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Feasibility of Dual-Task Gait Assessment and Association with Cognitive Impairment Subtypes in a Memory Clinic Setting

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Abstract

The objectives of this thesis were 1) to assess feasibility and practicality of gait performance to help differentiate cognitive diagnoses, 2) to assess differences in gait speed and dual-task gait cost across the cognitive spectrum, and 3) to determine if poor baseline gait performance is associated with future cognitive decline, all within a clinical setting. Patients at the Aging Brain and Memory Clinic completed gait assessment, consisting of a usual gait trial and three dual-task gait trials, in addition to cognitive and clinical assessments. Patients who had two clinic visits during the study period were also included in a longitudinal analysis. Gait speed decreased across the cognitive spectrum and was associated with a more severe cognitive impairment. Dual-task gait performance on the naming animals condition was also associated with future cognitive decline. This thesis presents an investigation of gait performance in a clinical setting with a large diverse cohort.

Keywords

Aging, older adults, cognition, dual-task, gait testing, gait velocity, gait speed

Summary for Lay Audience

This thesis explores the usefulness and feasibility of using a dual-task test, or "walking while talking" test, to predict which patients in memory clinics are at higher risk of progressing to dementia. In the past, it has been shown that patients with a more pronounced slowdown when walking and talking (when compared to just walking) may be more likely to progress to dementia, but this test has not been thoroughly studied in a clinic setting. We performed this test on patients who were attending the memory clinic at Parkwood Institute for evaluation of their memory concerns. We found that this test was feasible to complete, as a large majority of patients were able to complete the test. We also found that participants with slow walking speed and those who further slowed down when dual-tasking were more likely to have been diagnosed with dementia and may be more likely to decline in the following years. While we would need a larger study with more participants for each diagnosis and a longer follow-up period to better understand this relationship, these results show that dual-task gait testing in a clinical setting may be useful in better evaluating risk of dementia.

Acknowledgments

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Key Terms Glossary

Cognition	The set of mental activities carried out by the brain that are involved in the acquisition, storage, retrieval, and use of information [1].
Mobility	The ability of a person to complete movement in any form, including walking, completing activities of daily living, exercising, and even using transportation [2].
Neurodegenerative diseases	Diseases that cause progressive damage to a group of neurons and have residual cognitive or motor effects (ex. Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis (ALS)) [3].
SCI	Subjective Cognitive Impairment. A clinical condition characterized by subjective cognitive complaints but normal scores on tests of cognition [4].
MCI	Mild Cognitive Impairment. A clinical condition characterized by subjective cognitive complaints and lower than normal scores on tests of cognition, but without impairments on activities of daily living and with absence of dementia [5].
Dementia	A clinical neurocognitive syndrome caused by multiple underlying diseases which cause chronic decline in cognition [6]. Usually characterized by objective cognitive impairment which is impacting activities of daily living [7,8]. The most common cause is thought to be Alzheimer's disease.
Gait	The pattern of movement of the human body during locomotion [9]. Mainly used to describe walking [10].
Dual-task gait	Walking while performing a cognitively demanding task.
Dual-task gait speed cost	The amount of slowdown in gait speed due to the added cognitive task, expressed as a percent of usual gait speed.

Chapter 1

1 Literature Review

As the current population is aging, with this comes cognitive impairments and disability, of which the most extreme expression is dementia syndromes. Although cognitive impairment is not the norm in aging, it is very prevalent among older adults [5]. Worldwide, approximately 50 million people are living with dementia, with almost 10 million new cases each year [11]. There are currently over half a million Canadians living with dementia, and this number is expected to grow by 66% in the next ten years [12]. However, when an older adult has cognitive complaints, it is difficult to discern in the early stages if they are due to the aging process or to dementia syndromes. In the search for good biomarkers to detect dementia, those that are easy to perform and clinically available will be of extreme importance. In this regard, motor biomarkers and physical performance abilities, including gait performance, are emerging as candidates to detect those at higher risk of dementia [13]. Recently, it has been postulated that gait performance while executing a cognitively demanding task can detect those older adults with subtle brain damage and who are more likely to progress to dementia. Therefore, this thesis aims to study the association between gait performance, specifically dual-task gait testing, and cognitive outcomes for older adults at risk of dementia in a clinical setting, with the goal of establishing feasibility of this testing in real clinical scenarios and confirm potential predictive abilities. Chapter 1 will provide an overview of cognitive impairments, gait testing, and the dual-task paradigm. This chapter will discuss the motor-cognitive interface and how it affects mobility in aging. We conclude by presenting the study rationale, purpose, and hypotheses.

1.1 Introduction

As research into motor biomarkers of cognition has expanded, dual-task gait testing has emerged as a “brain stress test” to evaluate the interaction between motor and cognitive performance [14]. Dual-task gait testing, defined as “walking while performing a cognitively demanding task”, was found to be associated with future dementia in patients

with mild cognitive impairment (MCI), a pre-dementia state [15]. As cognitive decline varies drastically in these prodromal states, both in timing and in magnitude [5], it is important to determine who is at high risk for dementia as early as possible. Research has shown that dual-task gait testing may be able to help with this early detection [15], however this theory has not been thoroughly studied in a memory clinic setting. Demonstrating feasibility and usefulness in a clinical setting would encourage clinicians to adopt this testing as part of assessment for memory complaints in older adults. This thesis will aim to apply previously described dual-task testing methodologies [14] in a large memory clinic cohort, to determine its feasibility and association with various cognitive diagnoses.

1.2 Cognition

While there are many definitions of cognition, it is usually conceptualized as "the set of mental activities involved in the acquisition, storage, retrieval, and use of information" [1]. Cognition can be broken down into several functions, including memory, speech and language, and executive functions, such as planning and attention, along with many others [16]. Several of these cognitive functions will be further explored below as they relate to Miyake's models of cognition [17,18]. This model was chosen this model to follow as it has been applied to dual-task research from its earliest days in cognitive psychology [19].

1.2.1 Executive Function

Executive function is a higher level cognitive process that produces, regulates, and monitors goal-directed behaviours [17,20]. Executive function can be further divided into smaller processes, such as volition, planning, shifting between information sets, multi-tasking, monitoring and updating working memory, and inhibition [17,20]. Executive function is commonly linked to the frontal lobe, an anatomical region of the brain which has an important role in both cognitive and motor networks [17,21]. Patients with damage to the frontal lobe often show detriments in cognitive processes that are part of executive function [22]. Earlier research in psychology often referred to executive function tests as

"frontal tasks" [17]. However, imaging studies have shown that other regions of the brain, mainly in the parietal lobe, are also activated in tasks of executive function [23].

The frontal lobe is sensitive to age related changes in structural integrity [21,24], which creates the high prevalence of executive dysfunction in older adults. This is attributed to the increase in vascular risk factors often seen in older adults, as these can lead to changes and ultimately damage to white matter in the brain [24]. Decline in executive function may also precede impairments in memory in both normal aging and in neurodegenerative diseases [25]. Impairments in executive function are also highly correlated with falls and slow gait speed in older adults [26]. In a large cohort of older adults, 35% of patients with low executive function experienced a fall within one year, compared to only 15% with higher executive function scores [27].

1.2.2 Working Memory

Working memory is a cognitive function that allows the brain to maintain and retrieve task relevant information [18]. In the past, working memory was often confused with short term memory. However, there is evidence that the systems function separately, as those with short term memory impairments are still able to process information to perform activities of daily living [28]. More recently, working memory has been associated more with executive function than memory under the model described by Miyake [17]. While working memory does require some aspects of information storage, the use of working memory is often more the ability to monitor and update information during cognitive tasks, which is an important executive function [17]. Working memory is also associated with walking, as it is required to follow a route or process changing surroundings [29]. In a study of patients with MCI, poor performance on tests of working memory was associated with slow usual gait speed and poor performance on dual-task gait tests [30].

1.2.3 Processing Speed

Processing speed is the speed at which information is processed during higher level cognitive functions associated with executive function [31]. Processing speed peaks in adolescence and declines with aging [31]. The processing speed theory of aging

described by Salthouse [32] proposes that age related decline in cognition can be attributed to decreased processing speed. Under this theory, slow processing speed causes decrease in cognitive function in tasks that require time sensitive response and in tasks that require input from multiple steps to complete later steps of processing. In relation to mobility, some studies suggest slow walking speed may be due to slowing in processing speed associated with aging and cognitive decline [33]. An additional study of processing speed and gait in older adults found that performance on multiple tests of processing speed explained the association between smaller prefrontal area volume and slow gait speed [34].

1.2.4 Attention

Attention is described as a number of different processes that are related aspects of how the brain becomes receptive to stimuli and how it may begin processing these stimuli [35]. While attention has no one definition, it can be thought of as a subprocess of executive function [20]. Attention as a process can be separated into focused, sustained, and divided or alternating attention [20]. Selective attention, or concentration, is the selection of relevant stimuli and the concurrent suppression of irrelevant stimuli [35]. Sustained attention is the ability to detect stimuli that are unpredictable over a long period of time [36]. Divided attention is the ability to perform more than one task at once, while alternating attention is the ability to switch between the two [20,35]. Attentional capacity varies between individuals and can be affected by many factors, including fatigue, brain injury, and aging [35]. Divided attention is of particular interest, as it is most sensitive to changes due to these factors [35] and is representative of the real world condition, as individuals are often susceptible to multiple attentional demands. Gait as an isolated task in healthy individuals requires limited attentional resources [37,38]. However, in those with neurodegenerative or neuromuscular diseases, or when an additional attention demanding task is added, attention is needed to maintain postural control and maintain steadiness in walking [37,39].

1.3 Cognition in Aging

Observed decline in cognition with aging can be attributed to slower processing speed [32] and depletion of cognitive reserve [40]. Decreased processing speed leads to cognitive operations not being completed within the required time limit for response. It can also cause breakdown in simultaneous cognitive operations due to products from earlier steps being forgotten once later steps are completed [32]. Alternatively, cognitive reserve is the idea that how different individuals process tasks makes some more resistant to deficits due to brain pathology [40]. The cognitive reserve theory of decline postulates that individuals have different levels of processing capacity, but all have a critical threshold and once one's capacity declines below this level, clinical and functional impairments are seen [40]. However, these impairments present differently in different people, which leads to the differential diagnoses of cognitive impairments seen in clinical settings.

1.3.1 Spectrum of Cognitive Impairment

There are many diagnoses associated with cognitive impairment that are seen with aging, but three of these are commonly used in clinical practice. In order of increasing severity, they are subjective cognitive impairment (SCI), mild cognitive impairment (MCI), and dementia (see Figure 1.1). SCI, also called subjective cognitive decline (SCD) [4], is characterized by the presence of memory complaints or worry about decline in cognition (e.g. slowness and word finding difficulties), with no objective impairment on cognitive testing (normal for their age and education level). While these patients do not have objective cognitive impairments, they are still at heightened risk of future cognitive decline over those without these subjective concerns [41].

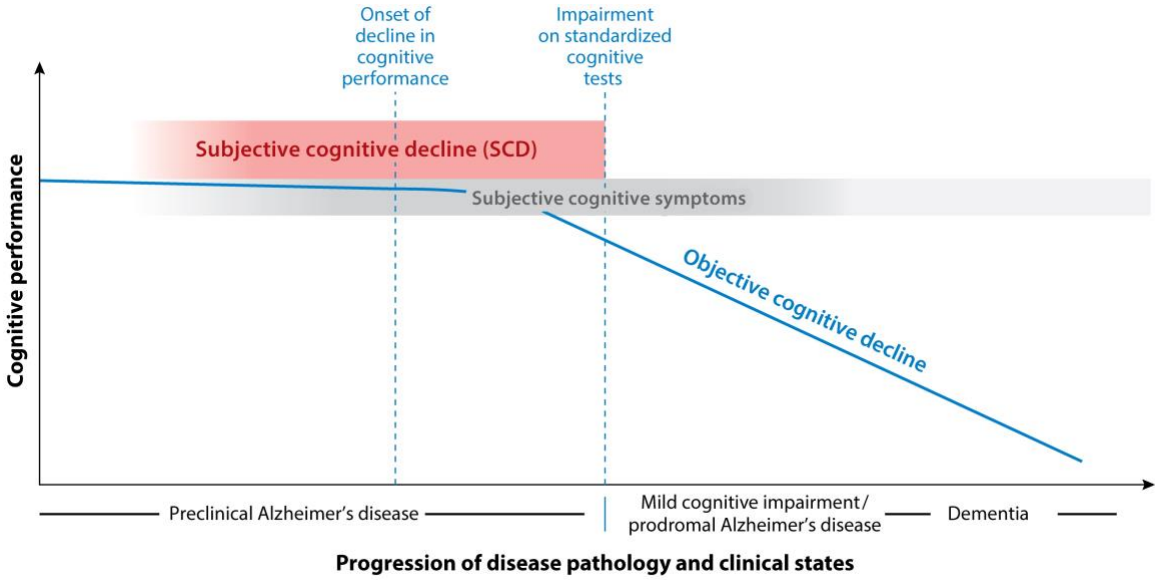

Figure 1.1 Model of the course of cognitive decline in relation to progression of Alzheimer's Disease pathology. Republished with permission of Annual Reviews, from Rabin, Smart, & Amariglio (2017) [4]**; permission conveyed through Copyright Clearance Center, Inc.**

1.3.2 Mild Cognitive Impairment

MCI is described in the literature as a pre-dementia state, as it is characterized by both subjective memory complaints and objective decline on cognitive testing greater than expected for normal aging [42]. To be diagnosed as MCI, patients must not have deficits in their activities of daily living due to their changes in cognition, but they are at higher risk for converting to dementia [42]. It is estimated that 10-20% of older adults over the age of 65 meet these criteria for MCI [5]. While 5-15% of those with MCI may progress to dementia each year, up to 30% of those with MCI will remain stable or revert back to normal cognition [5,43]. MCI may present in many different cognitive domains, and decline in each domain may present differently throughout the course of MCI [44]. In general, MCI that affects any memory domains is termed amnestic MCI, while non-amnestic MCI affects other domains of cognition, usually including attention, executive function, language or visuospatial skills [45]. MCI may also be present in more than one domain (multi-domain MCI) or a single domain. While memory is the most commonly

cited domain to have impairment in MCI, impairments of executive function are the second most prevalent [5,46] and may also be associated with increased depression and anxiety in patients with MCI[47].

1.3.3 Dementia

Dementia is a clinical syndrome resulting from several different underlying diseases which cause chronic impairment in cognition [6]. Dementia diagnosis is also characterized by subjective cognitive impairment, usually memory complaints with an objective impairment on cognitive testing greater than expected for normal aging, both affecting the patient's activities of daily living [8,48]. The four major types of dementia are Alzheimer's Disease, Lewy Body Disease, Frontotemporal dementia, and vascular dementia [49]. Alzheimer's disease dementia is the most common of these and accounts for 60-80% of total cases of dementia [50]. Five hundred sixty-four thousand Canadians are currently living with dementia, which costs the Canadian healthcare system $10.4 billion annually [51]. In 2018, Alzheimer's disease was the eighth highest overall cause of death in Canada and the sixth highest for those aged 85 and older [52].

Currently, treatment options for dementia are limited. Pharmacological treatments are aimed mainly at treating symptoms of the diseases, not the diseases themselves, and may come with physical and neuropsychiatric side effects [53]. Many multi-domain treatment studies including lifestyle interventions have shown promise in improving cognition in patients with dementia, however these may have issues of adherence and often require healthy lifestyle adaptation throughout the entire lifespan to show maximum benefits [54]. Therefore, the search for in depth knowledge on the causes of dementia and methods of early detection and diagnosis has become of the utmost importance in research [55].

1.4 Gait

Gait can be defined as "the pattern of movement of the human body during locomotion" [9]. Gait is commonly used to describe the manner or style of one's walking [10], and is one key component of overall mobility [56]. While there are normal fluctuations in gait parameters, gait is generally stable between each stride even in changing external

environments [57]. However, gait abnormalities are highly prevalent in older adults, both in those with neurologic diseases and healthy older individuals [58]. Population based studies estimate 30% of older adults over 60 have a gait disorder, but this may increase to up to 60% for those over 80 years old [59,60]. Gait disturbances, known as a deviation from a normal gait pattern, may be either continuous, when caused by an underlying neuromuscular condition, or episodic, when in response to a change in the environment [61]. Increased gait variability, or step-to step fluctuations in time or distance, may be either of these, as it can be due to many conditions, such as stroke, neuropathy and depression, or due to environmental changes, such as negotiating an obstacle or performing multiple tasks at once [62]. Gait disturbances, and specifically high gait variability, have been associated with future risk of falls [63–66], frailty [67], mobility impairments and disability [68–70], and cognitive impairments and dementia [15,71–74].

1.4.1 Gait Cycle

The gait cycle is made up of both stance and swing phases (see Figure 1.2), with the stance phase marking when the foot is on the ground, and the swing phase marking when the foot is moving through the air [10,75]. The stance phase comprises about 60% of the gait cycle, and begins and ends with both feet on the ground [76]. The swing phase makes up the other 40% of the cycle, and begins with toe-off and ends with heel strike [76]. Once full gait cycle, or stride, is the interval between when one foot strikes the ground until the same foot strikes the ground again [75].

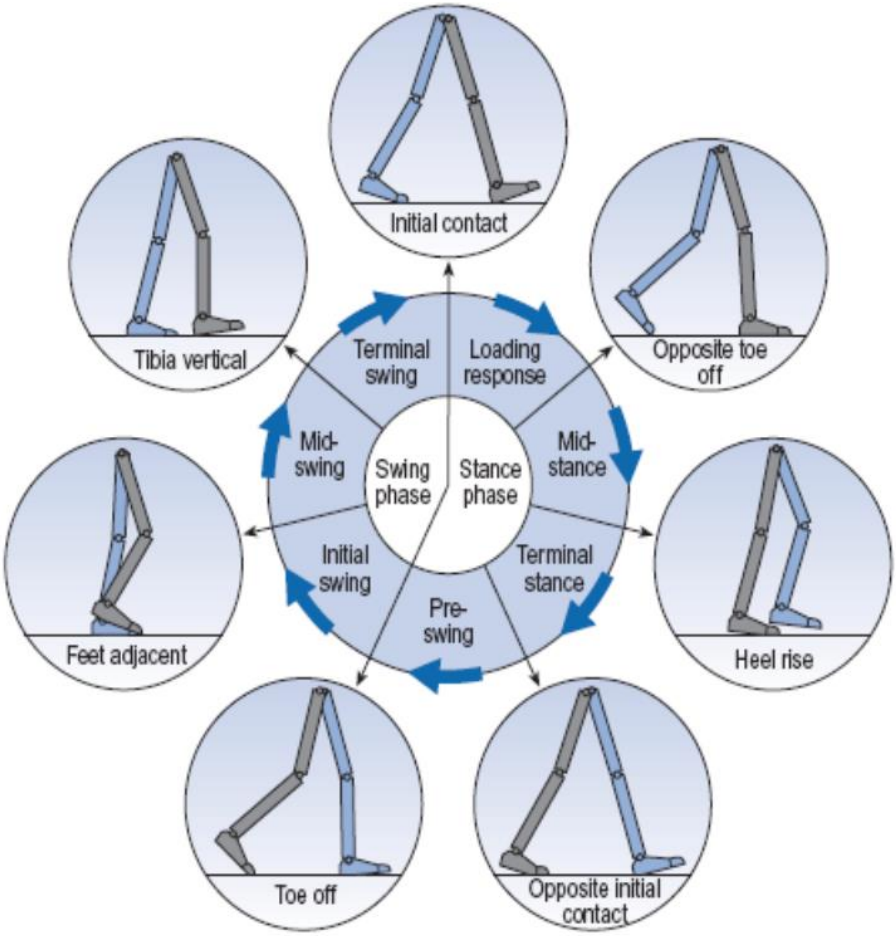

Figure 1.2 Phases of the gait cycle. From Kharb et al. (2011) [75]

1.4.2 Gait Assessment

Gait can be assessed by simple clinical observation or by quantitative testing. Quantitative gait testing can be done using various technologies, such as video recordings, electronic walkway, or accelerometer and wearable sensors. Gait testing technologies can give extended information about a person's walking and defined spatio-temporal quantitative variables can be assessed and recorded (see Table 1.1). For example, computerized walkways using pressure sensors to detect each footprint have become popular in research as they do not require a trained clinician and are highly reliable [77,78]. However, these technologies may be too expensive and the outputs too complex for use in clinical settings.

Alternatively, clinical observation of gait has some benefits as well. Clinical observation of gait includes an individual performing a number of walks while a trained clinician observes one or more parameters of the individuals gait pattern. These parameters may include: initiation, posture, gait speed/velocity, arm swing, freezing and more [76]. During clinical observation of gait, one important and clinically relevant quantitative variable, gait speed, can simply be assessed using a stop watch and a marked path of a known distance [14]. Using our previously published guidelines [14], gait testing can be done in a clinical setting using a measured path on the floor (ideally six meters) and a stop watch. While clinical observation of gait gives less quantitative information overall, it can give clinicians useful information and it has been validated against traditional technologies [79]. However, this approach may require more nuanced training for assessment and classification of results.

Table 1.1 Definitions of Commonly Used Quantitative Spatiotemporal Gait Variables. From Cullen et al. (2018) [14]

Variable	*Units*	*Definition*
Velocity	meters/second	Distance covered by the time to ambulate
Cadence	steps/minute	Number of steps by the time to ambulate
Stride length	meters	Distance between heel points of two consecutive footfalls of the same foot
Step length	meters	Anterioposterior distance between the heel points of two consecutive footfalls of the opposite foot
Step width	meters	Mediolateral distance between the heel points of two consecutive footfalls of the opposite foot
Stride time	seconds	Duration to ambulate one stride length
Step time	seconds	Duration to ambulate one step length
Double support time	seconds	Duration of when both limbs are in contact with the ground

1.4.3 Gait Speed

Gait speed can be defined as "the distance covered by the time to ambulate", and is a simple to collect but effective measure of mobility [14,80]. It can be measured using either quantitative gait testing technologies, or the simple stop watch collection method as described above. Gait speed has been described as the sixth vital sign in older adults due to its sensitivity to detecting changes in different settings and clinical conditions [81–83]. It was found that a decrease in gait speed of 0.1m/s was associated with poorer health status and disability, while an increase of the same amount of associated with overall well-being [82]. Gait speed has also been called the functional vital sign due to its predictive abilities and ease of collection [83]. The term "bradypedia" has even been suggested as a clinical diagnosis for slow gait speed [84].

Slow gait speed has also been associated with falls, limitations in activities of daily living, dementia and even mortality [65,81,85–88]. In a pooled analysis of several large cohort studies (n=27,220), a difference of 0.1m/s faster in gait speed was associated with a decrease in risk of mobility disability by 26% in men and 27% in women (see Figure 1.3), and a decrease in risk of mortality over four years between 18% and 24% [89]. These associations between slow gait speed and poor cognitive function can already be seen in midlife, and may even be related to poor development in childhood [90,91]. However, accelerated decline in gait speed in aging has been associated with an increase in energy demands of walking, specifically due to changes in body composition, lower extremity pain, poor balance, and other biomechanical and neuromuscular factors [92,93].

While usual or self-selected gait speed is the most commonly studied, other measurements of gait speed may be of interest. Maximum walking speed, where the participant walks as fast as they can without running, has been suggested as a useful measure in detecting changes in mobility performance and is associated with mobility disability [14,83,94]. Additionally, gait speed while performing an added cognitive task, or dual-task gait speed, has been associated with cognitive impairments and future risk of cognitive decline [15,95,96].

Changes in gait speed may be one of the earliest physical symptoms of dementia and are associated with severity of the disease [97]. Therefore, tests of gait and motor performance may be useful in detecting early signs of cognitive impairment, before cognitive symptoms are detectable [98].

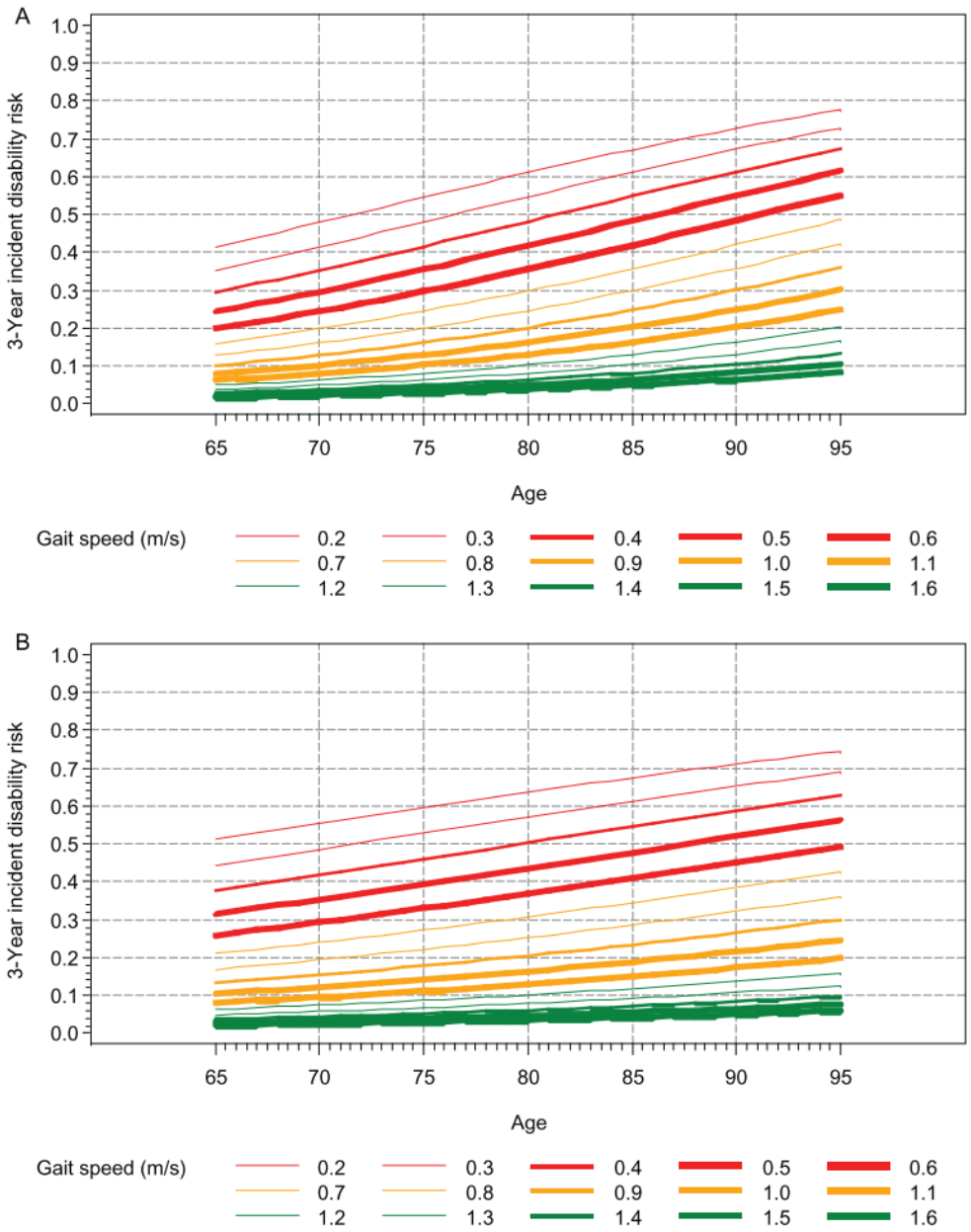

Figure 1.3 Gait speed in association with mobility difficulty for men (A) and women (B). Used with permission of Oxford University Press, from Perera et al. (2016) [89]

1.4.4 Gait and Cognition

While gait was once thought to be an automatic process requiring little cognitive input, recent evidence has shown that gait and cognition may be more highly correlated than once thought [38]. Firstly, gait performance and cognition both decline with age, and large cohort studies have shown they often coexist in older adults [63,99–101]. Poor gait performance has specifically been associated with low performance on tests of executive function, as this higher level cognitive process collects information from the sensory systems and uses it to produce and monitor behaviour and movements [20]. Gait performance, particularly speed, has also been linked to other cognitive domains, such as memory [102] and attention [39]. Additionally, decreased gait speed is one of the earliest physical symptoms of dementia and may manifest years before cognitive impairments are detectable [97].

1.5 Motor-Cognitive Interface

The presented evidence linking gait and cognition creates the theory of a motor-cognitive interface (see Figure 1.4). This relationship between mobility and cognitive domains is not fully understood yet [62], but it is known that regulation and control of gait and cognitive processes rely on shared brain areas and networks that are susceptible to damage during aging, diseases associated with aging, and neuropathology. Completing both a motor and cognitive task at once can put stress on these systems and even overload them if there are already cognitive challenges present. This overload can lead to deficits in one or both tasks that can be measured, and provides an opportunity to use a dual-task gait test as a “brain stress test” [14].

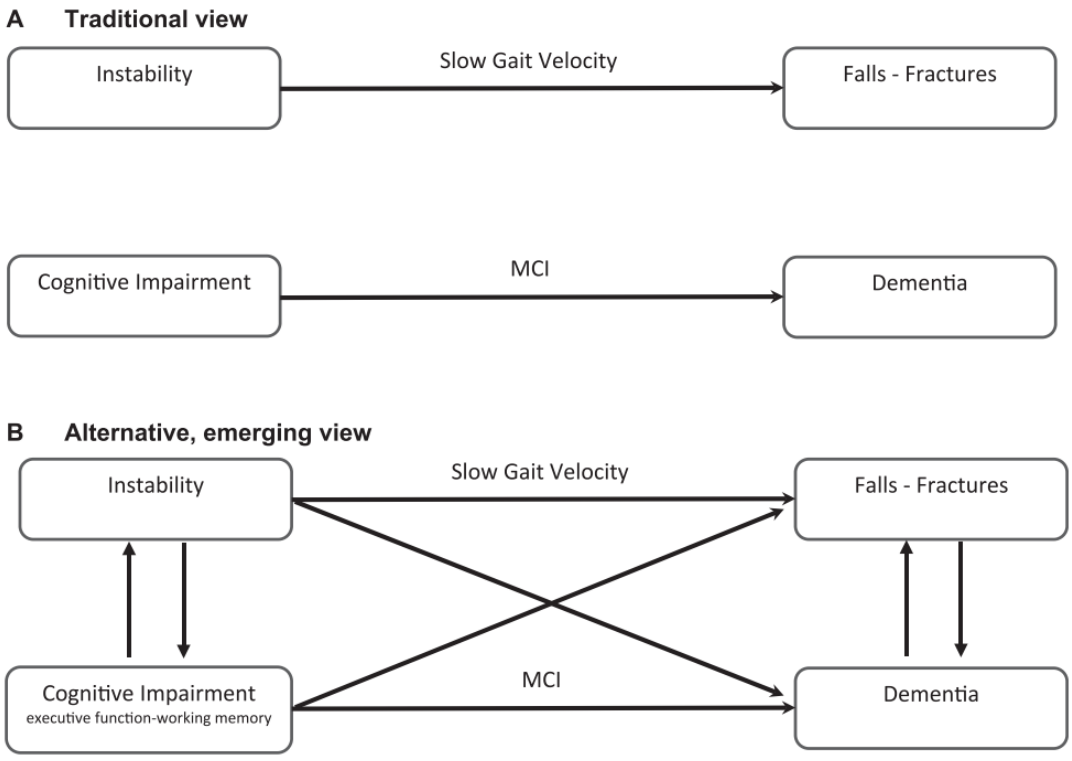

Figure 1.4 (A) Traditional view of cognitive and gait decline with aging and (B) the emerging view based on evidence of the cognitive-motor interface. From Montero-Odasso et al. (2012) [63]

1.5.1 Dual-Task Paradigm in Gait and Cognition Assessment

The dual-task paradigm suggests that two tasks done at the same time creates competition between the two tasks for a limited amount of brain resources, and this competition creates a detriment in one or more of the activities [20]. Dual-task gait testing, defined as "walking while performing a cognitively demanding task", applies this paradigm to the interaction of mobility and cognition. Walking and cognitive tasks rely on shared networks in the brain, and while these shared networks are also not fully known, the most commonly described areas include the frontal lobe (ex. prefrontal and supplementary motor areas) and temporal lobe (ex. hippocampus) [103–105]. This testing was derived from a seminal study showing that nursing home residents who were not able to hold a conversation while walking were at a higher risk of falls [106].

1.5.2 Theories of Dual-Tasking

There are three main theories for how dual-tasking is processed in the brain. The first of these is the capacity sharing model, which is based on the idea that attentional tasks performed at the same time compete for a limited capacity of neural resources [39,107,108]. The competing tasks can overload these resources, therefore causing the disturbances we see in gait and cognitive tasks while dual-tasking [20]. The degree of this effect, and in which of the two tasks it shows up in, is dependent on the type and difficulty of both the cognitive task and the walking task [39,108]. The instructions given can also influence which task is given priority (ie. higher attentional resource allocation) [107], which is why in dual-task gait testing it is suggested to instruct participants to equally prioritize both tasks [14] in order to best mimic what happens naturally while walking [109,110].

A second theory of the processing of dual-tasking is the bottleneck theory, which proposes that if two tasks require the same processor and that processor can only process one task at a time, the second task is put on hold until the first is completed [107,108]. It is also possible that multiple bottlenecks occur during the entire response process at different stages, such as response selection and response execution [107,108].

Finally, a third theory of dual-tasking has to do with the similarities and differences between the two tasks, and is called the cross-talk theory [108,111]. This theory relates to decreasing peripheral overload, and postulates that similar tasks are more easily processed together due to the "turning on" and use of similar processors [108]. For example, it was found that performance in a rhythmic cognitive task, counting backwards by ones, could be improved while walking when compared to just sitting, as walking also has a rhythmic component [112]. However, there is some criticism of this theory that suggests similar tasks processed together may cause side effects or "confusion" that negatively affect performance [108].

1.5.3 Dual-Task Gait Cost

From dual-task gait testing we can calculate dual-task gait cost (DTGC), which is a measure of the "cost" incurred by dual-tasking versus doing either the mobility or

cognitive task alone (see Figure 1.5). DTGC measures how the added cognitive task impairs gait performance, and can be calculated with any of the quantitative variables collected in gait testing [14]. Dual-task cognitive cost (DTCC) can also be calculated, depending on the cognitive task being completed, using response rate, number of correct answers, or reaction time [14]. Older adults may prioritize gait and balance over cognitive tasks [113], which cause DTCC to be larger than DTGC. However, DTGC for gait speed is the more commonly reported measure of dual-task gait testing, without consideration of DTCC, possibly due to differences in calculation of DTCC based on type of cognitive task used and the difficulty of determining an accurate rate of enumeration for the cognitive task, both by itself and while walking [114].

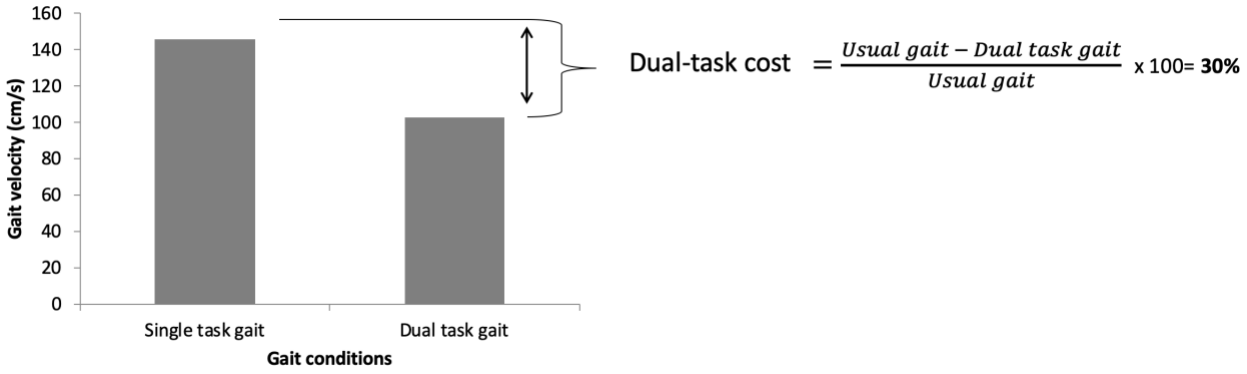

Figure 1.5 Visual representation of the dual-task cost calculation for gait speed. Unpublished, used with permission from Dr. Manuel Montero-Odasso.

1.5.4 Studies of Dual-Task Gait Testing in a Clinical Setting and Current Gaps in the Literature

To date, there are only three published studies of dual-task gait testing in a memory clinic setting that we are aware of. The first of these was by MacAulay and colleagues [115], which found patients with MCI made more cognitive errors while dual-tasking and slowed down more when dual-tasking, in comparison to just walking, than healthy controls (this was not quantified as dual-task cost but represents the same phenomenon). Another study by Nielsen and colleagues [96] showed that dual-task cost using the Timed

Up and Go test was able to separate healthy controls from patients with MCI and from patients with dementia patients, but that it had a low prognostic value for future cognitive decline. Furthermore, both of these studies had small sample sizes (*n*=61 and 86, respectively), and these studies did not examine patients with a diagnosis of SCI. The final study available was published by our group [116], and is a preliminary analysis of the results that will be presented in this thesis. However, this previously published work only included cross-sectional data and about half of the sample that will be presented within this thesis. This previously published work concluded that using the three main cognitive subtypes: SCI, MCI, and dementia, patients diagnosed with dementia had slower gait speed and higher dual-task cost.

1.6 Overview of Thesis

1.6.1 Rationale

The presented literature supports the potential use of dual-task gait testing as a "stress-test" on the brain and its allocation of resources, which may be useful for detecting those individuals at high-risk for future cognitive decline. Specifically, dual-task gait performance was associated with progression to dementia in patients with MCI [15]. However, with only two relatively small studies of dual-task gait testing in clinical settings [95,96], there exists a gap in the literature of a large, long-term clinical cohort with a wider spectrum of cognitive diagnoses who are tested under multiple different dual-tasks.

1.6.2 Purpose

The purpose of this thesis is to, within a clinical setting, 1) assess feasibility and practicality of gait performance to help differentiate cognitive diagnoses, 2) assess differences in gait speed and dual-task gait cost across the cognitive spectrum, and 3) determine if poor gait performance at baseline is associated with future cognitive decline.

1.6.3 Hypotheses

At the cross-sectional level, it was hypothesized that 1) gait speed will be slower and dual-task gait cost will be higher for older adults attending a memory clinic that are

diagnosed with more severe cognitive impairment and 2) poorer performance on the dual-task gait assessment will be predictive of worse cognitive impairment.

Within the longitudinal sub-study, it was hypothesized that slow gait speed and higher dual-task gait cost at baseline will be predictive of cognitive decline at the follow-up visit.

Chapter 2

2 Methods

We have previously published a sub-set of this data in the Journal of Alzheimer's Disease and the following methods have been adapted from this publication [116].

2.1 Study Design and Participants

Clinic-based study that included all consecutive older adults who were assessed for memory complaints at the Aging Brain and Memory Clinic at Parkwood Institute in London, Ontario, Canada between July 2015 and May 2019. In order to be included in the current study, participants had to (1) be over 50 years of age, (2) be able to safely ambulate six meters without an assistive device, and (3) be fluent in English and able to understand test instructions. In order to be included in longitudinal analysis, participants had to meet baseline inclusion criteria and have a second visit in the clinic minimum of twelve months after their first visit. Follow-up visits in the clinic were usually scheduled two to three years after the baseline visit. To maximize inclusion and to ensure an accurate representation of the population seen in our clinics, no additional exclusion criteria were used. Participants were grouped into three categories based on final diagnosis: SCI, MCI and dementia. Diagnosis was achieved using a consensus conference and established criteria (Petersen criteria for MCI [5] and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition revised (DSM IV-TR) criteria for dementia [8]) after assessment performed by a geriatrician specialized in cognitive aging and dementia. Petersen criteria for MCI was ascertained by satisfying the following four criteria i) subjective cognitive complaints; ii) objective cognitive impairment in at least one of the following cognitive domains: memory, executive function, attention, and language; iii) preserved activities of daily living; confirmed by a geriatrician specialized in cognitive aging and dementia; iv) absence of dementia using criteria from the DSM IV-TR. This study was approved by the Health Science Research Ethics Board at

Western University and the Clinical Research Impact Committee at Lawson Health Research Institute, both in London, Ontario, Canada.

2.2 Demographic and Clinical Variables

All participant information and gait testing results were collected from patient charts. Demographic and clinical information collected included age, sex, falls history in the past 12 months, years of education, medications and comorbidities (see Appendix B). Comorbidities were measured as total number of "yes" responses on a clinical comorbidities checklist. Cognitive variables include Mini Mental State Examination (MMSE) score and the Montreal Cognitive Assessment (MoCA) score.

2.3 Gait Testing Procedure

All gait assessments were performed at the start of the clinical visit in a hallway outside the clinic room using a six-meter path. Six meters was chosen as it has been shown to be an appropriate length to be used for older adults without mobility impairments to ensure steady state walking is achieved [117]. Lines were marked on the floor to determine the stop and start points. One meter was added to each end of the pathway (as shown in Figure 2.1) to ensure acceleration and deceleration phases were not recorded. Walking trials were timed using a handheld stopwatch and recorded to two decimal places. Speed was calculated by dividing the known distance by the time spent walking from start to end points marked on the floor, in each trial, for each participant, and then converted to cm/s.

All participants were asked to complete a total of four walk trials. The first trial was always the preferred or usual gait speed trial. For this trial, the participants were asked to walk at their normal, every-day walking speed. The next three trials were the dual-task walking trials, which comprised walking at usual speed while preforming an added cognitively demanding task. The order of dual-task trials was fully randomized. The three tasks used for this study were counting backwards by 1's from 100 out loud, naming animals out loud, and counting backwards by 7's from 100 out loud, which have been previously validated and are listed here in order of increasing cognitive demand [37,118–

120]. Participants were instructed to equally prioritize both walking and the cognitive task to accurately replicate normal daily activities[20,109]. Number of enumerations and errors per each dual-task trial was also recorded in the patient's chart along with the speed for each trial. Participants were included in the analysis as long as they completed the usual gait speed trial and at least one of the dual-task trials. This gait protocol followed the Canadian guidelines for gait assessment we have published [14].

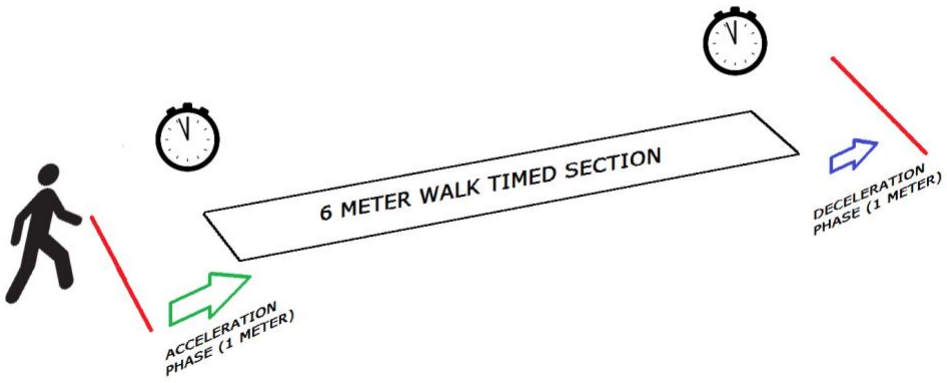

Figure 2.1 View of the gait testing pathway used in the Aging Brain and Memory Clinic. From Cullen et al. (2018) [14]

2.4 Feasibility Measures

For cross-sectional feasibility investigations, both quantitative and qualitative measures were used. Participant agreement was measured quantitatively as the percentage of eligible participants who completed a gait assessment at the clinic visit. Participants were included if they completed the usual gait walk and at least one dual-task walk. In order to establish the feasibility and practicality of gait testing in a busy clinical setting, after the study was completed we surveyed the two primary assessors who completed the gait testing. Assessor satisfaction was measured using the following questions:

Using a Likert scale from 1 ('Very Easy') to 5 ('Very Hard'):
1) How easy was the dual-task gait assessment to complete?

2) How easily was the dual-task gait assessment integrated into the flow and timing of the clinic appointment?

There was also the option to add additional comments to any of the ratings given above.

2.5 Calculation of Dual-Task Gait Cost (DTC)

DTC was calculated for each dual-task trial using the appropriate velocities. DTC was calculated in Microsoft Excel 2010 using the following formula: DTC = [(usual gait speed – dual-task gait speed)/usual gait speed] x 100. DTC is expressed as a percentage of slowing from the usual gait speed as a result of the added cognitive task [121]. For this thesis, DTC will refer only to dual-task gait cost, as dual-task cognitive cost was not examined.

2.6 Outcome Variables and Criteria

Following the objective of this thesis to determine if poor baseline gait performance was associated with future cognitive decline, three outcome variables were used to quantify cognitive decline at the follow-up visit. The first of these was a progression to a more severe diagnosis of cognitive impairment, which was categorized as conversion from SCI to MCI or dementia, MCI to dementia, or early/prodromal dementia to moderate or severe dementia. While this outcome is important for clinical use and for comparison to other studies measuring conversion to dementia [15,71], there is an inherent heterogeneity in these various changes and the potential for subjective bias. For example, conversion from MCI to dementia, based on some criteria, can be a result of the patient themselves or their caregiver reporting a change in activities of daily living (ADLs) and not due to changes in cognition [122–124]. For this reason, we have also decided to investigate if gait performance predicts decline in scores on cognitive tests, specifically the Mini Mental State Exam (MMSE) and Montreal Cognitive Assessment (MoCA). These objective measures have been thoroughly studied, and it was determined based on previous studies that cognitive decline would be operationalized as a drop of greater than two points per year on the MoCA [72,125]. For example, it was previously found in a study of MCI patients that the mean drop in total MoCA score was 2.19 points per year in

those who eventually converted to dementia and 1.72 points per year for those who remained MCI [125]. Estimates of average rate of decline on the MMSE vary and have been reported between less than one point per year for older people with normal cognition [126] and up to and over four points per year for patients with dementia [127–129]. Given the mixed diagnosis groups in our sample and to remain consistent with our criteria for MoCA decline, this outcome variable was also operationalized as a drop of greater than two points per year. Given the average follow-up period in our sample is at least two years, these values are also consistent with the minimal detectable change of three points on the MMSE and four points on the MoCA [130].

2.7 Statistical Analyses

Data were checked for normality and homogeneity of variances using the Kolmogorov-Smirnov and Levene's tests, respectively. Demographic and clinical characteristics were summarized as means and standard deviations or frequencies and percentages, as appropriate. Baseline demographic characteristics were compared between groups using one-way analysis of variance (ANOVA) or Chi-Square tests. Statistical significance was set at $p<0.05$. Statistical analyses were conducted using SPSS, version 25 (IBM Corporation).

2.7.1 Cross-sectional Analyses

Gait speed and dual-task gait cost were compared across groups using a repeated measures two-way analysis of variance (ANOVA), both unadjusted and adjusted for age, to evaluate the effect of cognitive diagnosis (diagnosis) across the different gait tasks (task) and their interaction (diagnosis x task).

The association between gait performance and diagnosis of an objective cognitive impairment MCI or dementia) was analyzed using a multi-factor regression with SCI as the reference category, with gait speed and dual-task cost as the independent variables and adjusted for age and sex. The association between gait performance and dementia diagnosis was also analyzed using a logistic regression, with dementia and pre-dementia (SCI or MCI) as the dichotomous outcome variable.

Receiver Operating Curves (ROC curves) with corresponding area under the curve (AUC) were created to determine the optimal cut-off point for slow gait speed in each gait test. AUC was classified using the clinical categorizations of low accuracy (0.5-0.7), moderate accuracy (0.7-0.9) and high accuracy (0.9 and higher). Moderate accuracy (0.7 or higher) is considered clinically relevant [131]. Sensitivity and specificity were determined for each cut-off point from these curves. Association between dementia diagnosis and slow gait speed using these cut-off points was assessed using a binary logistic regression.

2.7.2 Longitudinal Analyses

Cox regression analyses were completed to assess risk of progressing to a worse diagnosis, as measured by hazards ratios (HR), based on gait performance (usual and dual-task gait speed and dual-task cost) as continuous and dichotomous variables. Cut-off values for gait speed and dual-task cost were set at the mean of each variable for the sample. Proportional hazards were checked using visual inspection of Kaplan-Meier curves. Time was calculated as the number of months between the baseline visit and the follow-up visit in the clinic. To account for different follow-up periods, decline on cognitive tests was measured as points per year decline.

Chapter 3

3 Cross-Sectional Gait Performance and Measurement in a Clinical Setting

This chapter will explore the use of gait testing in a memory clinic setting from a cross-sectional standpoint. Specifically, this chapter will focus on the previously stated goals of this thesis, to determine 1) differences in gait speed and dual-task gait cost across the cognitive spectrum in a clinical setting and 2) if measuring gait performance is feasible in a clinic setting and useful to help differentiate cognitive diagnoses.

3.1 Results

3.1.1 Participant Characteristics

Three hundred seventy-two participants (mean age 72.83 ± 10.05 years; 50.8% female) met inclusion criteria. This sample included eighty-one participants with SCI, one hundred fifty-five participants with MCI and one hundred thirty-six with dementia. Characteristics of the study sample stratified by cognitive diagnosis are presented in Table 3.1. Mean age of participants was significantly higher across the spectrum of cognitive impairment. As expected, MMSE and MoCA scores were significantly lower in groups with more severe cognitive impairment diagnosis. The SCI group had significantly higher years of education than both the MCI and dementia groups. All three groups had similar number of comorbidities, number of medications, and twelve month falls histories.

Table 3.1 Demographic and clinical characteristics of study participants in sample stratified by cognitive diagnosis

		Stratified by Cognitive Diagnosis			
Variable	**Total Cohort** (*n*=372)	**SCI** (*n*=81)	**MCI** (*n*=155)	**Dementia** (*n*=136)	***p*-value**
Age (mean, SD)	72.83 (10.05)	65.57 (10.38)	71.97 (9.30)	78.13 (7.38)	**<0.001**
Female (n, %)	189 (50.8%)	47 (58.0%)	75 (48.4%)	69 (50.7%)	0.281
Years of education (mean, SD)	12.7 (3.4)[b]	14.0 (3.1)[c]	12.3 (3.3)[d]	12.3 (3.5)[e]	**0.001[a]**
No. of Comorbidities (mean, SD)	5.7 (3.3)	5.6 (3.7)	5.9 (3.2)	5.5 (3.1)	0.636
No. of medications (mean, SD)	7.9 (4.5)	8.0 (5.0)	7.8 (4.3)	8.0 (4.3)	0.921
MMSE score (mean, SD)	25.4 (4.6)[f]	29.0 (1.6)	26.6 (2.8)[g]	21.8 (4.9)	**<0.001[a]**
MoCA score (mean, SD)	21.1 (5.0)[h]	26.8 (2.0)[i]	21.1 (3.6)[j]	16.8 (4.0)[k]	**<0.001[a]**
Falls (n, %)[l]					
No falls	276 (74.2%)	63 (77.8%)	119 (76.8%)	94 (69.1%)	0.230
1 fall	59 (15.9%)	14 (17.3%)	22 (14.2%)	23 (16.9%)	
2+ falls	37 (9.9.1%)	4 (4.9%)	14 (9.0%)	19 (14.0%)	

Statistically significant values are bolded.

Abbreviations: SCI = Subjective Cognitive Impairment. MCI = Mild Cognitive Impairment. MMSE = Mini-Mental State Examination. MoCA = Montreal Cognitive Assessment.

[a], p-value reported from Welch's Test for unequal variance.

[b], data available for *n*=332.

[c], data available for *n*=74.

[d], data available for *n*=143.

[e], data available for *n*=115.

[f], data available for *n*=370.

[g], data available for *n*=153.

[h], data available for *n*=339.

[i], data available for *n*=80.

[j], data available for *n*=152.

[k], data available for *n*=107.

[l], in the past 12 months only.

3.1.2 Differences in Gait Speed Across the Diagnosis Groups

Gait speed for each group in each gait condition is summarized in Figure 3.1, Figure 3.2, and Table 3.2. Gait speed was lower in each group from usual gait to dual-tasking and with increasing dual-task difficulty. The repeated-measures ANOVA was significant when unadjusted and adjusted for age. Post-hoc analysis revealed that in the usual gait, counting backwards and naming animals tasks, the SCI and MCI groups were statistically similar to each other, but the dementia group was significantly different from both of those groups. In the serial sevens condition, only the SCI and dementia groups were statistically different (p=0.01). Within groups analysis showed that in the SCI and dementia groups the counting backwards and naming animals tasks were statistically similar (p=0.07 and p=0.31, respectively). All other within groups comparisons were significantly different ($p<0.05$).

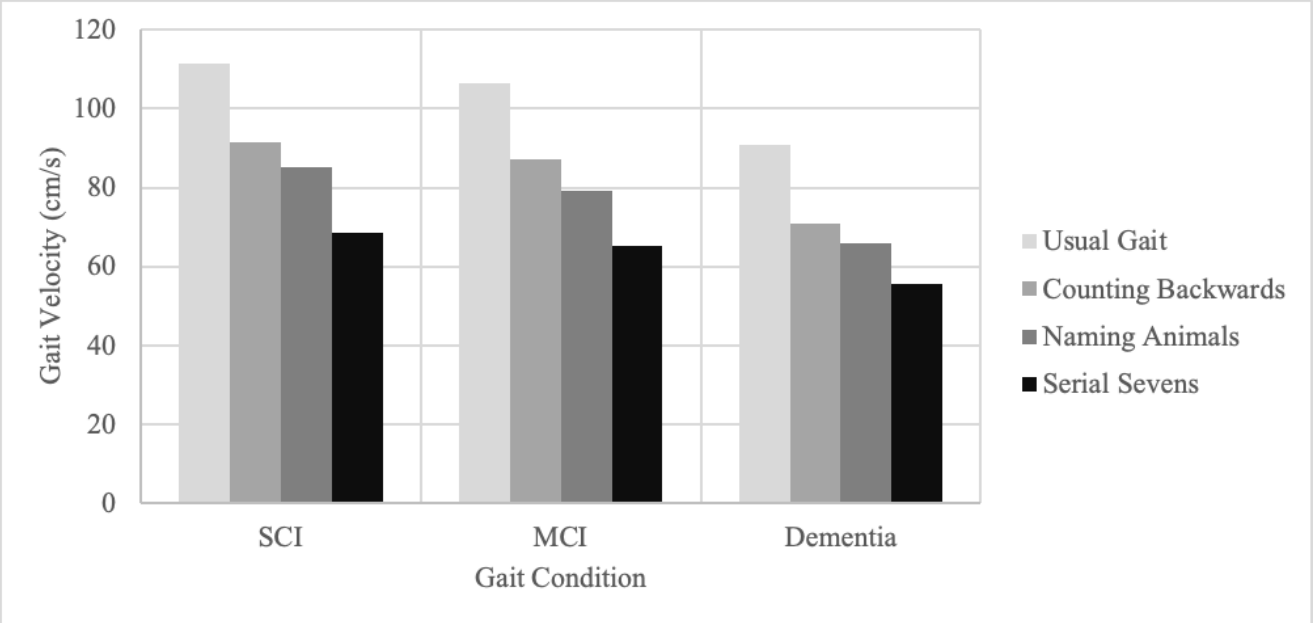

Figure 3.1 Gait speed (cm/s) stratified by diagnosis group

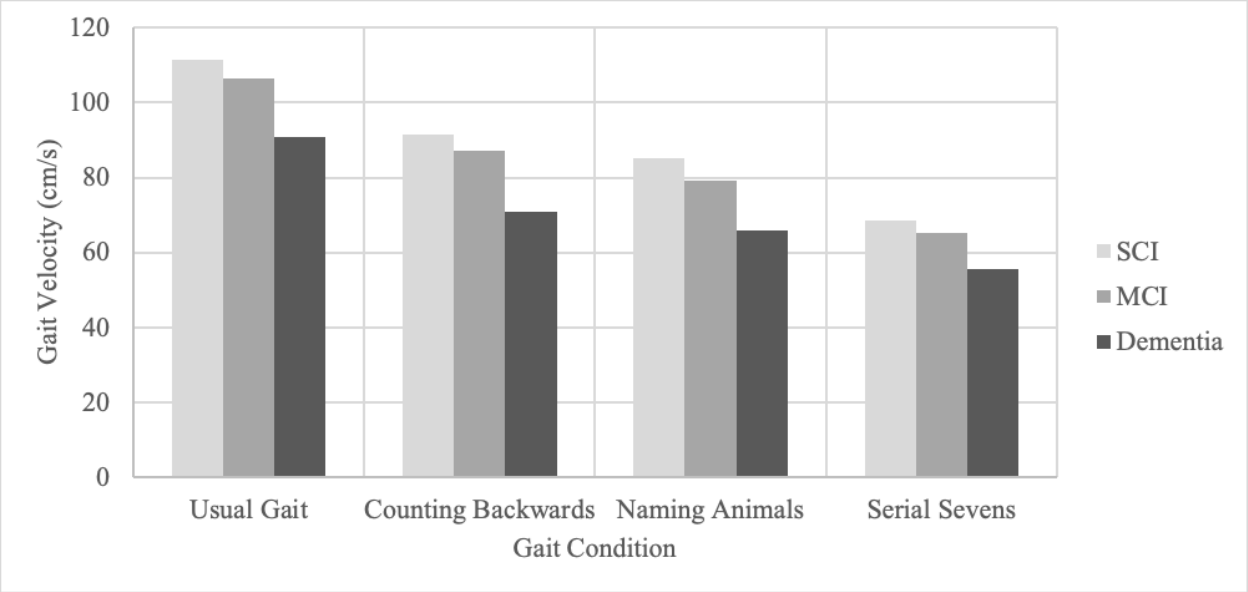

Figure 3.2 Gait speed (cm/s) stratified by gait condition

Table 3.2 Gait Speed performance (cm/s) by cognitive diagnosis and gait condition

Gait Condition [mean (SD)]	**Total cohort** (*n*=296)	**SCI** (*n*=74)	**MCI** (*n*=128)	**Dementia** (*n*=94)	***Effects* *p*-value** Model 1	***Effects* *p*-value** Model 2
Usual gait	102.69 (24.64)	111.39 (24.19)	106.27 (22.89)	90.96 (23.13)	Diagnosis: **<0.001** Condition: **<0.001**	Diagnosis: **<0.001** Condition: **<0.001**
Counting backwards	83.02 (24.25)	91.63 (24.72)	87.01 (22.26)	70.79 (21.83)	Interaction (Diagnosis*Condition): **0.04**	Interaction (Diagnosis*Condition): 0.21
Naming animals	76.42 (23.11)	85.02 (23.03)	79.26 (21.04)	65.79 (22.11)		
Serial sevens	62.98 (21.22)	68.61 (22.51)	65.14 (19.77)	55.61 (20.25)		

Statistically significant values are bolded.

n=76 excluded due to missing data in one or more gait conditions.

Model 1: Unadjusted. Model 2: Adjusted for age.

p-values reported are using the Greenhouse-Geisser correction for sphericity.

3.1.3 Differences in Dual-Task Gait Cost (DTC) Across the Diagnosis Groups

DTC for each group is summarized in Figure 3.3, Figure 3.4, and Table 3.3. The repeated measures ANOVA showed that DTC performance was only significantly associated with which dual-task condition was being performed ($p<0.001$). Within each diagnosis group, DTC increased with increasing task difficulty. There was no statistically significant difference in DTC between diagnosis groups ($p=0.43$).

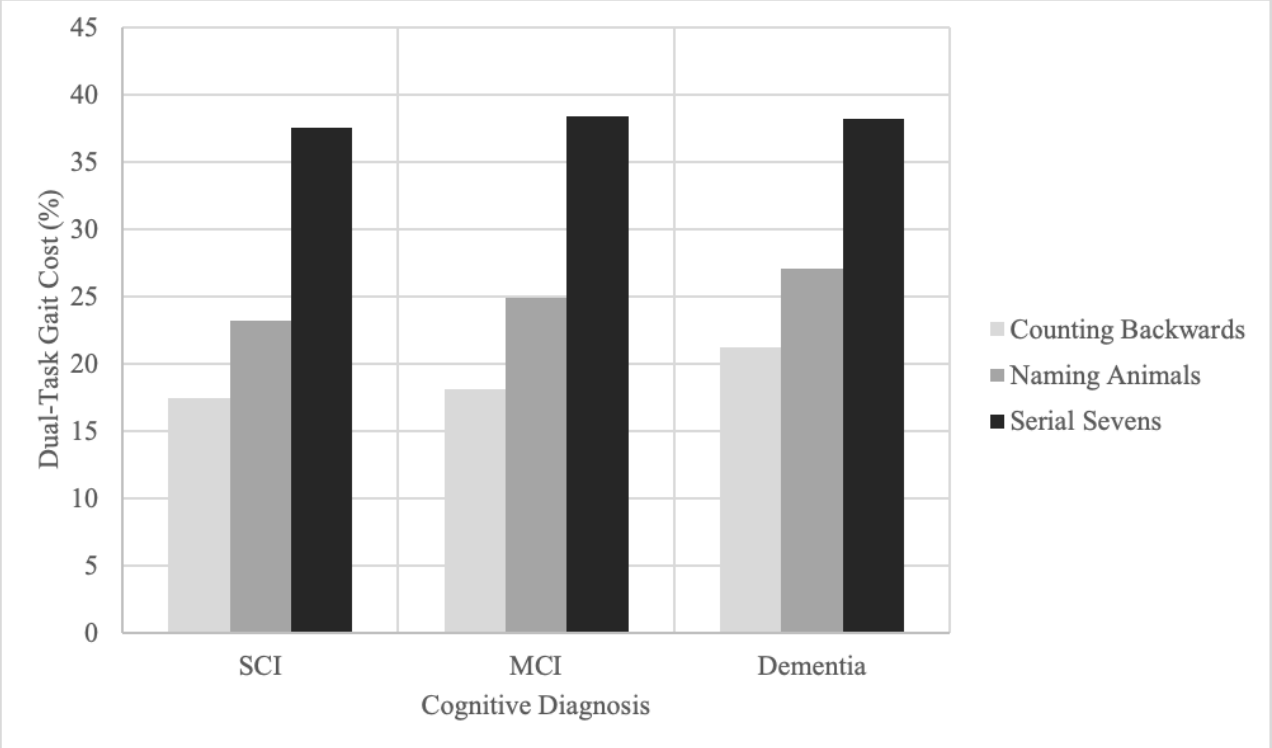

Figure 3.3 Dual-task gait cost (%) stratified by diagnosis group

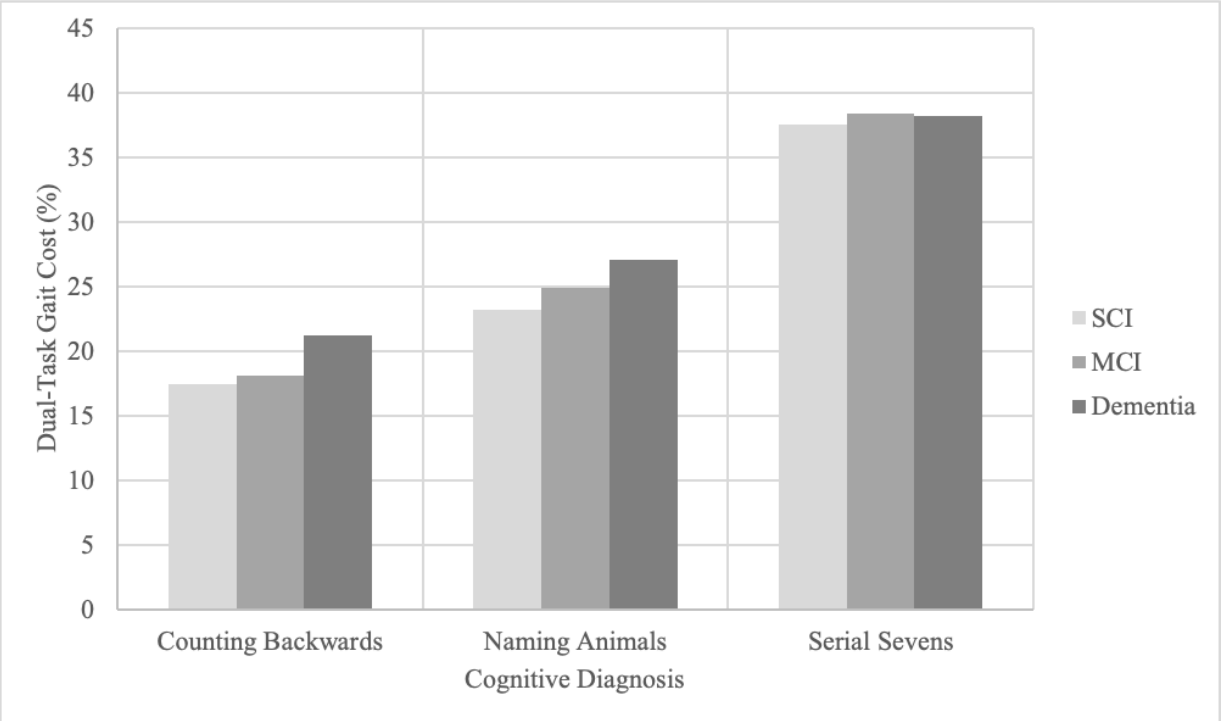

Figure 3.4 Dual-task gait cost (%) stratified by gait condition

Table 3.3 Dual-task Cost (%) by cognitive diagnosis and gait condition

Gait Condition [mean (SD)]	**Total cohort** (*n*=296)	**SCI** (*n*=74)	**MCI** (*n*=128)	**Dementia** (*n*=94)	***Effects* *p*-value** Model 1	***Effects* *p*-value** Model 2
Counting backwards	18.94 (14.62)	17.47 (15.30)	18.13 (12.23)	21.21 (16.81)	Diagnosis: 0.43 Condition: **<0.001**	Diagnosis: 0.10 Condition: **0.03**
Naming animals	25.21 (15.65)	23.26 (24.95)	24.95 (14.72)	27.14 (16.81)	Interaction (Diagnosis*Condition): 0.40	Interaction (Diagnosis*Condition): 0.30
Serial sevens	38.13 (17.39)	37.60 (18.41)	38.41 (17.32)	38.18 (16.86)		

Statistically significant values are bolded.

n=76 excluded due to missing data in one or more gait conditions.

Model 1: Unadjusted. Model 2: Adjusted for age.

p-values reported are using the Greenhouse-Geisser correction for sphericity.

3.1.4 Association between Gait Performance and Objective Cognitive Impairments

The association between gait performance on each dual-task condition and cognitive diagnosis was examined with SCI as the reference level (Table 3.4). For all gait conditions, MCI and SCI were statistically similar, except for gait speed in the naming animals condition, where slower speed was associated with an MCI diagnosis (presented as 1/exp(B): OR=1.01; 95% CI=1.00-1.02; p= 0.048). In contrast, poor performance (slower speed and higher DTC) was associated with diagnosis of dementia in almost all gait conditions. The exception to this was dual-task cost in the serial sevens condition, which was not associated with higher risk of dementia diagnosis (OR=1.01; CI=0.99-1.03; p=0.46).

Table 3.4 Association between gait performance and cognitive impairment (MCI or Dementia) vs subjective impairment (SCI)

Gait Condition	Odds Ratio (95% CI)	*p*-value
Usual gait speed		
MCI	1.00 (0.99-1.01)	0.66
Dementia	1.02 (1.01-1.04)	**0.001**
Counting backwards		
Speed		
MCI	1.01 (1.00-1.02)	0.16
Dementia	1.05 (1.03-1.06)	**<0.001**
Dual-Task Gait Cost		
MCI	1.01 (0.99-1.03)	0.25
Dementia	1.04 (1.02-1.06)	**<0.001**
Naming animals		
Speed		
MCI	1.01 (1.00-1.02)	**0.048**
Dementia	1.04 (1.02-1.06)	**<0.001**
Dual-Task Gait Cost		
MCI	1.02 (1.00-1.03)	0.09
Dementia	1.03 (1.01-1.05)	**0.001**
Serial sevens		
Speed		
MCI	1.01 (0.99-1.02)	0.42
Dementia	1.03 (1.01-1.04)	**0.004**
Dual-Task Gait Cost		
MCI	1.01 (0.99-1.02)	0.51
Dementia	1.01 (0.99-1.03)	0.46

Statistically significant values are bolded.

SCI is the reference category.

Adjusted for age and sex.

For speed, Odds Ratio presented as 1/Exp(B).

3.1.5 Association between Gait Performance and Dementia Diagnosis

Based on the previous results, the association with gait performance was also compared between dementia and the pre-dementia states (SCI and MCI) (Table 3.5). Again, slower gait speed and higher dual-task cost were significantly associated with dementia diagnosis in all gait conditions, except for dual-task cost in the serial sevens condition (OR=1.00; 95% CI=1.00-1.02; *p*=0.675).

Table 3.5 Association between gait performance and dementia diagnosis

Gait Condition	Odds Ratio (95% CI)	*p*-value
Usual gait		
Speed	1.02 (1.01-1.03)	**<.001**
Counting backwards		
Speed	1.04 (1.02-1.05)	**<.001**
Dual-task gait cost	1.03 (1.02-1.05)	**<.001**
Naming animals		
Speed	1.03 (1.02-1.04)	**<.001**
Dual-task gait cost	1.02 (1.01-1.04)	**0.004**
Serial sevens		
Speed	1.02 (1.01-1.04)	**0.003**
Dual-task gait cost	1.00 (1.00-1.02)	0.675

Statistically significant values are bolded.

Adjusted for age and sex.

For speed, Odds Ratio presented as 1/Exp(B).

3.1.6 Optimal Cut-off Values for Gait Speed

ROC Curve analysis showed a moderate ability to separate dementia patients from pre-dementia diagnoses for all gait conditions (Figure 3.5 and Table 3.6). While the AUC for each of the four gait tests were all statistically significant ($p<0.001$), only the counting backwards condition had moderate accuracy (AUC=0.711). The naming animals (AUC=0.698) and usual gait (AUC=0.693) conditions had low accuracy just below the moderate accuracy cut-off (AUC > 0.7). The optimal cut-off points for each gait test were as follows: 99.18 cm/s for usual gait, 80.54 cm/s for counting backwards, 82.72 cm/s for naming animals and 71.85 cm/s for serial sevens. These all gave moderate sensitivity (62.8%-72.3%) and specificity (60.0%-64.9%).

Using these cut-off values, a dichotomous gait variable was created (slow or fast gait speed). Binary logistic regression showed that slow gait speed was significantly associated with dementia diagnosis in all gait conditions (Table 3.7). The highest odds ratio was for speed while counting backwards (OR=3.73; 95% CI=2.22-6.26; $p<0.001$), while the lowest was for usual gait speed (OR=1.70; 95% CI=1.04-2.76; $p=0.034$). Naming animals and serial sevens were both in between these [NA(OR=2.73; 95% CI=1.54-4.82; $p=0.001$); S7 (OR=1.97; 95% CI=1.06-3.68; $p=0.033$)].

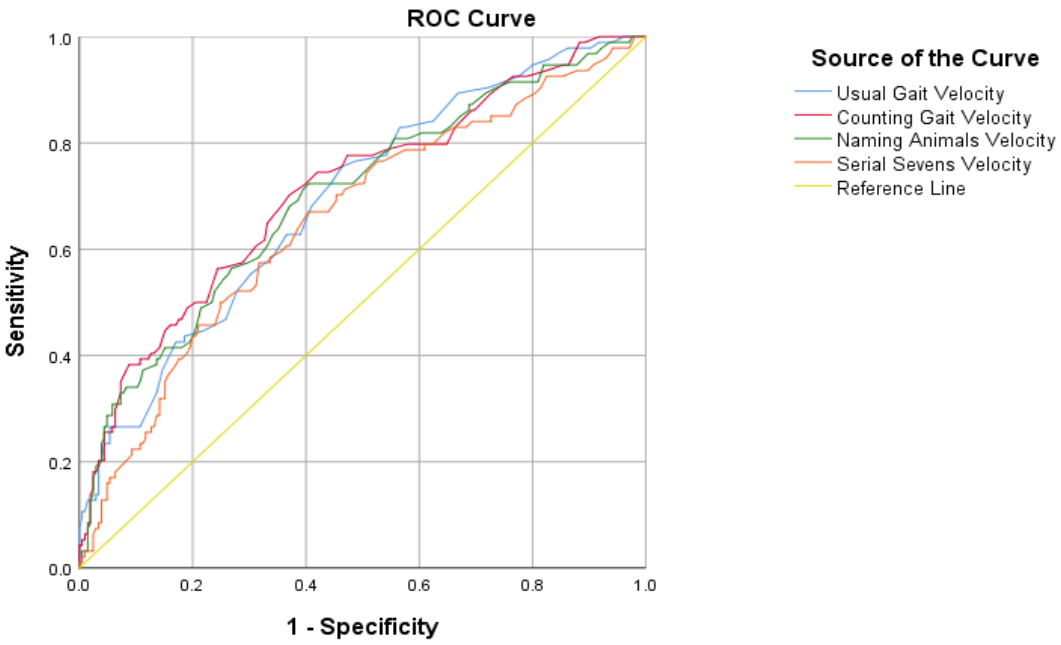

Figure 3.5 Receiver-operating characteristic (ROC) curves for gait speed's ability to separate dementia from SCI and MCI patients in each gait condition

Table 3.6 Gait speed cut-off values and associated sensitivity, specificity, and area under the curve (AUC) for each gait condition

Gait Condition	Optimal Cut-Off point (cm/s)	Sensitivity	Specificity	Area Under the Curve (AUC)	*p*-value
Usual gait	99.18	62.8%	64.0%	.693	**<.001**
Counting backwards	80.54	70.2%	62.9%	.711	**<.001**
Naming animals	82.72	72.3%	60.0%	.698	**<.001**
Serial sevens	71.85	63.8%	64.9%	.657	**<.001**

Statistically significant values are bolded.

Table 3.7 Association between slow gait speed on each test condition and dementia diagnosis

Gait Condition	Odds Ratio (95% CI)	*p*-value
Usual gait	1.70 (1.04-2.76)	**0.03**
Counting backwards	3.73 (2.22-6.26)	**<.001**
Naming animals	2.73 (1.54-4.82)	**0.001**
Serial sevens	1.97 (1.06-3.68)	**0.03**

Statistically significant values are bolded.

3.1.7 Feasibility Measures

There were four hundred sixty-seven clinic visits marked as eligible during the study period. Of these, forty-three charts were missing from the clinic at the time of data collection. The total number of charts accessed was four hundred twenty-four. Fifty-two participants were excluded from data collection for reasons summarized in Table 3.8. The most common reason gait testing was not done was due to barriers of the participants (59.6%), including communication issues (28.8%) and being unable to ambulate the path freely (23.1%). Assessor issues accounted for 13.5% of those participants who could not be included. The final study sample (n=372) represents 87.7% of the total potential participants who had data available, showing that gait testing can be successfully performed in a large majority of clinic patients.

Results from the feasibility survey of the assessors who completed the dual-task gait testing in the clinic are summarized in Table 3.9. Overall, both the physician and nurse clinician said that gait testing was “pretty easy” or 2 on a 5-point Likert scale for both ease of completing the test and ease of integrating it into the clinic visit. The additional comments made suggested that the gait collection form (see Appendix C), physical space to perform the test, and the timing of the appointment were all important aspects to successfully complete the test.

Table 3.8 Reasons for exclusion from study for patients with an eligible clinic visit and available data

Reason for Exclusion	***n***	***%***
Participant issues	*31*	*59.6*
Using gait aid/unable to walk	12	*23.1*
Communication issues/language barrier	15	*28.8*
Refused	1	*2.0*
Shortness of breath/cannot exert	3	*5.8*
Assessor issues	*7*	*13.5*
No trained assessor available	4	*7.7*
Incorrectly recorded	3	*5.8*
Study criteria	*11*	*21.2*
Under age limit (50 years old)	8	*15.4*
Not in one of three diagnosis groups	3	*5.8*
Reason not listed	*3*	*5.8*

Table 3.9 Assessor feedback on feasibility of the dual-task gait assessment

Assessor's Position	***Ease of completing the assessment***	***Ease of integrating the assessment into the flow and timing of the clinic appointment***	***Additional Comments***
Memory Clinic Physician	2 - "pretty easy"	2 - "pretty easy"	
Nurse Clinician	2 - "pretty easy"	2 - "pretty easy"	"is relatively easy to complete **with the template form"** "Space in an office setting may be a limiting factor" "Sometimes it's a challenge… depending upon how [early] patients arrive/ [how busy it is at] time of arrival"

Notes: Numeric responses collected on a 5-point Likert Scale.

Chapter 4

4 Longitudinal Analysis

Poor gait performance, as indicated by slow gait speed and high dual-task cost, has been associated with future risk of falls and cognitive decline [15,106]. As gait testing can be a cost effective and easy to measure clinical marker, it may act as a complement to current cognitive assessments to detect those at high risk for future cognitive decline. This chapter will explore the relationship between poor gait performance at baseline and cognitive status at the next clinical follow-up at least one year later. The three outcome variables explored for cognitive status at follow-up visit are 1) progression to a more severe diagnosis, which was categorized as conversion from SCI to MCI or dementia, MCI to dementia, or early/prodromal dementia to moderate or severe dementia 2) global cognitive decline of >2 points per year on the MoCA and 3) global cognitive decline of >2 points per year on the MMSE.

4.1 Results

4.1.1 Participant Characteristics

One hundred and seven patients met baseline inclusion criteria and had a second clinic visit at least twelve months later but still within the study period. Of these, nineteen had a baseline diagnosis of SCI, fifty-one had a baseline diagnosis of MCI, and thirty-seven had a baseline diagnosis of dementia. Sixty-one participants had progressed to a more severe diagnosis at their follow-up visit, while forty-six participants had remained stable or improved at follow-up. Characteristics of the study sample stratified by diagnosis change status are shown in Table 4.1. Participants who progressed in diagnosis and those who were stable were statistically similar in all baseline variables.

Characteristics of the study sample stratified by decline on cognitive testing are shown in Table 4.2 and Table 4.3. Twenty-nine participants showed significant decline in MoCA performance at follow-up (>2 points per year). Fifteen participants were missing MoCA score at one or both visits and therefore decline could not be calculated. Participants who showed significant decline on the MoCA and those who did not were statistically similar

in all baseline variables. Thirty participants showed significant decline on MMSE (>2 points per year). Participants who showed decline on MMSE testing were significantly older, had worse baseline cognitive test scores, and more severe baseline cognitive diagnosis.

Table 4.1 Baseline demographic and clinical characteristics of study participants in sample stratified by follow-up diagnosis status

		Stratified by Diagnosis Status		
Variable	**Total Cohort** (*n*=107)	**Stable/improved diagnosis** (*n*=46)	**Progression in diagnosis** (*n*=61)	***p*-value**
Age (mean, SD)	73.11 (9.47)	71.46 (10.60)	74.25 (8.43)	0.17[a]
Female (n, %)	57 (53.3%)	27 (58.7%)	30 (49.2%)	0.33
Years of education (mean, SD)	12.80 (3.01)[b]	12.34 (2.95)[c]	13.16 (3.03)[d]	0.18
No. of Comorbidities (mean, SD)	5.94 (2.99)	6.39 (2.71)	5.60 (3.15)	0.18
No. of medications (mean, SD)	8.28 (3.86)	8.56 (4.34)	8.06 (3.48)	0.52[a]
MMSE score (mean, SD)	25.76 (4.01)	26.57 (3.71)	25.15 (4.16)	0.07
MoCA score (mean, SD)	20.76 (5.18)[e]	21.76 (4.95)[f]	19.98 (5.25)[g]	0.08
Baseline diagnosis (n, %)				
SCI	19 (17.8%)	10 (21.7%)	9 (14.8%)	0.57
MCI	51 (47.6%)	22 (47.8%)	29 (47.5%)	
Dementia	37 (34.6%)	14 (30.4%)	23 (37.7%)	

Statistically significant values are bolded.

Abbreviations: SCI = Subjective Cognitive Impairment. MCI = Mild Cognitive Impairment. MMSE = Mini-Mental State Examination. MoCA = Montreal Cognitive Assessment.

[a], p-value reported from Welch's Test for unequal variance.

[b], data available for *n*=99.

[c], data available for *n*=44.

[d], data available for *n*=55.

[e], data available for *n*=103.

[f], data available for *n*=45.

[g], data available for *n*=58.

Table 4.2 Baseline demographic and clinical characteristics of study participants in sample stratified by follow-up MoCA change status

		Stratified by MoCA score change		
Variable	**Total Cohort** (*n*=92)	**Stable or normal decline** (*n*=63)	**Accelerated decline** (*n*=29)	***p*-value**
Age (mean, SD)	72.54 (9.54)	71.76 (10.22)	74.24 (7.75)	0.20[a]
Female (n, %)	51 (55.4%)	37 (58.7%)	14 (48.3%)	0.35
Years of education (mean, SD)	12.78 (2.96)[b]	12.38 (2.61)[c]	13.69 (3.51)[d]	0.10[a]
No. of Comorbidities (mean, SD)	6.18 (2.83)	5.85 (2.73)	6.90 (2.96)	0.10
No. of medications (mean, SD)	8.46 (3.98)	8.68 (4.45)	7.96 (2.68)	0.34[a]
MMSE score (mean, SD)	26.55 (3.40)	26.60 (3.84)	26.45 (2.23)	0.84
MoCA score (mean, SD)	21.34 (5.04)	21.16 (5.33)	21.72 (4.40)	0.62
Baseline diagnosis (n, %)				
SCI	19 (20.6%)	14 (22.2%)	5 (17.2%)	0.86
MCI	45 (48.9%)	30 (47.6%)	15 (51.7%)	
Dementia	28 (30.4%)	19 (30.2%)	9 (31.0%)	

Statistically significant values are bolded.

Abbreviations: SCI = Subjective Cognitive Impairment. MCI = Mild Cognitive Impairment. MMSE = Mini-Mental State Examination. MoCA = Montreal Cognitive Assessment.

[a], p-value reported from Welch's Test for unequal variance.

[b], data available for *n*=86.

[c], data available for *n*=60.

[d], data available for *n*=26.

Table 4.3 Baseline demographic and clinical characteristics of study participants in sample stratified by follow-up MMSE change status

		Stratified by MMSE score change		
Variable	**Total Cohort** (*n*=107)	**Stable or normal decline** (*n*=77)	**Accelerated decline** (*n*=30)	***p*-value**
Age (mean, SD)	73.11 (9.47)	71.99 (9.78)	76.00 (8.09)	**0.048**
Female (n, %)	57 (53.3%)	45 (58.4%)	12 (40.0%)	0.09
Years of education (mean, SD)	12.80 (3.01)[b]	12.81 (3.16)[c]	12.76 (2.59)[d]	0.94
No. of Comorbidities (mean, SD)	5.94 (2.99)	6.12 (2.79)	5.50 (3.45)	0.34
No. of medications (mean, SD)	8.28 (3.86)	8.45 (4.10)	7.83 (3.18)	0.41[a]
MMSE score (mean, SD)	25.76 (4.02)	26.44 (3.74)	24.00 (4.22)	**0.004**
MoCA score (mean, SD)	20.76 (5.18)[e]	21.92 (5.08)[f]	17.48 (3.97)[g]	**<0.001**
Baseline diagnosis (n, %)				
SCI	19 (17.8%)	19 (24.7%)	0 (0.0%)	**0.003**
MCI	51 (47.6%)	37 (48.0%)	14 (46.7%)	
Dementia	37 (34.6%)	21(27.3%)	16 (53.3%)	

Statistically significant values are bolded.

Abbreviations: SCI = Subjective Cognitive Impairment. MCI = Mild Cognitive Impairment. MMSE = Mini-Mental State Examination. MoCA = Montreal Cognitive Assessment.

[a], p-value reported from Welch's Test for unequal variance.

[b], data available for *n*=99.

[c], data available for *n*=74.

[d], data available for *n*=25.

[e], data available for *n*=103.

[f], data available for *n*=76.

[g], data available for *n*=27.

4.1.2 Gait Performance and Association with Progression in Cognitive Diagnosis

Table 4.4 reports the association between progression in cognitive diagnosis and gait speed and DTC as continuous variables as determined by the cox regression models. Only performance on the naming animals dual-task test was significantly associated with future decline in cognitive diagnosis. Both gait speed (presented as 1/exp(B): HR=1.02; 95% CI=1.00-1.03; p=0.004) and DTC (HR=1.02; 95% CI=1.01-1.04; p=0.011) in the naming animals condition were associated with diagnosis progression. These associations remained significant when adjusted for age, sex, and comorbidities. Performance in usual gait speed and the other dual-tasks were not significantly associated with the outcome variable.

Modeling gait speed and DTC as dichotomous variables using a mean split showed that only slow gait speed on the naming animals dual-task condition was associated with diagnosis progression (HR=1.73; 95% CI=1.03-2.91; p=0.037) (Table 4.5). This association did not remain significant when adjusted for covariates.

Table 4.4 Cox proportional hazard regression of the association of continuous gait speed and dual-task cost with cognitive diagnosis progression

Variable	Model 1 (Unadjusted)		Model 2 (Adjusted)	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Speed				
Usual	1.01 (0.99-1.02)	0.31	1.00 (0.99-1.01)	0.80
Counting backwards	1.01 (1.00-1.02)	0.08	1.01 (1.00-1.02)	0.14
Naming animals	1.02 (1.00-1.03)	**0.004**	1.02 (1.00-1.03)	**0.01**
Serial sevens	1.01 (0.99-1.02)	0.38	1.00 (0.99-1.02)	0.55
Dual-Task Cost				
Counting Backwards	1.01 (0.99-1.02)	0.39	1.01 (1.00-1.03)	0.15
Naming animals	1.02 (1.01-1.04)	**0.01**	1.02 (1.01-1.04)	**0.008**
Serial sevens	1.00 (0.98-1.02)	0.88	1.01 (0.99-1.02)	0.61

Statistically significant values are bolded.

Abbreviations: HR = Hazard ratio.

Model 1: unadjusted. Model 2: adjusted for age, sex and comorbidities.

For gait speed, Hazard Ratio presented as 1/Exp(B).

Table 4.5 Cox proportional hazard regression of the association of dichotomous gait speed and dual-task cost with cognitive diagnosis change

Variable	Model 1 (Unadjusted)		Model 2 (Adjusted)	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Speed				
Usual (<102.6cm/s)	1.26 (0.76-2.09)	0.38	1.12 (0.65-1.93)	0.68
Counting backwards (<81.6cm/s)	1.05 (0.63-1.77)	0.84	1.15 (0.68-1.96)	0.60
Naming animals (<75.1cm/s)	1.73 (1.03-2.91)	**0.04**	1.60 (0.94-2.72)	0.09
Serial sevens (<60.7cm/s)	1.22 (0.69-2.16)	0.49	1.07 (0.60-1.94)	0.81
Dual-Task Cost				
Counting Backwards (>21.1%)	1.19 (0.71-2.00)	0.51	1.45 (0.85-2.49)	0.17
Naming animals (>27.0%)	1.50 (0.90-2.50)	0.12	1.57 (0.97-2.63)	0.09
Serial sevens (>41.0%)	1.15 (0.65-2.00)	0.62	1.28 (0.72-2.29)	0.40

Statistically significant values are bolded.

Abbreviations: HR = Hazard ratio.

Model 1: unadjusted. Model 2: adjusted for age, sex and comorbidities.

4.1.3 Gait Performance and Association with Decline on the Montreal Cognitive Assessment (MoCA)

Table 4.6 shows the association between continuous gait variables and decline on the Montreal Cognitive Assessment (MoCA). Higher DTC in the naming animals condition was significantly associated with decline on the MoCA (HR=1.03; 95% CI=1.00-1.05; p=0.027). This association remained significant when adjusted for age, sex, and comorbidities. No other gait variables showed a significant association with decline on the MoCA.

When modeled as dichotomous variables, none of the gait variables were significantly associated with future decline on the MoCA (Table 4.7).

Table 4.6 Cox proportional hazard regression of the association of continuous gait speed and dual-task cost with MoCA score decline

Variable	Model 1 (Unadjusted)		Model 2 (Adjusted)	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Speed				
Usual	1.00 (0.98-1.02)	0.99	0.99 (0.97-1.01)	0.31
Counting backwards	1.01 (1.00-1.03)	0.18	1.01 (0.99-1.02)	0.43
Naming animals	1.01 (1.00-1.03)	0.08	1.01 (0.99-1.03)	0.25
Serial sevens	1.01 (0.99-1.03)	0.24	1.01 (0.99-1.03)	0.56
Dual-Task Cost				
Counting Backwards	1.02 (0.99-1.04)	0.16	1.02 (1.00-1.04)	0.13
Naming animals	1.03 (1.00-1.05)	**0.03**	1.02 (1.00-1.05)	**0.03**
Serial sevens	1.02 (0.99-1.04)	0.22	1.01 (0.99-1.04)	0.27

Statistically significant values are bolded.

Abbreviations: MoCA= Montreal Cognitive Assessment. HR = Hazard ratio.

Model 1: unadjusted. Model 2: adjusted for age, sex and comorbidities.

For gait speed, Hazard Ratio presented as 1/Exp(B).

Table 4.7 Cox proportional hazard regression of the association of dichotomous gait speed and dual-task cost with MoCA score decline

Variable	Model 1 (Unadjusted)		Model 2 (Adjusted)	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Speed				
Usual (<102.6cm/s)	1.21 (0.58-2.51)	0.61	0.98 (0.44-2.15)	0.95
Counting backwards (<81.6cm/s)	1.35 (0.64-2.83)	0.43	1.32 (0.60-2.90)	0.49
Naming animals (<75.1cm/s)	1.71 (0.82-3.59)	0.15	1.56 (0.72-3.36)	0.26
Serial sevens (<60.7cm/s)	2.16 (0.93-5.01)	0.08	1.72 (0.71-4.16)	0.23
Dual-Task Cost				
Counting Backwards (>21.1%)	1.54 (0.74-3.20)	0.24	1.67 (0.79-3.55)	0.18
Naming animals (>27.0%)	1.65 (0.79-3.43)	0.18	1.71 (0.82-3.59)	0.16
Serial sevens (>41.0%)	1.77 (0.78-4.00)	0.17	1.76 (0.74-4.15)	0.20

Statistically significant values are bolded.

Abbreviations: MoCA= Montreal Cognitive Assessment. HR = Hazard ratio.

Model 1: unadjusted. Model 2: adjusted for age, sex and comorbidities.

4.1.4 Gait Performance and Association with Decline on the Mini Mental State Exam (MMSE)

Table 4.8 shows the association between continuous gait variables and decline on the Mini Mental State Exam (MMSE). Slower gait speed in the naming animals condition was significantly associated with decline on the MMSE (presented as 1/exp(B): HR=1.02; 95% CI=1.00-1.04; *p*=0.01). This association remained significant when adjusted for age, sex, and comorbidities. No other gait variables showed a significant association with decline on the MoCA.

When modeled as dichotomous variables, none of the gait variables were significantly associated with future decline on the MMSE (Table 4.9).

Table 4.8 Cox proportional hazard regression of the association of continuous gait speed and dual-task cost with MMSE score decline

Variable	Model 1 (Unadjusted)		Model 2 (Adjusted)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Speed				
Usual	1.01 (1.00-1.03)	0.16	1.01 (0.99-1.02)	0.48
Counting backwards	1.01 (0.99-1.03)	0.20	1.01 (0.99-1.02)	0.43
Naming animals	1.02 (1.00-1.04)	**0.01**	1.02 (1.00-1.04)	**0.04**
Serial sevens	1.02 (0.99-1.04)	0.15	1.01 (0.99-1.03)	0.38
Dual-Task Cost				
Counting Backwards	1.00 (0.98-1.03)	0.78	1.01 (0.98-1.03)	0.59
Naming animals	1.02 (1.00-1.05)	0.08	1.02 (1.00-1.05)	0.07
Serial sevens	1.00 (0.98-1.03)	0.87	1.01 (0.98-1.03)	0.68

Statistically significant values are bolded.

Abbreviations: MMSE = Mini Mental State Exam. HR = Hazard ratio.

Model 1: unadjusted. Model 2: adjusted for age, sex and comorbidities.

For gait speed, Hazard Ratio presented as 1/Exp(B).

Table 4.9 Cox proportional hazard regression of the association of dichotomous gait speed and dual-task cost with MMSE score decline

Variable	Model 1 (Unadjusted)		Model 2 (Adjusted)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Speed				
Usual (<102.6cm/s)	1.32 (0.64-2.71)	0.45	1.12 (0.52-2.42)	0.76
Counting backwards (<81.6cm/s)	1.06 (0.50-2.23)	0.87	1.08 (0.50-2.33)	0.84
Naming animals (<75.1cm/s)	1.76 (0.84-3.72)	0.14	1.55 (0.72-3.33)	0.26
Serial sevens (<60.7cm/s)	2.21 (0.91-5.39)	0.08	1.64 (0.65-4.18)	0.23
Dual-Task Cost				
Counting Backwards (>21.1%)	0.78 (0.36-1.69)	0.53	0.88 (0.40-1.95)	0.75
Naming animals (>27.0%)	1.47 (0.71-3.05)	0.30	1.62 (0.77-3.40)	0.20
Serial sevens (>41.0%)	1.32 (0.58-3.00)	0.51	1.49 (0.64-3.44)	0.35

Statistically significant values are bolded.

Abbreviations: MMSE = Mini Mental State Exam. HR = Hazard ratio.

Model 1: unadjusted. Model 2: adjusted for age, sex and comorbidities.

4.1.5 Data Attrition Measures

As only about a quarter of the original sample *(n=107)* was included in the longitudinal analysis, it was also investigated why those who were not included did not have a second visit within the study period. A summary of these findings is presented in Table 4.10.

The most common reasons for not being included in longitudinal analysis were related to study criteria (*n*=134). One hundred and seventeen patients had a follow-up visit scheduled, but it landed outside of the approved period of data collection, which ended in June 2019. Sixteen patients had a second visit at the clinic that was less than twelve months after their first. These were mostly consults and did not often include any new testing. One patient was not able to be included in analysis as they were not able to verbally communicate at the follow-up visit.

Thirty-four patients did not have any further follow-up scheduled in the Aging Brain and Memory clinic. Thirty-two of these patients were referred to another service or department for follow-up. Two of these patients were discharged at their baseline visit, as they did not wish to be followed in the clinic.

Twenty-four patients were lost to follow-up. These included ten cancellations and twelve patients who did not show-up for their appointments. Additionally, one patient rescheduled their visit to after June 2019, making it no longer eligible, and one patient moved out of the province.

No data was available for seventy-three patients at the time of data collection for follow-up visits.

Table 4.11 shows the comparison of baseline clinical and demographic characteristics between those who were included in the longitudinal study (had a follow-up visit) and those who weren't. The two groups were statistically similar in all characteristics, except MMSE score (*p*=0.008). However, the mean score for each of the two groups were less than one point apart, so this is likely not a clinically significant difference.

Table 4.10 Reasons for exclusion from longitudinal analysis for patients without a second clinic visit

Reason for Exclusion	***n***	***%***
Lost to follow-up	*24*	*6.5*
Cancelled	10	2.7
No show	12	3.2
Rescheduled out of study period (after June 2019)	1	0.3
Moved out of province	1	0.3
No follow-up scheduled	*34*	*9.1*
Referred to another service[a]	32	8.6
Discharged at baseline	2	0.5
Study criteria	*134*	*36.0*
Next visit after study end date (June 2019)	117	31.4
Next visit less than 12 months from baseline	16	4.3
Not able to complete cognitive testing at follow-up[b]	1	0.3
No data available	*73*	*19.6*

Percentage value is in comparison to total cohort.

Total cohort size n=372. Longitudinal analysis n=107.

[a], these included neuropsychology, long-term care, psychiatry, research, and other clinics (due to geographic location).

[b], this patient had lost verbal communication skills.

Table 4.11 Baseline demographic and clinical characteristics of study participants stratified by inclusion in longitudinal study

Variable	**Included (had follow-up visit)** (*n*=107)	**Not included (no follow-up visit)** (*n*=265)	***p*-value**
Age (mean, SD)	73.11 (9.47)	72.81 (10.32)	0.18
Female (n, %)	57 (53.3%)	132 (49.8%)	0.58
Years of education (mean, SD)	12.80 (3.01)[a]	12.59 (3.60)[b]	0.18
No. of Comorbidities (mean, SD)	5.94 (2.99)	5.49 (3.34)	0.93
No. of medications (mean, SD)	8.28 (3.86)	8.58 (3.40)	0.54
MMSE score (mean, SD)	25.76 (4.02)	25.12 (4.88)[c]	**0.008**
MoCA score (mean, SD)	20.76 (5.18)[d]	21.31 (4.98)[e]	0.74
Baseline diagnosis (n, %)			
SCI	19 (17.8%)	62 (23.4%)	0.30
MCI	51 (47.6%)	104 (39.2%)	
Dementia	37 (34.6%)	99 (37.4%)	

Statistically significant values are bolded.

Abbreviations: SCI = Subjective Cognitive Impairment. MCI = Mild Cognitive Impairment. MMSE = Mini-Mental State Examination. MoCA = Montreal Cognitive Assessment.

[a], data available for *n*=99.

[b], data available for *n*=233.

[c], data available for *n*=263.

[d], data available for *n*=103.

[e], data available for *n*=236.

Chapter 5

5 General Discussion and Conclusions

5.1 Discussion

This thesis aimed to assess dual-task gait performance in a memory clinic setting across the spectrum of cognitive impairment diagnoses. It was hypothesized that slow gait speed and high dual-task cost would be associated with a more severe baseline cognitive diagnosis, and would be associated with accelerated cognitive decline at a follow-up visit. Our results showed that slow usual gait speed and slow gait speed while dual-tasking was associated with a diagnosis of dementia at baseline. Also, dual-task gait testing was able to be completed with almost 88% of eligible participants over a four year period, demonstrating that gait testing is feasible to perform in clinics. In our longitudinal analysis, there was a signal that poor dual-task gait performance at baseline, specifically in the naming animals task, may be associated with cognitive decline at the follow-up visit.

5.1.1 Cross-Sectional Gait Performance

Our results show that gait speed decreases across the spectrum of cognitive impairments, confirming in a clinical setting the relationship between gait and cognition that has been seen is other studies [132]. Gait speed was significantly different both across diagnosis groups and between different dual-tasks with each group. Interestingly, in all four dual-task conditions the SCI and MCI groups had statically similar performance. This means the SCI group had normal scores on tests of global cognition [133,134], but performed similar in the dual-task test to the MCI group, who have objective cognitive impairments. As we know patients with SCI are at increased risk for future cognitive decline [41], it is possible the dual-task test is able to detect these early subtle changes in cognition that cannot yet be seen on global cognitive testing. For example, the level of stress put on the brain as a result of the dual-task gait test may be more than or target different resources than traditional cognitive tests, and is therefore able to detect deficits at even the earliest stage. Further studies using a healthy control group with no cognitive complaints and a longer follow-up period would be needed to confirm this theory.

All groups had a mean usual gait speed of over 80 cm/s, with the SCI group at 111 cm/s, the MCI group at 106 cm/s, the dementia group at 91 cm/s, and 102cm/s as the mean for the whole cohort. Eighty cm/s is considered to be the cut-off for slow gait speed in association with gait pathologies and falls risk [70]. This means our sample had moderate to high mobility function [88,117], and using this cut-off alone would not have been sufficient to detect differences across the cognitive impairment groups. While mean gait speed for the dementia group was still above 80 cm/s, the difference in mean gait speed from the SCI and MCI groups was >10 cm/s, which is considered clinically meaningful [135].

While the exact neural mechanisms behind the dual-task paradigm are not yet understood, it is thought that both gait and cognitive tasks compete for a limited amount of resources in overlapping brain regions. This is supported by imaging studies that have shown higher activation in prefrontal brain regions when imagining walking while talking versus just walking [105]. Alternatively, damage or atrophy in these shared brain areas also causes detriments in both gait and cognition [103,104,136,137]. Our results are in line with this theory, as those with more severe cognitive diagnoses had slower gait speed, both in usual gait speed and while dual-tasking. Future neuroimaging studies would be needed to expand on this theory.

Interestingly, dual-task gait cost was not significantly different between the diagnosis groups. This goes against our original hypothesis and several other studies [96,132,138]. However, in the counting backwards and naming animals tasks, dual-task gait cost did increase slightly across the groups as we hypothesized, although when using all four gait tests together and excluding missing data this was not significant due to a power issue. Due to our statistical analysis design and the clinical nature of our study, we had to exclude a large number of participants from this analysis as they refused one or more of the dual-task conditions. It is possible that those who refused one of the tasks had a higher level of cognitive impairment and were embarrassed or fearful of attempting the task. This would lead to the mean DTC in these groups being lower than it truly would be if all participants had attempted the task. DTC did increase within each diagnosis group with increasing task difficulty, as has been shown in previous studies [118].

Regression analysis showed that slow gait speed and high dual-task cost were significantly associated with diagnosis of dementia. Receiver operating characteristic (ROC) curve analysis also showed that gait speed on each of the four gait tasks was low to moderate, with area under the curve (AUC) ranging from .657 to .711. Sensitivity and specificity for dementia diagnosis were also moderate, ranging from 62.8%-72.3% and 60.0%-64.9%, respectively. In comparison, the gold standard tests for cognitive impairment, the MoCA and MMSE, were found to have sensitivity of 83% and 72% and specificity of 86% and 83%, respectively, for predicting dementia [139]. While dual-task gait testing is not as strong as these tests alone, it can be used in conjunction with these traditional assessments as a quick and easy measure of the cognitive-motor interaction, which these tests cannot measure, and to improve diagnosis and treatment plans for patients. For example, a high dual-task gait cost may inform clinicians to send a patient for more in depth neuropsychological evaluation or for brain imaging, which may catch deficits at an earlier stage or give insight to the cause of these deficits.

Finally, our study has shown that dual-task gait testing is feasible to perform in a clinical setting. Eighty-eight percent of eligible patients completed at least part of the gait testing and could be included in analysis. A recent study of gait testing in an outpatient neurology clinic had a similar rate of test completion (81%) [140]. This, in addition to other studies done in a memory clinic setting [95,96], shows that dual-task gait testing can be done even in busy clinic settings. Both assessors reported the testing was “pretty easy” to complete and to add into the clinic visit. Some important tips for integration were presented, including the use of a standard collection form and the requirement of physical space. The methodology used here is quick, cost-effective, and requires minimal equipment to be completed. While our results have shown some differences in sensitivity and specificity between the different dual-tasks, it is still recommended to complete all three tests. Even in a busy clinical setting, it usually takes under five minutes to complete all four walks together, and it has been shown that the different cognitive tasks are needed as they assess different domains of cognition and may together create the optimal level of difficulty for all patients [141].

5.1.2 Longitudinal Gait Performance

While the previous sub-study answered our research questions regarding feasibility and practicality of gait testing and differences between diagnosis groups, there was still a gap in the literature of a longitudinal study of gait testing across the cognitive spectrum in a memory clinic cohort. Therefore, we decided to perform longitudinal analysis for any participants who had a second clinic visit during the study period. It was hypothesized that slow gait speed and greater dual-task gait cost at baseline would be predictive of cognitive decline at the follow-up visit. Previous research has shown that dual-task gait cost was a predictor of progression from MCI to dementia [15], however the limited studies of dual-task gait testing in a clinical setting have not shown the same results [96]. Our results show a signal that dual-task performance in the naming animals condition may be associated with change in diagnosis, which was a composite outcome including change from SCI to MCI, MCI to dementia, and early to late dementia. Both continuous gait speed and dual-task cost were associated with diagnosis change, even when adjusted for covariates. Dichotomous slow gait speed (using a median split) while naming animals was also associated with decline in diagnosis, although this association was not robust to adjustment for confounders. Several past studies have also found usual gait speed to have a weaker association with cognitive status and future cognitive decline [15,132,142,143]. However, differential associations between the dual-task conditions has not been thoroughly examined previously. It is possible that because the naming animals condition relies more purely on recall and semantic memory [144], while the arithmetic tasks rely on executive functions [145], that the naming animals task was most sensitive to changes as clinic patients were often being assessed for memory complaints. Alternatively, it is also possible that the naming animals task provides the optimal level of difficulty while also keeping patients' mental engagement (ie. not "giving up"). Naming animals is also a more universal task for a wide range of patients, as it has less influence from education level [146]. Additional cognitive testing to determine which cognitive domains are impaired in our cohort would be needed to examine this further.

Additionally, the association between poor gait performance at baseline and decline on cognitive testing was examined. It was found that again, the only condition to show a

signal of association was the naming animals task. Continuous dual-task cost while naming animals was significantly associated with decline of >2 points per year on the Montreal Cognitive Assessment (MoCA). Continuous slow gait speed while naming animals was associated with decline of >2 points per year on the Mini Mental State Exam (MMSE). Both of these associations remained significant even when adjusted for covariates. Similarly to the previous result, it is possible that the differential domains and pathways used in these dual-tasks could explain why only the naming animals dual-task shows a signal of association. Also, because the MoCA and MMSE are both measures of global cognitive function and not any domain specifically, it is possible that cognitive tests tailored to one specific cognitive domain would show a higher association with gait performance, especially in subtypes of each cognitive diagnosis.

While only 28.8% of participants could be included in longitudinal analysis, only 6.5% of participants were confirmed lost to follow-up. Thirty six percent of participants could not be included as their second visit to the clinic fell outside of the time range of the study. Nine percent (9.1%) of patients were not scheduled to be followed in the clinic for reasons not related to the study, and 19.6% of patients were not able to be included in follow-up analyses due to missing data. As the largest proportion of patients were excluded due to time constraints, both directly by the study design and indirectly by the scheduling constraints in a busy clinic, the study follow-up period should be extended in future studies to better capture the entire study sample. Still, even if we assume all patients who could not be included due inaccessible data were lost to follow-up, we only had an annual dropout rate of 6.5% of patients, which is comparable to other large observational memory clinic studies [147,148].

5.1.3 Strengths

This study is the largest investigation of dual-task gait testing in clinical patients to date, and includes all three common diagnosis groups. This demonstrates the feasibility of performing dual-task gait testing in a busy clinical setting, as a high percentage of total patients completed the assessment. Also, this thesis presents both cross-sectional and longitudinal analyses of gait and cognitive performance. Finally, we used previously

published gait testing guidelines [14], which will make comparison of our data to other large cohorts possible.

5.1.4 Limitations

Our analyses also have several limitations that we acknowledge. Firstly, using limited exclusion criteria allowed us to sample a large majority of the clinic population, but could lead to increased heterogeneity in each diagnosis group. Subtypes of MCI and dementia were grouped together, which may have implications on the relationship between gait performance and cognitive outcomes. For example, it has been shown in the past that dual-task gait testing may better predict conversion to vascular dementia than Alzheimer's disease [149]. The associations found in this current study may be influenced by strong associations within one subtype, even with weaker associations or no association at all possible in other subtypes. Our statistical analysis design for cross-sectional comparisons of gait speed and DTC required that any patients who did not complete all three dual-task be excluded from analysis. This could affect external validity, as participants who refused one or more tasks could actually have worse cognitive or mobility impairments than could be represented in the presented data. If those excluded had worse performance on the other remaining dual-tasks the mean dual-task cost in these tasks is actually under-estimated in this sample and between group differences may actually be larger than estimated here within. Additionally, we focused on dual-task gait cost only, but adding dual-task cognitive cost to our methodology would have improved our understanding of the dual-task paradigm in this sample. Information on education level of patients was collected but was not used as a covariate in analyses, which may impact the associations shown as education has a protective role in cognitive function and decline. Finally, our study was only completed at one hospital based clinic site in London, Ontario with a supervising team of one physician and one nurse clinician, which may limit it's generalizability to other clinic.

5.1.5 Future Directions

While our results fill in some of the current gaps in this area of literature, there are many other research questions that still need to be addressed. Firstly, while we explored

feasibility, sensitivity, and specificity of dual-task gait testing, it still needs to be determined how this test could be useful in clinical practice and how it would fit with the current gold standards of assessment. With the new results from this thesis, we have shown that dual-task gait testing is associated with cognitive impairments in a clinical setting, but how this could aid in differential diagnosis and treatment plans is still unclear. Previously, we have published instructions to easily perform gait testing in clinics and created videos to aid in the training of clinicians in this form of testing (see Appendix D). This will assist greatly to facilitate the dissemination of this testing to additional clinic sites and to allow the use of this testing to be further studied in other clinical settings.

Our results have shown a signal that dual-task performance at baseline may be associated with future cognitive outcomes. However, larger studies with more homogenous samples would be needed to further explore this relationship. For example, how this relationship manifests in SCI to MCI, MCI to dementia, and early to late stage dementia transitions should all be explored independently. They have unique factors that may influence the how this association is expressed and how it can be applied in clinical diagnoses and treatments.

Studies with a longer follow-up period may also show a stronger association between baseline gait performance and cognitive decline. The follow-up period for our study ranged from approximately one to three years. While some studies have found meaningful changes in cognition in a similar time span [150], some studies report the mean time needed to see clinically relevant symptoms may be more than twice as long as this [151,152]. Therefore, the follow-up period of our study may have been too short to capture the full picture of cognitive decline in our sample. Extending this follow-up period in the future may show a stronger relationship between gait performance and cognitive outcomes in a clinical setting.

5.2 Conclusions

This thesis has examined gait performance, specifically when dual-tasking, in a large cohort of memory clinic patients, both cross-sectionally and longitudinally. Our result show that gait speed and dual-task performance decline across the cognitive spectrum.

Motor performance testing was feasible to perform in a real clinical scenario and results were collected with minimal missing data. Additionally, we found a strong signal that results from this testing can help to differentiate between cognitive diagnoses across the spectrum of cognitive impairments seen in clinical settings. Our longitudinal analysis showed that poor dual-task performance may be an indicator of risk of future cognitive decline, however a larger sample with the opportunity to analyze each diagnosis group separately would be needed to determine this.

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Appendices

Appendix A: Research Ethics Board Study Approval

Western Research

Date: 24 February 2020

To: Dr. Manuel Montero- Odasso

Project ID: 110768

Study Title: Dual-Task Gait Assessment to Differentiate Cognitive Impairment Subtypes in a Clinical Setting

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

REB Meeting Date: 10/Mar/2020

Date Approval Issued: 24/Feb/2020

REB Approval Expiry Date: 09/Mar/2021

Dear Dr. Manuel Montero- Odasso,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

[redacted]

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix B: Demographic and Clinical Information Collection Form

Version Date: 08 February 2018

Dual-Task Gait Study Summary Sheet

Study ID: _____

Date of Assessment (MM/DD/YYYY)			
Birthdate (MM/YYYY)			
Age			
Sex	Male ☐	Female ☐	
Years of Education			
Diagnosis	SCI ☐	MCI ☐	Dementia ☐
Falls in last 12 months: _____ **Injuries from fall:** Yes ☐ No ☐	0 ☐	1 ☐	2+ ☐

Cognitive Testing

MMSE Score (Using WORLD)	
MoCA Total Score	
GDS Score	

Medication Information:

Number of Medications Currently Taking **Total:..... Others:.....**

Types of Medications:

Yes ☐ No ☐ Neuroleptics: .....
Yes ☐ No ☐ Diuretics: .....
Yes ☐ No ☐ Beta-Blocker: .....
Yes ☐ No ☐ Vasodilators: .....
Yes ☐ No ☐ SSRI: .....
Yes ☐ No ☐ Multi-Vitamins: .....
Yes ☐ No ☐ Calcium: .....
Yes ☐ No ☐ Benzodiazepines: .....
Yes ☐ No ☐ Thyroid (ATD): .....
Yes ☐ No ☐ Alpha-Blocker: .....
Yes ☐ No ☐ Aspirin: .....
Yes ☐ No ☐ Statins: .....
Yes ☐ No ☐ Vitamin D: .....

Version Date: 08 February 2018

Comorbid Issues and Complaints:					
Number of Comorbid Issues and Complaints: _____					
Hypertension	Yes☐	No☐	Lung Disease	Yes☐	No☐
CHF	Yes☐	No☐	Osteoarthritis	Yes☐	No☐
Diabetes	Yes☐	No☐	Cancer	Yes☐	No☐
Parkinson's Disease	Yes☐	No☐	Hearing Problems	Yes☐	No☐
Anemia	Yes☐	No☐	Major Joint Replaced	Yes☐	No☐
Osteoporosis	Yes☐	No☐	Dyslipidemia	Yes☐	No☐
Stroke	Yes☐	No☐	Depression	Yes☐	No☐
TIA	Yes☐	No☐	Anxiety	Yes☐	No☐
Does the patient currently/have they ever smoked? Yes ☐ No ☐ Years since quitting: _____					
Visual Problems:					
Glasses:	Yes ☐	No☐	Cataracts:	Yes ☐	No☐
Macular degeneration:	Yes ☐	No☐	Cataract surgery:	Yes ☐	No☐
Glaucoma:	Yes ☐	No☐	Legally blind:	Yes ☐	No☐
Cardiac Problems:					
Myocardial infarct:	Yes ☐	No☐	Pacemaker:	Yes ☐	No☐
Atrial fibrillation:	Yes ☐	No☐	Bypass:	Yes ☐	No☐
Angioplasty:	Yes ☐	No☐	Angina:	Yes ☐	No☐
Other: _____ _____ _____					

Gait Condition	**Velocity (cm/s)**	**Number of verbal answers**	**Errors in verbal answers**
Usual gait			
Counting gait			
Naming animals			
Serial Sevens			

Appendix C: Gait Information Collection Form

Patient Name _____ P # _____ Date _____ New pt ( ) Review pt ( )

Indicate Trial 1, 2 3, or 4	#Errors/ Repetitions	# seconds for 6 metre walk	Gait speed in cm/second	Indicate Trial 1, 2, 3, or 4	# Errors/ Repetitions	# seconds for 6 metre walk	Gait speed in cm/second
		3.5	171.4			9.6	62.5
		3.6	166.66			9.7	61.85
		3.7	162.16			9.8	61.22
		3.8	158.89			9.9	60.60
		3.9	154.84			10	60
		4	150			10.1	59
		4.1	146.34			10.2	58.8
		4.2	142.85			10.3	58.25
		4.3	139.53			10.4	57.69
		4.4	136.36			10.5	57.14
		4.5	133.33			10.6	56.60
		4.6	130.43			10.7	56.07
		4.7	127.65			10.8	55.55
		4.8	125			10.9	55.04
		4.9	122.44			11	54.54
		5	120			11.1	54.05
		5.1	117.64			11.2	53.57
		5.2	115.38			11.3	53.09
		5.3	113.20			11.4	52.63
		5.4	111.11			11.5	52.17
		5.5	109.09			11.6	51.72
		5.6	107.14			11.7	51.28
		5.7	105.26			11.8	50.84
		5.8	103.44			11.9	50.42
		5.9	101.69			12	50
		6	100			12.1	49.58
		6.1	98.36			12.2	49.18
		6.2	96.77			12.3	48.78
		6.3	95.23			12.4	48.38
		6.4	93.75			12.5	48
		6.5	92.30			12.6	47.61
		6.6	90.90			12.7	47.24
		6.7	89.55			12.8	46.87
		6.8	88.23			12.9	46.51
		6.9	86.95			13	46.15
		7.0	85.71			13.1	45.80
		7.1	84.50			13.2	45.45
		7.2	83.33			13.3	45.11
		7.3	82.19			13.4	44.77
		7.4	81.08			13.5	44.44
		7.5	80			13.6	44.11
		7.6	78.94			13.7	43.79
		7.7	77.92			13.8	43.47
		7.8	76.92			13.9	43.16
		7.9	75.94			14	42.85
		8	75			14.1	42.55
		8.1	74.07			14.2	42.25
		8.2	73.17			14.3	41.95
		8.3	72.28			14.4	41.66
		8.4	71.42			14.5	41.37
		8.5	70.58			15	40
		8.6	69.76			15.1	39.73
		8.7	68.96			15.2	39.47
		8.8	68.18			15.3	39.21
		8.9	67.41			15.4	38.96
		9	66.66			15.5	38.70
		9.1	65.93			15.6	38.46
		9.2	65.21			15.7	38.21
		9.3	64.51			15.8	37.97
		9.4	63.82			15.9	37.73
		9.5	63.15			16	37.5

Gait Speed with 6 metre walk. < 100 cm/second = slow gait

Trial # 1 Walking 6 metres only

Trial # 2 Walking 6 metres while counting down from 100, specify # errors in column above. Total number of subtractions given _____

Trial # 3 Walking 6 metres while naming animals, specify # of repetitions in column above. Total number of animals given _____

Trial # 4 Walking 6 metres while doing serial seven subtraction, specify # errors, 93_____, 86_____, 79_____, 72_____, 65_____,

83_____, 76_____,69_____, 62_____, 55_____,

Appendix D: Byproducts of this Thesis and Links to Media

The following instructional video is included as a byproduct to this thesis. It outlines instructions for how gait assessments are to be performed and recorded in a clinical setting. This video was produced and edited by myself (Stephanie Cullen) and Manuel Montero-Odasso with the help of the Gait and Brain Lab team.
Link: https://www.youtube.com/watch?v=DVAEENexaac&feature=emb_title

During my Masters, I also recreated our lab website with many online resources for researchers and for patients who would like to learn more about gait testing and mobility. These can be found at www.gaitandbrain.com.

More details about my research productivity and outputs during my Masters can be found in my CV below.

Curriculum Vitae

Name: Stephanie Cullen

Post-secondary Education and Degrees:

M.Sc. Kinesiology (Integrated Biosciences)
Western University
London, Ontario, Canada
2018-2020

B.Sc. (Honours) Kinesiology
Western University
London, Ontario, Canada
2014-2018

Honours and Awards:

CIHR Frederick Banting and Charles Best Canada Graduate Scholarship in Health Research (CGS – Master's) (2019-2020)

Alzheimer's Society of London and Middlesex Master's Scholarship in Alzheimer's Related Research (2018-2019)

Dr. Micheal S. Yuhasz Gold Medal in Kinesiology (2018)

Western Continuing Admission Scholarship (2014-2018)

Related Work Experience

Clinical Research Assistant
St. Joseph's Health Care London, Division of Geriatric Medicine and Lawson Health Research Institute
London, Ontario, Canada
2016-2020

Graduate Teaching Assistant
Western University
London, Ontario, Canada
2018-2019

Publications:

Cullen S, Borrie M, Carroll S, Sarquis-Adamson Y, Pieruccini-Faria F, Mckay S, Montero-Odasso M (2019) Are Cognitive Subtypes Associated with Dual-Task Gait Performance in a Clinical Setting? J. Alzheimer's Dis. 71, 57–64.

Cullen S, Montero-Odasso M, Bherer L, Almeida Q, Fraser S, Muir-Hunter S, Li K, Liu-Ambrose T, McGibbon CA, McIlroy WE, Middleton LE, Sarquis-Adamson Y, Beauchet O, McFadyen BJ, Morais JA, Camicioli R, The Canadian Gait and Cognition Network (2018) Guidelines for Gait Assessments in the Canadian Consortium on Neurodegeneration in Aging (CCNA). Can. Geriatr. J. 21, 157–165.

Cullen S. Effects of Aerobic and Resistance Exercise on Brain-Derived Neurotrophic Factor and Cognitive Benefits in Alzheimer's Disease. 2017 Undergraduate Awards. 13 Nov 2017; 21. https://ir.lib.uwo.ca/undergradawards_2017/21

Oral and Poster Presentations:

Cullen S, Borrie M, Carroll S, Mahon J, Sarquis-Adamson Y, Montero-Odasso M. Dual-task gait assessment may predict future cognitive decline in a memory clinic setting: a longitudinal study.
Poster presentation at 10th Canadian Conference on Dementia.

Cullen S, Borrie M, Carroll S, Montero-Odasso M. Association Between Cognitive Impairment Subtypes and Dual-Task Gait Performance in a Clinical Setting.
Oral presentation at Schulich Department of Medicine Resident Research Day (10 May 2019).

Cullen S, Borrie M, Carroll S, Montero-Odasso M. "Walking Performance Decline Across the Cognitive Spectrum in a Clinical Setting".
Poster presentation at Kinesiology Graduate Student Research Symposium (12 April 2019 – second place poster award), Parkwood Institute Research Day (26 April 2019), Canadian Geriatrics Society ASM (3 May 2019).

Conference and Event Participation:

Canadian Medical Hall of Fame 2017/2018/2019
Discovery Days Volunteer/Presenter
Co-lead 2018 and 2019 presentations for high school students (titled "Walking the Walk").

Kinesiology Graduate Students Association 2018 – 2019
Graduate Student Seminar Leader
Act as a liaison between graduate students and invited speakers for monthly seminars in bioscience stream topics.

CCNA Public Forum on Dementia Risk Reduction 2018
Montreal, Quebec
Chosen to represent the Mobility, Exercise and Cognition team during the trainee poster session. Gained experience presenting to a lay audience and prepared a poster on the administration and use of gait testing in CCNA projects.