the ability to independently and safely navigate in one’s environment, is a facet of gait and an essential feature of functional independence (Coppin et al., 2006). Goal-oriented locomotion (e.g., walking across an uneven surface) in daily life requires the ability to adapt to changes in the environment and these adaptations are the result of complex, integrated interactions between the central nervous system (CNS), the musculoskeletal system and the somatosensory systems (Woollacott & Shumway-Cook, 2002; Trew & Everett, 2005).

1.2.1 The Gait Cycle:

The gait cycle (Figure 1.1) describes the actions occurring between the initial contact of the heel on the ground to the successive heel strike of the same foot (Kirtley, 2006; Perry & Burnfield, 2010; Whittle, 2007). A normal gait cycle is divided into two phases: stance and swing. Sixty percent of the cycle is comprised of the weight bearing stance phase, which occurs when the foot makes initial contact with the ground and ends once the same foot is lifted off the ground. The remaining forty percent is comprised of the swing phase, which is initiated when the foot leaves the ground and ends when the same foot makes contact with the ground, moving the lower limbs in a progressive manner (Perry & Burnfield, 2010, Whittle, 2007).

Figure 1.1: Illustration of a normal gait cycle

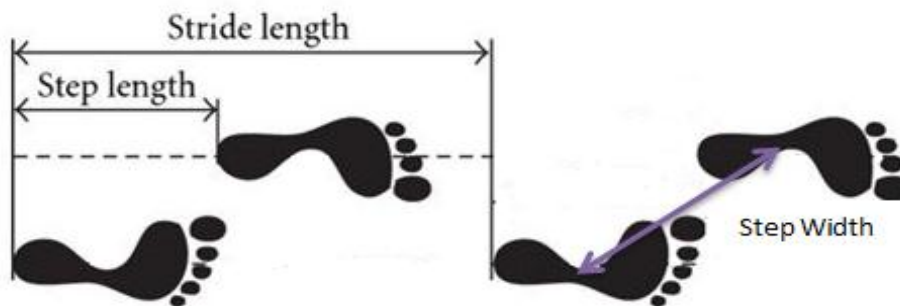


Adapted from Lim M. et al. (2007)

Gait is a complex activity and can be described using terms to identify timing components (temporal variables) or distance features (spatial variables). Temporal variables of gait include: single limb support time, the period of time during a stride

where only one foot is in contact with the ground; double limb support, the period of time where both feet are in contact with the ground at the same time (Perry & Burnfield, 2010); stride time, the time required to complete one full stride. The spatial variables of gait include: stride length, the distance between the heel points of two successive foot falls of the same foot and consists of two step lengths (Perry & Burnfield, 2010; Whittle, 2007); step length, the distance measured from the heel of the lead foot to the heel of the previous footfall on the opposite foot; step width, the distance between the midpoints of the lead foot to the midpoint of the trailing foot (Figure 1.2). Additional terms to characterize the features of gait include cadence, the number of steps taken within a given time frame and reported as steps per minute, and gait velocity, the distance covered in a given time (for example in centimeters per second, cm/sec) (Perry & Burnfield, 2010; Whittle, 2007). The combination of cadence and stride length determines gait velocity and influences almost all other gait variables (Craig, 1988; Elble et al., 1991) which is why they have considerable utility in the quantitative assessment of mobility (Masdeu, Sudarsky & Wolfson, 1997; Wolfson, 1990).

Figure 1.2: Spatial gait variables; step length, stride length and step width



Adapted from Wang, F. et al. (2010)

1.2.2 Methods of Gait Analysis:

1.2.2.1 Observational Gait Analysis

Observational gait analyses are used regularly in a clinical setting to evaluate gait and functional performance to provide information to estimate joint angles, muscle activity and some objective gait parameters (Cutlip, Mancinelli, Huber & DiPasquale, 2000; Whittle, 2007). These methods include the paper and pencil test (chalking/markings on subjects' soles as they walk on a paper walkway), stop watches and video-based analysis (Bilney, Morris & Webster, 2003; McDonough, Batavia, Chen, Kwon, & Ziai, 2001; McDonough & Nelson, 1994; Nelson, 1974). Observational methods may appear useful in healthy populations, but have poor retest reliability for assessing gait disorders in patient populations (Bilney et al., 2002). The simplicity of these methods limits the amount of gait information collected, makes them vulnerable to observer error and post test data collection can be time consuming (McDonough et al., 2001; Saleh and Murdock, 1985).

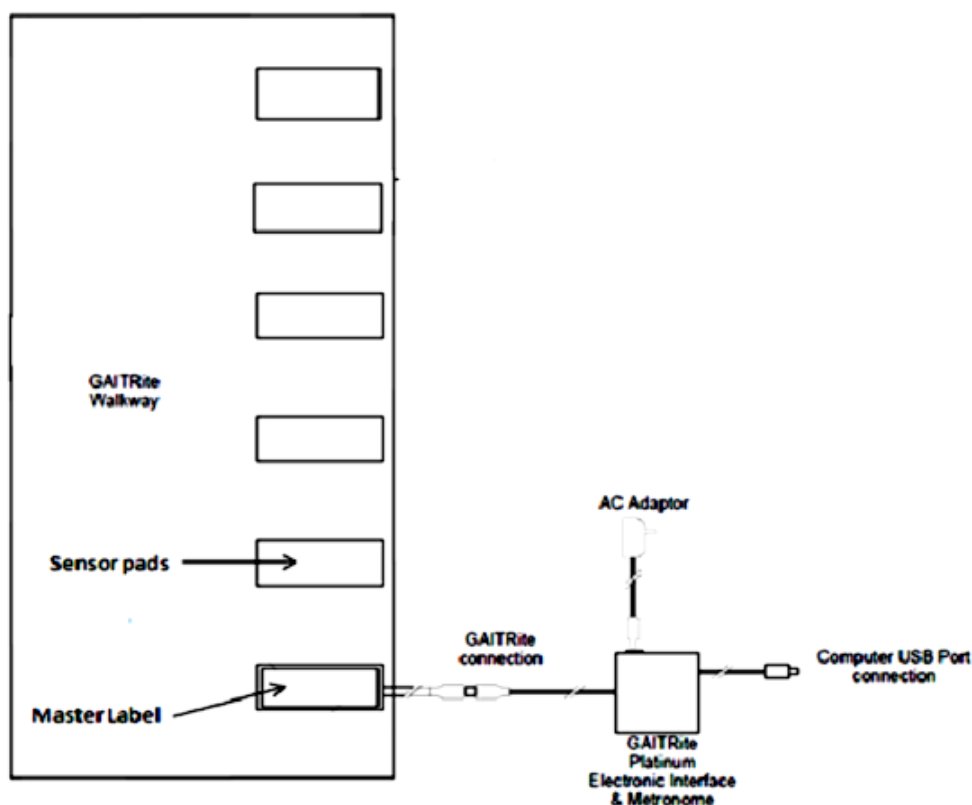
1.2.2.2 Instrumented Gait Analysis:

Three dimensional (3D) motion gait analysis is the most sophisticated method of instrumented gait analysis, providing information on kinematic, spatial and temporal gait variables (Scholz, 1989). This system uses visual, magnetic or opto-electric systems to track limb movement. Markers are placed on a subject's joint and limb segments and then wall-mounted cameras track movement as the person walks past (Perry & Burnfield, 2010; Scholz, 1989). This method of analysis is highly accurate and detailed in assessing gait kinematics, but it is expensive and impractical for clinical and limited for research use (Bilney et al., 2003; Cutlip, Mancinelli, Huber & DiPasquale, 2000; McDonough, Batavia, Chen, Kwon & Ziai, 2001).

The use of instrumented walkways in a clinical setting has become more common (van Uden & Besser, 2004; McDonough et al., 2001). Carpeted electronic mats (e.g.

GAITRite®) are embedded with pressure-sensitive sensors that capture spatial and temporal gait information as a subject walks over the mat (van Uden & Besser, 2004; McDonough et al., 2001) (Figure 1.3). Electronic readings of each footfall and calculations of different gait parameters are displayed in specialized software on a connected personal computer (McDonough et al., 2001). Instrumented walkways have excellent test-retest reliability (van Uden & Besser, 2004) and are a valid tool for measuring spatial and temporal gait parameters in young, elderly and patient populations (Menz, Latt, Tiedemann, Kwan & Lord, 2003). Instrumented walkways provide an accurate and quick alternative to objectively observe and diagnose gait disorders, eliminating error seen in observational methods.

Figure 1.3: Simplified schematic of the computerized GAITRite® Walkway



Adapted from CIR Systems at <http://www.gaitrite.com/downloads/WI-02->

15_Technical_Reference_L.pdf

1.3 Gait Velocity

The propulsion component of gait is illustrated through gait velocity (Verghese et al., 2008). Gait velocity as an assessment tool has been reported to be a valuable measure for the evaluation of older adults at risk for adverse events (Abellan van Kan et al., 2009; Montero-Odasso et al., 2005; Studenski et al., 2003). Maintaining gait velocity requires the synchronization of multiple physiological systems, from the neurologic and musculoskeletal to cardio-pulmonary and sensory systems (Alexander, 1996; Montero-Odasso et al., 2005). As one ages, their functional physiological systems begin to deteriorate resulting in an inability to maintain gait speed. Therefore, it has been proposed that a reduction in gait speed over time could represent an early manifestation of pathology in multiple physiological systems and be an early warning sign in identifying older adults at higher risk for adverse events (Montero-Odasso et al., 2005; Studenski et al., 2003).

1.3.1 Gait Velocity as a Marker of Adverse Events

Physical performance measures like gait velocity are universally accepted for assessing functional capabilities in a clinical setting (Cesari et al., 2005; Montero-Odasso et al., 2005; Studenski et al., 2003). Gait velocity measurements have proven to be a strong indicator of health status and a predictor of adverse health outcomes. In healthy older adults, researchers have identified a clinically meaningful cut-off for usual gait speed to be 100cm/sec (Bendall, Bassey & Pearson, 1989; Bohannon, 1997; Cesari et al., 2005; Imms & Edholm, 1981). Older adults with gait speed below this cut-off value should be considered high risk for adverse health outcomes (Cesari et al., 2005). Furthermore, Brach et al. (2010) determined a 10cm/sec decrease in velocity to be considered a substantial meaningful change.

Individuals with diminished gait speed (less than 100cm/sec) are at an increased risk for mobility disability, hospitalizations, institutionalization, falls, and mortality (Cesari et al., 2005; Montero-Odasso et al., 2005; Studenski et al., 2003). Gait speed

alone was found to be as good an objective predictor of disability (Guralnik et al., 2000), hospitalizations and declines in health status as complete physical function performance batteries (Studenski et al., 2003). Additionally, several studies suggest motor dysfunction, defined by gait velocity slower than 100cm/sec, predicts risk of future onset of dementia and Alzheimer's disease (AD) and progression of further cognitive decline (Camicioli, Howieson, Lehan & Kaye, 1997; Holtzer, Verghese, Xue & Lipton, 2006; Kuo et al., 2007; Waite et al., 2005; Wang, Larson, Bowen & van Belle, 2006). Testing to determine gait velocity is relatively easy to administer and does not require any special training of the evaluator. These reasons support the recommendation to use gait velocity testing to improve clinical and research assessments in identifying older adults at higher risk of major health related events (Abellan van Kan et al., 2009).

1.4 Gait Variability

Gait requires and demonstrates complex ongoing adjustments, or variation, in the temporo-spatial characteristics, even in predictable environments (Hausdorff, Peng, Ladin, Wei & Goldberger. 1995; Hausdorff, 2005; Beauchet et al., 2009). Stride-to-stride variability refers to fluctuations within the gait cycle from one stride to the next for any spatiotemporal gait characteristics. Historically, variability observed within gait was considered external noise which was filtered out of an analysis rather than considered a marker of interest (Hausdorff, 2007).

Stride-to-stride variability reflects walking rhythm and is believed to provide detailed physiological information in understanding motor control beyond measures based on average gait variable values (Hausdorff, 2007). In healthy adults, stride time and stride length variability values are generally below 3% (Beauchet, Herrmann, Dubost, & Kressig, 2005; Beauchet et al., 2009; Frenkel- Toledo et al., 2005; Montero-Odasso et al., 2012). Low gait variability reflects the efficiency of the automatic rhythmic stepping mechanism (Beauchet et al., 2005; Gabell & Nayak, 1984; Montero-Odasso et al., 2012) and the neuromuscular systems' ability to regulate gait (Hausdorff, 2005; Montero-Odasso et al., 2012). Though gait variability is a normal feature needed to adapt to

changing walking conditions, high gait variability (above 3%) is considered an indicator of abnormal gait regulation, an independent predictor of future falls and mobility disability (Brach et al., 2001; Hausdorff et al., 2001; Brach et al., 2007; Muir et al., 2012). Greater gait variability has also been associated with neurodegenerative diseases such as Alzheimer's disease (AD) (Nakamura, Meguro & Sasaki, 1996; Sheridan, Solomont, Kowall & Hausdorff, 2003; Webster, Merory & Wittwer, 2006; Wittwer, Webster & Menz, 2010) and Parkinson's disease (PD) (Frenkel- Toledo et al., 2005; Hausdorff et al., 2003; Muir et al., 2012; Schaafsma et al., 2003; Yogev- Seligmann et al., 2005). There is also evidence to suggest low step width variability indicates a failure to respond to changes in the environment leading to increased fall risk (Gabell & Nayak, 1984; Brach et al., 2005). Evaluating the magnitude of stride to stride fluctuations offers insights into fall risk and mobility function in older adults and a method to quantify pathological and age-related changes within the locomotor system (Hausdorff, 2007).

1.4.1 Quantification and Assessment of Gait Variability

Gait variability can be measured using spatial and temporal variables and is commonly quantified in the literature using either the standard deviation (SD) or the coefficient of variation (CoV) (Brach et al., 2008). The SD reports the magnitude of the deviation from mean values (Brach et al., 2008). Unlike the SD, the CoV is independent of the units in which variables are collected; it is calculated as the ratio of the SD to the mean, expressed as a percentage ($\text{CoV} = [(\text{SD}/\text{Mean}) * 100]$) (Brach et al., 2008; Hausdorff et al., 2005; Hausdorff, 2005). It is particularly useful for the comparison of values with different units or extensively different means (Hausdorff, 2005).

Montero-Odasso et al. (2009) demonstrated in an older adult population, the re-test reliability of gait variability was "excellent" using an electronic walkway under usual and dual task walking conditions. Brach et al. (2008) determined a limited number of steps (i.e., 5-6) measured using 4m walks had poor reliability for step width, step length and stance time variability. However, the use of additional steps (i.e., 10-12) to some extent improved the reliability for the gait variability parameters. Inconsistencies

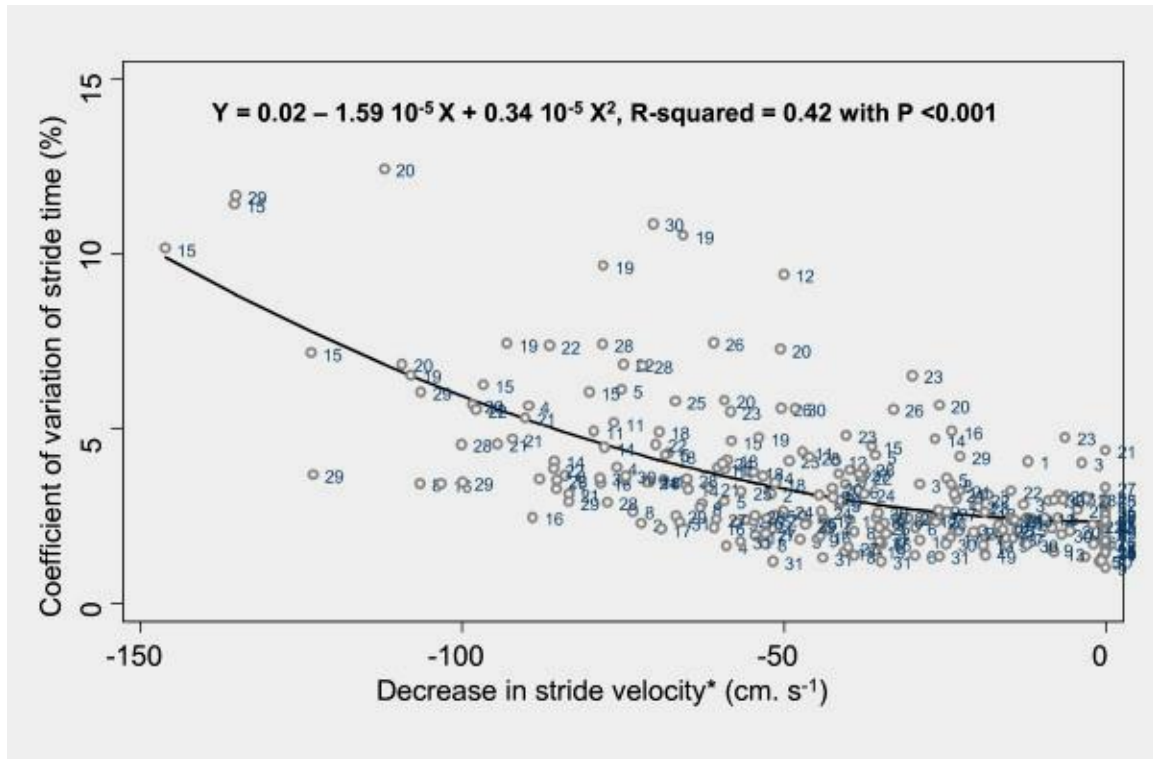
across the literature in data instrumentation, distances walked and analytical methods reveal controversies in what constitutes optimal protocols for measuring gait variability (Lord, Howe, Greenland, Simpson & Rochester, 2011).

1.4.2 Gait Velocity and Gait Variability

Changes observed in stride-to-stride gait variability over a period of time may be a more valuable measure in clinical settings to identify at risk older adults compared to gait velocity (Verghese et al., 2008; Brach et al., 2007). Many features of gait are highly correlated and despite several studies indicating gait speed influences gait variability (Beauchet et al., 2009; Belli et al., 1995; Dubost, 2006; Heiderscheit, 2000), there is evidence to suggest gait variability, specifically stride time variability (STV), is independent of walking speed (Brach et al., 2007; Danion, Varraine, Bonnard & Pailhous, 2003; Frenkel- Toledo et al., 2005; Grabiner, Briswas & Grabiner, 2001; Hausdorff et al., 2003; Maki, 1997).

As mentioned, gait velocity has been shown to influence gait variability. Increased STV was found as walking speed was systematically increased or decreased beyond comfortable walking pace (Van Emmerik, Wagenaar, Winogrodzka & Wolters, 1999). Thus, a U-shaped relationship between STV and gait velocity was then suggested, where higher STV was observed in very slow or fast speeds (Heiderscheit, 2000). Furthermore, Belli et al. (1995) reported a significant increase in STV as walking speed changed from preferred speed to maximum speed. More recently, in healthy young adults, Beauchet et al. (2009) demonstrated a curvilinear U-shaped relationship, demonstrating STV increased as walking speed decreased ($p < 0.001$) (Figure 1.4). Taken together, these results suggest that individuals choose optimal gait speeds for which energy consumption and stride time variability are minimal (Belli et al., 1995; Beauchet et al., 2009; Danion et al., 2003).

Figure 1.4: Curvilinear relationship between stride time variability (CoV) and decrease in self-selected walking speed in healthy adults. Normal self-selected walking speed used as the reference level and coded as 0 cm/sec.



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Several studies suggest gait variability is a reflection of the central neuromuscular control systems ability to regulate gait and an increase is not necessarily a by-product of slow gait (Hausdorff, 2004). This idea suggests gait variability as an entirely influenced by gait speed should be disregarded. Age-related changes in gait variability were found even when walking speed was held constant (Danion et al., 2003; Kang & Dingwell, 2007) and a study observing older adults with and without a history of falls found no differences in gait speed, but those who fell had significant increases in gait variability ($p < 0.001$) (Hausdorff, Edelberg, Mitchell, Goldberger & Wei, 1997). Maki (1997) demonstrated in older adults that gait variability was related to fall risk while walking speed was related to fear of falling. Furthermore, Frenkel- Toledo et al. (2005) were among the first to identify swing time variability as an independent parameter from gait

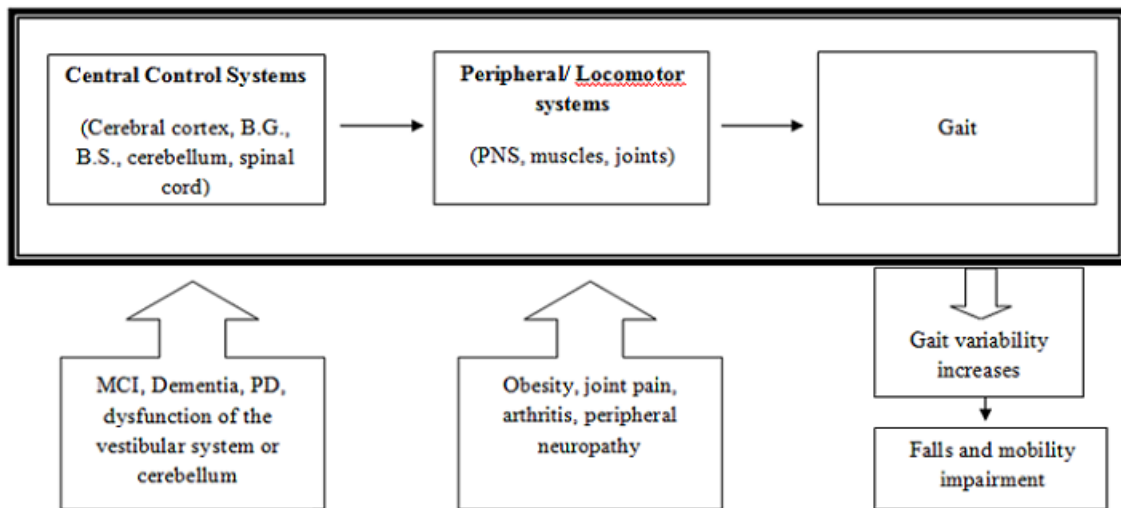
speed. Additionally, Brach et al. (2007) found stance time variability, when controlled for gait speed, to be independently associated with future mobility disability. In a study of AD patients, stride time variability was found to be significantly increased ($p < 0.001$), even though they walked at similar speeds as healthy controls (Webster et al., 2006).

In summary, although a relationship between gait speed and variability is evident, velocity cannot be solely responsible for stride to stride fluctuations (Frenkel- Toledo et al., 2005). Gait variability appears to be affected during extreme walking speeds, while during self selected usual pace, variability is minimized. Overall, evidence suggests gait variability may be a more sensitive marker compared to gait velocity of gait control and stability (Hausdorff, Edelberg, Mitchell, Goldberger & Wei, 1997; Hausdorff, Schweiger, Herman, Yogev-Seligmann & Giladi, 2008), an indicator of underlying pathologies (Gabell & Nayak, 1984) and a better determinant of fall risk in an older adult population (Hausdorff et al., 2001; Maki, 1997; Verghese et al., 2009).

1.4.3 Gait Variability as a Marker of Adverse Events

Stride to stride fluctuations have increasingly become a common area of research as it provides a window for the study of locomotor control (Hausdorff, 2007; Montero-Odasso et al., 2012). An increase in variability may be caused by changes in a number of physiological factors related to aging or underlying disease, such as neuromuscular control, peripheral systems, musculoskeletal function and postural control. Additionally, subtle physiological changes can also influence gait variability, including cognitive impairments (Figure 1.5). Thus, gait variability can be useful in providing insight into the neural control of locomotion. Falls are a common geriatric syndrome with many negative consequences (Speechley, 2011; Tinetti, Speechley & Ginter, 1988). Annually, approximately 30% of Canadian adults over the age of 65 experience at least one fall. Fall survivors often experience soft tissue injuries, restricted mobility and fractures (Speechley, 2011; Tinetti, Speechley & Ginter, 1988). It is well established that effective strategies for fall prevention and reduction are necessary for high risk older adults (Hausdorff, 2007; Tinetti, 1987; Tinetti, Speechley & Ginter, 1988; Speechley, 2011).

Figure 1.5: Illustration of the possible underlying mechanisms affecting gait variability. (Abbreviations: B.G., Basal Ganglia; B.S., Brainstem; MCI, mild cognitive impairment; PD, Parkinson's Disease; PNS, Peripheral nervous system).

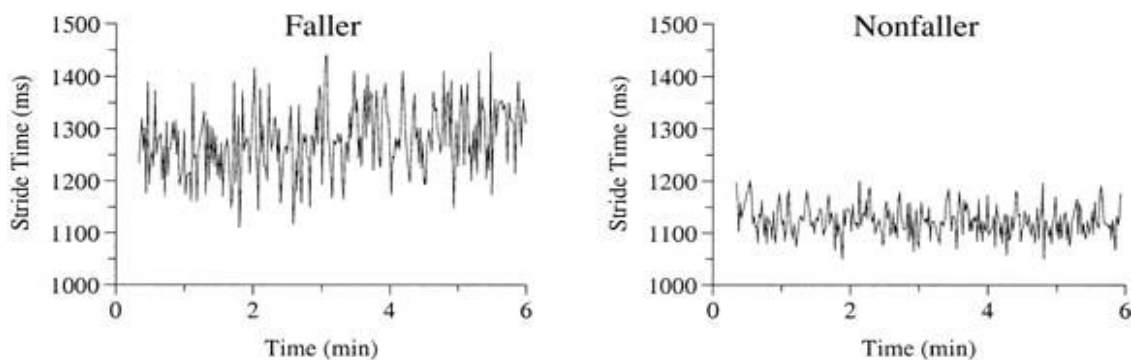


Adapted from Rosano, C. et al. (2007)

Current evidence supports gait variability as a useful measure to help identify older adults at risk for falls (Callisaya et al., 2011; Hausdorff et al., 2001; Hausdorff, 2005; Maki, 1987; Owings & Grabiner, 2003; Verghese et al., 2009). Guimaraes & Isaacs (1980) were among the first to demonstrate older adults who fell, walked with increased gait variability (step time and step length) compared to non-falling older adults. Maki (1997) showed among older adults that a decreased step width variability and an increased step width prospectively discriminated individuals who fell from those who did not. It was also found that gait speed was related only to fear of falling and not to the actual risk of falling, while gait variability measures predicted future falls. Furthermore, although gait speed, mental status and ability to perform activities of daily living (ADLs) were similar between fallers and non-fallers in this community-dwelling older adult population, increased stride time variability was associated with an increased risk for future falls (Hausdorff et al., 2001) (Figure 1.6). Among patients with AD, significant associations between increased stride length variability and falls were found and it was suggested to be the best predictor of falls in this population (Nakamura et al., 1996;

Sheridan & Hausdorff, 2007). These results were confirmed by Verghese et al. (2009) in an elderly population, where fall risk was predicted by increased swing time and step length variability. Taken together, these studies demonstrate that the magnitude of variability in several gait parameters may be more closely related to fall risk when compared to conventional measures of averages of gait speed. The studies also highlight the clinical utility of gait variability in quantitative gait assessments for the evaluation of mobility and fall risk in the elderly.

Figure 1.6: Stride-to-stride fluctuations in stride time measured at baseline, in an elderly subject who subsequently fell during the 1 year follow-up period and an elderly subject who did not fall.



Copyright © Archives of Physical Medicine and Rehabilitation from Hausdorff, J. et al. (2001)

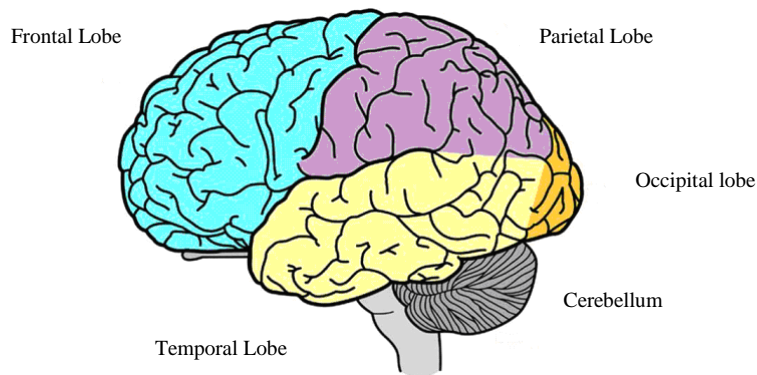
1.4.4 Neural Control of Gait and Gait Variability

Many physiological systems are involved in gait regulation. The following section will describe and highlight important brain structures and neural systems required for locomotion.

1.4.4.1 Neural Control of Gait

Human locomotion and many other movements are achieved through complex, hierarchical processes in the central nervous system (CNS) (Nakazawa, Obata & Sasagawa, 2012; Fukuyama et al., 1997). The highest level of control for motor function within the CNS (brain and spinal cord) is the cerebral cortex, basal ganglia and the cerebellum (Fukuyama et al., 1997; Takakusaki, Nozomi & Masafumi, 2008). The cerebral cortex is divided into four lobes: frontal, parietal, temporal and occipital (Trew & Everett, 2005; Widmaier, Raff & Strong, 2006) (Figure 1.7). The cerebral cortex performs the most complex information integration and is responsible for higher cognitive functions such as planning, attention, memory storage and perception (Trew & Everett, 2005; Widmaier, Raff & Strong, 2006). Different lobes are responsible for gait at different stages, but the exact role of each lobe in human gait remains unknown (Fukuyama, et al., 1997; Nakazawa et al., 2012).

Figure 1.7: Four separate lobes of the brain



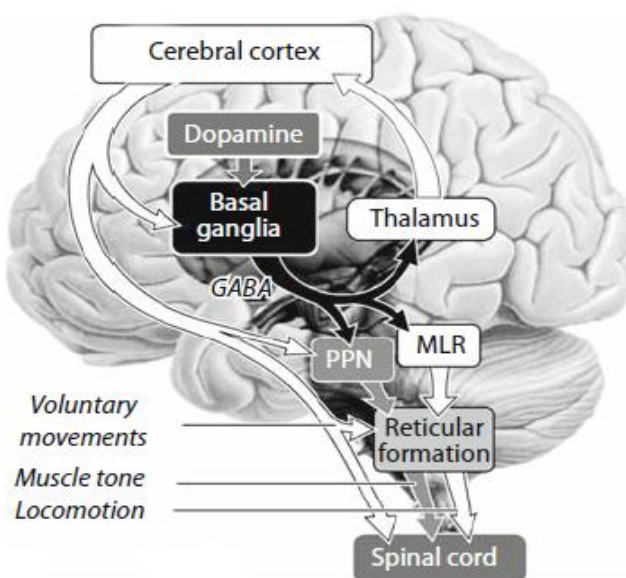
Adapted from Widmaier, E. et al. (2006).

The cerebral cortex, specifically the supplementary motor area (SMA) and the basal ganglia (a sub-cortical structure) initiate locomotion and integrate information from all somatosensory, visual and motor areas of the brain to allow for the planning, execution and coordination of voluntary movements. Located in the posterior portion of the frontal lobe, the primary motor cortex is responsible for integrating afferent brain information and sending the final global motor command via fibre connections to the

brainstem and spinal cord (Graziano, Taylor, Moore & Cook, 2002; Takakusaki et al., 2008; Trew & Everett, 2005).

A neural pathway called the cortical-basal ganglia-thalamocortical loop provides connections for communication between the cerebral cortex, the basal ganglia, thalamus, cerebellum and the brainstem (Figure 1.8). The current understanding of the loop is that it is necessary for accurate control of voluntary movements requiring intention, cognition and attention (Elble, 2007; Middleton & Strick, 2000; Takakusaki et al., 2008). The primary role of the brainstem in motor function is to initiate contractions of postural muscles to maintain body posture and balance during changing environmental

Figure 1.8: Schematic representing the cortical-basal ganglia-thalamocortical loop in the control of voluntary movements, locomotion and muscle tone. (Abbreviations: MLR, midbrain locomotor region; PPN, pedunculopontine nucleus)



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circumstances (Elble, 2007; Takakusaki et al., 2008; Trew & Everett, 2005). The pedunculopontine nucleus (PPN) is a brainstem structure which plays a central role in

neural communication important for movement between the higher level control centers in the brain and the spinal (Elble, 2007; Mena-Segovia, Bolam & Magill, 2004; Takakusaki et al., 2008). The PPN is highly interconnected with the basal ganglia and together they are responsible for the automatic regulation of postural muscle tone, the execution of rhythmic limb movements and inhibition of unwanted movements (Mink, 2003; Takakusaki et al., 2008).

The spinal cord's crucial role in human movement is to act as a relay system transmitting neural signals between the brain and the rest of the body. It also contains neural circuits which control reflexes and central pattern generators (CPGs) (Dietz, 2003; Nakazawa et al., 2012; Trew & Everett, 2005). Central pattern generators (CPGs) are neural networks between the brainstem and the spinal cord (Dietz, 2003; Duysens & Van de Crommert, 1998; Trew & Everett, 2005). CPGs are described as complex neuronal networks within the spinal cord that can generate self-sustained rhythmic motor patterns that drive movements, even in the absence of input from higher level brain centers (Dietz, 2003; Nakazawa et al., 2012). Even though it is generally accepted that CPGs are responsible for locomotion in mammals, the underlying principles of CPGs function are based on results in experimental animals models and the role of CPGs do not translate directly to our understanding of human locomotion (Dietz, 2003; Fukuyama et al., 1997; Nakazawa et al., 2012).

Classical research experiments completed by Brown in 1911 and 1912 demonstrated cats with a transected spinal cord, causing deprivation of supraspinal and proprioceptive input, were still able to initiate and display complex rhythmic motor output. These results suggested that higher level cortical processing was unnecessary during automatic locomotion execution. (Dietz, 2003; Duysens & Van de Crommert, 1998; Nakazawa et al., 2012; Takakusai et al., 2008). In humans, current evidence suggests sufficient muscular force cannot be generated from subcortical neural networks alone to sustain stepping patterns of a gait cycle (Nakazawa et al., 2012). The current understanding of CPGs in human locomotion is that they likely receive information from higher level cortical control centers as well as sensory afferents from visual, auditory,

vestibular and proprioceptive receptors (McCrea & Rybak, 2008; Rossignol, Dubuc & Gossard, 2006; Saint-Cyr, Taylor & Nicholson, 1995). Human locomotion is more unstable and additional descending cortical control is most likely required (Takakusai et al., 2008).

The cerebellum is essential for movement coordination. It utilizes feedback circuits to integrate ‘real time’ input signals from visual, auditory, vestibular and somatosensory cortices to perform smooth, correct and synchronized motor actions (Takakusai et al., 2008; Trew & Everett, 2005). The cerebellum also works closely with the brain stem to regulate aspects of posture control and maintain equilibrium of limb movements during locomotion (Takakusai et al., 2008; Widmaier, Raff & Strong 2006).

In summary, gait is a highly complex task which depends on both automatic and intentional processes. The basal ganglia and structures within the brain stem are required for the automatic regulation of gait, where adaptive functional gait navigation depends on higher level cortical control centers. Failure in the ability of these systems to communicate effectively results in motor dysfunction and gait impairments.

1.4.4.2 Neural Control of Gait Variability

Little is known about the mechanisms underlying the stride-to-stride fluctuations quantified in gait variability (Brach et al., 2007; Hausdorff, 2005). In a healthy locomotor system, inputs from the basal ganglia, cerebral cortex and cerebellum, in combination with feedback from the vestibular, visual and proprioceptive systems are integrated to generate limb movements that are smooth, accurate and coordinated. Subsequently, the output of this integration is expressed through spatial and temporal gait parameters (Hausdorff et al., 2008). Evidence suggests each gait variable may be regulated by different physiological mechanisms and raises the importance of investigating the parameters separately in an attempt to understand the organization and regulation of gait control (Hausdorff, 2007).

Early work by Gabell & Nayak (1984) proposed variability in step length and stride time were representative of the rhythmic, automatic stepping mechanisms brought about by repeated sequential contractions and relaxation of muscle firings producing forward propulsion. Through studies of neurological diseases and their associations with increased gait variability, it was suggested that these characteristics are more dependent on central neural control and cognition than musculoskeletal performance (Beauchet et al., 2005; Montero-Odasso et al., 2012). In humans, the PPN forms part of the rhythmic locomotor center which has direct projections to the spinal cord (Mena-Segovia et al., 2004; Takakusaki et al., 2008), suggesting it may have a role in the control of CPGs (Jahn et al., 2008). With that said, we can conclude that the magnitude of stride time and stride length variability are controlled largely in part by the brainstem and basal ganglia in addition to frontal and prefrontal cortices (Brach, Studenski, Perera, VanSwearingen & Newman, 2007; Hausdorff, 2008).

Variability in the gait parameters, of step width and double support time are predominately determined by balance control mechanisms (Gabell & Nayak, 1984). These variables are more closely associated with sensorimotor functions such as muscular strength (Callisaya et al., 2010). A disruption in balance control would result in an increase in step width and double support time variability indicating a lack of compensation for instability (Brach et al., 2007; Gabell & Nayak, 1984). However, recent evidence suggests older adults who walk with extreme step width variability (either high or low) are at increased risk for falls and has led to inconsistencies in published normative values for these parameters (Brach et al., 2005). The control or generation of gait variability is likely multi-factorial and a thorough understanding of the underlying mechanisms of each gait parameter will help explain locomotor functions and factors which can be modified in therapeutic interventions for gait impairments.

1.5 Cognition

Cognition is not an easily definable term as it can be interpreted differently depending on an individual's background or area of study (Benjafield, 2007). For the purpose of this study, it is simply defined as the mental processes involved in the acquisition, storage, transformation and use of knowledge (Matlin, 1998). The countless pathways of obtaining knowledge is why cognition is associated with several other concepts including awareness, comprehension, intelligence, recognition, skill and understanding, all of which are involved at some level to one or more cognitive domains (Matlin, 1998).

1.5.1 Cognitive Domains

The unique and distinct characteristics of each specific cognitive domain will be highlighted here. These domains are outlined based on various hypotheses suggesting their role on gait and mobility. It is important to understand that these terms are not distinct independent features and some overlaps exist between domains.

1.5.1.1 Executive Function

Executive function (EF) refers to a set of higher level cognitive functions, working collectively to modify cortical sensory input to produce behaviour required for regulation of goal directed movements (Sheridan et al., 2003; Yogev-Seligmann et al., 2008). EF is also involved in the control of attention and aspects of working memory resources (Yogev-Seligmann et al., 2008; Sheridan & Hausdorff, 2007). The functions of EF include initiation or intention of action, planning, problem solving, action monitoring and attention (Lezak, 1995; Sheridan & Hausdorff, 2007; Yogev-Seligmann et al., 2008). The frontal and prefrontal lobes, predominately the dorso-lateral prefrontal cortex and the anterior cingulate cortex, have been related to the cognitive features of EF (Yogev-Seligmann et al., 2008). However, there is evidence to suggest EF activates other areas

of the brain and are not only localized to the frontal cortex (Collette, Hogges, Salmon & Van der, 2006; Lorenz-Reuter, 2000; Stuss & Levine, 2002).

1.5.1.2 Attention

Attention is often considered a specific example of EF. The term describes different processes driven by sensory perception that are related to how an organism becomes receptive to stimuli and how it overlooks or begins to process incoming internal or external excitation (Lezak, 1995; Sheridan et al., 2003; Yogev-Seligmann et al., 2008). Attention can be further subdivided into three types: selective, sustained and divided. Selective attention refers to the filtering of irrelevant stimulation and suppression of distracters (Lezak, 1995). Sustained attention is the ability to maintain attention on a task for a period of time. Lastly, divided attention is the ability to perform multiple tasks at the same time, shifting attention from one task to the other (Lezak, 1995). This type of attention not only plays an important role in complex challenging environments but is also important, to a lesser degree, in routine walking environments (Yogev-Seligmann et al., 2008). Similar to EF, attention is associated with the prefrontal cortex, primarily the dorsolateral prefrontal cortex and the anterior cingulate gyrus. Evidence also suggests aspects of attention are associated with the parietal lobe (Perry & Hodges, 1999).

1.5.1.3 Memory

Working memory refers to a set of linked information processing systems necessary to maintain or retrieve newly acquired information for short term storage and manipulation while a subject is engaged in complex cognitive tasks (Baddeley, 1992). Early work suggested working memory was associated with hippocampal systems (Olton, Becker & Handelman, 1979) but were based on single cell non-human animal models. Follow-up studies in humans indicated that areas typically associated with language processing (Broca's area) and the posterior parietal cortex were also associated with working memory (Baddeley & Hitch, 1974; Markowitsch et al., 1999; Shallice & Vallar, 1999; Vallar, Betta & Silveri, 1997). However, the most recent evidence credits the

dorso-lateral and ventro-lateral regions of the prefrontal cortex with the central role in working memory (D'Esposito, Postle & Rypma, 2000; D'Esposito, 2007; Müller & Knight, 2006).

Episodic memory is one of the two distinct features of declarative memory and refers to a long term memory network, which is unique because it is oriented in the past and accompanied by the conscious capability to store, recollect and re-experience personal past events in the context of space and time (Tulving, 1972). Declarative memory refers to memories which can be consciously stored and recalled such facts, events or knowledge (Tulving, 1972). Functional neuro-imaging studies indicate episodic memory is primarily supported by neural connections in the medial temporal lobe, predominately the hippocampus, which also interacts with other cortical areas (Fletcher, Frith & Rugg, 1997; Nyberg, 1997; Squire et al., 1992). Evidence has also found cortical activation in the prefrontal cortex and superior parietal lobe activation during encoding and retrieval aspects of episodic memory (Buckner et al., 1995; Buckner & Tulving, 1995; Kapur et al., 1995; Schacter, Wagner & Buckner, 2000), which is for active management and monitoring of episodic memory (Fletcher et al., 1997).

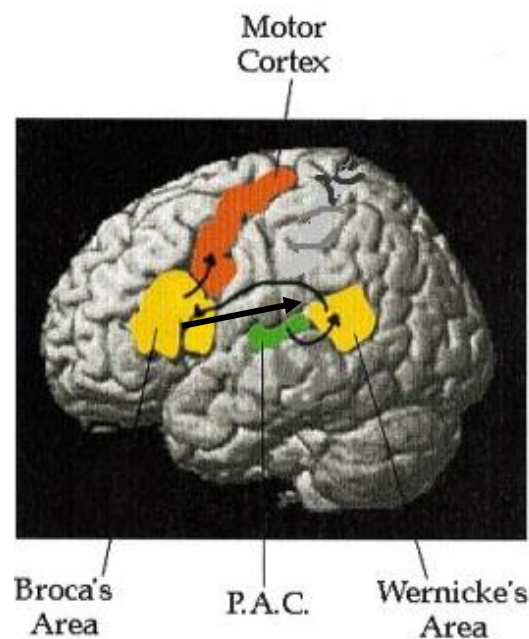
Semantic memory is the second distinct feature of declarative memory and is comprised of knowledge of facts, vocabulary and concepts learned through everyday experiences independent of personal experiences (Tulving, 1972; Tulving 1991). Through various neuro-imaging studies, the inferior temporal lobe and pre-frontal cortex are the two regions which tend to be consistently activated during semantic memory tasks (Martin, Haxby, Lalonde, Wiggs & Ungerleider, 1995; Martin, Wiggs, Ungerleider & Haxby, 1996; Vandenberghe, Price, Wise, Josephs & Frackowiak, 1996).

1.5.1.4 Language

Language refers to a structured system of communication which uses written or spoken words and symbols to explain the external environment or personal thoughts (Price, 2000). The language domain consists of categories related to speech expression,

auditory comprehension, naming, reading and writing (Price, 2000; Strauss, Sherman & Spreen, 2006). Aphasia is a general term used to describe deficits in language comprehension and expression (Damasio & Geschwind; 1984). Broca's area and Wernicke's area communicate extensively between each other and are usually located on the left in frontal and temporal lobes respectively. These areas also share neural connections to the motor cortex which generates speech (Price, 2000). Traditionally, Broca's area is associated with correct speech production and articulation, whereas Wernicke's area is associated with language comprehension and processing (Obler et al., 2010; Friederici, 2002; Vigneau et al., 2006).

Figure 1.9: Lateral left hemisphere view of the brain and areas associated with language and speech production. (Abbreviations: P.A.C., primary auditory cortex)



Adapted from Price, C. (2000).

1.6 Identifying Individual Cognitive Domain Contribution on Gait

Many of the cortical and sub-cortical regions involved in higher level cognitive functions discussed above, overlap with areas involved in motor control. However, the act of walking alone cannot be used to evaluate the relationship between

individual cognitive domains and gait. Methods for isolating cognitive components from musculoskeletal components of gait and going beyond observing discrete pathology (i.e. brain lesions) are needed. This section will describe the technique, the dual task paradigm, used to evaluate how functions of the individual cognitive domains influence gait performance. Studies in both healthy and cognitively impaired adults confirm such a relationship by demonstrating dual-task (DT) effects on gait and associations between cognitive deficits and gait dysfunction

1.6.1 Evaluating Cognitive Control on Gait: Theories of Dual Task (DT)

Interference

Performing two tasks simultaneously can result in detrimental effects on one or both tasks. The “outcome conflict” where one task produces output which prevents the processing of another task is referred to as DT interference (Navon & Miller, 1987; Pashler, 1994). The underlying mechanisms of DT interference provide pertinent details on the functional structure of the brain and help explain an individual’s ability or inability to simultaneously manage multiple tasks in different environmental situations (Pashler, 1994). Explanations of DT interference generally revolve around three theoretical approaches.

The first model, the bottle neck theory, proposes processing systems are only capable of handling input from one task at any given time. Under these circumstances, when two tasks are presented concurrently and require the same neural networks, they both compete for resources resulting in a delayed or impaired response in one or both tasks (Pashler, 1994; Tombu & Jolicoeur, 2003). The second model, the cross-talk model suggests interference is caused not by the capacity of the information processing systems, but by the type of input presented and the consequent responses (Pashler, 1994). This model posits two tasks from similar cognitive domains recruit the same neural networks allowing easier performance of both tasks concurrently. Conversely, it becomes difficult to perform the two tasks if they are from different cognitive domains (Pashler, 1994).

The third model and the most widely accepted model of DT interference in gait research is the capacity sharing theory. The model is based on the assumption that an individual is able to multi-task and can voluntarily allocate attention to the components of the combined given task, although the type of task may determine processing priority (Pashler, 1994; McLoed, 1977; Tombu & Jolicoeur, 2003). Information processing centers are considered to have finite resources that are shared among tasks and processing capacity decreases as additional tasks are introduced to the system or as the time between stimuli presented is reduced, resulting in a diminished ability to perform one or both tasks. (Kahneman, 1973; McLoed, 1977; Navon & Miller, 2002; Tombu & Jolicoeur, 2003). For example, the performance of additional tasks while walking alters gait performance, the secondary task or both (Yogev-Seligmann et al., 2008). Studying the DT interference phenomenon has relevant clinical implications as it more closely simulates real life situations and begins to explain approaches to practical problems with multi-tasking in activities of daily living (ADLs).

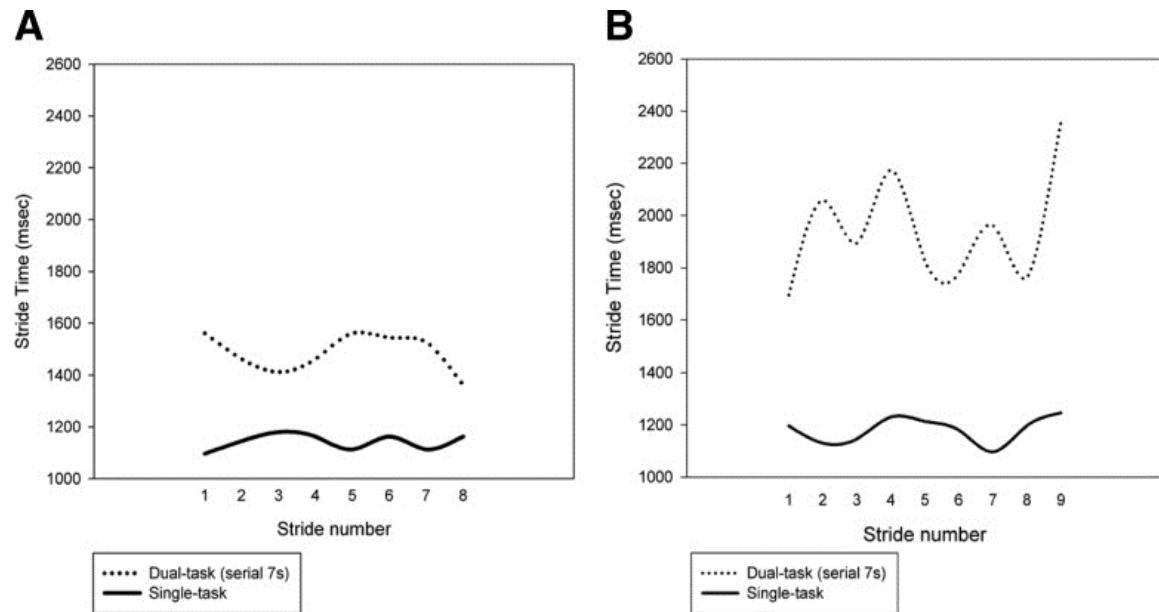
1.6.2 Dual-Task Paradigm

The concept of the DT paradigm is based on the capacity sharing theory and empirical evidence supports the influence of cognition in gait control (Amboni et al., 2013; Montero-Odasso et al., 2012). The ‘stops walking while talking’ study was the first to demonstrate that an inability to continue a conversation while walking, a DT activity, was a marker for future falls in institutional-dwelling older adults (Lundin-Olsson, Nyberg & Gustafson, 1997). Since then, observing individuals performing a secondary cognitive task while walking is referred to as the DT paradigm and has been used to assess the relationships between gait, cognition and risk of falling. How the instructions are communicated for performing DT testing influences test performance (Beauchet, Dubost, Aminian, Gonthier & Kressig, 2005; Verghese et al., 2007), without explicit cues to rank the task the DT paradigm forces the brain to prioritize tasks when no specific instructions on prioritization are provided (Amboni et al., 2013). The DT effect on gait performance depends on the nature of the secondary task, as the secondary task can be cognitive, motor, auditory or visual (Beauchet et al., 2009; Verghese et al., 2007). In

general, when challenged under DT conditions, healthy subjects will prioritize maintaining gait and posture over a secondary task; this is known as the “posture first” strategy (Bloem, Grimbergen, van Dijk & Munneke, 2006). The mean differences between gait velocity or variability from a single task to DT indicates the extent of the cognitive reserve and is referred to as the “dual-task cost” (Amboni et al, 2011; Montero-Odasso et al., 2012).

Even though healthy young and older adults alter their gait pattern with decreases in gait speed and increased stride-to-stride variability in response to DT, the changes are likely to be less detrimental to stability (Beauchet et al., 2005; Dubost et al., 2006; Ebersbach, Dimitrijevic & Poewe, 1995; Hausdorff et al., 2008; Verghese et al., 2007). In a study of healthy young adults, DT gait speed decreased from 130cm/sec to 123 cm/sec (5% change) and the CoV of stride time increased from 1.8% to 2.1% (0.3% change). Even though the change leaves their gait velocity well above the “normal” threshold for these parameters, the literature does not definitively state whether it is the magnitude of change or decreases below a certain threshold which indicate reduced attentional capacities. Additionally, greater DT costs in gait are seen in older adults with history of falls (Beauchet et al., 2009; Hausdorff et al., 2008) and in individuals with cognitive impairments (i.e. MCI, AD). Moreover, it was also determined that as the severity of cognitive impairment or DT complexity increases, gait performance measures worsen (Figure 1.10). (Camicioli et al., 1997; Montero- Odasso et al., 2012; Muir et al., 2012; Sheridan et al., 2003).

Figure 1.10: The effect of complex dual task conditions (serial 7 subtractions) in stride time in an older adult with normal cognition (A) compared to an older adult with mild cognitive impairment (B).



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1.6.3 Evidence Supporting the Relationship between Gait and Cognition

Recently many studies have examined the complex relationship between specific cognitive functions and gait performance with use of the DT paradigm. In their study of non-demented older adults, Hausdorff and colleagues (2005) were among the first to demonstrate that even steady-state walking could be considered a complex task, requiring higher level cognitive resources. In the years following, many studies established a relationship between gait dysfunction and impairments in EF and attention in healthy older adults. These studies consistently show that poorer performance in EF and attentional domains are associated with slower velocity (Ble et al., 2005; Coppin et al., 2006; Holtzer, Wang & Verghese, 2012; Springer et al., 2006; Watson et al., 2010) and increases in gait variability (swing time, step length, stride time and length) (Dubost et al., 2006; Hausdorff et al., 2005; Verghese et al., 2007; Verghese et al., 2008; Yogev-

Seligmann et al., 2008) during DT conditions, not seen during simple motor tasks. These results were also replicated in MCI patients (Montero-Odasso et al., 2012; Muir et al., 2012). Additionally, increased gait variability measures and poor executive function during DT conditions was found to predict falls in older adults (Herman et al., 2010; Mierlman et al., 2012; Sheridan & Hausdorff, 2007). These results imply intact executive function and attention are necessary in older adults to perform complex mobility tasks.

There are inconsistent findings concerning the role of memory in gait control. A computerized tomography study showed that a deficit in overall motor performance was associated with temporal lobe atrophy (Guo et al., 2001). A few studies have demonstrated an association between deficits in episodic and working memory with decreased gait velocity in normal aging (Holtzer et al., 2006; Holtzer et al., 2012) and MCI (Montero-Odasso et al., 2010). One study found memory impairment, in addition to EF impairments, were associated with greater gait speed decline (Watson et al., 2010). In contrast, many studies fail to find an association between memory (working or episodic) and gait performance measures (Herman et al., 2010; Martin et al., 2012; van Iersel et al., 2008), and to date no studies indicate a significant association between memory deficits and increases in gait variability (van Iersel et al., 2008).

Evidence is scarce with respect to demonstrating involvement of the language domain in gait control. Many studies assessing language function on gait have used a factor analysis approach, which likely is not a true independent representation of the language domain specifically (Verghese et al., 2008). Using factor analysis, Holtzer et al. (2006, 2012) found the language domain was related to gait velocity, but became insignificant during DT testing. Additionally they had found deficits in language were not related to falls in normal older adults. Conversely, one study which looked at language independently, found faster gait speed was associated with less decline in the language domain (Mielke et al., 2013). Currently, no studies indicate a significant association between language impairments and increased gait variability.

The use of neuro-imaging techniques within this field of research has developed over time and they have provided additional support to confirm the cognitive control of gait. A Proton Emission Tomography (PET) study demonstrated activation of the dorsolateral prefrontal cortex, cingulate cortex, superior and inferior parietal lobes while subjects imagined standing, walking and avoiding obstacles (Malouin, Richards, Jackson, Dumas & Doyon, 2003). Magnetic resonance imaging (MRI) studies have assessed the role of white matter abnormalities and/ or focal neuronal loss on gait and cognitive impairment in older adults (Rosano, Brach, Studenski, Longstreth & Newman, 2007; Rosano et al., 2008). Gait variables and their respective variability values were independently associated with subclinical brain infarcts, white matter abnormalities and focal neuronal loss in regions related to motor, attention and executive control (Rosano et al., 2007; Rosano et al., 2008). Rosano and colleagues (2008) also found that diminished volumes in the sensorimotor (motor) and fronto-parietal (cognitive) regions were associated with reduced stride length and increased double support time. In a subsequent study, a smaller prefrontal area was related to slower gait and processing speed, suggesting shared neural basis for both functions (Rosano et al., 2012). Furthermore, a study of neuro-chemical and functional changes in a cognitively intact elderly population found reduced stride length was associated with smaller hippocampal volume and decreased hippocampal metabolism was associated with increased stride length variability (Zimmerman, Lipton, Pan, Hetherington & Verghese, 2009). Taken together, these findings refute complete locomotor automaticity and suggest higher level cognitive contribution is involved in regulation of gait speed and variability.

1.7 Mild Cognitive Impairment (MCI)

Recent investigations have identified MCI as a transitional stage between normal cognitive functioning and dementia. MCI is a relatively new concept and despite extensive supporting evidence of the syndrome there are contentious debates on defining MCI, its clinical significance, prevalence, and determining the appropriate guidelines for diagnosis (Albert & Blacker, 2006; Larrieu et al., 2002; Ritchie, 2004; Gauthier et al., 2006). MCI is a controversial concept and is now the focus of natural history, biomarker

and AD prevention studies in an attempt to identify the earliest stages of cognitive decline (Chertkow, 2002). Many aging adults are likely to develop cognitive impairments, but not all cases will develop into dementia.

1.7.1 Characteristics of Mild Cognitive Impairment

With age cognitive function can remain stable, decline gradually over time to a state of MCI, or further progress to dementia (Feldman & Jancova, 2005). Fundamental work by Petersen et al. (1999) developed the foundations for MCI classification. They determined MCI patients could be differentiated from cognitively normal and those with mild Alzheimer's disease. Petersen's initial criteria only included deficits inconsistent with one's age within the memory domain. Subsequently, Winblad et al. (2004) revised and established a more recent criteria for MCI diagnosis incorporating additional domains of cognition beyond memory. Petersen then revised his initial criteria to be more consistent with the consensus criteria by Winblad and colleagues (2004). The current criteria identifies a period in time when an individual's cognitive decline is greater than expected at a given age and education level (>1.5 standard deviations below normal on tests of cognitive function), but the change does not meet the criteria for dementia. These individuals have consistent memory complaints, usually verified by a close informant and reinforced by objective validated cognitive and neuropsychological assessments. MCI patients will display evidence of cognitive decline over time while maintaining the ability to perform ADLs (Petersen et al., 1999; Petersen et al., 2001; Petersen, 2004 Winblad et al., 2004).

There are inconsistencies regarding the prevalence of MCI due to the recent classification of the term (Albert & Blacker, 2006), discrepancies in the operationalization of subtypes (Ward, Arrighi, Michels & Cedarbaum, 2012), differing diagnostic measures (Petersen et al., 1999) and the differences between population and clinic-referred study samples (Feldman & Jancova, 2005). The prevalence in clinic-referred samples is assumed to be greater than the general population of older adults. Based on a recent systematic review in North America, the prevalence for MCI in older

adults over the age of 65 varies and is estimated to range anywhere between 20% and 26% (Ward et al., 2012), increasing to 29% in older adults over 85 years old (Lopez et al., 2003). Studies estimate 10–15% of older adults with MCI progress to dementia annually (DeCarli, 2003; Petersen et al., 1999; Petersen, 2004), whereas older adults without MCI develop dementia at a rate of 1-2% annually (Petersen et al., 1999).

Individuals with MCI are at an increased risk for mobility impairment and further cognitive decline (Bennett et al., 2002; Liu-Ambrose et al., 2008; Verghese et al., 2008). As a result, greater focus has been directed to the early identification of patients at high risk for cognitive decline and to interventions at the earliest stages of ‘pre-dementia’ such as MCI (Albert & Blacker, 2006; Burns & Zaudig, 2002; Thompson & Hodges, 2002). MCI likely represents a stage within the neurodegenerative disease process of dementia which may respond to treatment to alter disease trajectory and the severity of the impairment is subtle enough to allow a higher threshold of cognitive testing in order to uncover the influences of different cognitive domains on gait performance (Montero-Odasso et al., 2009).

1.7.2 Heterogeneity of Mild Cognitive Impairment

It is unknown whether every MCI case can be considered a prodrome for neurodegenerative diseases, such as AD, as not all people diagnosed with MCI will progress to dementia. Approximately 40% of MCI cases will remain stable over time (i.e., their cognitive status neither gets better or worse) (Burns & Zaudig, 2002; Ritchie, 2004; Ganguli, Dodge, Shen, & DeKosky, 2004). Heterogeneity within this population likely contributes to the variation of clinical outcomes and underlying physiological pathology that can develop over time, such as functional impairments, AD and other types of dementia (Albert & Blacker, 2006). MCI has been divided into two different subtypes: amnesic and non-amnesic (Petersen, 2004). Amnesic MCI (aMCI) is the most common and it is often thought of as a precursor to AD (Ghosh, Libon & Lippa, 2013; Petersen, 2004). These patients have subjective memory complaints (usually episodic memory) which is beneficial if corroborated by an informant accompanied by

objective memory impairments (Albert & Blacker, 2006; Ghosh et al., 2013; Petersen, 2004). Those with non-amnesic MCI (naMCI), have impairment(s) in a non-memory domain, such as executive function, attention or language (Ghosh et al., 2013; Petersen, 2004). Due to the relative rarity of a pure MCI subtype, it is likely that most MCI samples include a combination of both aMCI and naMCI (Alladi, Arnold, Mitchell, Nestor & Hodges, 2006).

1.7.3 Pathophysiology of Mild Cognitive Impairment

There is currently limited evidence to support a pathological process in MCI. There are no reported cases of death from MCI; therefore, studies attempting to determine a pathophysiology have been conducted post-mortem on individuals with an MCI diagnosis who died from unrelated causes (Petersen et al., 2001). These studies demonstrated that these patients had an accumulation of disfigured tau proteins within a nerve cell, called neurofibrillary tangles, in the hippocampus and entorhinal cortex, which is typically viewed as a hallmark of AD histopathology (Du et al., 2001; Petersen, 2001; Chertkow et al., 2007; Thompson & Hodges, 2002). Additionally, a neuro-imaging study found that individuals with MCI with lower hippocampal volume at baseline were found to be more likely to convert to dementia after a 2-4 year follow-up period (Jack et al., 1999).

In the absence of histopathology studies, neuro-imaging has provided information on structural changes of the brain. A neuro-imaging study by Bennett, Schneider, Bienias, Evans & Wilson (2005), found brain changes in individuals with MCI were intermediate between normal and AD. These changes were intermediate not only in terms of the presence of plaques and tangles (hallmark features of AD), but also in terms of cerebral infarcts and Lewy body pathology. Several studies have identified apolipoprotein E status as a strong predictor of progression from MCI to AD (Petersen et al., 1995; Fleisher et al., 2007), while others have failed to find an association (Aggarwal et al., 2005; Devanand et al., 2005). There has been a lot of controversy regarding the role of genetic testing in detecting MCI cases that will convert to AD, though a lack of

substantial evidence does not support routine genetic screening in patients with MCI (Ghosh et al., 2013).

1.7.4 Neuropsychological Screening and Diagnosis of Mild Cognitive Impairment

Differentiating symptoms that are attributable to MCI and normal aging can be challenging, as forgetfulness and difficulty recalling common names or words are often apart of the normal aging process (Ghosh et al., 2013). There is currently no treatment for MCI, yet early detection provides an opportunity to introduce therapeutic interventions to treat modifiable risk factors that have the potential to alter disease trajectory (Feldman & Jacova, 2005). The Mini-Mental State Examination (MMSE), the most widely accepted screening tool for dementia, has been found to be insensitive in diagnosing MCI (Chertkow, 2007; Petersen, 2004). The MMSE is very general and only successful in detecting those with severe cognitive impairment. The Montreal Cognitive Assessment (MoCA) is often used to complement the MMSE when screening for MCI. It is a brief cognitive screening test proven to have greater sensitivity and specificity to detect MCI (Chertkow et al., 2007; Nasreddine et al., 2005). The MoCA differs from the MMSE in that it is more difficult and includes a wider range of tests assessing a greater number of cognitive functions including executive function, delayed recall, language, attention and visuospatial skills. The MoCA also puts less scoring weight on orientation to time and place (Nasreddine et al., 2005). There is no generally accepted neuropsychological testing battery for MCI, but evidence suggests in order to properly diagnosis MCI testing of multiple domains is necessary (Lonie, Tierney & Ebmeier, 2009).

1.8 Rationale for Study

Gait and cognitive impairments will increase as the population ages, exposing these older adults to an increased risk to a wide variety of adverse events. Given the fact that these two conditions are often coincident in the same individual, it is important to completely understand the cognitive factors which may affect and contribute to gait control. Despite growing interest, the exact cortical mechanisms involved in gait control are not well known and we lack a thorough understanding of the neural centers that regulate gait. Existing literature evaluating the relationship between gait and cognition has focused almost exclusively on executive function (EF) and attention, where as the role of additional cognitive domains in gait performance remains unknown. Furthermore, existing studies tend to use very few gait variables or stride-to-stride variability characteristics. Increases in gait variability have been proven repeatedly to be associated with fall risk in older adults, therefore, discerning cognitive mechanisms of gait variability may provide another approach to risk assessment and treatment. Additionally, a well-documented limitation in the previous literature has been the lack of integration between neuropsychological and gait assessments for identifying older adults at risk for cognitive and mobility decline.

Limited work has been devoted to investigating the interactions between a cognitive abilities and gait performance in older adults with mild cognitive impairment (MCI). Many of the studies that have examined associations between cognitive function and gait control are primarily focused in high functioning populations or patients with PD, unfortunately the results cannot be directly extrapolated to MCI populations. MCI is a relatively understudied population, especially during DT testing conditions. Individuals with MCI provide a patient population which has a higher threshold for tolerance of testing allowing the ability to explore the contributions of multiple cognitive domains in gait control (Montero-Odasso et al., 2009). Those with MCI also represent a highly vulnerable population because they are at an increased risk for falls, mobility decline and dementia (Bennett et al., 2002). For these reasons, it is of interest to study a broader range of associations in an attempt to understand changes in prodromal entities to AD.

If associations are found between gait performance and individual cognitive domains, it will support the idea that gait is controlled by multiple cognitive processes beyond EF. The associations would further enhance our understanding of the shared neural networks and highlight the benefits of a clinical assessment that includes multiple cognitive domains when identifying older adults at high risk for mobility decline.

1.9 Purpose

This investigation evaluated the associations between deficits in several cognitive domains (i.e., executive function, attention, language, episodic memory and working memory) and quantitative gait variables (temporal, spatial and variability) in people with MCI through the use of the DT paradigm. The results will provide evidence to support and understand the underlying cognitive processes involved in gait control.

1.10 Hypotheses

It was hypothesized that: 1) performance in quantitative gait variables (spatial, temporal and variability) will be associated with deficits in multiple cognitive domains beyond EF and that the associations would be greater when a secondary task was added to the gait task, 2) gait variability parameters would be able to identify more associations in cognitive domains than mean gait variables and 3) stride time variability would show the most associations with cognitive domains when compared with other evaluated gait parameters of interest and in our sample of older adults with MCI.

Chapter 2: METHODOLOGY

2.1 Study Design

This study was a secondary analysis of baseline data collected from three longitudinal studies. The first study was a 5 year prospective cohort study; “Gait Velocity as an Independent Predictor of Dementia in Older Persons with Mild Cognitive Impairment” which began recruitment of participants in May of 2007. The main objective of this cohort study was to assess whether quantitative gait variables could predict progression to dementia. The second study was a 3 year prospective cohort study; ‘Gait Variability as a Predictor of Cognitive Decline and Risk of Falls in MCI’, participant recruitment began in November 2010 and involved follow up assessment every 6 months. This cohort study was primarily designed to determine if gait variability was associated with impairment in executive function (EF), attention and memory as well as determining the anatomical neural substrate of gait variability. Lastly, the study entitled ‘Can cognitive enhancers reduce the risk of falls in older people with mild cognitive impairment (MCI)?’ began data collection in December 2009. This study was a randomized control trial and the main objective was to determine the effect of a cognitive enhancer (donepezil) on gait and balance performance in people with MCI over a 6 month time frame.

All projects were approved by the University of Western Ontario Health Sciences Research Ethics Board (Appendix A).

2.2 Study Population

The three studies aforementioned initially recruited their samples in London, Ontario from the ‘Aging Brain and Memory Clinic’ at Parkwood Hospital, retirement homes, family physicians and the community. MCI participants were eligible to participate if there was a recent clinical diagnosis of MCI, aged 65 and older and the ability to walk without a mobility aid. Participants were excluded in these studies based

on the inability to understand English, any neurological disorder with residual motor deficits (e.g., stroke, parkinsonism, epilepsy, AD), a neuromuscular disorders or a history of hip or knee replacement 6 months prior to study participation, the use psychotropic medication which can affect motor performance, or active major depression (measured by a score $>8/15$ on the Geriatric Depression Scale) (Yesavage et al., 1982; Yesavage, 1988). The exclusion criteria were determined to reduce statistical noise presented by diseases or disabilities known to have detrimental effects on gait.

To obtain the study sample of MCI patients used in the secondary analysis performed for this thesis, participants needed to meet the inclusion criteria of having scores on all cognitive testing outlined in section 2.3 and data for single and dual-task (DT) gait test conditions. Across the three studies there were a total of 130 unique individuals and 72 met the inclusion criteria for the present study.

2.3 Medical and Cognitive Status Assessments

Trained research assistants completed a comprehensive interview for sociodemographic characteristics, co-morbidities, medications, history of falls within 12 months, self-reported levels of physical activity (Physical Activity Scale for the Elderly) and preserved functionality in activities of daily living (BADL) (Katz score for ADLs and Lawton-Brody score for Instrumental Activities of Daily living (IADLs) (Lawton & Brody, 1969). Patients were also administered the Geriatric Depression Scale (GDS) is a reliable and valid screening tool used for measuring depressive symptoms in the elderly. Scores range from 0-15, where higher scores reflect severity of depression. A cut off score of >6 was used to exclude participants (Sheikh et al., 1991).

Objective global cognitive status was assessed using the MMSE (scored 0-30) (Folstein, Folstein & McHugh, 1975) and the MoCA (scored 0-30) (Nasreddine et al., 2005), with lower scores indicating poorer performance of each test. Cognitive impairment in the MCI population was operationalized by a combination of a low MoCA

score (< 26) and normal MMSE (>26) (Nasreddine et al., 2005). These scores were used for descriptive purposes only.

The Trail Making Test (TMT) version A and B, a well-established psychomotor test, was used to determine deficits in executive cognitive functions (Coppin et al., 2006; Lezak, 1995; Strauss, Sherman & Spreen, 2006). Version A was used in this analysis to assess attention and required participants to draw lines connecting consecutively numbered circles (1-25) randomly ordered on a page. Version B added a measure of cognitive flexibility, mental shifting and planning (Corrigan & Hinkeldey, 1987; Korte, Horner & Windham, 2002). Participants were asked to draw lines to connect circles in an alternating order of letters and numbers on a page. Both versions are timed and the time to completion is measured in seconds. The difference between version B and A (Δ TMT) was used in this study to model EF. Delta TMT is used to control for the effect of motor speed and is considered a more accurate measure of EF (Lezak, 1995).

Digit Span Test (forwards and backwards) was used to measure attention. In Digit Span Test forward (DSTF), participants are asked to repeat a list of random numbers starting at two digits and increasing to eight in the same order (scored 0-16). In Digit Span Test backwards (DSTB), they are then asked to listen to a series of numbers and repeat them in the reverse order (scored 0-14) (Wechsler, 1987). DSTF is more a measure of immediate attention and DSTB in this study was used as a measure of complex attentional tasks (Choi et al., 2014; Lezak, 1995; Yogev-Seligmann et al., 2008). The difference between the digit span forward and backward test (Δ DST) was used in this analysis as an index of the central executive component of working memory, where better scores indicated better memory (Liu-Ambrose, Nagamatsu, Graf, Beattie, Ashe & Handy, 2010).

The Letter Number Sequencing Test (LNS) was used to assess working memory. The test examined the ability to retain and process a sequence of letters and numbers and then were asked to recite numbers first in increasing order followed by letters in alphabetical order (scored 0-21) (Becker & Morris, 1999).

The Rey Auditory Verbal Learning Test (RAVLT) was used to assess episodic memory. The participant listens to list of 15 nouns (List A) repeated five times, after each trial they are asked to recall as many words as possible from the list. A second interference list (List B) is presented and the participant is asked to recall as many words as they can from List B. After the interference trial, the participant is immediately asked to recall the words from List A and the score is calculated based on the number nouns retained from List A (Lezak, 1995).

The reduced 15-item version of the Boston Naming Test (BNT) was used to assess the language domain, requiring participants to clearly identify and verbalize the objects depicted in pictures. The score (0-15) was calculated from those items correctly named spontaneously and named correctly after semantic cues (Stern et al., 1992).

2.4 Gait Assessment

In a well-lit area, gait performance was assessed using 6m x 0.64m electronic walkway system (GAITRite®) with pressurized sensors activated with each footfall as a subject walks over the mat. A connected personal computer displayed electronic imprints and collected spatial and temporal gait parameters from each footfall. To measure steady state walking, 1 meter acceleration and deceleration regions were added to either end of the mat but were not included in gait parameter calculations. The GAITRite® system has shown excellent validity and reliability collecting spatial and temporal characteristics in various populations, including the elderly (Bilney et al., 2003; McDonough et al., 2001; Verghese et al., 2002). Gait velocity (cm/s), stride time (msec), stride length (cm), step width (cm) and double support time (msec) were the primary variables of interest and measured under single and cognitively challenging DT conditions. The variability in four gait parameters (stride time, stride length, double support time and step width) was quantified using the CoV ($\text{CoV} = [(\text{SD}/\text{Mean}) \times 100]$). Because the SD is reported in the same unit as the mean, a measurement scale with larger units (e.g. 50 to 100) will not necessarily have a larger SD than a measurement scale with smaller units (e.g. 1 to 50)

even if the shapes of the two frequency distributions are different, and thus the degree of dispersion is identical. This property invalidates the use of the SD to directly compare variability across different scales. By dividing the SD by the mean, the CoV becomes a standardized estimate of dispersion, which can then be directly compared between scales based on different units. The variables were selected based on the interrelationship, between cognitive control of gait, stability, posture and fall risk in the elderly described in the literature (Brach et al., 2005; Hausdorff, 2001; Hausdorff, 2005; Montero-Odasso, 2012). Other gait characteristics captured by the GAITRite® system were not included for this analysis because of the high correlation with the included variables.

Participants were asked to walk at a self-selected usual comfortable pace while completing each walking trial. The single task condition consisted of simply walking the length of the mat. The DT conditions consisted of counting backwards from 100, serial 7 subtractions from 100 and naming animals out loud. These conditions were selected based on previous research indicating arithmetic tasks relies on attention and working memory (Hittmair-Delazer, Semenza & Denes, 1994), where naming animals is related to verbal fluency (Weiss et al., 2003). Standardized verbal instructions were given before each walking condition and did not provide instruction on task prioritization during the DT conditions

2.5 Statistical Analysis

Baseline demographic and medical characteristics of the study sample were summarized using means, standard deviations (SD) or frequencies expressed as a percentage as appropriate. The CoV was calculated for the gait variability of four parameters (stride time, stride length, step width and double support time). Preliminary analysis of the raw data identified the presence of outliers, these cases were further investigated to ensure absence of measurement error. The normality of the gait characteristics were evaluated with skewness, kurtosis and normality tests. Log transformations were used to obtain normal distribution in highly skewed gait variability parameters (dependant variable) and can be seen in Appendix B.

Pearson correlation analysis between each of the gait parameters was completed to determine highly correlated variables. A correlation co-efficient greater than 0.6 were considered highly correlated and were excluded from the analysis.

One way analysis of variance (ANOVA) with repeated measures design was performed to determine mean difference between all four walking conditions (one independent variable with four levels) and gait characteristics (dependant variables). Statistically significant findings from the ANOVA were followed by post-hoc analysis of pairwise comparisons using the Bonferroni test for all possible comparisons to adjust for multiple comparisons and to reduce chance of type I errors. Analysis was completed for the mean, the CoV and log transformed gait variables.

Multiple linear regression analysis was performed to further investigate cross-sectional associations between cognition (as measured by TMTA & B, DSTs, LNS, RAVLT & BNT) and gait (velocity, stride time, stride length, step length and double support time) with and without DTs. Gait variables were the dependant variables and exposure variables of interest were the neuropsychological test scores. All assumptions for linear regression models were fulfilled by examination of scatter-plot and histogram graphs. The regression analysis was adjusted for age, body mass index (BMI), total number of medications and total number of co-morbidities to account for potential confounding effects. All data was analyzed using Statistic Package for the Social Sciences (SPSS) software version 20.0 (SPSS, Chicago, IL). Statistical significant was accepted at 0.05 for all analysis.

Chapter 3: RESULTS

3.1 Study Population and Demographics

For this study, data on 72 participants with mild cognitive impairment (MCI) were used for our initial sample. Four subjects were excluded from the study, due to an inability to speak or understand English (1) or measurement error (3). The final sample consisted of 68 participants. All demographic characteristics are summarized in Table 3.1. The average age of the participants was [Mean (SD)] 74.1 (10.1) years, of whom 54% were male with an average Body Mass Index (BMI) of 26.8 (4.5). Depression scores were low and all subjects were able to perform instrumental activities of daily living.

Table 3.1: Demographic characteristics of study participants in total sample

Variable	Mean \pm Standard Deviation n=68
Age (years)	75.9 \pm 6.9
Level of Education (years)	12.9 \pm 3.1
Gender (%)	
Male	54%
Female	46%
Body Mass Index (height/meters ²)	26.8 \pm 4.5
Total Number of Medications	7.2 \pm 4.2
Total Number of Co-Morbidities	6.6 \pm 2.7
General Depression Scale (Total Score)	2.0 \pm 1.9
Lawton Brody ADL Scale (Total Score)	5.91 \pm 7.3
Lawton Brody IADL Scale (Total Score)	7.69 \pm 1.2

Notes: ADL =Activities of Daily Living, IADL= Instrumental activities of daily living, n = sample size

Participants neuropsychological test scores are summarized in Table 3.2. Participants mean scores on global cognitive tests were consistent with a diagnosis for MCI since a pattern of normal MMSE scores (>26) of 28.2 (1.8) and low MoCA scores of 24.0 (3.1) was found among participants. Performance on Trial Making Test A (TMTA) and B (TMT B) and Rey Auditory Verbal Learning Test (RAVLT) were below normal ranges, while the mean performance in Digit Span Tests (DST), Letter Number Sequencing (LNS) and Boston Naming Test were within normative data for older adults

over 65 (Choi et al., 2014; Montero-Odasso et al., 2009 Strauss, Sherman & Spreen, 2006; Tombaugh, 2004).

Table 3.2: Descriptive statistics of neuropsychological tests (raw scores) in 68 participants with mild cognitive impairment

Variable	Mean \pm Standard Deviation
MMSE	28.2 \pm 1.8
MoCA	24.0 \pm 3.1
TMT A	48.1 \pm 16.1
TMT B	131.7 \pm 77.7
Δ TMT	83.6 \pm 68.5
DST-F	11.03 \pm 1.9
DST-B	7.03 \pm 2.3
Δ DST	4.0 \pm 2.2
LNS	7.6 \pm 2.5
RAVLT	4.75 \pm 2.8
BNT	13.5 \pm 1.3

Notes: MMSE= Mini Mental State Examination, MoCA= Montreal Cognitive Assessment, TMT=Trail Making Test, DST-F= Digit Span Test Forward, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ =delta

3.2 Gait Performance

3.2.1 Exclusion of Gait Variables

Pearson correlation analysis identified significant correlations between gait variables and the following variables were excluded due to their high correlation with the included measures. The excluded variables were step length, swing time and step time (Table 3.3).

Table 3.3: Pearson Correlation Matrix between all gait variables captured by the GAITRite® system.

Pearson Correlation Co-Efficient (p-values)									
	<i>Velocity</i>	<i>Stride Time</i>	<i>Step Time</i>	<i>Stride Length</i>	<i>Step Length</i>	<i>Double Support Time</i>	<i>Swing Time</i>	<i>Stride Width</i>	<i>Step Width</i>
<i>Velocity</i>	1	-0.643 (<0.001)	-0.508 (<0.001)	0.913 (<0.001)	0.912 (<0.001)	-0.685 (<0.001)	-0.155 (0.206)	-0.189 (0.122)	0.794 (<0.001)
<i>Stride Time</i>	-0.643 (<0.001)	1	0.821 (<0.001)	-0.293 (0.015)	-0.293 (<0.001)	0.598 (<0.001)	0.704 (<0.001)	0.052 (0.674)	-0.275 (0.028)
<i>Step time</i>	-0.508 (<0.001)	0.821 (<0.001)	1	-0.222 (0.68)	-0.223 (0.068)	0.449 (<0.001)	0.650 (<0.001)	-0.079 (0.522)	-0.201 (0.111)
<i>Stride Length</i>	0.913 (<0.001)	-0.293 (<0.001)	-0.222 (0.068)	1	0.999 (<0.001)	-0.559 (<0.001)	0.171 (0.163)	-0.206 (0.091)	0.862 (<0.001)
<i>Step Length</i>	0.912 (<0.001)	-0.293 (<0.001)	-0.223 (0.068)	0.999 (<0.001)	1	-0.560 (<0.001)	0.174 (0.156)	-0.211 (0.084)	0.0864 (<0.001)
<i>Double Support Time</i>	-0.685 (<0.001)	0.598 (<0.001)	0.449 (<0.001)	-0.559 (<0.001)	-0.560 (<0.001)	1	-0.023 (0.853)	0.234 (0.055)	-0.531 (<0.001)
<i>Swing Time</i>	-0.155 (<0.001)	0.704 (<0.001)	0.650 (<0.001)	0.171 (0.163)	0.174 (0.156)	-0.023 (0.853)	1	-0.200 (0.102)	0.183 (0.148)
<i>Stride Width</i>	-0.189 (0.122)	0.052 (0.674)	-0.079 (0.522)	-0.206 (0.91)	-0.211 (0.084)	0.236 (0.055)	-0.200 (0.102)	1	-0.086 (0.498)
<i>Step Width</i>	0.794 (<0.001)	-0.275 (0.028)	-0.201 (0.111)	0.862 (<0.001)	0.864 (<0.001)	-0.531 (<0.001)	0.183 (0.148)	-0.086 (0.498)	1

Note: bold values indicate statistical significance at $p < 0.05$

3.2.2 Effects of Dual-Task Testing

All participants were able to perform the walking tasks. The mean number of responses and errors during the dual task conditions are presented in Table 3.4. Mean and gait data during single and DT conditions (counting backwards by 1's, serial 7 subtractions and naming animals), as well as significant differences between each dual task condition are summarized in Table 3.5. There was a significant reduction in mean gait speed across all walking conditions ($p > 0.001$). The CoV and log transformed variables showed similar results. Mean CoV parameters, except for the CoV of double support time, were significantly increased across the four walking conditions ($p > 0.001$). Bonferroni correction analysis showed no significant difference between walking conditions and double support time variability.

Table 3.4: Response totals and errors for each dual task walking condition.

	Counting by 1's Gait	Serial 7 Subtractions Gait	Naming Animals Gait
Total Number of Responses			
Mean \pm SD	11.0 \pm 2.01	4.2 \pm 1.80	6.8 \pm 1.81
Total Number of Errors			
Mean \pm SD	.03 \pm .17	.51 \pm .89	----

Notes: SD= standard deviation

Table 3.5: One-way ANOVA with repeated measures for baseline gait characteristics for all walking conditions.

	Usual Gait	Counting by 1's Gait	Naming Animals Gait	Serial Seven's Gait	p-value
<i>Velocity</i>					
Mean (cm/s):	109.0 ± 21.3	103.5 ± 25.4	93.6 ± 26.6	88.2 ± 28.5	<.001
<i>Stride Time</i>					
Mean±SD(msec):	1146.2 ± 96.7	1212.6 ± 150.0	1307.2 ± 210.6 ^a	1402.0 ± 377.1 ^a	<.001
CoV(%)±SD:	2.6 ± 1.3	2.7 ± 2.0 ^a	4.4 ± 2.9 ^{a,b}	5.8 ± 5.6 ^b	<.001
CoV (log) ±SD:	0.41 ± 0.11	0.43 ± 0.30 ^a	0.64 ± 0.46 ^{a,b}	.076 ± 0.75 ^b	<.001
<i>Stride Length</i>					
Mean±SD (cm):	124.1 ± 19.3 ^a	123.5 ± 21.9 ^a	118.8 ± 24.4 ^b	117.2 ± 23.6 ^b	<.001
CoV(%)±SD:	3.4 ± 2.2 ^a	4.0 ± 2.3 ^{a,b}	4.6 ± 3.3 ^{a,b}	5.3 ± 4.5 ^b	<.001
CoV (log) ±SD:	0.53 ± 0.34 ^a	0.60 ± 0.36 ^{a,b}	0.66 ± 0.52 ^{a,b}	0.72 ± 0.65 ^b	<.001
<i>Double Support Time</i>					
Mean±SD (sec):	.37 ± .07	.39 ± .08	.44 ± .13	.47 ± .13	<.001
CoV(%)±SD:	7.5 ± 6.0 ^a	8.0 ± 4.2 ^a	8.3 ± 4.8 ^a	9.1 ± 5.2 ^a	.270
CoV (log) ±SD:	0.88 ± 0.78 ^a	0.90 ± 0.62 ^a	0.92 ± 0.68 ^a	0.96 ± 0.71 ^a	.091
<i>Step Width:</i>					
Mean±SD (cm)	63.9 ± 9.5 ^a	62.6 ± 10.0 ^a	60.4 ± 11.0 ^b	60.5 ± 11.1 ^b	<.001
CoV(%)±SD:	4.8 ± 2.5 ^a	5.7 ± 2.5 ^{a,b}	6.4 ± 3.5 ^b	7.1 ± 4.8 ^b	<.001
CoV (log) ±SD:	0.68 ± 0.40 ^a	0.75 ± 0.39 ^{a,b}	0.80 ± 0.54 ^b	0.85 ± 0.68 ^b	<.001

Notes: ± SD= standard deviation, one-way ANOVA (analysis of variance) with repeated measures CoV= coefficient of variation, statistical significance set at p<0.05, a,b denote statistically significant between group differences determined by the Bonferroni test, values with the same letter are not significantly different from one another, different letters or no letters indicate statistical differences.

3.2.3 Associations between Specific Cognitive Domains and Quantitative Gait Variables

Results from the unadjusted linear regression analysis comparing individual cognitive test scores on gait variables during single task and dual-task (DT) gait are presented in Appendix C. In brief, during the single task usual gait speed condition poor scores on measures of executive function (EF) and attention were significantly associated with increased (worse) double support time. Poorer scores on measures of working memory were significantly associated with increased (worse) stride time and poorer performance on language tests were associated with decreased (worse) stride length. During DT conditions, poorer performance on measures of attention, working memory, episodic memory and language were significantly associated with poorer gait performance.

In the adjusted linear regression analysis, during the single task usual walking speed condition increased double support time remained significantly associated with poorer scores on cognitive measures of attention and executive function (EF) (Table 3.6). During the dual-task (DT) conditions of counting backwards by 1's gait, poor performance on cognitive tests measuring attention remained significantly associated with decreased gait velocity and increased stride time. Poor performance on working memory tests remained significantly associated with decreased velocity and increases in stride time and double support time. Better scores on tests of episodic memory were significantly associated with decreases in double support time and better scores on tests assessing language were significantly associated with increased stride length (Table 3.7). During the DT condition of naming animals, decreased velocity and step width were associated with poor working memory scores (Table 3.8). During serial seven subtraction gait, no significant associations were found (Table 3.9).

Table 3.6: Adjusted linear regression analysis comparing the associations of cognitive test score on the outcome of gait variables during single task usual gait speed.

Unstandardized Regression Coefficients, (95% CI)					
	Gait Variables during single task gait:				
	Velocity (cm/s)	Stride Time (msec)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	-0.22 (-0.47, 0.03) p= .104	0.55 (-0.70, 1.8) p= .381	-0.181 (-0.44, 0.074) p= .161	1.18 (0.27 – 2.10) p= .012	-0.080 (-0.215 - 0.055) p=.240
ΔTMT	-0.024 (-0.082, 0.033) p= .399	0.100 (-0.186, 0.39) p= .486	-0.014 (-0.074, 0.045) p=.627	0.223 (0.016 - 0.44) p= .016	-0.015 (-0.046 - 0.016) p= .326
DST-B	0.72 (1.02, 2.46) p= .411	-4.06 (-12.68, 4.55) p= .349	0.41 (-1.38, 2.20) p= .649	-3.66 (-10.27 – 2.95) p=.273	0.21 (-0.754 – 1.18) p= .663
ΔDST	-1.02 (-2.88, 0.84) p= .278	5.20 (-4.02, 14.43) p= .264	-0.54 (-2.46, 1.39) p= .579	2.87 (-4.27 – 10.01) p= .425	-0.65 (-1.67 - 0.375) p= .210
LNS	1.89 (-0.38, 2.75) p= .134	0.39 (-7.52, 8.30) p= .921	1.50 (-0.142, 3.04) p= .074	-4.74 (-10.71 – 1.23) p= .117	0.55 (-0.313 – 1.42) p= .206
RAVLT	-0.15 (-1.61, 1.30) p= .833	-3.52 (-10.67, 3.63) p= .329	-0.54 (-2.02, 0.94) p= .470	-3.14 (-8.63 – 2.35) p= .257	-0.056 (-0.84 - 0.73) p= .887
BNT	1.67 (-1.40, 4.74) p= .280	6.53 (-8.74, 21.81) p= .396	2.91 (-0.182, 5.99) p= .065	-7.77 (-19.44 – 3.90) p= .188	1.48 (-0.179 – 3.13) p= .080

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities; TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.

Table 3.7: Adjusted linear regression analysis comparing the association of cognitive test scores on the outcome of gait variables during dual task testing using a secondary task of counting backwards by 1's.

Unstandardized Regression Coefficients, (95% CI)					
	Gait Variables during counting by 1's gait:				
	Velocity (cm/s)	Stride Time (msec)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	-0.40 (-0.728, -0.064) p= .020	2.17 (-0.002, 4.34) p= .050	-0.22 (-0.510, 0.073) p= .137	0.59 (-0.57, 1.76) p= .312	-0.11 (-.247, .031) p=.124
ΔTMT	-0.058 (-0.136, 0.020) p= .140	.41 (-0.096, 0.908) p=.111	-0.024 (-0.092, 0.045) p= .496	0.26 (0.001, 0.522) p= .001	-0.013 (-0.045, 0.020) p= .440
DST-B	2.26 (-0.073, 4.59) p= .057	-16.42 (-31.33, -1.50) p= .032	0.880 (-1.19, 2.96) p= .399	-5.35 (-13.37, 2.65) p=.186	0.076 (-0.927, 1.08) p= .880
ΔDST	-3.0 (-5.45, -0.512) p= .019	22.18 (6.51, 37.85) p= .006	-1.15 (-3.37, 1.07) p= .304	10.23 (1.88, 18.56) p= .017	0.75 (-1.80, 0.309) p= .162
LNS	1.80 (-0.35, 3.94) p= .099	-4.48 (-18.58, 9.62) p= .528	1.70 (-0.156, 3.55) p= .072	-4.04 (-11.39, 3.31) p= .276	0.47 (-0.49, 1.37) p= .298
RAVLT	0.12 (-1.88, 2.12) p= .906	-7.90 (-20.63, 4.83) p= .220	-0.47 (-2.20, 1.26) p= .593	-6.75 (-13.29, -0.22) p=.043	-0.24 (-1.05, 0.57) p= .557
BNT	3.08 (-1.11, 7.26) p=.147	-3.85 (-31.30, 23.61) p=.780	3.79 (.22, 7.35) p= .038	-10.57 (-24.72, 3.58) .140	1.21 (-.527, 2.94) p=.169

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities; TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.

Table 3.8: Adjusted linear regression analysis comparing the association of cognitive test scores on the outcome of gait variables during dual task testing using a secondary task of naming animal's.

Unstandardized Regression Coefficients, (95% CI)					
	Gait Variables during naming animal's gait:				
	Velocity (cm/s)	Stride Time (msec)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	-0.27 (-0.64, 0.11) p= .159	2.64 (-0.58, 5.87) p= .106	-0.120 (-0.45, 0.22) p= .477	0.93 (-1.04, 2.90) p=.351	-.096 (-0.250, 0.058) p= .219
ΔTMT	-0.043 (-.13, 0.041) p= .310	0.46 (-0.28, 1.20) p= .223	-0.007 (-0.083, 0.070) p=.864	0.300 (-0.14, 0.74) p= .181	-0.011 (-0.047, 0.025) p= .543
DST-B	1.80 (-0.76, 4.36) p= .164	-8.15 (-30.75, 14.46) p= .474	1.14 (-1.15, 3.44) p= .324	-2.73 (-16.34, 10.90) p= .690	0.45 (-0.65, 1.5) p= .414
ΔDST	-3.36 (-6.02, -0.681) p= .015	20.08 (-3.90, 44.06) p= .099	-2.01 (-4.46, 0.45) p= .107	11.16 (-3.30, 24.63) p= .128	-1.20 (-2.35, -0.060) p= .039
LNS	1.06 (-1.33, 3.46) p= .378	-3.05 (-24.11, 18.01) p= .773	1.34 (-0.788, 3.46) p= .213	-4.49 (-17.01, 8.23) p= .489	0.48 (-0.512, 1.48) p=.335
RAVLT	0.008 (-2.14, 2.16) p= .994	-11.23 (-28.6, 7.30) p= .230	-0.76 (-0.267, 1.14) p=.427	-8.42 (-19.48, 2.65) p= .133	-0.23 (-1.13, 0.660) p= .602
BNT	1.77 (-2.78, 6.33) p= .440	-9.40 (-49.34, 30.56) p= .640	20.74 (-1.29, 6.77) p= .178	-20.75 (-44.20, 2.71) p= .082	0.99 (-0.938, 2.91) p= .309

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities;
TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.

Table 3.9: Adjusted linear regression analysis comparing the association of cognitive test scores on the outcome of gait variables during dual task testing using a secondary task of serial seven subtractions.

Unstandardized Regression Coefficients, (95% CI)					
	Gait Variables during serial seven subtraction gait:				
	Velocity (cm/s)	Stride Time (msec)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	-0.38 (-0.800, 0.047) p= .081	3.12 (-2.82, 9.22) p= .293	-0.18 (-0.51, 0.151) p= .280	0.69 (-1.32, 2.69) p= .497	-0.12 (-0.28, 0.042) p= .146
ΔTMT	-0.064 (-0.62, 0.034) p=.197	0.52 (-.86, 1.91) p= .452	-0.021 (-0.097, 0.055) p= .584	0.33 (-0.12, 0.78) p= .149	-0.019 (0-.056, 0.018) p= .305
DST-B	1.93 (-1.03, 5.0) p= .197	-16.34 (-58.2, 25.52) p= .438	1.10 (-1.12, 3.40) p= .342	-2.79 (-16.67, 11.11) p= .690	0.45 (-0.70, 1.59) p= .437
ΔDST	-0.85 (-7.03, 5.33) p= .785	-5.01 (-91.61, 81.43) p= .907	-0.076 (-4.83, 4.69) p= .975	12.21 (-16.22, 40.63) p= .394	-.302 (-2.61, 2.0) p= .794
LNS	1.01 (-1.73, 3.74) p= .465	-5.37 (-43.74, 33.0) p= .781	1.36 (-0.73, 3.44) p= .199	-2.46 (-15.13, 10.22) p= .700	0.65 (-0.38, 1.67) p=.213
RAVLT	-0.52 (-3.02, 1.98) p= .678	11.10 (-23.77, 45.98) p= .527	-0.83 (-2.74, 1.09) p= .392	-1.66 (-13.22, 9.90) p= .775	-0.15 (-1.06, 0.78) p= .752
BNT	1.23 (-4.1, 6.55) p= .646	11.63 (-62.89, 86.15) p= .756	2.12 (-2.0, 6.19) p= .302	-4.12 (-28.79, 20.46) p= .737	1.08 (-0.91, 3.07) p= .282

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities; TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.

3.2.4 Associations between Specific Cognitive Domains and Gait Variability Parameters

Overall, a greater number of associations were found between deficits in cognitive performance and increases in gait variability parameters across all walking conditions with the exception of serial subtractions gait. Stride time variability (STV) was found to be the most consistent gait variability parameter, associated with the most cognitive domains across single and the three DT conditions. Results from the unadjusted linear regression analysis comparing the associations of individual cognitive domains on an outcome of gait variability are presented in Appendix D. In brief, during single task usual gait poor performance in measures of EF and working memory were significantly associated with worse gait performance in STV and stride length variability. During DT conditions, deficits in EF, attention, working memory, episodic memory and language were all significantly associated with increases in gait variability parameters.

In the adjusted linear regression analysis, during single task usual gait speed deficits in EF and working memory were significantly associated with increases in the variability of stride time and stride length. Double support time showed statistically significant associations with deficits in working memory and episodic memory (Table 3.10). During the DT walking condition of counting backwards by 1's deficits in EF were significantly associated with increases in STV. Deficits in attentional cognitive domains were significantly associated with increases in STV and stride length variability. Poorer scores on measures of working memory were associated with increases in STV, stride length variability and double support time variability. Better performance on tests of episodic memory was associated with decreases in STV and double support time variability (Table 3.11). During the DT walking condition of naming animals, deficits in attentional domains were significantly associated with increased STV and stride length variability. Poorer performance on tests of working memory was associated with increased STV, stride length variability and step width variability. Better scores on tests of the language domain were significantly associated with decreased STV (Table 3.12).

There remained no significant associations found during serial seven subtraction gait between cognitive test scores and gait variability measures (Table 3.13).

Table 3.10: Adjusted linear regression analysis comparing the association of cognitive test scores on the outcome of gait variability during single task usual gait speed.

Unstandardized Regression Coefficients, (95% CI)				
	Gait Variability during single task gait (log):			
	Stride Time (msec)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	0.0024 (-0.003, 0.003) p= .987	0.001 (-0.004, 0.006) p= .729	0.000 (-0.004, 0.004) p= .927	-0.001 (-0.004, 0.002) p= 0.550
ΔTMT	0.001 (0.00, 0.001) p= .045	0.001 (0.00, 0.002) p= .023	0.001 (0.00, 0.002) p= .059	0.00 (0.00, 0.001) p= .234
DST-B	-0.014 (-0.034, 0.007) p= .185	-0.020 (-0.054, 0.014) p= .234	0.001 (-0.026, 0.028) p= .945	-0.004 (-0.027, 0.020) p= .763
ΔDST	0.049 (0.008, 0.089) p= .020	0.080 (0.012, 0.148) p= .022	0.054 (0.001, 0.108) p= .046	0.039 (-0.007, 0.085) p= .097
LNS	-0.031 (-0.048, -0.014) p= .001	-0.047 (-0.076, -0.018) p= .002	-0.022 (-0.046, 0.002) p= .075	-0.019 (-0.040, 0.002) p= .071
RAVLT	-0.014 (-0.031, 0.003) p= .094	-0.023 (-0.051, 0.005) p= .106	0.013 (-0.010, 0.035) p= .026	-0.017 (-0.036, 0.001) p= .069
BNT	-0.002 (-0.039, 0.034) p= .903	-0.005 (-0.066, 0.056) p= .866	-0.039 (-0.086, 0.008) p= .099	0.006 (-0.035, 0.047) p= .777

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities; TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.

Table 3.11: Adjusted linear regression analysis comparing the association of cognitive test scores on the outcome of gait variability during dual task testing using a secondary task of counting backwards by 1's.

Unstandardized Regression Coefficients, (95% CI)				
	Gait Variability during counting by 1's gait (log):			
	Stride Time (msec)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	0.004 (0.00, 0.007) p= .026	0.006 (0.002, 0.010) p= .002	0.002 (-0.002, 0.005) p= .349	0.002 (0.00, 0.005) p= .071
ΔTMT	0.001 (0.00, 0.002) p= .006	0.001 (0.00, 0.002) p= .081	0.001 (0.00, 0.001) p= .168	0.00 (0.00, 0.001) p= .259
DST-B	-0.023 (-0.046, -0.001) p= .043	-0.030 (-0.057, -0.003) p= .030	-0.015 (-0.037, 0.008) p= .192	-0.010 (-0.029, 0.010) p= .322
ΔDST	0.025 (0.001, 0.049) p= .041	0.015 (-0.016, 0.045) p= .338	0.006 (-0.018, 0.030) p= .599	0.005 (-0.016, 0.026) p= .647
LNS	-0.017 (-0.038, 0.003) p= .101	-0.037 (-0.061, -0.013) p= .003	-0.024 (-0.044, -0.005) p= .016	-0.014 (-0.031, 0.003) p= .106
RAVLT	-0.023 (-0.042, -0.005) p= .013	-0.012 (-0.035, 0.012) p= .318	-0.023 (-0.041, 0.005) p= .012	-0.011 (-0.023, 0.005) p= .115
BNT	-0.031 (-0.071, 0.101) p= .134	-0.030 (-0.079, 0.019) p= .231	-0.025 (-0.064, 0.014) p= .209	0.009 (-0.034, 0.34) p= .996

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities; TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.

Table 3.12: Adjusted linear regression analysis comparing the association of cognitive test scores on the outcome of gait variability during dual task testing using a secondary task of naming animal's.

Unstandardized Regression Coefficients, (95% CI)				
	Gait Variability during naming animal's gait (log):			
	Stride Time (msec)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	0.006 (0.001, 0.010) p= .011	0.003 (-0.001, 0.007) p= .181	0.00 (-0.003, 0.004) p= .949	0.002 (-0.002, 0.005) p=.282
ΔTMT	-0.004 (-0.010, 0.001) p= .122	-0.003 (-0.009, 0.002) p= .218	-0.001 (-0.006, 0.003) p= .565	-0.001 (-0.006, 0.004) p= .636
DST-B	-0.018 (-0.048, 0.012) p= .236	-0.029 (-0.056, -0.002) p= .037	-0.003 (-0.028, 0.021) p= .777	-0.022 (-0.046, 0.003) p= .081
ΔDST	0.025 (-0.008, 0.057) p= .131	0.042 (0.014, 0.071) p= .004	0.009 (-0.017, 0.036) p= .492	0.044 (0.020, 0.068) p= .001
LNS	-0.029 (-0.057, -0.002) p= .038	-0.021 (-0.047, 0.004) p=.101	-0.004 (-0.026, 0.019) p= .745	-0.011 (-0.033, 0.012) p= .348
RAVLT	-0.004 (-0.029, 0.022) p= .767	-0.009 (-0.032, 0.015) p= .464	0.002 (-0.018, 0.023) p= .817	-0.101 (-0.030, 0.010) p= .331
BNT	-0.067 (-0.118, -0.015) p= .012	-0.026 (-0.076, 0.023) p= .293	-0.018 (-0.061, 0.025) p= .410	-0.018 (-0.062, 0.025) p= .404

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities; TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.

Table 3.13: Adjusted linear regression analysis comparing the association of cognitive test scores on the outcome of gait variability during dual task testing using a secondary task of serial seven subtractions

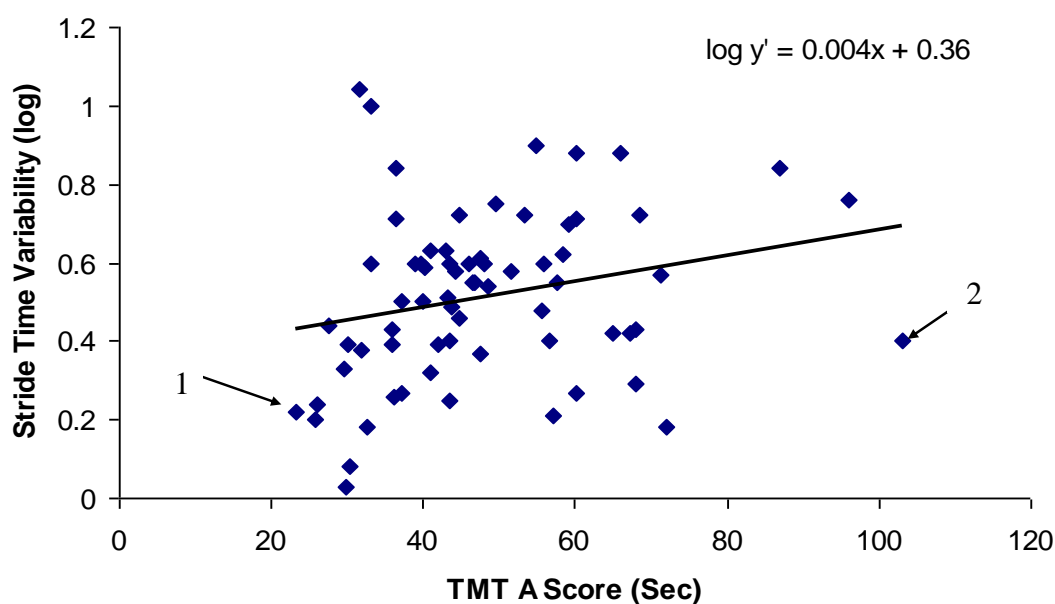
Unstandardized Regression Coefficients, (95% CI)				
	Gait Variability during serial seven subtraction gait (log):			
	Stride Time (msec)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	0.003 (-0.002, 0.007) p= .237	0.00 (-0.004, 0.005) p= .832	-0.002 (-0.006, 0.002) p= .382	0.001 (-0.003, 0.005) p= .620
ΔTMT	0.001 (-0.001, 0.002) p= .326	0.00 (-0.001, 0.001) p= .724	0.00 (-0.001, 0.001) p= .561	0.00 (-0.001, 0.001) p= .491
DST-B	-0.005 (-0.037- 0.028) p= .769	-0.025 (-0.056, 0.006) p= .110	0.010 (-0.017, 0.037) p= .472	-0.010 (-0.039, 0.018) p= .467
ΔDST	0.029 (-0.005, 0.064) p= .091	0.029 (-0.004, 0.062) p= .085	0.007 (-0.022, .036) p= .635	0.022 (-0.008, 0.057) p= .152
LNS	-0.008 (-0.037, 0.022) p= .613	-0.016 (-0.045, 0.012) p= .252	0.011 (-0.013, 0.036) p= .356	-0.007 (-0.033, 0.018) p= .568
RAVLT	0.016 (-0.011, -0.043) p= .245	-0.001 (-0.028, 0.025) p= .916	0.011 (-0.012, 0.033) p= .338	-0.002 (-0.025, 0.021) p= .859
BNT	-0.023 (-0.080, 0.035) p=.435	0.042 (-0.013, 0.097) p= .128	0.033 (-0.015, 0.080) p= .174	0.036 (-0.013, 0.085) p= .149

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities; TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.

3.2.5 Interpretations of Log Transformations

The log transformed variables do not make intuitive sense for clinical applications; therefore, examples of patients with good and poor cognitive test scores were selected to assist with the interpretation of the results for the gait variability regression analysis. STV and stride length variability were selected because they were found to be the most consistent of all variables in terms of associations with cognitive test scores. Since the dependant variable is log transformed and the independent variable is not, the beta co-efficient can be interpreted as: every 1 unit change in the independent variable is expected to multiply the original dependent variable by 10^b , where b is the beta co-efficient.

Figure 3.1: Linear regression analysis for the association of raw Trail Making Test A scores on the outcome of stride time variability (log) during counting backwards by 1's gait.



Notes: Cases numbered are ones used in example calculations, 1= good cognitive test score; 2= poor cognitive test score, y' = predicted dependant variable score

Trail Making Test A (attention):

An individual with a good cognitive score on a measure of attention (23.16 seconds) would be predicted to have a STV value of 2.88:

$$\text{Log } y' = B_1X_1 + a$$

$$\text{Log } y' = 0.004x + 0.36$$

$$\text{Log } y' = 0.004(23.16) + 0.36$$

$$\text{Log } y' = 0.457$$

Transformation back to original CoV %:

$$y' = 10^{0.457}$$

$$y' = 2.88$$

An individual with a poor cognitive score on a measure of attention (103 seconds) would be predicted to have a STV value of 5.86:

$$\text{Log } y' = B_1X_1 + a$$

$$\text{Log } y' = 0.004x + 0.36$$

$$\text{Log } y' = 0.004(103) + 0.36$$

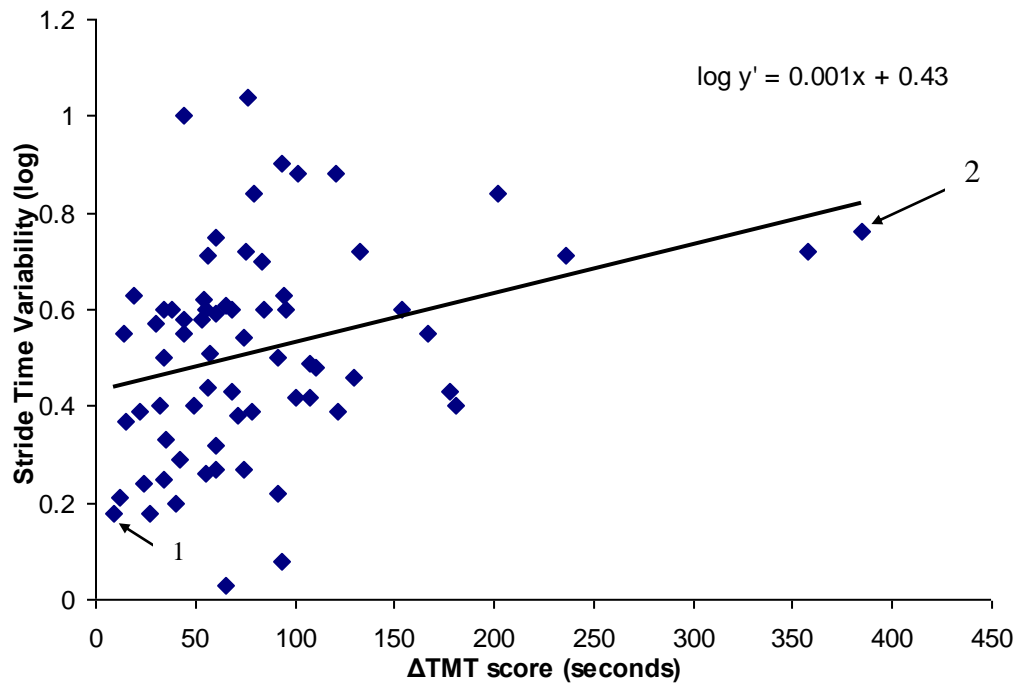
$$\text{Log } y' = 0.786$$

Transformation back to original CoV%:

$$y' = 10^{0.786}$$

$$y' = 5.86$$

Figure 3.2: Linear regression analysis for the association of raw Δ Trail Making Test scores on the outcome of stride time variability (log) during counting backwards by 1's gait.



Notes: Cases numbered are ones used in example calculations, 1= good cognitive test score, 2= poor cognitive test score, y= predicted dependent variable

Δ Trail Making Test (EF):

An individual with a good cognitive score on a measure of EF (9 seconds) would be predicted to have a STV value of 2.75:

$$\text{Log } y' = B_1 X_1 + a$$

$$\text{Log } y' = 0.001x + 0.43$$

$$\text{Log } y' = 0.001(9) + 0.43$$

$$\text{Log } y' = 0.439$$

Transformation back to original CoV %:

$$y' = 10^{0.439}$$

$$y' = 2.75$$

An individual with a poor cognitive score on a measure of EF (385 seconds) would be predicted to have a STV value of 6.53:

$$\text{Log } y' = B_1 X_1 + a$$

$$\text{Log } y' = 0.001x + 0.43$$

$$\text{Log } y' = 0.001(385) + 0.43$$

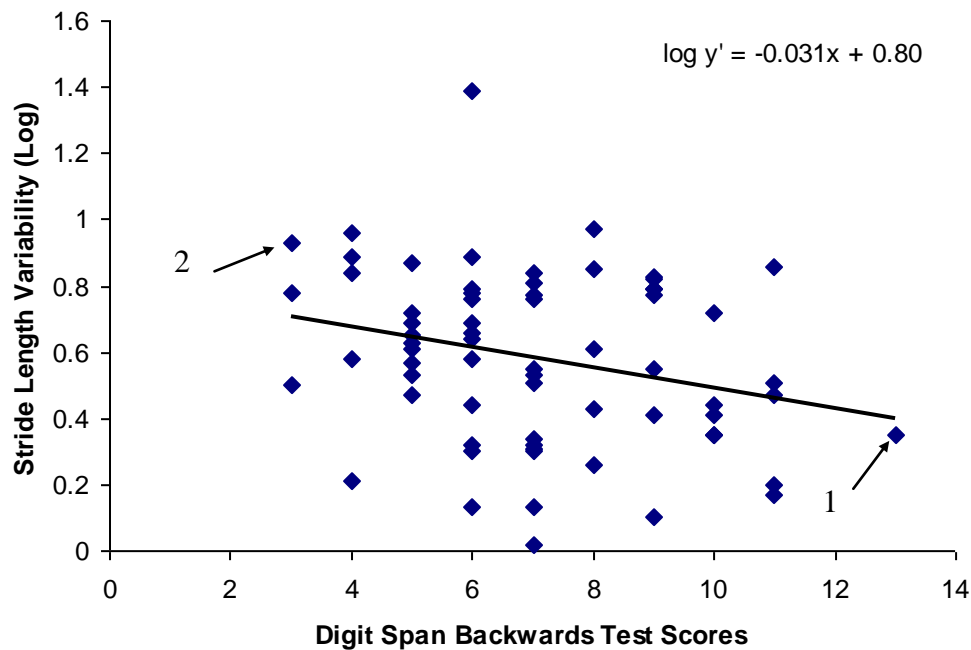
$$\text{Log } y' = 0.815$$

Transformation back to original CoV%:

$$Y' = 100^{0.815}$$

$$Y' = 6.53$$

Figure 3.3: Linear regression analysis for the association of raw Digit Span Test backwards scores on the outcome of stride length variability (log) during naming animal's gait.



Notes: Cases numbered are ones used in example calculations, 1= good cognitive test score, 2= poor cognitive test score, y' = predicted dependent variable score

Digit Span Test Backwards (attention):

An individual with a good cognitive score on another measure of attention (13) would be predicted to have a stride length variability value of 2.49

$$\text{Log } y' = B_1 X_1 + a$$

$$\text{Log } y' = -0.031x + 0.80$$

$$\text{Log } y' = -0.031(13) + 0.80$$

$$\text{Log } y' = 0.397$$

Transformation back to original CoV %:

$$y' = 10^{0.397}$$

$$y' = 2.49$$

An individual with a poor cognitive score on a measure of attention (3) would be predicted to have a stride length variability value of 5.09:

$$\text{Log } y' = B_1X_1 + a$$

$$\text{Log } y' = -0.031x + 0.80$$

$$\text{Log } y' = -0.031(3) + 0.80$$

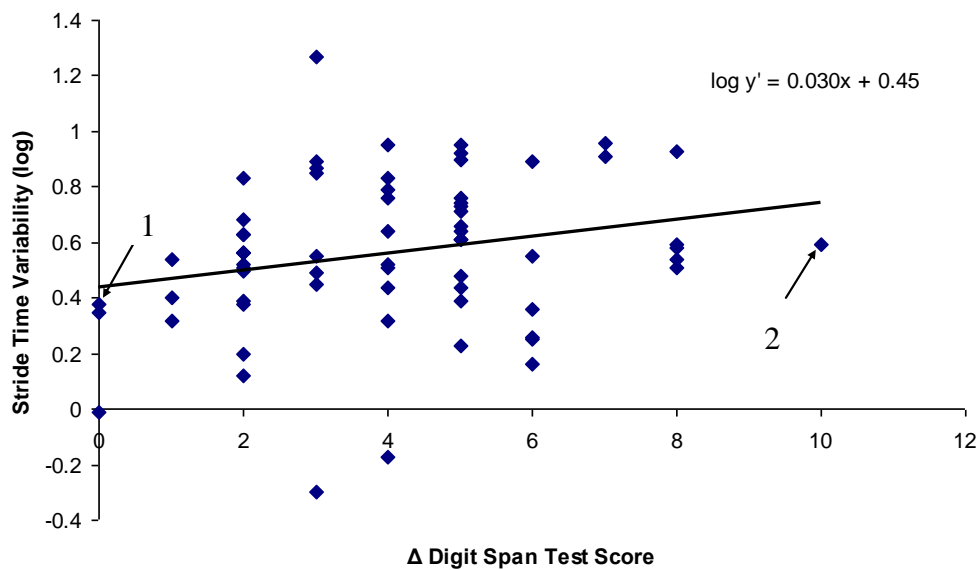
$$\text{Log } y' = 0.707$$

Transformation back to original CoV%:

$$y' = 10^{0.707}$$

$$y' = 5.09$$

Figure 3.4: Linear regression analysis for the association of raw Δ Digit Span test scores on the outcome of stride time variability (log) during naming animal's gait.



Notes: Cases numbered are ones used in example calculations, 1= good cognitive test score, 2= poor cognitive test score, y' = predicted dependent variable score

Δ Digit Span Test (working memory):

An individual with a good cognitive score on a measure of working memory (0) would be predicted to have a STV value of 1.11:

$$\text{Log } y' = B_1X_1 + a$$

$$\text{Log } y' = 0.030x + 0.045$$

$$\text{Log } y' = 0.030(0) + 0.045$$

$$\text{Log } y' = 0.045$$

Transformation back to original CoV %:

$$y' = 10^{0.045}$$

$$y' = 1.11$$

An individual with a poor cognitive score on a measure of working memory (10) would be predicted to have a STV value of 2.21:

$$\text{Log } y' = B_1X_1 + a$$

$$\text{Log } y' = 0.030x + 0.045$$

$$\text{Log } y' = 0.030(10) + 0.045$$

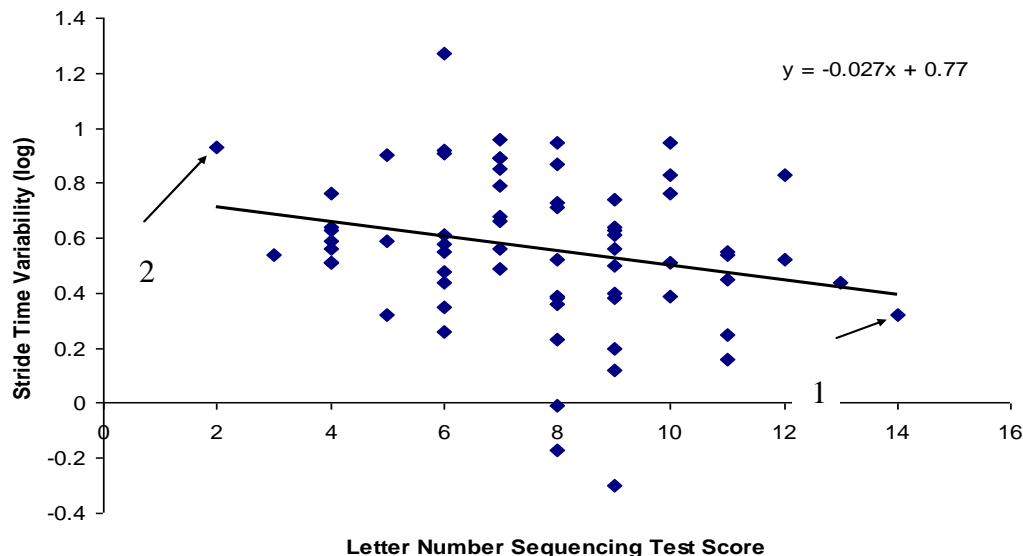
$$\text{Log } y' = 0.345$$

Transformation back to original CoV%:

$$y' = 10^{0.345}$$

$$y' = 2.21$$

Figure 3.5: Linear regression analysis for the association of raw Letter Number Sequencing Test scores on the outcome of stride time variability (log) during naming animal's gait.



Notes: Cases numbered are ones used in example calculations; 1= good cognitive test score; 2= poor cognitive test score, y' = predicted dependent variable

Letter Number Sequencing Test (working memory):

An individual with a good cognitive score on a measure of working (14) would be predicted to have a STV value of 2.47

$$\text{Log } y' = B_1X_1 + a$$

$$\text{Log } y' = -0.027x + 0.77$$

$$\text{Log } y' = -0.027(14) + 0.77$$

$$\text{Log } y' = 0.392$$

Transformation back to original CoV %:

$$y' = 10^{0.392}$$

$$y' = 2.47$$

An individual with a poor cognitive score on a measure of working memory (2) would be predicted to have a STV value of 5.20:

$$\text{Log } y' = B_1X_1 + a$$

$$\text{Log } y' = -0.027x + 0.77$$

$$\text{Log } y' = -0.027(2) + 0.77$$

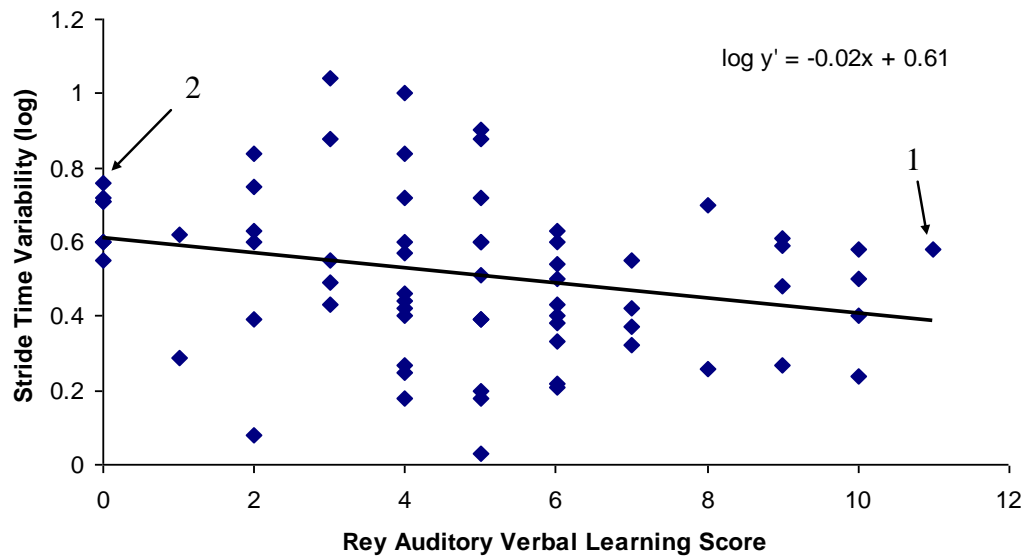
$$\text{Log } y' = 0.716$$

Transformation back to original CoV%:

$$y' = 10^{0.716}$$

$$y' = 5.20$$

Figure 3.6: Linear regression analysis for the association of raw Rey Auditory Verbal Learning Test Scores on the outcome of stride time variability (log) during counting backwards by 1's gait.



Notes: Cases numbered are ones used in example calculations, 1= good cognitive test score, 2= poor cognitive test score, y' = predicted dependent variable score

Rey Auditory Verbal Learning Test (episodic memory):

An individual with a good cognitive score on a measure of episodic memory (11) would be predicted to have a STV value of 2.45:

$$\text{Log } y' = B_1 X_1 + a$$

$$\text{Log } y' = -0.02x + 0.61$$

$$\text{Log } y' = -0.02(11) + 0.61$$

$$\text{Log } y' = 0.457$$

Transformation back to original CoV %:

$$y' = 10^{0.457}$$

$$y' = 2.45$$

An individual with a poor cognitive score on a measure of episodic memory (0) would be predicted to have a STV value of 4.07:

$$\text{Log } y' = B_1 X_1 + a$$

$$\text{Log } y' = -0.02x + 0.61$$

$$\text{Log } y' = -0.02(0) + 0.61$$

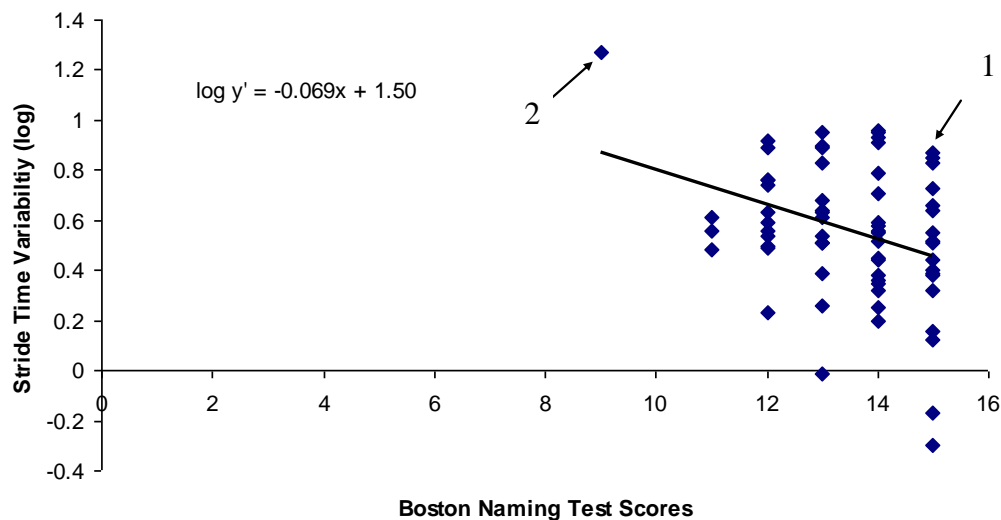
$$\text{Log } y' = 0.39$$

Transformation back to original CoV%:

$$y' = 10^{0.39}$$

$$y' = 4.07$$

Figure 3.7: Linear regression analysis for the association of raw Boston Naming Test scores on the outcome of stride time variability (log) during counting backwards by 1's gait.



Notes: Cases numbered are ones used in example calculations; 1= good cognitive test score; 2= poor cognitive test score

Boston Naming Test (language):

An individual with a good cognitive score on a measure of language (15) would be predicted to have a STV value of 2.92:

$$\text{Log } y' = B_1X_1 + a$$

$$\text{Log } y' = -0.069x + 1.5$$

$$\text{Log } y' = -0.069(15) + 1.5$$

$$\text{Log } y' = 0.465$$

Transformation back to original CoV %:

$$y' = 10^{0.465}$$

$$y' = 2.92$$

An individual with a poor cognitive score on a measure of language (9) would be predicted to have a STV value of 7.57:

$$\text{Log } y' = B_1X_1 + a$$

$$\text{Log } y' = -0.069x + 1.5$$

$$\text{Log } y' = -0.069(9) + 1.5$$

$$\text{Log } y' = 0.879$$

Transformation back to original CoV%:

$$y' = 10^{0.879}$$

$$y' = 7.57$$

Chapter 4: DISCUSSION

4.1 General Discussion

The overall goal of this study was to evaluate the associations between a wide range of specific cognitive domains and quantitative gait variables during single and dual-task (DT) test conditions. All three hypotheses were confirmed at the conclusion of this study. The present study has demonstrated that deficits in cognitive domains beyond executive function (EF) including memory and language are associated with quantitative gait measures. Previous studies have been limited in the measures of cognition evaluated, focusing almost exclusively on EF and attention, the present study has demonstrated that poor performance on tests evaluating working memory, episodic memory and language are also associated with DT declines in gait performance. This study has also demonstrated that measures of gait variability can be a more sensitive marker compared with mean values as It had a greater number of associations between cognitive domains when compared to mean values in individuals with mild cognitive impairment (MCI). Since DT conditions are used to assess shared cognitive resources during gait performance and stride-to-stride variations in gait are a reflection of dynamic gait regulation and stability, our results suggest that in our MCI sample gait regulation is indeed controlled by a number of higher level cognitive functions including resources from memory and language domains. Deficits in these cognitive domains may predispose an individual to gait abnormalities.

Our findings indicating deficits in memory and language were related to gait performance in addition to measures of EF and attention confirmed the first hypothesis. Of interest, DT test conditions were required to demonstrate additional relationships between deficits in language and memory domains and gait performance using quantitative gait measures. To explain why aspects of gait would be affected by the addition of a secondary task and how gait would be related to tests of cognition through the capacity sharing DT theory provides a framework to explain why gait is affected.... This model states that information processing centers have limited mental resources shared among tasks and the processing capacity decreases with the addition of a

secondary task leading to a decrease in one or both tasks (Pashler, 1994; McLoed, 1977; Tombu & Jolicoeur, 2003). Age- related deterioration to physiological systems controlling and maintaining gait create a greater need to recruit higher level cognitive functions to properly integrate information necessary to regulate gait and dynamic stability (Hausdorff et al., 2005). Thus, DT changes in gait, especially those requiring involvement of multiple cognitive skills highlights the shared higher level neural networks between gait regulation and cognition.

As hypothesized, gait variability demonstrated in the linear regression analysis more associations between cognitive domains than mean gait variables in MCI. Of the four gait variability parameters, stride time variability (STV) was the most consistent gait parameter demonstrating associations among the most cognitive domains. Revisiting the original hypothesis proposed by Gabell & Nayak (1984), STV and stride length variability are considered a reflection of the automatic stepping mechanisms, controlled by the brainstem and basal ganglia (Rosano et al., 2007). These variables are considered highly dependent on cortical control and less affected by musculoskeletal performance (Beauchet et al., 2005; Montero-Odasso et al., 2012). Variability in step width and double support time are primarily determined by balance control mechanisms (Gabell & Nayak, 1984). In the adjusted analysis, only the temporal parameter of double support time was associated with impairments in EF and attention during single task gait. The EF and attention cognitive tests used were timed, which may in part explain some of the associations found with temporal gait parameters. Meanwhile, both spatial and temporal gait variability parameters were able to detect associations between impairments in EF, attention, working memory and episodic memory during the same walking condition. These results suggest gait variability may be a better expression and more sensitive marker of the role of cortical resources during simple and dual gait tasks in MCI.

The significant declines in gait velocity and increases in gait variability while engaging in DT task activities found in our sample are consistent with previous research. The results adds further support to gait performance in healthy older adult and patient populations is less automatic and more dependant on cognitive control. (Beauchet et al.,

2005; Hausdorff et al., 2005; Hausdorff et al., 2008; Montero-Odasso et al., 2012; Muir et al., 2012; Sheridan et al., 2007; Woollacott & Shumway-Cook, 2002; Srygley, Mierlman, Herman, Giladi & Hausdorff, 2009; van Iersel et al., 2008). The present findings are consistent with other reports demonstrating gait performance declined as DT test conditions increased in complexity (Montero-Odasso et al., 2012; Muir et al., 2012; Woollacott & Shumway-Cook, 2002). Increases in gait variability seen during DT test conditions reflects failure of automatic stepping and balance mechanisms (Nutt et al., 1993), as a result of limited shared attentional capacities between cortical gait control and secondary cognitive tasks. Another possible explanation for the observed DT declines in gait could be a result of task prioritization. When asked to perform walking and cognitive tasks concurrently, our population may inappropriately allocate attentional resources, sacrificing resources needed for stable gait by using a “posture second” strategy (Bloem et al., 2006).

Many researchers argue that gait is an over-learned automatic task requiring little or no higher level cognitive resources (Christensen et al., 2000; Fukuyama et al., 1997). We found relationships between impairments in EF and memory with increases in gait variability even during single task gait. Our results are in part consistent with the results of Persaud et al. (1995) and Hausdorff et al. (2005) suggesting that routine walking can be considered a complex motor task requiring higher level cognitive input, especially in older adults.

EF is associated with areas in the frontal lobe, primarily the dorso-lateral prefrontal cortex and also plays an important role in older adults’ ability to divide attention (Sheridan et al., 2003; Woollcott & Shumway-cook, 2002; Yogev-Seligman et al., 2008). Executive dysfunction is considered a pervasive feature in AD (Sheridan et al., 2003) and has been associated with increased fall risk in the elderly (Herman et al., 2010; Mierlman et al., 2012; Springer et al., 2006). Similar to other studies, we found associations between deficits in EF and attention with increases in gait variability during single and DT conditions (Ble et al., 2005; Hausdorff et al., 2005; Holtzer et al., 2012; Persaud et al., 1995; Sheridan, 2003). A probable explanation for finding associations

between EF, attention and gait performance is that EF may be a central component of the ability to divide attention and maintain safe gait and goal oriented walking control systems (Ble et al., 2005; Yogev-Seligmann et al., 2008). These findings may partially explain why increases in gait variability would be related to fall risk and also help explain why DT conditions would increase gait variability in those with EF dysfunction (Hausdorff et al., 2003; Sheridan et al., 2003). Additionally, deficits in EF have been suggested to predict gait impairments although no definitive relationship has been demonstrated (Yogev-Seligmann et al., 2008). Our results demonstrated that deficits in EF were associated with gait abnormalities expressed through increased variability in stride time and stride length during simple and DT walking.

We found associations with measures of working memory and increased double support time variability and step width variability. These findings are consistent with results from previous studies showing that difficulty maintaining balance was associated with atrophy in the parietal cortex (Rosano, Aizenstein, Studenski & Newman, 2007; Rosano et al., 2008). It is possible that deficits in this cortical region may impair balance regulation and increased variability in these measures may be to compensate for these deficits (Rosano et al., 2008).

Hippocampal atrophy is related to memory impairments and is characteristic in MCI and AD (Du et al., 2001; Jack et al., 1999; Petersen, 2001). Studies have suggested the hippocampus also plays an essential role in locomotion through connections with the prefrontal cortex (Knight, 1996; Scherder et al., 2007; Song, Kim, Kim & Jung, 2005; Zimmerman et al., 2009). Studies identifying associations between memory deficits and decreased gait velocity (Holtzer et al., 2012; Mielke et al., 2013; Montero-Odasso et al., 2009; Verghese et al., 2007; Watson et al., 2010), as well as gait variability (Hausdorff et al., 2008) were consistent with our results. We found associations between deficits in episodic memory and increased variability in stride time and double support time during DT circumstances. Conversely, a number of studies have found no associations with memory function and gait disturbances (Hausdorff et al., 2005; Herman et al., 2010; Holtzer et al., 2006; Mierlman et al., 2012; Persaud et al.,

2008 Springer et al., 2006; van Iersel et al., 2008). Safe and stable locomotion through an environment relies on the integration of visual, vestibular and proprioceptive information (Hausdorff et al., 2008). The hippocampus is involved with all of these functions and shares close neural connections with the prefrontal cortex, an area involved with EF (Malouin et al., 2003). Thus, our results support the idea that memory retrieval and encoding in the hippocampus uses shared networks as those which maintain dynamic gait and stability, particularly in challenging or unfamiliar environments.

Additionally, previous studies have found that working and episodic memory are the first functions compromised in AD (Aggarwal et al., 2005; Petersen et al., 2001). A recent study showed that deficits in working memory can be a marker of progression to dementia in people with MCI (Missonnier et al., 2005) and other studies have shown that the presence and severity of episodic memory deficits in MCI was more robustly related to risk of AD than impairment in other domains (Aggarwal et al., 2005; Jack et al., 1999). The results from this study support future research on the prognostic utility of the associations found in predicting those who at high risk for progression to dementia.

As described previously, the cortical and sub-cortical control of gait is not well understood. Neuro-imaging studies have shown increased gait variability (i.e., stride time, stride length) and poor balance are primarily related to deficits in the frontal and temporal lobes, white matter abnormalities, brain infarcts and basal ganglia dysfunction (Guo et al., 2001; Malouin et al., 2003; Rosano et al. 2007; Rosano et al., 2008; Rosano et al., 2012). Areas such as the hippocampus and parietal lobe are also showing associations with motor control and gait stability (Malouin et al., 2003; Rosano et al., 2008; Zimmerman et al., 2009). The increased stride time and stride length variability observed in the present study could represent subtle mobility impairments related to early dysfunction of these cortical and sub-cortical areas regulating gait (Rosano et al., 2007). This is supported by studies which suggest gait impairments precede cognitive impairments (Mielke et al, 2013; Montero-Odasso et al., 2012; Buracchino et al., 2010; Verghese et al., 2007).

Of note, STV was also the only gait parameter to detect associations in the language domain during naming animal's gait testing. Faster gait speed has been found to be protective of language deficits (Mielke et al., 2013) however; to our knowledge this is the first study to demonstrate associations between deficits in the language domain and increased stride-to-stride variability. Language deficits often extend beyond Wernicke's and Broca's area to include other areas of the temporal lobe as well as areas in the parietal lobe (Hart & Gordon, 1990; McCroy, Firth, Brunswick & Price, 2000; Price et al., 1996; Wise et al., 1991). Thus, complete language comprehension and speech production involves additional areas outside of the temporal and prefrontal cortex. This suggests that increased STV may not only be a marker of deficits in EF and attention but also sensitive to detect deficits in other areas of the brain not typically known to be associated with gait control. Furthermore, these associations suggest that at least while walking and completing a secondary task requiring verbal fluency, there is a shared neural network among areas in the brain which control communication and language and areas that control gait stability.

Lack of associations found between gait and the language domain may be because our sample did not demonstrate deficits below normal values in this cognitive domain. Additionally, several studies have demonstrated that EF and attention impairments are the first non-memory domains affected in cognitive decline which usually occur before language impairments (Binetti et al., 1996; Lafleche & Albert, 1995; Reid et al., 1996). Lack of associations found may also be due to the insensitivity of the Boston Naming Test (15-item) in detecting language deficits. The test may not be challenging enough to detect aphasia. A more sensitive measure of deficits in language such as the full 60-item version of the Boston Naming Test may provide enough sensitivity to detect additional associations and should be further explored.

In summary, previous research has clearly demonstrated EF and attention are required for gait. We expand on this literature by demonstrating multi-tasking through an environment requires not only the higher level cognitive functions of EF and attention but also utilizes cognitive input from memory and language neural systems. In our analysis

we found relationships between deficits in several cognitive domains associated with the cortical areas involved in gait control. These findings are consistent with complex neural correlates for gait control believed to incorporate frontal, temporal and parietal cortical circuits and in addition to sub-cortical structures of the basal ganglia and brainstem (Guo et al., 2001; Malouin et al., 2003; Scherder et al., 2007; Sheridan & Hausdorff, 2007; Watson et al., 2010).

4.2 Strengths and Limitations

This study has the strengths of using a comprehensive evaluation of spatial and temporal gait variables in a well-defined population meeting the strict criteria for MCI. All MCI participants were identified by the same validated clinical criteria (Petersen, 2004; Winblad, 2004). This study also used a detailed and wide range of neuropsychological assessments to appropriately categorize the specific cognitive domains of executive function, memory, attention and language. The neuropsychological and gait assessments are well established and validated in samples for MCI (Montero-Odasso et al., 2009; Montero-Odasso et al., 2012). Few studies evaluating the relationship between gait and cognition in an MCI population use the DT paradigm. The present study makes use of multiple conditions of DT to assess the associations.

Some limitations need to be outlined. The cross-sectional design precludes us to infer causality or confirm the temporal order of the relationship between gait performance and cognitive measures. The sample size in the current study was relatively small and may have not been large enough to detect weaker associations and as a result some associations may have been missed. Despite this, to our knowledge this is the largest sample size assessing MCI older adults using DT gait conditions. Our findings need to be replicated and further investigated in longitudinal studies with larger sample sizes. This limitation creates biases towards the null hypothesis. Another limitation was the risk of type I error (asserting associations are true when they are not) due to evaluation of a large number of variables increases the chances of deeming a true non-significant associations significant. The Bonferroni test in post-hoc ANOVA analysis was

used to handle multiple testing conditions. Another area of concern would be the use of a short walkway and the number of strides collected. While the number of strides required to measure stride-to-stride variability is unknown, previous research has indicated that limited stride numbers can influence the reliability of the measures (Brach et al., 2008). Even with a short walkway we were still able to detect effects of DT testing and associations between the individual cognitive domains and gait performance suggesting study values are likely sufficient. It should be noted, dual-tasking over a long walkway is not ideal because an individual may not be able to sustain tasks over an extended period of time (Lord et al., 2011). The lack of associations found in this study may be due to limited number of gait data points. Future studies would be beneficial to evaluate these associations with a larger number of strides in a larger population. However, there may be trade-off issues between a need to collect more data and to limit participant burden that doesn't have an easy solution. Although the study used a large number of neuropsychological tests, episodic memory was assessed only with verbal tests. It is unknown whether the results from this test can be applied to episodic memory for non-verbal information as well. Thus, a more inclusive evaluation of episodic memory is warranted. Another potential limitation is that this study did not account for errors during dual tasking conditions; consequently the sincerity and accuracy during DT conditions could not be determined. The lack of associations found in the current study during serial 7 subtractions gait could be a result of our inability to determine and account for an individual's genuine effort while performing this DT test. For example, an individual may not have been able to perform serial 7 subtractions as a single task and during the DT condition their gait performance may be closer to a single task. This limitation biases our results towards the null hypothesis. Across the literature there are currently inconsistencies concerning how to handle errors and effort among DT conditions correctly but, in the future it would be better to evaluate the secondary task as a single task activity.

4.3 Future Directions

In line with previous research, our results highlight the importance of DT testing and gait variability in clinical settings. Future studies should focus on determining the temporal order of this relationship as this has the potential to determine whether gait variability can be used as a predictor for cognitive decline and progression to dementia. Differences in measures of mean, variance and quantity for gait performance are not consistent across the literature. Additionally, definitions of specific cognitive domains across the literature are not always uniform (Segev- Jacobovski et al., 2011). Future studies should focus on establishing standardized reference values for gait variables and refining descriptions of cognitive domains in order to understand differences across all parameters and enhance clinical interpretations. Typically gait and cognitive function are studied as distinct entities as a result neuropsychological tests are not integrated in routine assessments of mobility decline and fall risk. The findings of the present study suggest future studies should focus efforts to include cognitive measures in the traditional approaches to mitigate fall risk and determining the effects of cognitive training in cognitive domains such as memory and language will be able to improve gait. Cognitive training has also been shown to improve cognition in some older adult populations (Ball et al., 2002; Peretz et al., 2011; Willis et al., 2006). It would be of interest to further investigate the effects of training specific cognitive domains on gait characteristics. Lastly, future studies should corroborate findings with neuro-imaging results to help assess the anatomical and neural correlates between motor and cognitive functions. Gait variability is vital to the understanding of interactions underlying the cognitive control of gait; therefore, DT changes in gait variability can potentially serve as a clinical tool for targeting cognitively impaired older adults at risk for mobility and further cognitive decline.

Chapter 5: CONCLUSION

Walking is not automatic and emerging evidence shows that gait control relies on cortical processes; however, the exact mechanisms controlling gait are not completely understood. This study demonstrated that deficits in memory and language, which are beyond executive function (EF), are associated with poor to gait performance, more specifically gait variability measures. Decreases in various cognitive abilities were associated with poorer performance on gait variability measures.

Our findings suggest that gait variability is a sensitive marker for cognitive function because was associated with cognitive deficits while spatial and temporal gait parameters failed to do so. Gait variability is an expression of the cortical control on gait (Montero-Odasso et al., 2011; Beauchet et al., 2012) and detrimental gait changes in stride-to-stride variability observed while dual-tasking can not only identify cognitively impaired older adults at risk for gait disorders and falls, but could also represent the extent of the cognitive reserve. Thus, increased gait variability during dual-tasking may reflect subtle gait disturbances related to early stages of cortical and sub-cortical dysfunction.

Furthermore, we demonstrate the benefits of incorporating DT gait conditions as an appropriate tool to detect interactions and provide pertinent information concerning the relationship between motor control and specific cognitive functions. Since the magnitudes of the changes of dual-task gait variability are more related to cognitive deficits in our MCI population, we postulate that gait changes seen while dual tasking can be used as a biomarker of cognitive impairment and potentially help to better characterize those individuals who may progress to further cognitive decline and future dementia (Waite et al., 2005, Montero-Odasso et al. 2014). The combination of neuropsychological and gait assessments can provide the clinician with important information about multiple adverse events which otherwise would not be detected during a routine exam (Yogev-Seligman et al., 2008). Finally, the gait reduction seen in our study while dual tasking provides evidence that complex cognitive challenge in high function older individuals

with cognitive impairment pose them at risk of mobility decline at fall since their mean velocity decreased below the accepted threshold for fall risk (below 100 cm/s). This potential clinical added value of dual-task gait in the cognitive impaired can be tested in future longitudinal studies.

In summary, gait control is clearly multi-factorial and this study provides evidence to support gait as a complex motor function, its control shares similar underlying neural substrate with specific cognitive domains. Improved understanding of the relationship between gait and cognitive impairments can help identify older adults at higher risk for mobility decline, falls and progression to dementia.

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APPENDICES

Appendix A:

Ethics Approval Notice



Office of Research Ethics

The University of Western Ontario
Room 4180 Support Services Building, London, ON, Canada N6A 5C1
Telephone: (519) 661-3036 Fax: (519) 850-2466 Email: ethics@uwo.ca
Website: www.uwo.ca/research/ethics

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. M.M. Odasso

Review Number: 16086

Review Date: November 6, 2009

Revision Number: 1

Review Level: Expedited

Protocol Title: Can cognitive enhancers reduce the risk of falls in older people with Mild Cognitive Impairment? A Randomised Control Trial

Department and Institution: Geriatric Medicine, Parkwood Hospital

Sponsor: PSI-PHYSICIAN SERVICES INC FOUNDATION

Ethics Approval Date: November 12, 2009

Expiry Date: June 30, 2011

Documents Reviewed and Approved: Addition of co-investigator (S. Carter), revised inclusion/exclusion criteria, revised risks, revised letter of information & consent form dated November 6/09 & Poster

Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

- a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
- b) all adverse and unexpected experiences or events that are both serious and unexpected;
- c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. Joseph Gilbert

Ethics Officer to Contact for Further Information

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Use of Human Participants - Ethics Approval Notice

Research Ethics

Principal Investigator: Dr. Manuel Montero Odasso
 File Number: 6161
 Review Level: Delegated
 Approved Local Adult Participants: 140
 Approved Local Minor Participants: 0
 Protocol Title: Can cognitive enhancers reduce the risk of falls in older people with Mild Cognitive Impairment? A Randomised Control Trial (REB# 16086)
 Department & Institution: Schulich School of Medicine and Dentistry/Geriatric Medicine, St. Joseph's Health Care London
 Sponsor:
 Ethics Approval Date: October 12, 2012 Expiry Date: June 30, 2013
 Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Addition of Co-investigator	Elyse Gordon has been added as a Research Student.	

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.



Ethics Officer to Contact for Further Information



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Office of Research Ethics

The University of Western Ontario
 Room 4180 Support Services Building, London, ON, Canada N6A 5C1
 Telephone: (519) 861-3036 Fax: (519) 850-2466 Email: ethics@uwo.ca
 Website: www.uwo.ca/research/ethics

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. M.M. Odasso

Review Number: 17200

Review Date: June 15, 2010

Review Level: Full Board

Approved Local # of Participants: 100

Protocol Title: Gait Variability as Predictor of Cognitive Decline and Risk of Falls in MCI: A Cohort Study

Department and Institution: Geriatric Medicine, Parkwood Hospital

Sponsor: CIHR

Ethics Approval Date: September 07, 2010

Expiry Date: June 30, 2015

Documents Reviewed and Approved: UWO Protocol (including instruments noted in Section 8.1), Letter of Information and Consent Form dated 03 August 2010, Recruitment Letter dated 05 July 2010 and Advertisement Poster

Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

- a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
- b) all adverse and unexpected experiences or events that are both serious and unexpected;
- c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. Joseph Gilbert
 FDA Ref. #: IRB 0000940

Ethics Officer to Contact for Further Information

☐ (s)

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cc: ORE File
 LHRI

UWO HSREB Ethics Approval - Initial
 V. 2008-07-01 (rptApprovalNoticeHSREB_initial)

17200

Page 1 of 1



Use of Human Participants - Ethics Approval Notice

Research Ethics

Principal Investigator: Dr. Manuel Montero Odasso

File Number: 7162

Review Level: Delegated

Approved Local Adult Participants: 100

Approved Local Minor Participants: 0

Protocol Title: Gait Variability as Predictor of Cognitive Decline and Risk of Falls in MCI: A Cohort Study (REB #17200)

Department & Institution: Schulich School of Medicine and Dentistry/Geriatric Medicine, St. Joseph's Health Care London

Sponsor: Canadian Institutes of Health Research

Ethics Approval Date: October 12, 2012 **Expiry Date:** June 30, 2015

Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Addition of Co-investigator	Elyse Gordon has been added as a Research Student.	

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices; Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

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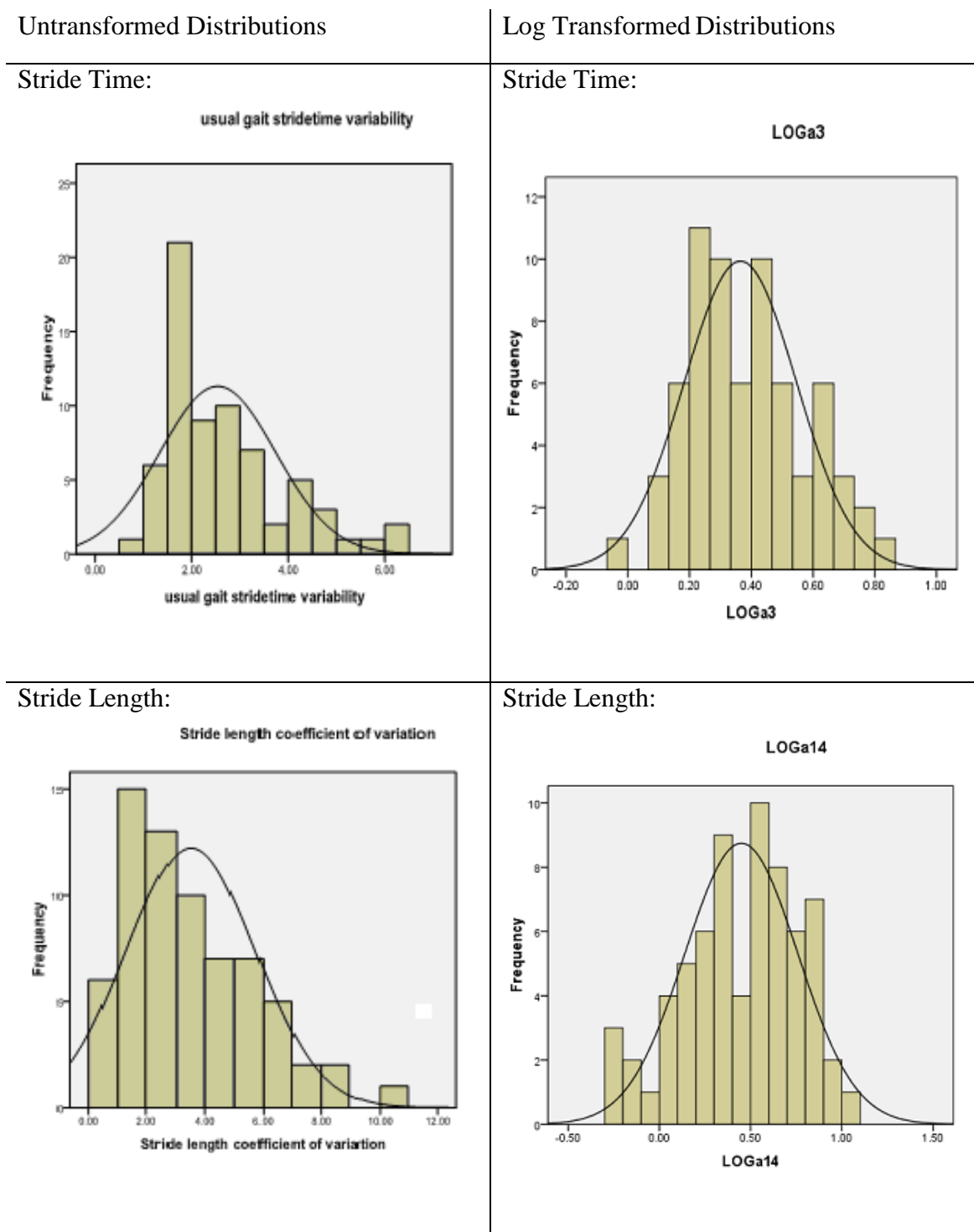
Ethics Officer to Contact for Further Information

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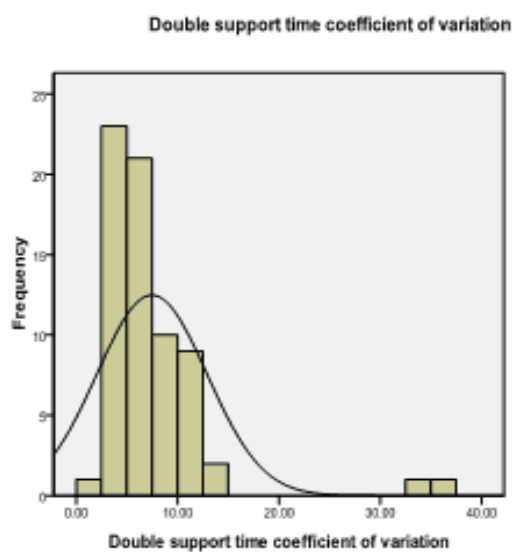
Appendix B:

Normal Distributions and Log transformed distributions for gait variability parameters

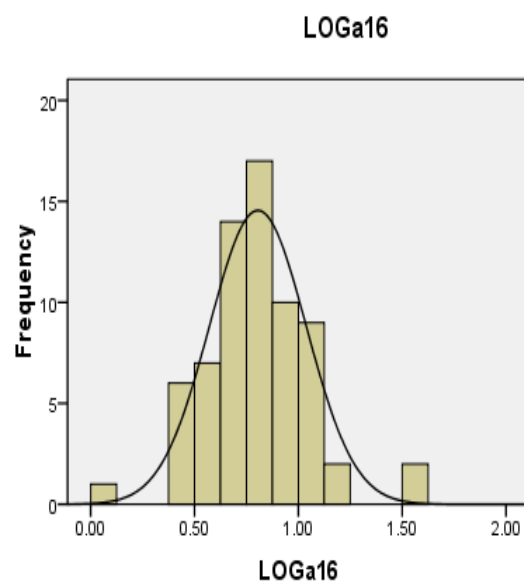
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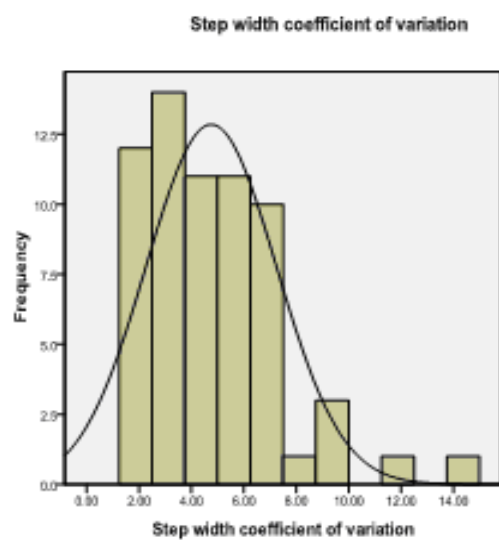
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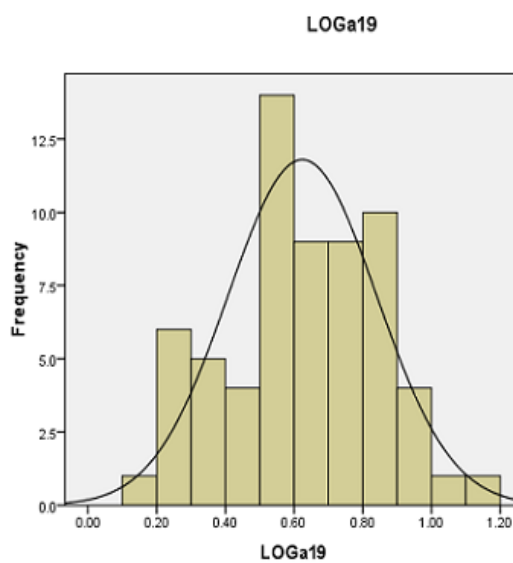
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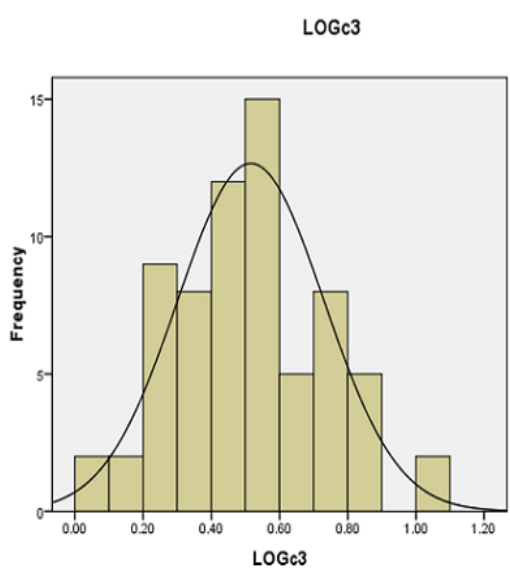
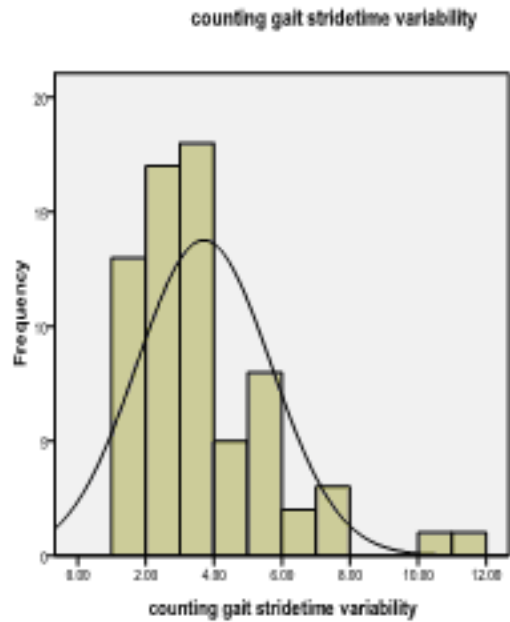
Counting backwards by 1's gait variability parameters:

Untransformed Distributions

Log Transformed Distributions

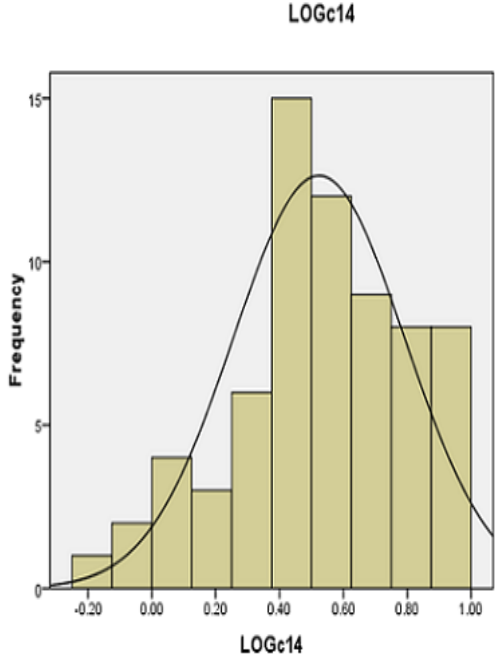
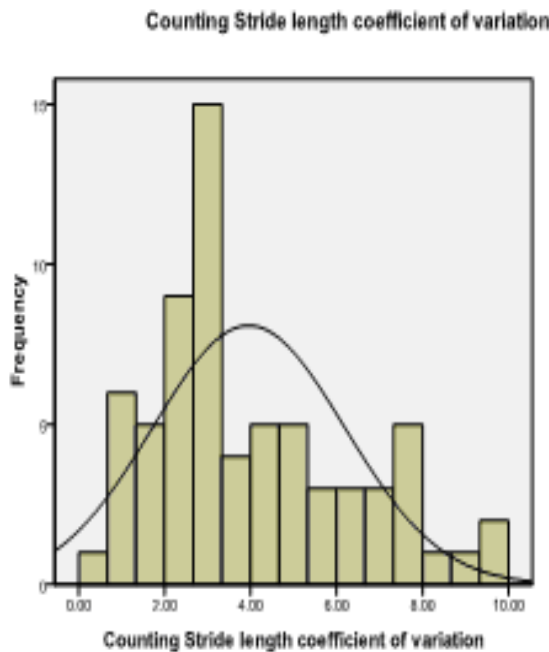
Stride Time:

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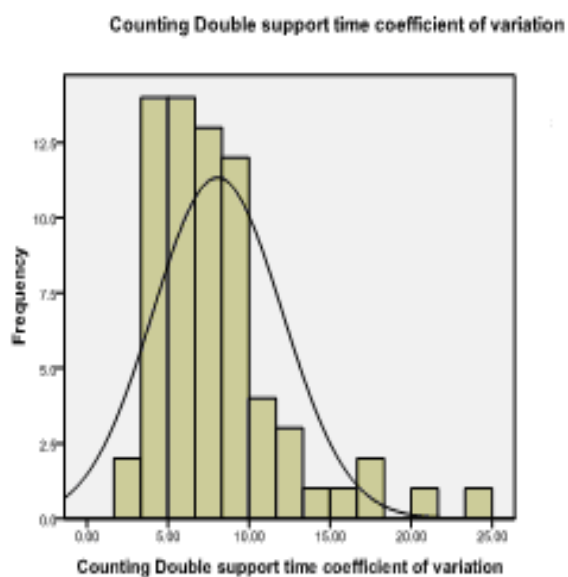


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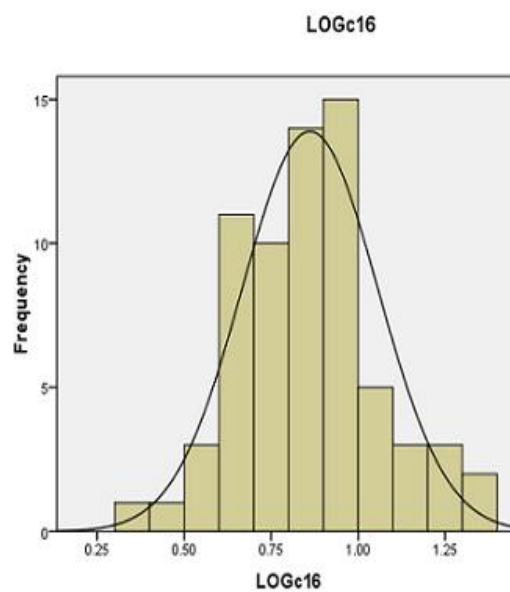
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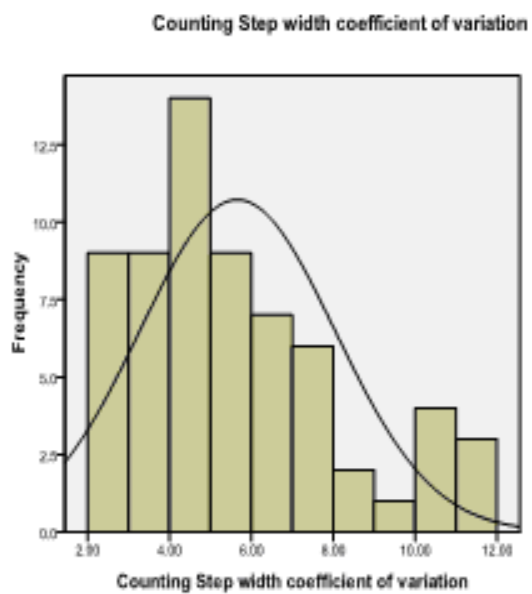
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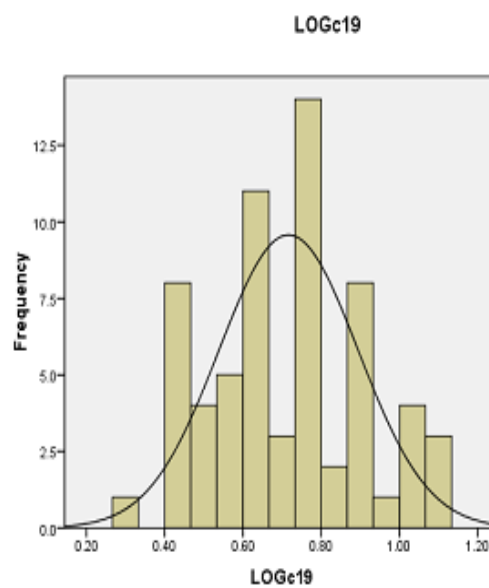
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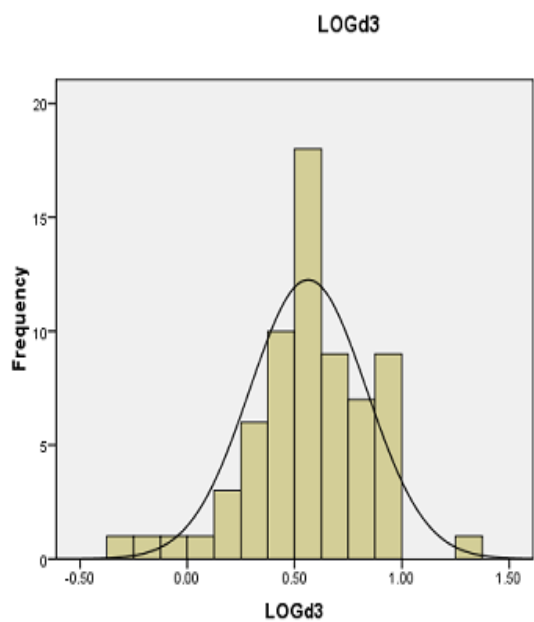
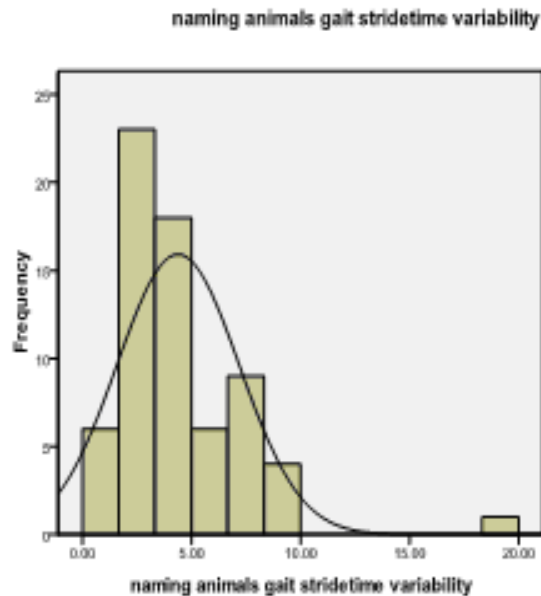
Naming animals gait variability parameters:

Untransformed Distributions

Transformed Log Distributions

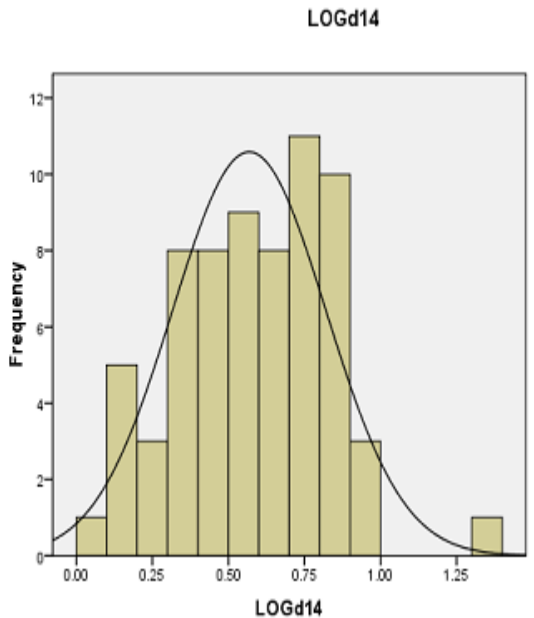
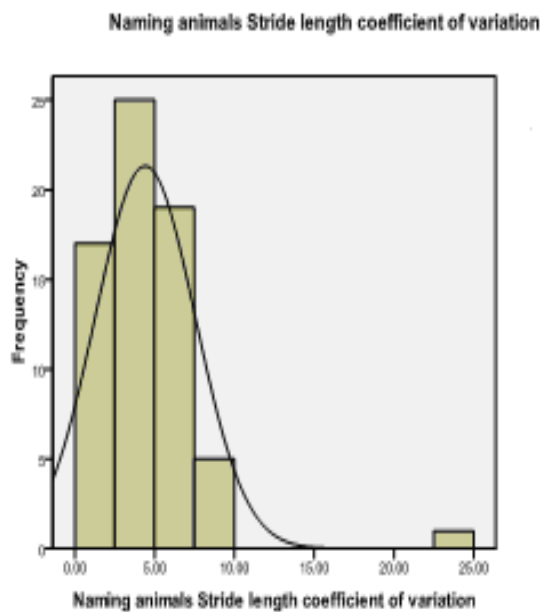
Stride Time:

Stride Time:

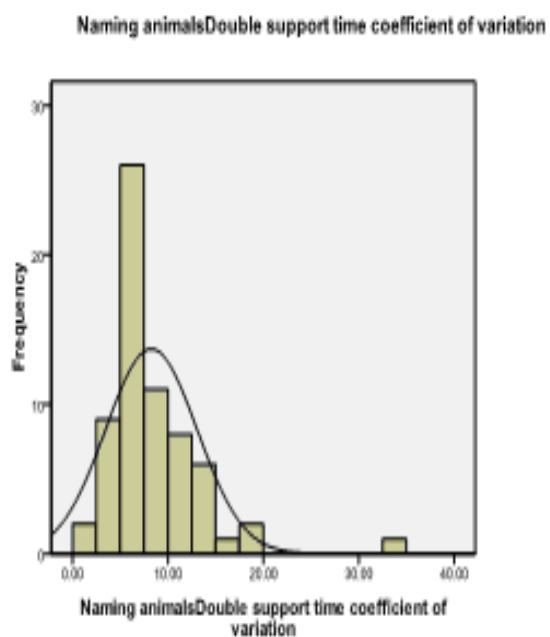


Stride Length:

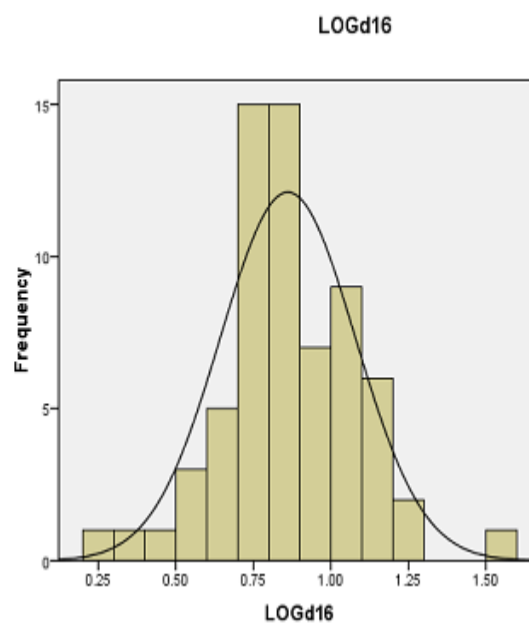
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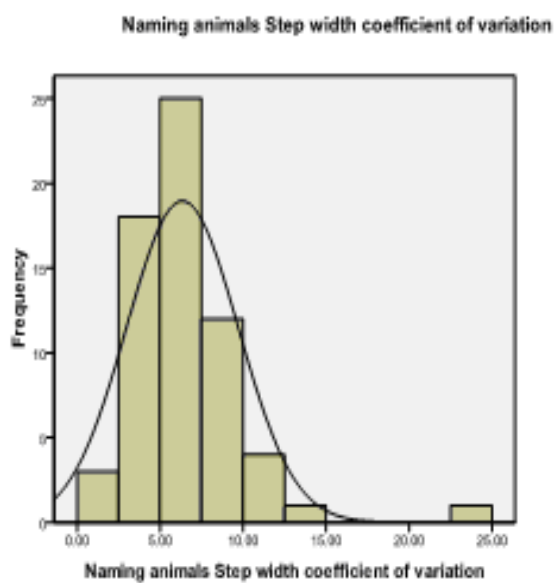
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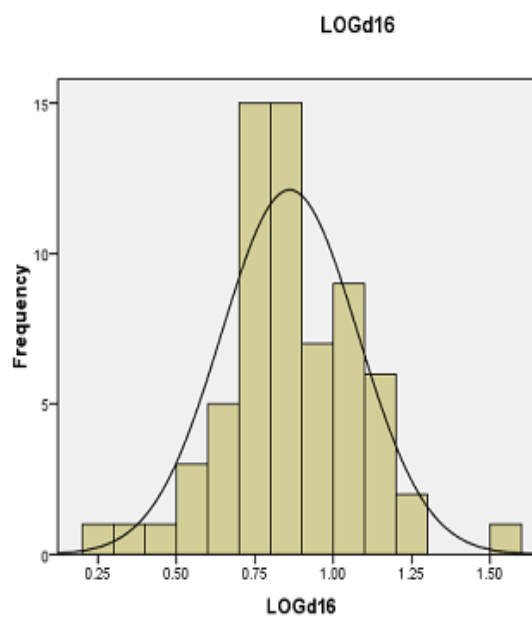
Double Support Time:



Step Width:



Step Width:



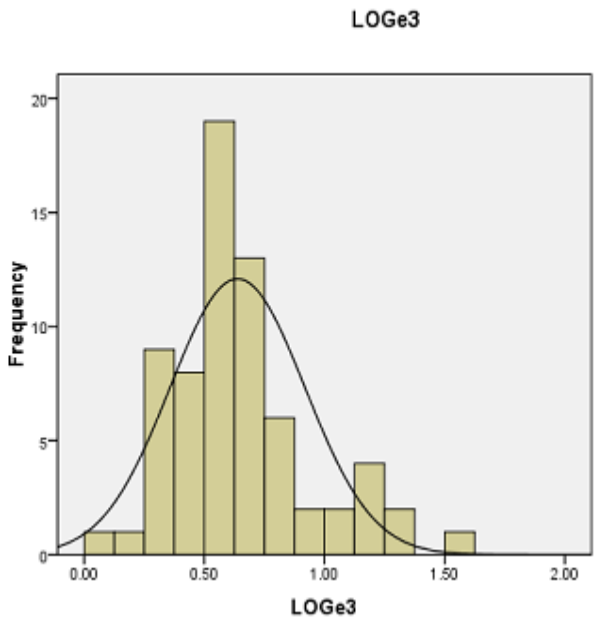
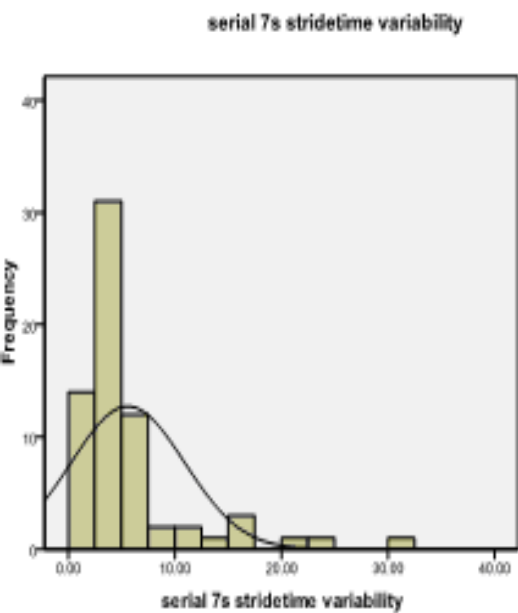
Serial seven subtraction gait variability:

Untransformed Distributions

Log Transformed Distributions

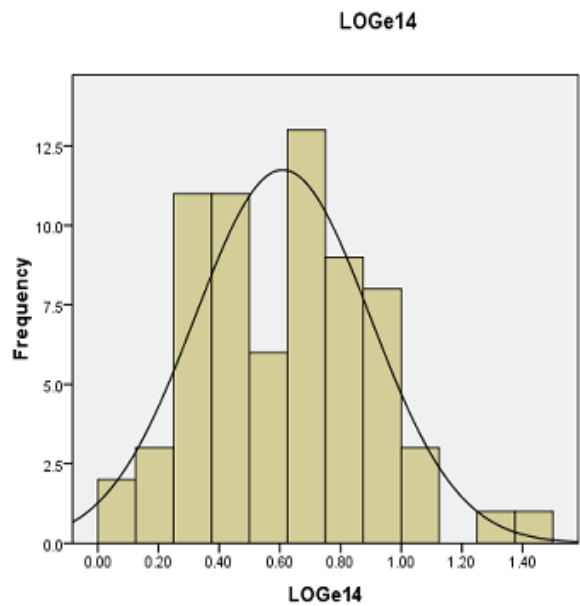
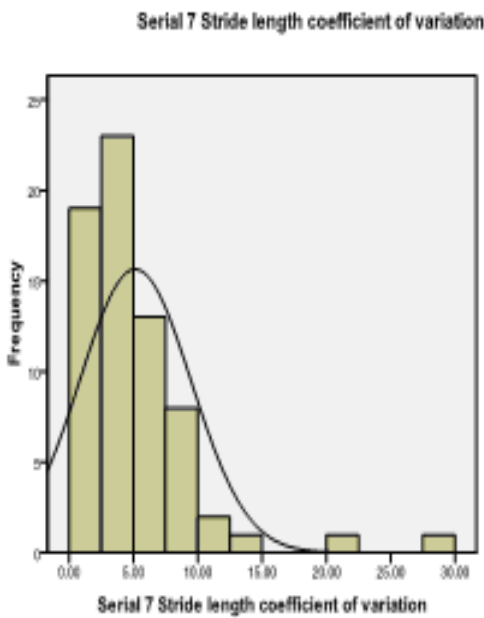
Stride Time:

Stride Time:

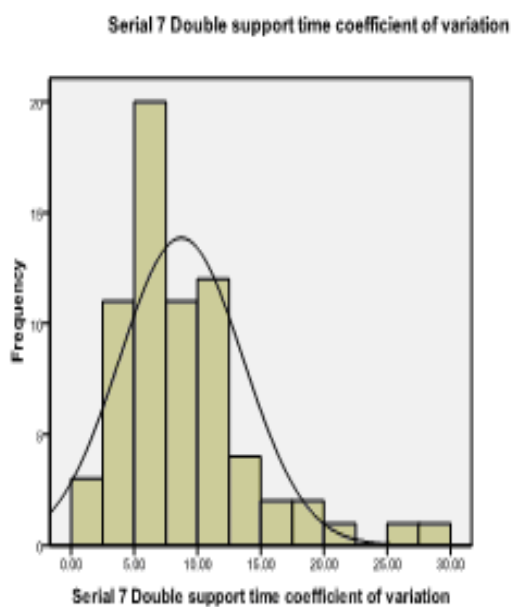


Stride Length:

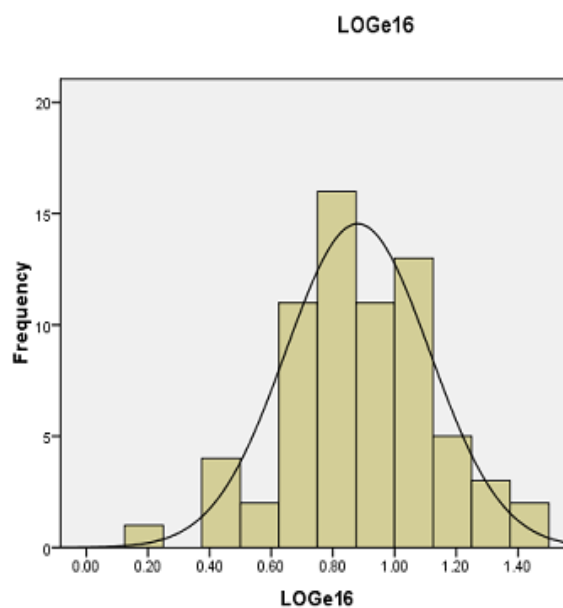
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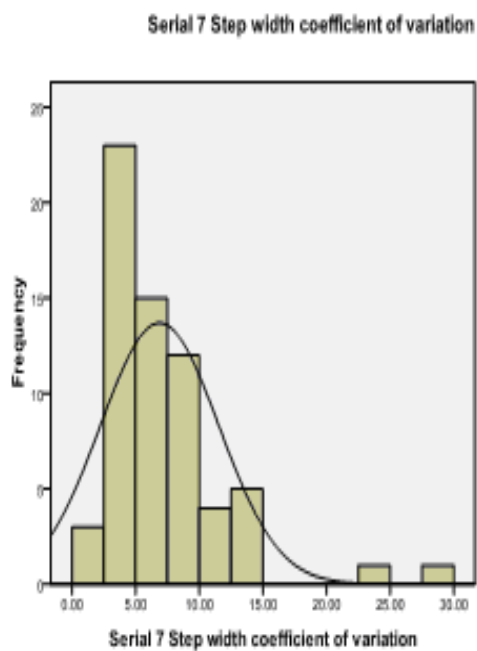
Double Support Time:



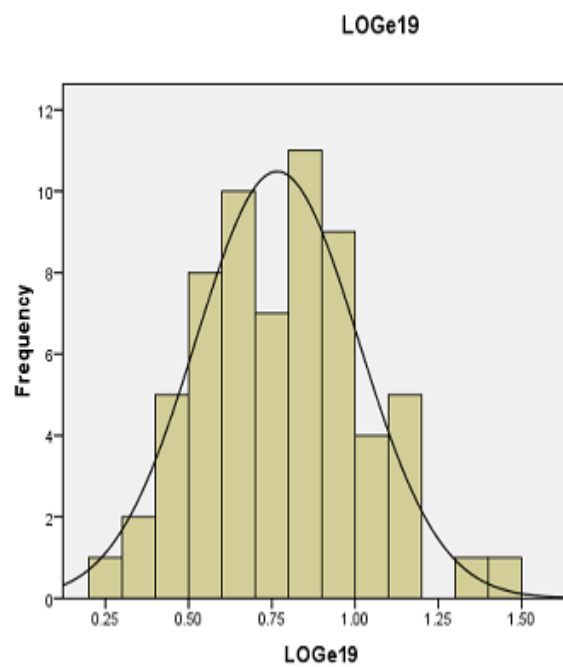
Double Support Time:



Step Width:



Step Width:



Appendix C:

Results from the unadjusted linear regression analysis comparing the associations of individual cognitive domains on an outcome of gait variables during single task and dual task walking conditions

Table D.1: Unadjusted linear regression comparing the association of cognitive test scores on an outcome of gait variables during usual gait

Unstandardized Regression Coefficients, (95% CI)					
	Gait Variables during usual gait:				
	Velocity (cm/s)	Stride Time (ms)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	-0.29 (-0.614, 0.016) p= .062	1.07 (-.380, 2.51) p= .146	-0.212 (-.50, .077) p= .147	1.31 (0.245, 2.37) p= .017	-0.098 (-0.243, 0.047) p= .181
ΔTMT	-0.031 (-0.106, 0.045) p= .418	0.130 (-0.214, 0.474) p= .453	-0.0018 (-0.087, 0.050) p= .597	0.272 (0.020, 0.524) p= .035	-0.018 (-0.052, 0.016) p= .302
DST-B	0.67 (-1.6, 3.0) p= .563	-3.35 (-13.77, 7.07) p= .523	0.407 (-1.68, 2.49) p= .698	-4.03 (-11.85, 3.80) p= .308	0.163 (-0.905, 1.23) p= .762
ΔDST	-2.2 (-4.5, 0.12) p= .063	10.41 (-0.182, 21.02) p= .054	-1.29 (-3.44, 0.867) p= .237	5.12 (-3.01, 13.25) p= .213	-1.02 (-2.08, 0.050) p= .061
LNS	0.69 (-1.35, 2.73) p= .501	.919 (-8.40, 10.24) p= .845	0.892 (-0.954, 3.74) p= .338	-2.35 (-9.36, 4.67) p= .507	0.344 (-0.598, 1.29) p= .468
RAVLT	0.27 (-1.6, 2.12) p= .767	-5.83 (-14.11, 2.44) p= .164	-0.246 (-1.92, 1.43) p= .770	-3.91 (-10.18, 2.35) p= .217	-0.004 (-0.838, -0.829) p= .992
BNT	2.72 (-1.18, 6.63) p= .169	-0.011 (-18.09, 18.07) p= .999	3.45 (-0.055, 6.95) p= .054	-12.79 (-26.07, 0.485) p= .059	1.69 (-0.079, 3.46) p= .061

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities; TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.

Table D.2: Unadjusted linear regression comparing the association of cognitive test scores on an outcome of gait variables during counting by 1's gait

Unstandardized Regression Coefficients, (95% CI)					
	Gait Variables during counting by 1's gait:				
	Velocity (cm/s)	Stride Time (ms)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	-0.441 (-.811, -.072) p= .020	2.52 (0.330, 4.72) p= .025	-0.243 (-0.570, 0.085) p= .144	0.721 (-0.55, 2.0) p= .263	-0.11 (-0.26, 0.041) p=.150
ΔTMT	-0.061 (-0.151, 0.028) p=.174	0.425 (-0.100, 0.950) p= .111	-0.025 (-0.103, 0.053) p= .520	0.283 (-0.010, 0.577) p= .058	-0.013 (-0.049, 0.023) p= .485
DST-B	2.08 (-0.608, 4.76) p= .127	-15.04 (-30.80, 0.717) p=.061	0.780 (-1.58, 3.14) p= .511	-5.14 (-14.18, 3.90) p= .261	-0.016 (-1.14, 1.11) p= .978
ΔDST	-3.82 (-6.52, -1.13) p= .006	25.44 (9.75, 41.13) p= .002	-1.86 (-4.29, 0.560) p= .130	12.32 (3.29, 21.35) p= .008	-0.99 (-2.12, 0.146) p= .086
LNS	1.21 (-1.20, 3.64) p= .318	-3.21 (-17.63, 11.21) p= .658	1.08 (-1.01, 3.17) p= .308	-1.59 (-9.72, 6.55) p= .698	0.208 (-0.789, 1.20) p= .678
RAVLT	0.579 (-1.61, 2.77) p= .600	-10.43 (-23.19, 2.32) p= .107	-0.147 (-2.05, 1.75) p= .878	-7.43 (-14.54, -0.330) p= .041	-0.111 (-0.990, 0.767) p= .801
BNT	3.86 (-0.77, 8.49) p= .101	-9.93 (-37.82, 17.95) p= .479	4.11 (0.152, 8.07) p= .042	-13.82 (-29.23, 1.6) p= .078	1.33 (-0.557, 3.22) p= .164

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities;
TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.

Table D.3: Unadjusted linear regression comparing the association of cognitive test scores on an outcome of gait variables during naming animals gait

Unstandardized Regression Coefficients, (95% CI)					
	Gait Variables during naming animal's gait:				
	Velocity (cm/s)	Stride Time (ms)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	-0.33 (0.73, 0.077) p= .111	3.03 (-.145, 6.2) p= .061	-0.167 (-0.54, 0.208) p= .377	1.23 (-0.85, 3.28) p= .244	-0.11 (-0.28, 0.059) p= .197
ΔTMT	-0.047 (-0.142, 0.048) p= .329	0.48 (-0.28, 1.23) p= .207	-0.008 (-0.096, 0.079) p= .849	0.33 (-0.14, 0.81) p= .168	-0.011 (-0.051, 0.029) p= .573
DST-B	1.53 (-1.35, 4.41) p= .292	-5.59 (-28.54, 17.36) p= .628	0.98 (-1.67, 3.64) p= .461	-2.0 (-16.73, 12.73) p= .787	0.34 (-0.90, 1.58) p= .586
ΔDST	-4.39 (-7.18, -1.52) p= .003	25.97 (2.86, 49.08) p= .028	-2.86 (-5.56, -0.177) p= .037	15.73 (0.850, 30.61) p= .039	-0.18 (-2.66, 2.31) p= .888
LNS	0.590 (-2.04, 3.22) p= .656	-2.72 (-23.62, 18.18) p= .796	0.73 (-1.69, 3.15) p= .548	-1.62 (-15.02, 11.78) p= .810	0.23 (-0.87, 1.33) p= .676
RAVLT	0.407 (-1.91, 2.72) p= .727	-12.36 (-30.46, 5.75) p= .178	-0.323 (-2.45, 1.80) p= .762	-9.45 (-20.99, 2.08) p= .107	-0.049 (-1.02, 0.921) p= .920
BNT	2.51 (-2.44, 7.46) p= .316	-13.39 (-52.81, 26.03) p= .500	3.26 (-1.25, 7.77) p= .154	-24.89 (-49.49, -0.29) p= .047	1.23 (-0.86, 3.33) p= .242

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities; TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.

Table D.4: Unadjusted linear regression comparing the association of cognitive test scores on an outcome of gait variables during serial seven's gait.

Unstandardized Regression Coefficients, (95% CI)					
	Gait Variables during serial seven's gait:				
	Velocity (cm/s)	Stride Time (ms)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	-0.42 (-0.840, 0.001) p= .050	3.38 (-2.30, 9.01) p= .239	-0.23 (-0.59, 0.12) p= .193	0.96 (-1.05, 2.97) p= .342	-0.13 (-0.30, 0.036) p= .122
ΔTMT	-0.070 (-0.170, 0.031) p= .171	0.62 (-0.72, 2.0) p= .360	-0.025 (-0.109, 0.058) p= .548	.375 (-0.089, 0.840) p= .112	-0.020 (-0.059, 0.020) p= .331
DST-B	1.72 (-1.33, 4.76) p= .265	-16.07 (-56.59, 24.45) p= .431	0.939 (-1.59, 3.47) p= .460	-2.39 (-16.72, 11.94) p= .740	0.33 (-0.92, 1.58) p= .601
ΔDST	-5.12 (-8.07, -2.17) p= .001	55.83 (15.63, 96.03) p= .007	-3.02 (-5.56, -.480) p= .021	23.56 (9.77, 37.35) p= .001	-1.73 (2.94, -0.53) p= .006
LNS	0.73 (-2.01, 3.46) p= .597	-6.51 (-42.79, 29.77) p= .721	0.92 (-1.34, 3.17) p= .420	-0.68 (-13.47, 12.11) p= .916	0.43 (-0.67, 1.53) p= .435
RAVLT	-0.25 (-2.72, 2.22) p= .840	11.95 (-20.63, 44.53) p= .467	-0.44 (-2.47, 1.60) p= .670	-2.40 (-13.90, 9.11) p= .679	-0.015 (-0.99, 0.96) p= .975
BNT	-2.07 (-3.44, 7.16) p= .486	6.58 (-63.81, 76.96) p= .853	2.75 (-1.59, 7.08) p= .210	-8.76 (-33.46, 15.94) p= .481	1.25 (-0.86, 3.35) p= .241

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities; TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.

Appendix D:

Results from the unadjusted linear regression analysis comparing the associations of individual cognitive domains on an outcome of gait variability during single and dual task walking conditions

Table E.1: Unadjusted linear regression comparing the association of cognitive test scores on an outcome of gait variability during single task gait.

Unstandardized Regression Coefficients, (95% CI)				
	Gait Variability during single task gait (log):			
	Stride Time (ms)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	0.0087 (-0.003, 0.003) p= .953	0.001 (-0.004, 0.006) p= .611	0.00 (-0.004, 0.003) p= .844	-0.001 (-0.004, 0.003) p= .704
ΔTMT	0.001 (0.00- 0.001) p= .062	0.001 (0.00, 0.002) p= .024	0.001 (0.00, 0.002) p= .064	0.00 (0.00, 0.001) p= .217
DST-B	-0.014 (-0.034, 0.006) p= .174	-0.021 (-0.054, 0.013) p= .224	0.00 (-0.026, 0.026) p= .978	-0.003 (-0.028, 0.022) p= .803
ΔDST	0.005 (-0.017, 0.26) p= .664	0.017 (-0.019, 0.052) p= .354	-0.004 (-0.031, 0.023) p= .748	0.008 (-0.017, 0.033) p= .536
LNS	-0.027 (-0.044, 0.010) p= .003	-0.041 (-0.070, 0.012) p= .006	-0.021 (-0.044, 0.001) p= .064	-0.013 (-0.035, 0.008) p= .217
RAVLT	-0.013 (-0.029, 0.004) p= .127	-0.025 (-0.051, 0.002) p= .070	0.012 (-0.008, 0.033) p= .243	-0.018 (-0.037, 0.001) p= .061
BNT	0.00 (-0.036, 0.036) p= .994	-0.011 (-0.070, 0.047) p= .699	-0.035 (-0.079, 0.009) p= .121	-0.003 (-0.045, 0.039) p= .884

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities; TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.

Table E.2: Unadjusted linear regression comparing the association of cognitive test scores on an outcome of gait variability during counting by 1's gait

Unstandardized Regression Coefficients, (95% CI)				
	Gait Variability during counting by 1's gait (log):			
	Stride Time (ms)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	0.003 (0.00, 0.006) p= .049	0.007 (0.003, 0.011) p= .001	0.001 (-0.002, 0.004) p= .342	0.003 (0.00, 0.005) p= .080
ΔTMT	0.001 (0.00, 0.002) p= .008	0.001 (0.00, 0.002) p= .104	0.00 (0.00, 0.001) p= .183	0.00 (0.00, 0.001) p= .318
DST-B	-0.022 (-0.045, 0.001) p= .060	-0.028 (-0.057, 0.001) p= .062	-0.015 (-0.037, 0.006) p= .157	-0.007 (-0.028, 0.014) p= .491
ΔDST	0.028 (0.004, 0.052) p= .020	0.024 (-0.006, 0.055) p= .119	0.008 (-0.015, 0.030) p= .500	0.009 (-0.013, 0.031) p= .404
LNS	-0.012 (-0.033, 0.009) p= .243	-0.033 (-0.059, -0.008) p= .011	-0.023 (-0.042, -0.005) p= .014	-0.010 (-0.028, 0.009) p= .293
RAVLT	-0.020 (-0.038, -0.002) p=.033	-0.016 (-0.040, 0.008) p= .184	-0.020 (-0.037, -0.003) p= .021	-0.013 (-0.029, 0.003) p= .104
BNT	-0.026 (-0.066, 0.014) p= .203	0.036 (-0.087, -0.015) p= .167	-0.020 (-0.058, 0.017) p= .281	-0.004 (-0.040, 0.032) p= .807

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities; TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.

Table E.3: Unadjusted linear regression comparing the association of cognitive test scores on an outcome of gait variability during naming animal's gait

Unstandardized Regression Coefficients, (95% CI)				
	Gait Variability during naming animals gait (log):			
	Stride Time (ms)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	0.006 (0.002, 0.010) p= .006	0.003 (-0.001, .007) p= .090	0.00034 (-0.003, 0.003) p= .984	0.002 (-0.001, 0.006) p= .173
ΔTMT	0.001 (0.00, 0.002) p= .062	0.00 (-0.001, .001) p= .628	0.00 (-0.001, 0.001) p= .502	0.00 (0.00, 0.001) p= .293
DST-B	-0.019 (-0.049, 0.011) p= .217	-0.031 (-0.058, -.003) p= .029	-0.006 (-0.030, 0.018) p= .623	-0.021 (-0.046, 0.003) p= .089
ΔDST	0.030 (0.00, 0.061) p= .053	0.043 (0.015, 0.070) p= .003	0.009 (-0.017, 0.034) p= .499	0.043 (0.020, 0.066) p<.001
LNS	-0.026 (-0.053, 0.00) p= .052	-0.019 (-0.045, 0.006) p= .135	-0.002 (-0.024, 0.019) p= .823	-0.009 (-0.031, 0.013) p= .437
RAVLT	-0.005 (-0.029, 0.019) p= .680	-0.012 (-0.035, 0.010) p= .271	0.004 (-0.015, 0.023) p= .681	-0.013 (-0.032, 0.006) p= .182
BNT	-0.068 (-0.117, -0.019) p= .007	-0.038 (-0.086, 0.010) p= .123	-0.015 (-0.056, 0.026) p= .463	-0.027 (-0.069, 0.015) p= .210

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities; TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.


Table E.4: Unadjusted linear regression comparing the association of cognitive test scores on an outcome of gait variability during serial sevens gait

Unstandardized Regression Coefficients, (95% CI)				
	Gait Variability during serial sevens gait (log):			
	Stride Time (ms)	Stride Length (cm)	Double Support Time (sec)	Step Width (cm)
TMT A	0.003 (-0.001, 0.007) p= .180	0.002 (-0.003, 0.006) p= .423	-0.001 (-0.005, 0.003) p= .566	0.001 (-0.003, 0.005) p= .502
ΔTMT	0.001 (0.00, 0.002) p= .265	0.00 (-0.001, 0.001) p= .683	0.00 (-0.001, 0.001) p= .596	0.00 (-0.001, 0.001) p= .571
DST-B	-0.005 (-0.036, 0.027) p= .765	-0.025 (-0.057, 0.006) p= .110	0.011 (-0.016, 0.038) p= .415	-0.009 (-0.037, 0.019) p= .512
ΔDST	0.033 (0.001, 0.065) p= .041	0.037 (0.005, 0.069) p= .024	0.012 (-0.015, 0.040) p= .378	0.022 (-0.006, 0.050) p= .117
LNS	-0.009 (-0.037, 0.020) p= .547	-0.019 (-0.047, 0.009) p= .182	0.007 (-0.017, 0.031) p= .550	-0.007 (-0.032, 0.018) p= .565
RAVLT	0.017 (-0.008, 0.042) p= .190	-0.006 (-0.031, 0.020) p= .656	0.010 (-0.012, 0.031) p= .372	-0.006 (-0.028, 0.016) p= .591
BNT	-0.022 (-0.076, 0.033) p= .426	0.030 (-0.025, 0.084) p= .282	0.033 (-0.013, 0.079) p= .154	0.031 (-0.016, 0.078) p= .188

Notes: Analysis adjusted for age, body mass index, total number of medications and total number of co-morbidities;
TMT=Trail Making Test, DST-B=Digit Span Test Backwards, LNS= Letter Number Sequencing, RAVLT= Rey Auditory Verbal Learning Test, BNT= Boston Naming Test, Δ=delta, bold values are statistically significance at p<0.05.

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CURRICULUM VITAE

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EDUCATION

- Masters of Science, Kinesiology** **September 2012- Present**
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 Specialization in Exercise Physiology
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 York University
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MSC THESIS

- Specific Cognitive Domains Associated with Gait Performance in Mild Cognitive Impairment
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AWARDS AND DISTINCTIONS

- Canadian Geriatric Society- Canadian Institute of Health Research- Travel Award 2014
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- Kinesiology Graduate Student Conference Travel Award, 2014
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RESEARCH EXPERIENCE

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REFEREED ABSTRACTS AND/OR PRESENTATIONS

Gordon E., Muir Hunter S., Speechley M., Montero Odasso M. Associations Between Impairments in Specific Cognitive Domains and Gait Parameters in Patients with Mild Cognitive Impairment. June 12, 2013; Ingersoll, Ontario (Podium Presentation)

Gordon E., Muir Hunter S., Montero Odaaso M. The role of specific cognitive domains in gait performance. Aging, Rehabilitation and Geriatric Care Program/ Faculty of Health Symposium. February 7, 2014; London, Ontario (Oral and Poster Presentation)

Gordon E., Muir Hunter S., Speechley M., Montero Odasso M. Deficits in Specific Cognitive Domains Affects Gait Performance: Results from the Gait and Brain Study. Canadian Geriatric Society Annual Meeting. April 10 – April 13; Edmonton, Alberta (Podium and Poster Presentation)

Gopaul K., **Gordon E.**, Speechley M., Oteng-Amoako A., Beauchet O., Annweiler C, Muir Hunter S., Montero-Odasso M. The Motor Signature of Mild Cognitive Impairment: Results from the Gait and Brain Study. Canadian Geriatric Society Annual Meeting. April 10 – April 13; Edmonton, Alberta (Podium and Poster Presentation)

Gordon E., Muir Hunter S., Speechley M., Montero Odasso M. The Role of Specific Cognitive Domains in gait performance; Results from the Gait and Brain Study. American Geriatric Society Annual Meeting. May 17-19; Orlando, Florida (Poster Presentation)

TEACHING EXPERIENCE

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Canadian Hall of Fame Discovery Day
Parkwood Hospital, London

May 2, 2014

- Coordinated and lead the “Walking the Walk” Workshop Seminar