Gait and Working Memory in Alzheimer's Disease, Aging and Small Vessel Cerebrovascular Disease

by

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Abstract

This thesis first explored the effects of concurrent spatial attention and working memory task performance on over-ground gait in healthy young and older adults. It then compared over-ground gait parameters and working memory performance in mild Alzheimer's Disease (AD) and normal controls (NC) and investigated costs of dual-tasking on working memory performance and cadence during treadmill walking at preferred walking speed in the two groups. Furthermore, it explored these differences in AD and NC groups in relation to their subcortical hyperintensities (SH) that were rated using standardized scales on MRI. Reaction times and accuracy on working memory performance measures were collected under single and dual task conditions. Over-ground gait parameters were measured on an automated walkway. Costs of dual-tasking on gait parameters and working memory performance were measured at a constant velocity on a treadmill. The hypotheses that working memory influences gait performance and that a higher SH burden negatively influences over-ground gait and costs of dual-task conditions, were supported in a series of experiments. Gait slowed down while performing working memory and spatial attention tasks in young and older adults. Patients with mild AD,

compared to NC, had a slower gait velocity, shorter stride length and lower cadence on the walkway. When the two groups were subdivided into higher and lower SH groups based on their median SH score, the NC group with lower SH burden walked significantly faster with a higher cadence and a longer stride length than the other three groups. Lastly, a higher SH burden negatively influenced working memory performance in NC while in mild AD patients, it had negative influences on adaptive changes in gait while dual-tasking. These results suggest that, in dual-task condition, SH interfere with processing speed in NC and on gait in AD. These findings provide new insights in to tradeoffs during dual tasking in relation to cerebrovascular disease. This has ecological implications because of the prevalence of small vessel disease in aging and dementia, may impact on predicting falls in AD.

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Chapter 1

1 Introduction

Canadians 65 years and older, are projected to outnumber children aged 15 and younger as early as 2015. By 2031, it is estimated that there would be between 8.9 million and 9.4 million people aged 65 and over in Canada (23% to 25% of total population) whereas in the USA the estimate is close to 70 million by 2030 [1]. The Canadian Study of Health and Aging, the largest longitudinal study of older adults in Canada, reported that almost 80% of seniors over 85 years reported stable health over a five-year period but over two-thirds reported a decline in their functional ability [2]. While a substantial proportion of older adults remain free of disease and disability, chronic health conditions such as hypertension, heart disease, falls, stroke and dementia account for a large proportion of functional disability in older adults. Gait impairment and cognitive impairment predict occurrence of falls and dementia respectively, and alone or together, can account for a large proportion of functional impairment in older adults.

In addition to coexisting co-morbidities that are commonly associated with aging, there are physiological changes that occur at several levels, which could amplify pathological states and propel functional disability. One such model described by Pugh and Lipsitz [3] illustrates the effect of cardiovascular risk factors such as hypertension, diabetes, etc, which are associated with microvascular damage commonly affecting the periventricular and subcortical structures of the brain. These are seen on MRI in almost 95% of elderly. Age-associated changes in the fronto-subcortical neural networks, further influenced by microvascular changes associated with aging, may underlie the phenotype of common geriatric syndromes such as gait impairment, urinary incontinence, executive dysfunction and low mood [3]. Therefore, studying the interaction of microvascular damage may be essential in any study implicating the fronto-subcortical system such as gait and cognition.

Amongst the various causes of functional decline in older adults, falls in older adults are an important contributor of mortality and morbidity. Ganz et al. [4] studied the prognostic value for risk factors for future falls in older adults from 18 studies that met their inclusion criteria for multivariate analysis. They calculated LR for falls and categorized LR for single falls and for 2 or more falls. The highest LR for risk factors for one or more falls were presence of CNS active drugs (LR:27), evidence of stroke on neurological exam (LR:15) and dementia (LR:15) . Falls are usually the result of multifactorial changes influenced by environmental constraints, however; one of the most important factors that contribute to falls are mobility impairment, cerebrovascular disease and cognitive impairment. These three factors are independently associated with functional impairment but also interact with one another and amplify their effect on disability.

Falls in the elderly are usually preceded by dysfunction in balance, gait and/or motor control[5, 6]. Age-related changes in musculoskeletal system (such as decreased muscle contraction, sarcopenia, decreased range of movements, decreased dorsiflexion), the peripheral nervous system (such as decreased audition, vision, sensations, nerve conduction velocity) and the central nervous system (such as decreased cerebral perfusion, decreased neurotransmitters, white matter changes, atrophy) can further modulate gait and postural control thereby contributing to falls. This study focuses on gait and cognitive ability in patients with Alzheimer's Disease (AD) in relation to the concomitant cerebrovascular disease. Specifically, this study explores the interaction between gait, executive cognitive function and age-associated white matter changes in the brain in healthy older adults and in those with mild stage AD.

1.1 Gait Parameters

Gait can be measured in two broad categories namely, temporal and spatial parameters. A few parameters discussed in this thesis are defined in table 1 and 2 below.

Table 1: Temporal Parameters

Gait-velocity or gait-speed

Cadence: The number of steps per minute

Stride-time: Time elapsed between the first contact of two consecutive footfalls of the same foot.

Double-support: The duration when both the feet are on the ground from point of heel-contact to the point of toe-off.

Stance time: The percentage of the gait cycle of the same foot when the foot is on the ground.

Swing time: The percentage of the gait cycle when the foot is off the ground. It is equal to the single-support time of the opposite foot.

Table 2: Spatial Parameters

Step-length: Distance measured on the line of gait propagation from the heel point of the current footfall to the heel point of the previous footfall of the opposite foot.

Stride-length: Distance measured on the line of gait propagation between the heel points of two consecutive footfalls of the same foot.

Base of support or step-width: Perpendicular distance from heel point of one footfall to the line of progression of the opposite foot.

1.2 Neuroanatomy of gait

Regions involved in gait control include the frontal lobes, cingulate cortex, the parietal cortices, white matter tracts connecting the frontal and parietal lobes that run in fasciculi through the centrum semiovale, basal ganglia, the supplementary motor area and the white matter tracts that connect the basal ganglia and SMA, dorsal brain stem, cerebellum and pyramidal tract through the spinal column[7-11]. Frontal regions are responsible for attentional control of gait while the agranular frontal cortex constitutes the motor cortex. Premotor areas are also involved in controlling gait speed especially on the treadmill[12]. Anterior prefrontal regions are involved in preparation of cued movement, while the medial mortor cortex and SMA mediate planning and execution of the movement[13]. The basal ganglia are critical subcortical structures associated with gait control. They contribute through connection with the SMA to maintain cortical tone leading to a state of readiness. Secondly, they provide internal cues to precise submovements and are associated with the timing and rhythmicity of these submovements. The internal cues are sent to the SMA where a correct submovement sequence is appropriately selected, and in turn triggers the motor cortex to produce the movement. Abnormal internal cues can disrupt submovements and impair gait.

For external cues, the pathways are different. The basal ganglia-SMA loop is bypassed and visual and auditory signals from the sensory cortex go directly to the premotor area, activating the motor cortex. Parietal cortices play an important role in sending sensory signals which also represent the movement of body parts in relation with each other as required when overcoming obstacles[14].

Several techniques have been used to study these pathways such as lesion studies, ERP, PET, SPECT,MRI, fMRI of motor imagery, magnetic resonance spectroscopy, diffusion tensor imaging and Near-infrared spectroscopic topography.

1.3 Gait and Aging

Healthy aging is associated with changes in the musculoskeletal system, peripheral and central nervous systems which affects several motor functions including gait and balance. Changes that occur in older adults include a decrease in stride-length and velocity,[15] shorter swing phase, reduced arm swing and widened step-width[16] and, an increase in variability of stride-width and stride-length[17]. Although gait velocity declines by about 0.7% to 1.6% per year after age 63, the age-related decline is apparently a result of decrease in stride-length rather than cadence [18, 19]. Therefore, the main differences in gait in healthy elderly as compared to young-adults have to do with age-related decline in gait speed. It is believed that the decrease in gait speed and stride-length allow for increased double-support time and therefore a more conservative gait pattern [20]. These responses are exaggerated under circumstances that threaten gait stability such as walking on an irregular surface [20]. Maki et al. have showed that in response to a rapid lateral displacement of the support surface (mechanical perturbation) older adults take multiple compensatory steps to avert a fall as compared to young adults [21]. Similarly, informational perturbations, which relate to rapid changes in somatosensory input such as a rapidly moving visual field that creates an illusion, and internal perturbations relating to disruption of the balance control system itself may lead to deleterious postural responses leading to falls [22].

Recently emerging literature on the cognitive demands of gait and postural control, suggest that attention plays an important role in maintaining a steady gait. Lack of attention due to distraction from walking can lead to changes in gait patterns. Therefore, this can be construed

as another form of endogenous perturbation, a cognitive perturbation that occurs through distraction or by enforcing additional demands on attentional capacity by engaging the individual in a cognitively demanding task, which may perturb the gait depending on the nature of the task. An overview of dual-task literature follows later in this chapter.

What is not clear from existing studies is whether the gait parameters that increase gait stability are the same as those that are associated with falling in the near future. In a study of 1815 elderly Chinese aged 70 and over, a decrease in gait speed and stride-length during a 16-foot walk was associated with an increase in falls in the subsequent 12 months [15]. In this cohort, those with cognitive impairment or depressive symptoms had a slower gait suggesting that within the healthy older adult sample there are other factors that can further interfere with gait. Gait slowing has also been related to depressive symptoms rather than to changes in fitness [23]. This may reflect age-associated changes in the fronto-subcortical system that are further compounded by microvascular damage [3]. Executive function, gait control and mood are in part mediated by fronto-subcortical systems, which can be injured by the small-vessel disease which commonly accompanies aging. In studies on dual-tasking in 'normal' elderly, the role of white matter changes, have not been adequately taken into account. Therefore, assessing vascular risk factors and including measures of vessel disease burden in the brain parenchyma is a main aim of this thesis. The role of vascular disease and its association with gait and cognitive impairment is reviewed below.

Treadmill walking, though in theory is mechanically similar to overground walking, in reality is quite different. Studies have found that gait speed, cadence and knee angle on treadmill is different form over ground walking even in unimpaired older adults. [24]. Patient with stroke had faster gait speed, longer stride lengths, and lower cadence over ground than on the treadmill[25]. Habituation on the treadmill in young adults varies up to 1-hour whereas in older adults, even 15 minutes of habituation was not found to equate to overground gait parameters[24, 26].

1.4 Gait and Cognition

Dual-task studies primarily look at the influence of one task on the performance of another task and vice versa. The functional neuroanatomy of dual tasking is of great interest to human research as these regions are relevant to routine functioning and can be compromised in disease. Several recent studies using functional neuroimaging of the performance of two competing tasks simultaneously point to increased neuronal activity in the frontal and parietal cortices[27, 28]. Specifically, the left frontal gyrus,iinferior frontal sulcus, the middle frontal gyrus, and the intraparietal sulcus are activated on functional neuroimaging of dual-task performance.[29]. This suggests that the dorsolateral prefrontal and superior parietal cortices are involved in the coordination of concurrent and interfering task processing[29].

From studies demonstrating changes in gait that occur when subjects simultaneously perform a secondary task, it is understood that attentional resources are essential to gait control. Limited attentional resources, sharing of common neuronal resources and bottlenecking of critical pathways, have been suggested to explain the costs of dual tasking. Healthy young and older adults demonstrate changes in their temporal or spatial gait parameters while dual-tasking by reducing gait velocity, shortening stride-length, increasing double-support and/or cadence. These changes signify one common compensatory mechanism, i.e. increasing gait stability by slowing down. It is also been reported that gait parameters change when concurrently performing a second task while walking; this is commonly referred to as the 'dual-task' condition. Such changes in gait have been demonstrated in elderly[30-32] and in patients with AD[33-35] by having the participants talk while walking either as a structured cognitive interference task or by engaging in casual conversation. These studies have shown that patients stop walking while talking or when they continue walking, they demonstrate increased variability in their velocity, stride-length and/or double-support[30-35]. Some researchers have associated these dual-task changes with their risk of sustaining a fall, for example, one study found that cessation of walking increased the odds of falling[30]. Review of current literature on dual-tasking studies related to gait is summarized in table 1.

Drawbacks of secondary tasks used in the previous dual-task literature include the following. Articulation of speech or even the changes in respiratory cycle while speaking can interfere with gait patterns, so considering speech as a purely cognitive secondary task, is misleading because of the confounding motor activities. To show that two tasks interfere with each other, it is essential that the two tasks share common neuronal resources and therefore compete for the same neuronal substrates. Cognitive interference tasks used in the existing dual-task literature have not consistently applied this principle. For example, Sheridan et al. have shown that executive function tasks induce an increase in gait variability and others have shown that visuo-spatial tasks also induce gait changes [34, 36]. Furthermore, just as dual-task can lead to gait slowing, similarly, reciprocal slowing in speed of information processing on the cognitive tasks can also occur, which has often not been considered in previous studies[37-39]. This thesis has tried to overcome some of these drawbacks, as will be detailed in the subsequent chapters.

1.5 Subcortical Hyperintensities

The advances in neuroimaging modalities such as computerized tomography (CT), particularly magnetic resonance imaging (MRI), and its use in older adults led to the identification of changes in the radiological appearance of periventricular white matter and subcortical regions whose clinical significance was unclear, at least initially. The term "leukoaraiosis" was coined by Hachinski for these areas on CT scan, to denote rarefaction or thinning of cerebral white matter[40]. On T2-weighted MRI sequences, these areas appeared 'bright' or hyperintense and were referred to initially as perventricular rims, caps and unidentified bright objects [41]. Over the last two decades, significant work in this arena has better characterized these lesions using various research techniques including epidemiological, pathological, biological and sophisticated neuroimaging approaches. These have helped to clarify that these lesions are very prevalent in the elderly, are associated with known cardiovascular risk factors, are of substantial clinical significance and can be associated with disability[42]. Several terms have been used to describe them including 'white matter hyperintensities', 'white matter lesions' and 'periventricular and deep white matter

lesions'. As these hyperintense areas are seen in both periventricular white matter and subcortical regions of the brain particularly sparing the U-fibres, we refer to them collectively as 'subcortical hyperintensities' (SH).

1.5.1 Prevalence of SH

The Cardiovascular Health Study, a large population-based cohort study, reported that SH were present in 87% of all participants and 83% of those without prior stroke on MRI of elderly participants who were not institutionalized, wheelchair-bound, or under treatment for cancer [43]. The Atherosclerosis Risk in Communities Study, found an overall prevalence of SH of 86% in their cohort aged 55-72 years (mean, 62 years) [44]. Some epidemiological studies such as the Rotterdam study (cohort age range: 55 – 85 years) and the Helsinki Aging Study (cohort age range: 55 – 90 years) reported prevalence of 27% and 36% respectively[45] where as others have reported prevalence as high as 92%[46]. Longstreth et al. reported in 1996 that some degree of SH was relavent in up to 96.6 % of those over 65 years[42]. In Alzheimer's Disease (AD), similar prevalence has been reported ranging from 38% to 95% [47, 48].

1.5.2 Risk Factors for SH

Large epidemiological studies have demonstrated an association between the presence of SH and increasing age and known cardiovascular risk factors[42, 44, 49, 50]. Two of these studies did not find an association between SH and diabetes [44, 49] but few prospective studies have shown a relationship between deep white matter hyperintensities and glycated hemoglobin levels [51, 52]. Increasing age and presence of diabetes was also associated with progression of diabetes in one study[53]. The association between the presence of hypertension and SH [41] was confirmed on several epidemiological studies [42, 44, 49] and its presence suggested the progression of SH [54]. The control of hypertension was associated with a reduced risk of SH

progression[55]. These studies suggest that since SH are associated with cardiovascular risk factors, controlling these factors should reduce the rate of SH progression[56].

1.5.3 Pathology of SH

SH on MRI represents the graveyard of dead or dying cerebral tissues in response to multiple etiological insults, leading to infarction (necroctic SH) or demyelination, astrocytic gliosis vacuolation(non-necrotic SH)[57-59]. The association with cardiovascular risk factors and cerebrovascular disease, and its histological similarity to chronic ischemic injury and structural changes in the vasculature, all suggest that SH are usually the result of cerebral ischemia (see Pantoni and Garcia[60]). Arteriolar changes often underlie focal necrosis, called lacunes, appearing as SH. Pathologically SH includes intimal hyperplasia, arteriosclerosis, lipohyalinosis, amyloidosis, aneurysms and vasculitis. In addition, increased tortuosity of vessels also occurs, which increases vascular resistance and contributes to white matter ischemia and hyperintensities [60, 61]. Penetrating end-arterioles in the white matter regions show the replacement of vascular smooth muscles by fibrohyaline changes leading to narrowing of vessel lumen, called arteriosclerosis. These changes are typical of SH seen in deep white matter; however, the periventricular hyperintensities are associated with disruption of the ependymal layer of the ventricle, demyelination and venous collagenosis, with characteristics typical of vasogenic edema [61]. Glutamate concentration, considered to result from cerebral ischemia, is elevated in the cerebrospinal fluid of those with SH compared to those without SH [62]. At the molecular level, elevated hypoxia-inducible factors and proteins in deep subcortical lesions and incidental white matter lesions suggest that tissue ischemia is associated with SH[63]. These studies considered together with epidemiological evidence showing a relationship with cardiovascular risk factors, support the evidence for an ischemic etiology of SH in older adults.

1.5.4 SH and Gait

Masdeu, Wolfson, et al. reported in a sample of 40 nursing home residents who had no evidence of neurological disease, that some of them experienced falls[64]. Significantly more white-matter hypodensities were seen on CT scan in 20 older adults, who had experienced one or more falls over a 2-year period, than in the 20 who did not fall during this period [64]. Around the same time another report associated impaired gait and balance with hyperintensities on MRI [65]. Thompson and Marsden, in studying gait in subcortical arteriosclerotic encephalopathy (Binswager's Disease), a condition with severe periventricular confluent hyperintensities also associated with lacunar infarcts, described a parkinsonian gait in their sample of 12 patients[66]. However, this raised a question as to whether a lesser burden of white matter lesion could also be associated with a milder gait impairment. Several reports followed associating gait and balance impairment with milder degrees of SH on MRI[64, 66-83]. A few recent studies indicate that gait may be related to the presence of SH, but also to the lesion volume[72-74, 79]. Some of these studies targeted populations with gait and balance impairment and used subjective clinical evaluations of the presence or absence of gait difficulty or more structured performance measures such as the Short Physical Performance Battery and Tinetti Balance and Mobility Scale [71-73, 84, 85]. Such studies highlight the importance of SH in mobility impairment but do not indicate which specific gait parameters are associated. Those who have looked at objective gait measures have focused on a limited number of gait parameters such as gait velocity [76, 78, 83, 86]. Camicioli et al. showed that the presence of SH in the periventricular region of the brain were associated with the number of steps and the time taken by participants to complete a 30-foot walk[78]. Similarly, Starr et al. also described correlations between gait speed and brain stem SH in 97 participants of the Aberdeen 1921 birth cohort[76]. A recent report examined temporo-spatial gait characteristics on a sample of 321 high-functioning older adults who had no dementia or stroke in the Cardiovascular Health Study and found that those with a slow gait speed, short stride and long double support time had higher white matter disease and subclinical strokes[87]. Presence of SH is also associated with more rapid progression of impaired mobility without any other apparent cause [85]. But in this report, the association between gait parameters and SH in healthy older adults was not observed. There is very little research looking at the association between gait characteristics in early stage of AD and underlying SH. Hence this project studied possible associations between SH and spatio-

temporal gait parameters in a convenience sample both patients with AD, and demographically matched elderly healthy controls.

There are limited studies on the regional association between SH burden and gait impairment. In the only report to date, frontal periventricular regions were reported to have a high sensitivity and a poor specificity, whereas the parieto-occipital regional SH load had a high specificity and a low sensitivity for mobility impairment [71]. Benson et al. [71] compared SH in 12 older adults with superior mobility and 16 with poor mobility and found that 64% of those with impaired mobility had posterior SH (mostly bilateral) where as none with superior mobility had any posterior SH. Four of the 5 with poor mobility had frontal SH in the absence of posterior SH. Thus, frontal SH had a sensitivity of 93%. A letter to the editor in response to this article supported the finding that frontal SH were correlated with gait impairment but not SH in any other region.

The mechanisms by which SH interferes with gait are not clearly understood but it is hypothesized to relate to: [1] interruption in the circuitry between the basal ganglia, cerebellum and their connections with the motor cortex[66], [2] impaired central somatosensory processing[74] and , [3] disruption of long-loop reflexes[64]. This also suggests that the presence of SH may also interfere the performance of another task while walking, which is common to everyday functioning (such as talking while walking). Therefore, this also studied the association of SH with such dual-tasking using controlled experimental paradigms.

1.5.5 SH and Cognition

An association between cognitive abilities and SH was described over twenty years ago by Steingart and colleagues [88] in a cohort of 105 normal elderly who participated as controls in a dementia study. They reported that those with SH on CT scans obtained lower scores on the Extended Scale for Dementia, reflecting difficulties in time orientation, construction of

sentences and memory. Subsequently, other reports emerged suggesting that in non-selected individuals with SH and without dementia, attention, speed of processing, visuo-spatial memory, and executive skills were primarily affected[50, 89, 90]. The Rotterdam Scan Study, a longitudinal population-based study of over seven thousand adults over 55, screened for cognitive impairment on the Mini-Mental Status Examination [91] and the Geriatric Mental schedule, showed that in a sub-sample of over 1000 adults, SH were associated with poorer cognitive performance independent of atrophy and infarcts. This study also found that SH in periventricular regions affected speed of processing assessed on timed measures such as the Stroop test, in keeping with studies reporting similar findings in smaller samples [50, 90]. They did not however, confirm findings that more superficially located SH were found to be related to performance on visuoperceptual skills, visuomotor tracking/psychomotor speed and, to a lesser degree, learning capacity and abstract and conceptual reasoning skills[92]. The inconsistent results probably relate to variable methodologies in classification of SH, cognitive tools used, and whether the target population had concomitant AD or not.

1.6 Alzheimer's Disease: Clinical features and pathology

Alzheimer's disease is typically known to occur after age 65. While the gold standard of diagnosis is currently autopsy alone, established guidelines require that the clinical picture demonstrate a progressive impairment in memory and in at least one other cognitive domain which represents a decline from the previous level of functioning in social and professional dependence in executive or basic activities of daily living, in the absence of other identifiable causes for dementia [93]. However, recent suggested guidelines in the diagnosis of AD include use of biomarkers, neuroimaging and cerebrospinal fluid analysis[94]. The initial stage of AD is characterized by episodic memory loss. Neuropsychological tests can reveal deficits in memory and also to a lesser extent deficits in attention, executive function, working memory, visuo-spatial attention and language[95]. As the disease progresses, impairments in these domains becomes apparent to family and friends, and there a progressive reliance on the caregiver for assistance in instrumental activities of daily living is needed to overcome these functional impairments[96-98]. Behavioral symptoms such as delusions, hallucinations and

wandering behaviours can be seen in the moderate stages of AD. In the later stages of the disease, functional impairments affect one's ability to care for self including difficulties in bathing, toileting and feeding is affected. At this stage gait changes become clinically apparent even to the untrained eye. Parkinsonism may also emerge at this stage[99]. Gradually there is marked limitation in ambulation with the need for 24-hour support. Death is usually caused not directly by the disease but as a complication of infections or respiratory failure.

The most relevant features in the pathological diagnosis of AD are neurofibrillary tangles (NFT) and amyloid plaques. Although other changes such as neuronal and synaptic loss, depletion of cortical cholinergic innervation and gliosis are seen frequently, using criteria such as the Consortium to Establish a Registry for Alzheimer's disease (CERAD) criteria and the 1997 criteria proposed by the National Institute of Aging and the Reagan Institute of Alzheimer's Association emphasize the presence of NFT and neuritic plaques in AD diagnosis. Specific regional predilection of NFT and neuritic plaques and the number of NFT in each microscopic field of vision determine the high, intermediate and low likelihood of AD[100, 101].

Lewy bodies are intracellular inclusion bodies that are typically seen in the substantia nigra of patients with Parkinson's disease. Wide spread presence in the cerebral cortex and brain stem indicates diffuse Lewy Body disease(DLB). Lewy bodies are seen frequently seen on pathological specimens in patients with AD; some reports suggest their presence in up to 60% in those with familial AD[102, 103]. Clinical features of DLB include recurrent falls caused by gait and postural instability, which is probably caused, in part, by extrapyramidal signs such as rigidity and bradykinesia[104]. Falls are more common in patients with DLB[105] than in those with AD. However, the clinical presentation of patients with mixed pathologies, such as DLB and AD or Lewy body variant of AD, includes features that are atypical of AD alone such as REM sleep disorder, fluctuations in attention and cognition, clinically recognizable gait instability and hallucinations, which can help to distinguish these clinically. While the use of established clinical guidelines significantly increases the accuracy of the diagnosis, as with all clinical studies of neurodegenerative disorders, the gold standard for diagnosis is neuropathology.

1.7 Gait and Alzheimer's Disease

In a longitudinal sample of AD, falls occurred in 36% of patients compared to 11% of age-matched controls[106]. Clinical features of AD that might play a role in increasing falls in this population could be stratified according to the clinical stage of AD. During the early stages of AD, executive dysfunction may play a role in increasing falls risk by impacting gait during dual-tasking. In addition, studies have shown that performance in visuo-constructional tasks correlate well with functional ability and it is likely that visuo-spatial deficits may lead to difficulties in obstacle avoidance or its successful clearance leading to trips and slips. Patients with AD may be less able to select appropriate responses quickly especially under constantly changing environmental conditions. This slower speed of central processing may contribute to clinically slow responses in averting falls and therefore, an increased risk of falling[107]. Furthermore, recent work suggests that the gait parameters in AD are different from healthy elderly, characteristics of which suggest gait instability[108]. In later stages of AD, parkinsonism becomes more prevalent and gait disturbances are clinically obvious further fuelling the risk of falls. In addition, behavioural symptoms such as wandering, increases the risk of falls in the severe stages of AD. Patients with AD have a 36% higher risk of falls [106, 109] even though gait impairment is not usually clinically apparent during the mild stage of AD [93, 110-112] . In fact, if gait impairment is present early in the course of dementia, this is regarded as evidence that the underlying etiology is likely not AD[112]. On routine clinical assessment including standardized scales such as the Tinetti balance and gait scale, mild AD patients are similar to age-matched controls [110]. This raises the possibility that, although gait in early AD appears to be no different from that of normal elderly on clinical examination, changes in gait-speed may become evident on more challenging walking tasks may elicit abnormalities in AD compared to normal controls, not evident on casual inspection. Also whether such differences can be detected by more careful measurement of temporal and spatial gait parameters in mild AD even under normal walking conditions has not been well studied.

A summary of studies relating to gait patterns in AD is summarized in Table 2. In terms of temporal parameters, comparisons in gait and balance between healthy controls and those with AD have focused on moderate and severe stage of AD (MMSE<18) and consistently showed that AD patients have a slower gait[5, 34, 110, 111, 113-115]. However, there is no consensus yet on whether there is even subtle gait impairment in mild-stage AD. A recent report from the Einstein Aging Study compared quantitative gait assessments in a group of 54 patients with amnestic mild cognitive impairment (MCI), a preclinical state of AD and 62 non-amnestic MCI in comparison with 295 normal elderly. The authors reported that both patient groups demonstrated abnormalities in gait[116]. Specifically, amnestic MCI patients showed decreased stride-length and non-amnestic MCI demonstrated decreased velocity, stride-length and cadence when compared to normal elderly. Between the two patient groups, nonamnestic MCI group had a significantly slower cadence[116]. In mild-stage AD, velocity was found to be slower than healthy older adults in one study[117], while another reported that in a sample of 95 AD patients with varying degrees of disease severity, none had gait impairment in the mild stage. However; these authors reported that 16% of the moderate and 32% of severe stage of AD had observable gait impairment[118]. Nakamura et al. studied postural sway and gait using a gravicorder and reflective markers mounted on bare-feet in AD in-patients grouped according to three grades of severity on the Clinical Dementia Rating scale (CDR) [111]. They reported that in their sample of 15 patients with mild-stage AD (CDR of 1.0), significant differences were seen in postural sway but not gait characteristics, whereas differences in the latter were also seen in two groups with more severe dementia. This could explain why patients with AD have increased risk of falls in later stages of the disease, but why the risk is higher than age-matched controls even in the early stage of AD despite clinically normal gait pattern is still unclear. In a sample of 157 patients with AD, Buchner et al. reported that 31% experienced falls in the first four years from the onset of memory difficulties[109]. This figure went up to 51% in the 117 patients who were followed over the subsequent three years. Moreover, the fracture-rate was more than three times the age- and sex-adjusted rate of the general population[109], raising the possibility that subtle gait and balance changes, not apparent in regular clinical gait assessment, may become more evident in more challenging tasks that better simulate daily life. One study reported that on more challenging bed-side gait measures, such as the Timed-up-and-go (TUG), 360-degree

turns and figure of '8' walk, patients with mild stage AD do more poorly than age-matched healthy controls[119].

There are a small number of studies that have looked at dual-tasking in AD while walking. There is evidence to suggest that gait relies on executive function abilities and that performance of executive function tasks may interfere with gait performance under dual-task conditions[33, 120-122]. Camicioli et al. compared dual-tasking effects in 15 patients with mild AD (MMSE: 21; age: 74 years) using a word-list generation task, considered an executive function task, with groups of younger and older adults, they found that the AD group took a significantly longer time to complete a 30 feet walk compared to the other two groups while dual-tasking [35]. Sheridan et al. described increased variability in gait and decreased speed while dual-tasking using a forward digit span task in 28 patients with mild AD[34]. Another study also demonstrated that performance of fluency tasks and digit recall tasks interfered with gait in patients with AD and in healthy elderly[33]. A few studies have targeted patients with Parkinson's disease and stroke including dementia samples with mixed etiologies. These have been summarized in Table 1.

1.8 Objectives and hypotheses

Taking into consideration the above studies, the objectives of this thesis were as follows.

1.8.1 Experiment #1: Effect Of Working-Memory And Spatial-Attention Task Performance On Gait Parameters In Young And Older Healthy Adults

The goal of this experiment was to determine whether two cognitive tasks, working memory and spatial attention, under dual-task conditions would lead to comparable changes in gait parameters in healthy young adults. The degree to which mental tasks interfere with walking increase with age suggesting that aging is associated with decreased capacity to allocate the

attentional resources required to efficiently carrying out both tasks[123-126]. Therefore, a smaller sample of healthy older adults was also studied to compare to the healthy young adults.

Hypothesis: The hypothesis for this experiment was that performance of cognitive tasks would lead to a decrease in gait velocity and stride-length and increase in double-support to provide a more stable gait pattern during dual-tasking, and that these dual-task related changes in gait would be larger in the older adult group compared to younger adult group. Additionally, it was predicted that the changes in gait parameters during dual-tasking would depend on the attentional load of the secondary task, such that under dual-task conditions, the working memory task, which was designed to be cognitively more demanding than the spatial attention task, would lead to larger effects on gait parameters than the spatial attention task.

1.8.2 Experiment #2: Over-Ground And Treadmill-Controlled Gait Parameters In Patients With Mild Alzheimer's Disease And Healthy Older Adults.

The objective of this experiment was to compare over-ground and treadmill-controlled gait parameters in mild stage-AD and healthy normal controls (NC) at their self-selected walking speed.

Hypothesis#2: The hypothesis for this experiment was that patients with AD would be slower than NC but that there would be no changes in over-ground spatial parameters between the groups. Furthermore, enforcing a steady velocity on a treadmill would minimize any differences in temporal parameters in the two groups.

1.8.3 Experiment #3: Gait in Relation to Severity of Subcortical Hyperintensities in Mild Alzheimer's Disease and Healthy Older Adults.

The primary aim of this experiment was to explore the association between the total burden of SH in the brain using a reliable rating scale, and gait parameters, specifically gait-velocity, stride-length and stride-width, in patients with mild AD compared to NC. The secondary objective was to explore the correlation between regional distribution of SH and the gait parameters (gait-velocity, stride-length and step-width).

Hypothesis #3: The hypothesis for this experiment was that in each group, those with a higher proportion of SH would have a slower velocity, a shorter stride-length and a wider step-width, as an adaptation to the increase double-support time and therefore stability. It was further predicted that in both groups, the SH scores for the frontal and basal ganglia regions, aw well as total SH score, would correlate with gait velocity and stride-length.

1.8.4 Experiment #4: Dual-task Effects of Treadmill Walking while Performing Working-Memory Tasks in Alzheimer's Disease and Healthy Older Adults: Relation to Subcortical Hyperintensities

The objectives of this experiment were to 1) explore the costs of working memory performance on cadence (steps/minute) while walking on the treadmill at preferred speed in patients with mild AD and NC; 2) to examine the costs of treadmill walking on working memory performance (accuracy and reaction time); and 3) to assess whether the overall burden of subcortical hyperintensities (SH) in AD and NC participants correlated with increased costs of dual-tasking.

Hypotheses#4: The hypothesis was that both groups, AD and NC, would increase their cadence while dual-tasking and that both groups would demonstrate a decline in performance measures on the working-memory tasks. In both groups, those with higher proportion of SH would have poorer dual-task costs on cadence compared to those with lesser SH burden.

Table 1: Summary of dual-task gait literature:

STUDY	POPULATION	DUAL-TASK	RESULTS
Lajoie et al.[127]	Young adults	Auditory reaction time	- fastest RT in sitting - slow RT in standing and walking - RT in SS<RT in DS in gait cycle - no change in gait parameters
Ebersbach et al.[128]	Young adults	(i) Digit span (ii) Opening/closing Coat Buttons (iii) tasks (i) & (ii) (iv) finger tapping	1) only task (iv) had ↓ in stride time 2) ↑ DS time with (iii) 3) ↓ digit span with walking
Beauchet et al. [129]	Young and older adults	Counting	- ↑ steps & ↑ time both Y & O; but O > Y - ↓ length of step & ↓ cadence ONLY in O - ↑ lateral deviation & number of steps ONLY in O
Lindenberger et al.[126]	Young, milddle-aged and older adults	Memory encoding task	Dual-task costs increased with age

Camicioli et al. [37]	- PD (19 with Hx of freezing [F] & 19 with no Hx of Freezing [NF]) vs normal controls	Gait Verbal Fluency	- PD-F: ↑ steps & ↑ time to complete walk vs PD-NF - PD-F more dependent on attention and frontal deficits influence freezing in PD
Bond & Morris [38]	PD vs. NC	1°: walk 2°: i) with tray ii) with 4 glasses on the tray	- PD: slow with (ii) but not with (i) when vs. NC - PD depends on attentional mechanisms with any movements due to BCR dysfunction
Camicioli et al.[35]	AD vs. NC And Young vs older adults	1°: walk 30' 2°: fluency	2° on 1°: ↑ time to complete walk
Lundin-Olssan et al.[30]	Dementia vs. Depression vs. Stroke patients	1°: walking 2°: talking (SWWT)	- 12/58 stopped walking while talking, of those 12, 10/12 fell at least once in the next 6 mos. - PPV of SWWT 83%, NPV 76%
Lundin-Olssan et al.[130]	Older adults	1°: TUCT 2°: Carrying a glass of water (TUCT manual) – used as a task of attention	- 10/42 took ≥ 4.5 sec more for TUCT manual than TUCT
Cocchini et al.[33]	AD vs age-matched healthy control adults	**EXPERIMENT 1:** 1°: Walking along an	**EXP 1** - walking for AD patients was more affected than it was for the normal elderly by a concurrent cognitive demand.

		irregular pathway, first at normal speed and then as quickly as possible 2°: Association fluency task **EXPERIMENT 2:** i) Walking along an irregular pathway as in 1° ii) Digit recall task	**EXP 2** – demonstrated that both groups were equally impaired under dual task conditions when the demands of the cognitive tasks were adjusted for individual levels of ability.
Bootsma-van der Wiel et al.[31]	Older adults 85+	Verbal Fluency dual-task as a fall predictor	Dual-task not a predictor of falls
de Hoon et al.[32]	Older adults	Were asked simple questions while walking	Those with slower speeds, stopped frequently while talking
Sheridan et al.[34]	Out-Patients with dementia	Repeating random digits	Increased gait variability in AD group
O'Shea et al.[131]	15 PD vs without PD	coin transference counting backwards	Type of task did not matter
Sparrow et al.[36]	6Young and 12 Older adults	RT task; Audio,Visual, Audio-Visual stimuli	Costs of walking on Visual and Audio-Visual RT in OA not in auditory stimuli
Bowen et al.[132]	11 post-stroke patients	GaitMatII- with verbal stimulus eliciting verbal resposnse- yes or no	↓vel and ↑DS%
Haggard et al.[133]	Stroke, SAH, TBI rehab patients va controls	spoken word generation mental arithmetic verbal paired assoc. monitoring	- 6-7% decrement in stride duration in all four tasks -No changes in gait variability on 4 dual-tasking

		verbal V/S decision task	
Lundin-Olsson et al.[130]	42 sheltered accommodation residents w/wo walking aids	1. TUG 2. TUG-manual-glass of water	7 of 10 who had >4.5 sec difference between TUG and TUG-m had subsequent falls
van Iersel et al.[134]	59 fit Older adults	1. 100-7 2. 100-13 3. phonemic fluency (K and O)	No change in stride width variability & body-sway with dt ↑variability stride -time & -length with dt ↓ gait velocity with dt Verbal fluency had largest effect
Springer et al.[122]	19Young adults and 41 Older adults (fallers & non-fallers)	simple DT-listening complex DT-1+phoneme monitorin 500-7 DT	↓speed in all 3 groups ↓swing time in the 2 OA groups not YA DT no affect on swing time variability in YA and nonfallers ↑swingtime var in fallers on all DT

Table 2: Summary of studies that have looked at gait in patients with AD

Study	Popln	Age	Stage	Method	Trials	Velocity	Stride length	Comments
Alexander [5]	AD=17	68-71	MMSE 12.6	Flat walkway 6m, LED,	5x no obstacle 5X 25mm obs	0.8±0.17 m/s (approach speed) *	496.8±75mm*	
	NC=39	72	MMSE 29.4		5x152mm obs	1.2±0.17 m/s (approach speed)	655.5±87mm	
Pettersson et al.[135]	AD=17	74	MMSE 25	BBS		TUG time:11s*		-360-Turn
	NC=18	75	MMSE 29.5	TUG Figure of 8		TUG time: 9s		-one-leg stand -Figure of 8: AD:13 vs 1 step outside the markings
Camicioli & Licis [113]	AD fallers=18	83±10	MMSE: 15.8	Gait RITE mat single and dual-tasking(counting by 1s)	3 traverses: 1:practice, 2:preferred pace 3, dual-task	62.4±19(single) 61.3±25 (dualtask)	81.5±19.6cm(s) 83.1±23.3cm(dt)	Cadence decreased on dual tasking
	AD non-fallers=24	82±7	MMSE: 14.7			70±17cm/sec(single task) 66.5±21(dualtask)	82.8 ±19.2cm(s) 83.2±22.9cm(dt)	
Visser et al.[136]	AD=11	79±3	Set test: Nl score	6m walk with reading from 4m, registration with aluminium foil to shoes		0.67±0.17m/s* Cadence:1.8±0.2*	0.43±1.1m*	AD diagnosed by excl of vascular and other causes. No staging of AD but patients had severe memory impairment and BPSD
	NC=11	78±3	Set test: Nl score			1.1±0.3 Cadence:2.1±0.2	0.58±0.1m	

O'Keefe et al.[114]	AD=55	78±5	CDR from 1-3					Cautious gait commonest with mild AD and frontal gait commonest with severe AD
Nakamura et al.[111]	AD=45	77	CDR 1,2,3 (15 each group)	SPECT regions selected a-priori. Postural sway – gravicorder; Walk- 10 m walkway with motion analyses; CV=(SD/M)x100	60 sec of eyes fixed stand; 3 trails of walk	CDR1:0.93±0.13 m/s CDR2:0.65±0.11* CDR3:0.57±0.18*	0.94±0.12 0.61±0.18* 0.49±0.13*	Postural sway in CDR 1 had $p<0.05$ otherwise they resembled NC in gait. IN CDR2, 3 rCBF in frontal and BG c' with stride length and variability.
	NC=15	77	MMSE 27			1.05±0.19	1.03±0.14	
Goldman et al.[117]	AD-v mild=40	72±7.5	CDR 0.5	Cog tests Finger tapping Gait:foot-switch RT	Gait: 10m walk RT: Fitts task	1.06±0.2		Simple RT was longer in mild AD thatn the other two groups. Very mild and mild differed on DSST
	AD-mild=20	74±7.8	CDR 1.0			0.89±0.2**		
	NC=43	73±7.7	CDR0			1.08±0.19		
Allan et al.[110]	AD=64		CAMCOG: 60±15	Tinetti balance and gait scale				Mild AD(CAMCOG>65): no gait/balance impr but non-AD (Camcog>65) had sign gait/nbalance imp
	Non-AD=163							
	NC=47		CAMCOG: 94					

Chapter 2

2 Effect of Working-memory and Spatial-attention Tasks on Gait in Healthy Young and Older Adults

ABSTRACT

Changes in gait parameters induced by the concomitant performance of one of two cognitive tasks activating working memory and spatial attention, was examined in healthy young adults (YA) and older adults (OA). There was a main effect of task condition on gait-speed ($p= 0.02$), stride-length ($p<0.001$) and double-support time ($p=0.04$) independent of the group. There were no significant differences between working memory and spatial attention associated gait changes. Working-memory and spatial-attention dual-tasking led to a decrease in gait-speed ($p=0.09$ and 0.01) and stride-length ($p=0.04$ and 0.01) and increase in double-support time ($p=0.01$ and 0.03) in YA and decrease in stride-length ($p=0.04$ and 0.01) alone in OA. Cognitive task associated changes in gait may be a function of limited attentional resources irrespective of the type of cognitive task.

2.1 INTRODUCTION

Dual-tasking studies on balance control and gait have enhanced our understanding of the influences of cognition on these functions (reviewed by Woollacott et al.[137]). Dual-tasking methodology involves the performance of secondary tasks while walking to determine the costs involved in performing the concurrent task [17, 30, 32, 35, 39, 128, 129, 131, 138, 139](see methodology review by Huang and Mercer [140]). Costs of dual-tasking on gait parameters are observed by studying changes in velocity, cadence, step-length and double support time

while performing secondary tasks; the decrements in gait parameters are presumed to be due to a limited attentional capacity depending on the complexity of the secondary task[137, 140].

Various secondary tasks have been used to demonstrate the interactions between cognition and gait. Most studies have used speech as the distraction task [30-35, 37, 39, 128, 129, 133, 134, 138, 141-146] where as others have used manual motor tasks[38, 130, 131, 147] or even electrical stimulation as the secondary tasks[148]. Interference effects of the secondary tasks depend on the study sample and complexity of the secondary task. For example, effects on gait parameters were observed on a counting-backwards task in older adults but not in young adults [138] and on a digit span task in patients with Alzheimer's Disease [34] but not in young adults [128]. Some studies suggest that the respiratory alterations associated with speech production and/or central interference between regions involved in motor control as well as articulation or the rhythmic components of speech may play a role in dual-task interference rather than the competing demands on attention[149, 150]. Ebersach et al. studied the effect on gait with concurrent secondary tasks including a digit span task, opening and closing buttons task and finger tapping and found that stride time decreased with concurrent finger tapping and double support time increased only when digit span was performed along with opening and closing buttons while walking; digit span or the button task independently had no effect on gait parameters[128]. Similarly, reaction time tasks in response to an auditory stimuli did not affect gait parameters but reciprocal effects of walking were seen on reaction time[36, 127]. These studies suggest that the interference effect of a secondary-task on gait may depend on the type of secondary task, which may relate to whether or not the two concurrent processes share common neuronal resources [140].

Executive function refers to the ability to conceptualize, abstract, organize, initiate and regulate complex behaviour [151] and comprises higher-level functions such as attentional capacity and working memory (the ability to mentally manipulate information). Dual-task studies indicate that executive function tasks influence gait performance in community-dwelling older adults[122, 152-154]. For example, arithmetic tasks but not semantic fluency (generating a list of animals) are more likely to lead to alterations in gait under dual-task

conditions in older adults [141]. Similarly, executive function tasks have also shown to alter gait parameters in patients with Alzheimer's Disease [34] and Parkinson's Disease [155]. Working memory is an executive function requiring transient maintenance and concurrent manipulation of information for a goal-directed activity, which is utilized in routine daily activites[156]. Spatial attention refers to the ability to shift the focus of awareness from one spatial location to the another [157]. Spatial attention involves the ability to align attention or focus from ones current source of visual stimulus to another stimulus that is spatially segregated from the previous stimulus. The orienting of attention from one location to another could be triggered by an overt or covert shift of attention. Spatial attention and working memory share common cognitive features (dynamic shifting of attentional resources) as well as few common brain activations on functional neuroimaging (supplementary motor areas and intra-parietal sulcus)[158]; however, these tasks differ in that the former is primarily a task of visuo-spatial attention associated with predominantly posterior brain regions whereas the latter is an executive-function task associated with predominantly anterior brain regions [159]. It is unclear whether these two different cognitive tasks independently interfere with walking if performed simultaneously while walking.

The goal of this study was to determine whether these two cognitive tasks under dual-task conditions would lead to comparable changes in gait parameters in healthy young adults. The degree to which mental tasks interfere with walking increase with age suggesting that aging is associated with a greater demand on attentional resources required for efficiently carrying out both tasks[123-126]. Therefore, we also studied a smaller sample of healthy older adults to compare to that of the healthy young adults. We hypothesized that performance of cognitive tasks would lead to a decrease in gait velocity, stride-length and double-support to provide a more stable gait pattern during dual-tasking and these dual-task related changes in gait would be larger in the older adult group compared to younger adult group. We also hypothesized that the changes in gait parameters during dual-tasking would depend on the attentional load of the secondary task such that under dual-task conditions, our working memory task, which was designed to be cognitively more demanding than the spatial attention task, would lead to larger effects on gait parameters than the spatial attention task.

2.2 METHODS

2.2.1 Participants:

Thirty-eight healthy participants were recruited for this study: 28 young adults (mean age: 27 years) and 10 older adults (mean age: 75 years). The older adults were recruited from a community-dwelling pool of healthy elders participating in the Sunnybrook Dementia Study, a longitudinal study with annual neuropsychological testing, neuroimaging and functional assessments. Cognitive impairment, gait impairment or any condition that interfered with gait were exclusionary. The older adult participants were within normal limits on detailed neuropsychological testing. The study was conducted in a gait laboratory of a university hospital with approval from the Institutional Research Ethics Board.

2.2.2 Apparatus

Gait parameters were measured using GaitRite® (CIR systems, Inc., Havertown, PA), a computerized walkway that records the temporal and spatial parameters of each participant's gait for subsequent analysis. It contains a grid of pressure-activated sensors that are encapsulated in a carpeted walkway measuring 12 x 2 feet. The accompanying software (GAITRite Gold, Version 3.2b) reconstructs each traverse across the walkway and automatically computes the spatial and temporal parameters for every traverse.

The stimuli for the cognitive paradigms were presented using Labview® software (National Instruments Corporation, Austin, TX) on a computer on a Windows XP background. The

stimuli were projected on a screen placed at either end of the walkway in the direct view of the participant's central gaze as they walked on the walkway. Reaction times were captured by means of a small hand-held button device attached to the computer via an analogue-to-digital converter. The data were acquired and analyzed through Labview software. The sampling frequency was set at 500Hz.

2.2.3 Gait

Gait-velocity, stride-length and double-support were measured at the participants' preferred-pace and captured during a steady-state gait. To ensure this, we instructed participants to start walking approximately 3 feet prior to stepping on the walkway and continue walking up to 3 feet beyond the end of the computerized walkway. Gait parameters were measured across three conditions: walking only, without concomitant cognitive tasking, or walking while performing the working memory task and walking while performing the spatial attention task. Each condition comprised five traverses across the walkway.

2.2.4 Cognitive tasks

2.2.4.1 Letter 2-back working memory task:

The working memory task was a verbal 2-back task[160]. In every trial, participants were shown a continuous stream of letters that were flashed on a screen. Participants were to respond by pressing the button if a presented letter was the same as the one that came up two stimuli back in the sequence. This task had a high working memory load as it required the

continuous maintenance of each stimulus in memory until two consecutive stimuli appeared and required continuous on-line monitoring of the presented stimulus in order to execute the response as soon as the stimulus matched the one that came up two stimuli prior to it. This task did not require shifts of spatial-attention as the letters appear continuously in the centre of the screen.

2.2.4.2 Spatial-attention task:

The spatial attention task[161] examined covert shifts of spatial attention. Participants maintained fixation on a central point on the screen where an arrow appeared pointing to the left or right. Immediately, a stimulus appeared in one of the two peripheral boxes located on either side of the centrally placed arrows. The stimuli were of two types either a "X "or a "2 ". The participants were instructed to respond to the target, an "X" only [not a "2"] by pressing the button on the hand-held device as rapidly as possible. The central cue remained visible until the stimulus appeared on the periphery triggering a covert shift of attention to the peripheral stimuli.

2.2.5 Study design

Participants were tested individually during a single session. At the start of the session all participants received detailed instructions on how to perform the cognitive conditions. Every participant practiced the cognitive conditions prior to testing sitting in front of a computer screen in order to achieve a minimal accuracy of 90% while performing the tasks. For analysis, session included a single-task walking condition, two single-task cognitive conditions (verbal 2-back working memory task and a covert spatial attention task) and two dual-task conditions (walking plus the two cognitive tasks). The single-task cognitive conditions consisted of five trials of 60 second duration each (detailed below). The single-

task walking condition consisted of five traverses across the walkway with a button device held in the dominant hand and with gaze fixated at a mark centered on the screen across the walkway. The dual-task conditions also comprised five trials of walking across the walkway while performing the two cognitive tasks described below, one at a time in succession. Participants registered their responses on the cognitive tasks by pressing a hand-held button held in their dominant hand. The display duration for every stimulus on the cognitive paradigms was set to 500ms with an inter-stimulus interval of 1500 seconds. Participants were encouraged to perform the task to the best of their ability and register their responses as quickly as possible. The order of condition was randomized but participants were informed about the task condition prior to every traverse across the walkway.

2.2.6 Statistical Analysis

The data were analyzed using a repeated measures analysis of variance (ANOVA) to study the main effects of condition (no cognitive task vs working-memory vs spatial-attention) on gait parameters (velocity, stride-length and double-support) in the two groups (young adults vs older adults). Task condition served as the within-subjects factors. We also reported partial eta squared values (η_P^2) as measures of effect size. To identify significant differences when there was a main effect of condition on gait parameters within-subjects, pairwise t-tests were used.

2.3 RESULTS

2.3.1 Demographic characteristics

The young adult group had a mean age of 27±4 years with an average height of 170±11 cm and an average weight of 68.4±15.4 kg. The mean age, height and weight of the older adult group was 75±7 years, 163.3±12.4 cm and 73±15.4 kg respectively.

2.3.2 Dual-task effect on gait parameters

2.3.2.1 Velocity (Figure1, Table 1):

There was a main effect of dual-task condition on velocity ($F(1,36)=3.991$, $p=0.02$, $\eta_P^2 = 0.1$) but this was independent of the group ($p=0.5$). Gait-velocity decreased significantly while performing working memory tasks (8.0 ± 17.0 cm/sec, $p=0.02$) and spatial-attention tasks (7.6 ± 14.8 cm/sec, $p=0.01$) in the YA group. In the OA group gait velocity decreased with concomitant working-memory (4.3 ± 12.7 cm/sec, $p=0.3$) and spatial-attention tasking (3.0 ± 8.5 cm/sec, $p=0.2$) but these did not attain statistical significance. There were no statistically significant differences in velocity between working-memory and spatial attention conditions in the two groups. Dual-task induced changes in velocity between the two groups were not significantly different.

2.3.2.2 Stride-length (Figure 2, Table 1)

There was a main effect of dual-task condition on stride-length ($F(1,36)= 10.032$, $p<0.01$, $\eta_P^2 = 0.2$) and this was independent of the group ($p=0.8$). The decrease in stride-length with concurrent working-memory task (5.6 ± 11.0 cm , $p<0.01$) and spatial-attention (6.2 ± 9.2 cm, $p<0.01$) were significant in YA group. The decrease in stride-length in the OA group was also significant during concurrent working-memory (6.0 ± 8.2 cm, $p<0.05$) and spatial-attention (5.0 ± 5.0 cm, $p<0.05$) tasks. There were no statistically significant differences in stride-length between working-memory and spatial attention conditions in the two groups. Dual-task induced changes in stride-length between the two groups were not significantly different.

2.3.2.3 Double-support time (Figure 3, Table 1):

There was a main effect of dual-task condition on double-support ($F(1,36)=3.188$, $p<0.05$, $\eta_P^2 = 0.1$) and this was independent of the group ($p=0.6$). In the YA group, the changes in double-support with concurrent working memory task and spatial attention (both -0.02 ± 0.04 sec, $p<0.05$) were statistically significant but again there was no significant change in double-support between working-memory and spatial attention conditions. In the OA group, there was an increase in double-support time during concurrent working-memory and spatial-attention but this did not attain statistical significance. Dual-task induced changes in double-support between the two groups were not significantly different.

2.4 DISCUSSION

Results of this study support the hypothesis that changes in gait parameters occur with concomitant performance of cognitive tasks in older and younger adults. Specifically, young adults reduce their gait speed significantly while performing spatial-attention and working memory tasks while walking. The decrease in gait-velocity is also reflected by an increase in double-support time on dual-tasking in this group. The older adults showed similar changes in temporal parameters but the differences did not attain statistical significance. Both groups also showed a significant decrease in stride-length in the two dual-task conditions. Furthermore, changes on tasks expected to more cognitively demanding, showed a trend towards greater magnitude of changes in gait velocity, stride length and double-support but this did not reach statistical significance. The changes in dual-tasking in older adults were not significantly different from the changes in dual-tasking in the young adult group.

These findings are consistent with other studies showing decrements in temporal gait and spatial gait parameters such as a report on increase in double-support time in young adults with concurrent performance of a digit span and a manual dexterity task[128] and

increased cadence along with a decrease in gait speed while counting task in young and older adults [129]. However, the current study extends previous knowledge by demonstrating that concurrent cognitive activity alone can influence gait parameters that is, without interference effects from concurrent manual or speech activity which is noteworthy as previous studies have also shown that postural stability may be directly influenced by speech production while performing word generation tasks, and talking while walking or repetition of digits[150].

We found that the changes in gait parameters were similar for both working memory and spatial-attention tasks. The changes were more marked during the working memory task but there were no statistical significant differences on costs of gait parameters between the two tasks although the lack of difference may reflect the small sample size. The mechanism underlying dual-task interference with gait is not fully understood. Decrease in gait speed on dual tasking has been commonly reported in patients with dementia and stroke [35, 39, 133] and in healthy older adults[122, 134, 145]. Gait slowing associated with dual-tasking is thought to be a compensatory strategy, to maintain gait stability though it is not clear why these parameters associated with more stable gait are also associated with an increase risk of falling in older adults[162]. It is postulated that under dual-task situations, resource sharing of common neuronal areas that sub-serve individual tasks involved may lead to "capacity-sharing" and/or "bottle-necking" of common resources, leading to decrements in both tasks [163]. The interference effects for different concurrent motor or cognitive tasks may then depend on whether or not these concurrent processes compete for the same neuronal resources[140]. This may be one reason why some secondary-tasks such as listening have no effect on gait parameters when performed concurrently[124, 127] , whereas others such as the ones we used in this study show an effect.

Functional MRI studies of working memory and spatial attention tasks have revealed that these tasks evoke a network of activations in multiple frontoparietal regions such as the supplementary motor area, banks of the intraparietal sulcus, striatum and cerebellar vermis [158]. Functional neuroimaging studies have also suggested that these regions may play an important role in human locomotion[7, 9, 14]. The premotor and prefrontal regions appear to be

involved in the maintenance of an individual's walking pace[12] , while areas within the parietal lobe such as the banks of the intraparietal sulcus may play a role in informing about relative positions of body parts and modulating limb movements [164]. Therefore, working memory and spatial attention may also share in part the neuronal resources that control gait speed and other temporal parameters, which may be a mechanism for dual-task interference in this study.

This study differs from other dual-task studies on gait in that the secondary tasks used in this study targeted unitary cognitive functions, namely working memory and spatial attention. The paradigms were designed to minimize interference by other concurrent cognitive processes and limit motor interference to only a button-press in the dominant hand. We used sensitive gait assessment devices in capturing specific gait parameters in two groups of healthy young and older adults. This study has its limitations as well. Firstly, the advantage of using an automated walkway to enable accurate and easy capture of gait parameters was compromised by the relatively short length of the walkway (12 feet), as we were unable to capture continuous gait parameters beyond the duration required to complete a single traverse. To mitigate this drawback we averaged gait parameters over 5 traverses for each condition. Secondly, there was a significant main effect of dual-task condition on gait parameters in the two groups but the effect sizes (denoted by partial eta squared values (η_P^2)) for the main effects were small (in range of 0.1 to 0.2). The small effect size indicates that the changes in gait parameters using these concomitant tasks would likely be too subtle to be noticed by the naked eye and was only picked up on sensitive automated gait assessment systems used in this study. Effect sizes are not usually reported in dual-task gait studies in healthy individuals and comparisons with those targeting gait-impaired populations cannot be made.

In summary, a concurrent working-memory and spatial-attention task performed while walking in healthy young and older adults led to a decrease in gait velocity and stride-length and an increase in double-support time. There was a trend for increased costs of working-memory task performance on gait parameters in comparison to spatial-attention task

performance in both groups. Whether the change in temporal gait parameters is an innate compensatory response to increase stability of gait while dual-tasking, or results from competition of the concurrent processes for common neuronal resources, needs to be further investigated. The dual task used in this study can be used to elucidate possible interactions between working memory and gait control in pathological conditions associated with compromised neuronal resources such as in neurodegenerative and cerebrovascular disease.

<u>Table 1</u>: Changes in regular paced gait parameters with concurrent spatial-attention and working-memory task performance in young adult and older adult groups (*p* values indicate level of significance in differences between respective dual-task conditions as compared to regular paced gait parameters).

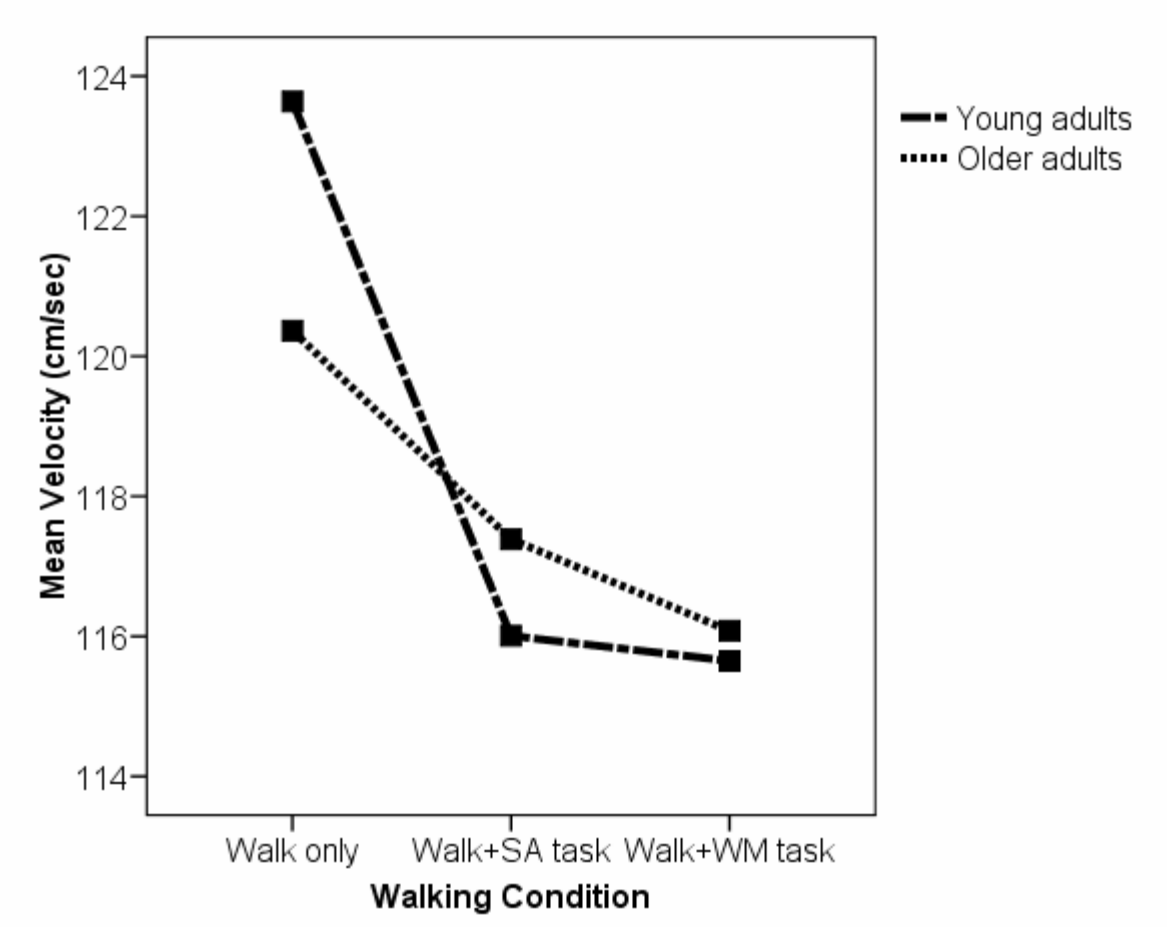
<u>1a.</u> Young adults:

	Regular paced walking (mean±SD)	Dual-tasking, i.e, walking +	
		Spatial-attention (mean±SD/ p value)	Working memory (mean±SD/ p value)
Velocity (m/sec)	123.6±16.2	116.0±21.3 P<0.001	115.7±22.9 P<0.001
Stride-length (cm)	139.6±15.7	133.4±19.3 P<0.001	133.7±20.0 P<0.001
Double-support (sec)	27±4	29±5 P<0.001	30±6 P<0.001

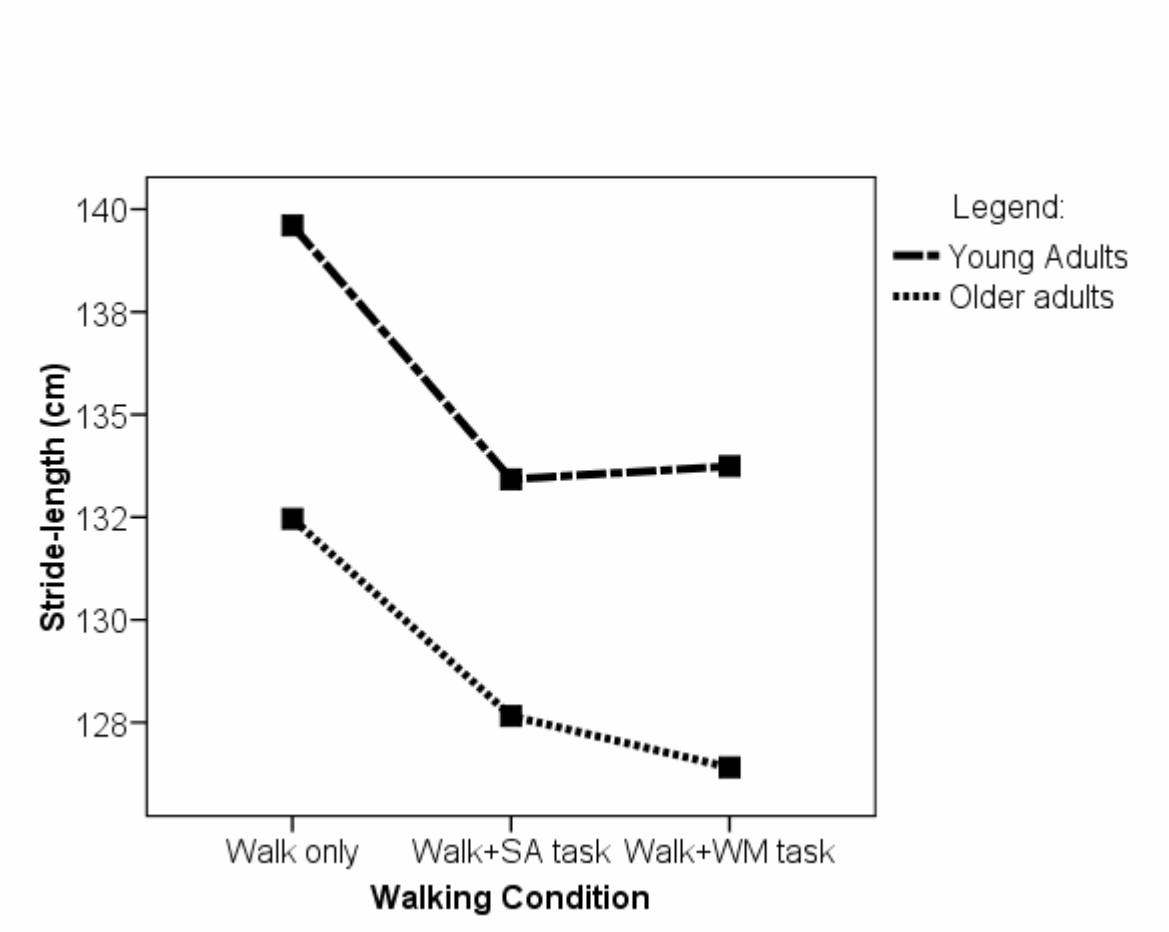
1b. Older adults:

	Regular paced walking (mean±SD)	Dual-tasking, i.e, walking +	
		Spatial-attention (mean±SD/ p value)	Working memory (mean±SD/ p value)
Velocity (m/sec)	120.4±22.1	117.4±23.3 P<0.001	116.1±27.2 P=0.001
Stride-length (cm)	132.5±20.7	127.7±21.2 P<0.001	126.4±23.9 P<0.001
Double-support (sec)	0.29 ± 0.04	0.29 ± 0.04 P>0.05	0.30 ± 0.06 P=0.02

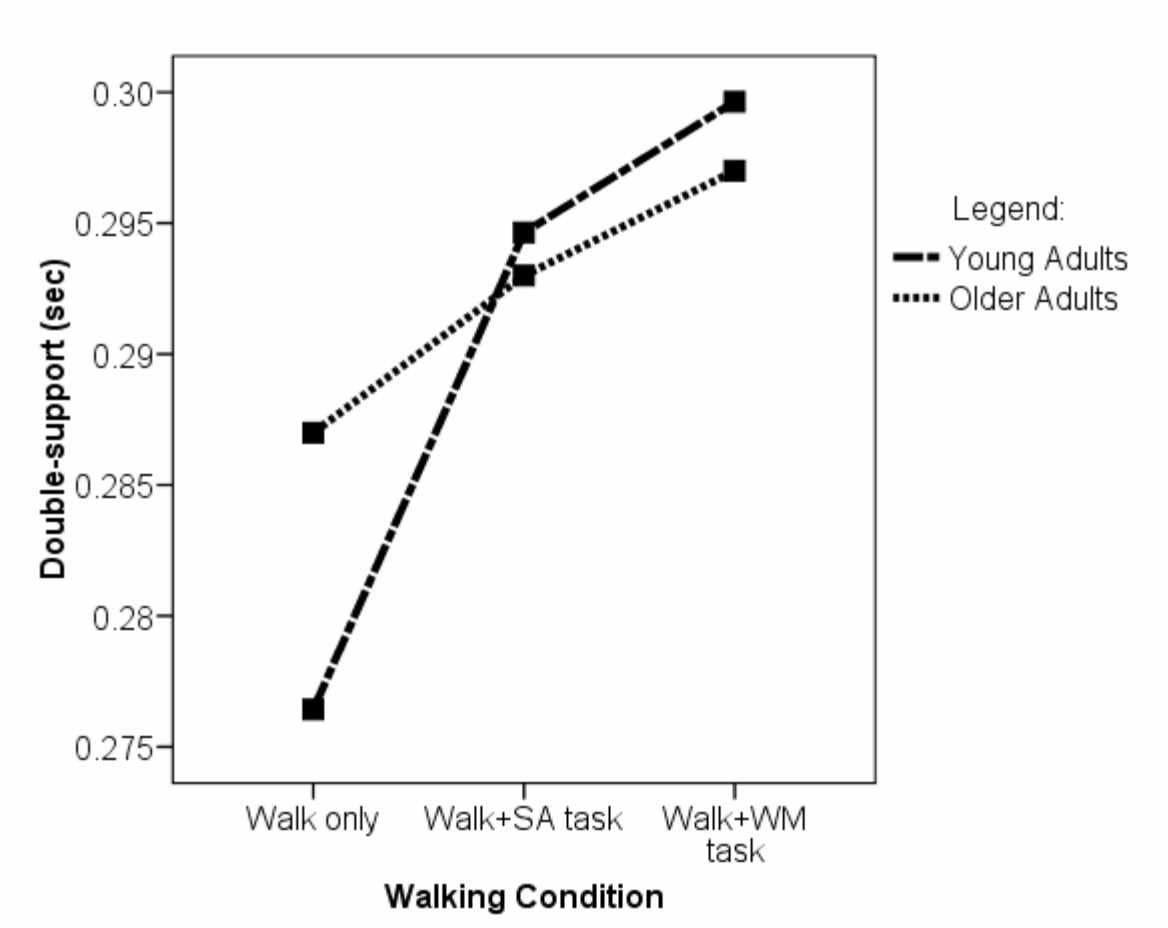
<u>Figure 1:</u> Changes in velocity in young adults and older adults with dual-tasking.



<u>Figure 2:</u> Changes in stride-length in young adults and older adults with dual-tasking



<u>Figure 3:</u> Changes in double-support time in young adults and older adults with dual-tasking.



Chapter 3

3 Over-ground and Treadmill-controlled Gait in Patients with Mild Alzheimer's Disease

Abstract

OBJECTIVE: To compare gait parameters in patients with mild stage Alzheimer's Disease (AD) and cognitively normal elderly.

DESIGN: Cross-sectional.

SETTING: University-affiliated tertiary centre.

PARTICIPANTS: Forty patients with mild stage AD and 27 normal controls (NC).

METHODS: Mini-mental Status Examination (MMSE), Timed-up-and-go task, body morphometric data, Unified Parkinson's Disease Rating Scale (UPDRS), and white matter disease burden on MRI, were obtained in both groups. Over-ground gait parameters (velocity, cycle-time, cadence, stride-length, stride-width and double-support time) were captured at preferred pace on an automated walkway. Treadmill-controlled parameters (cadence, cycle-time and double-support time) were obtained in a subset of this sample using footswitches at a preferred belt speed.

RESULTS: The groups were well matched on baseline characteristics. Patients with AD, compared to NC, had a lower MMSE (25±3 vs 29±1, $p<0.001$) and were slower on the Timed-up-and-go task (12±4 vs 9±3, $p=0.001$). The AD group had a higher UPDRS score than NC (7±9 vs 2±4, $p<0.01$). AD patients differed significantly from NC on their over-ground gait-velocity (99.4±19.2 cm/sec vs 119.5+14.7 cm/sec, $p<0.0001$), cadence (101.7±9.2 steps/min vs 110.9±9.2 steps/min, $p<0.001$) and stride-length (117.6±18.7cm vs 130.3±15.4cm, $p<0.01$). Upon adjusting for UPDRS score, the group differences in gait-velocity and stride-length (both $p<0.001$) remained significant. On the treadmill, patients with AD preferred a slower belt-speed than NC (60±20 cm/sec vs 74±23 cm/sec, $p<0.05$) but otherwise no significant differences were observed in treadmill-controlled parameters.

CONCLUSION: Patients with mild stage AD have decrements in gait-speed, stride-length and step-timing. These differences are minimized when steady speed is enforced on a treadmill.

Key words: Alzheimer's Disease, gait-velocity, cadence, stride-length, treadmill

3.1 INTRODUCTION

Falls as a result of gait and balance dysfunction are common in older adults and can occur in up to one-third of community dwelling elderly [165-168]. Those with early stage of AD have up to 36% higher risk of falls [106, 109] even though gait impairment is not usually clinically apparent during the mild stage of Alzheimer's Disease (AD) [93, 110-112] . Certain changes in gait such as an increase in variability of stride-width and stride-length[17], decrease in stride-length and velocity,[15] shorter swing phase, reduced arm swing and widened step-width[16] are associated with normal aging and at the onset of AD gait remains unchanged[110]. In fact, if gait impairment is present early in the course of dementia, the underlying etiology is thought not to be AD[112]. This suggests that while gait in early AD appears to be no different from that of normal elderly on visual examination, specific high-risk gait indices such as shortened

step-length on gait-initiation[169] and an increased stride-to-stride variability in velocity and double-support time, which independently predict risk of falling[162], may be more evident in early stages of AD with sensitive gait assessments.

In terms of temporal parameters, comparisons in gait and balance between healthy controls and those with AD have focused on moderate and severe stage of AD (MMSE<18), consistently showing that AD patients have a slower gait[5, 34, 110, 111, 113-115]. The data from CSHA showed that gait and postural impairment was present in 47-52% of patients with dementia and 44% to 46% in patients with CIND[170]. While this study separately assessed parkinsonism and gait impairment in the same sample it did not differentiate the subtypes of dementia[170]. In mild-stage AD, the results are mixed. While one study reported that mild AD patients have lower gait-velocity than healthy older adults[117], another reported that in a sample of 95 AD patients with varying degrees of disease severity, those in the mild stage had no obvious gait impairment while 16% in the moderate and 32% of severe stage of AD had observable gait impairment[118]. Nakamura et al. studied postural sway and gait using a gravicorder and reflective markers mounted on bare-feet in AD in-patients grouped according to three grades of severity on the Clinical Dementia Rating scale (CDR) [111]. They reported that in their sample of 15 patients with mild-stage AD (CDR of 1.0) significant differences were seen in postural sway but not gait characteristics whereas differences in the latter were seen in two groups with more dementia severity. This could explain why patients with AD have increased risk of falls in later stages of the disease, but why the risk is higher than age-matched controls even in early stage of AD despite clinically normal gait pattern is unclear. In a sample of 157 patients with AD, Buchner et al. reported that 31% experienced falls in the first four years from the onset of memory difficulties[109]. This figure went up to 51% in the 117 patients who were followed over the subsequent three years. Moreover, the fracture-rate was more than three times the age- and sex-adjusted rate of the general population[109], raising the possibility that subtle gait changes, not apparent in regular clinical gait assessment, may become more evident in more challenging tasks that better simulate daily life. A study reported that on more challenging bed-side gait measures such as Timed-up-and-go (TUG), 360-degree turns and figure of '8' walk, patients with mild stage AD do more poorly than age-matched healthy controls[119].

Innovative portable gait-analysis systems are now available that enables accurate capture of temporal and spatial gait parameters without compromising the participant's natural gait [171]. Specific differences in spatial and temporal characteristics of gait in relatively high-functioning, community-dwelling mild-stage AD compared to healthy older adults are not well documented. We therefore aimed to compare over-ground gait parameters in mild stage-AD and healthy normal controls (NC) at their self-selected pace. Our hypothesis was that patients with AD would be slower than NC on such sensitive gait assessments and that there would be no changes in over-ground spatial parameters between the groups. Furthermore, we hypothesized that enforcing a steady velocity, such as on a treadmill, would minimize the differences in temporal parameters in the two groups.

3.2 METHODS

3.2.1 Participant population

Participants were recruited from the Sunnybrook Dementia Study, a longitudinal study based in a university cognitive neurology clinic, which prospectively follows patients with cognitive impairment including AD and other dementia and a cohort of age-matched community-dwelling healthy elderly. All participants consent to undergo standardized neuroimaging and neuropsychological assessments annually for up to three years. Patients additionally undergo a thorough diagnostic including clinical history, neurological and general physical examination and standardized detailed mental status assessments[172], blood work to rule out secondary causes, standardized neuropsychological and neuroimaging examinations. Clinical data are reviewed independently by two knowledgeable clinicians to determine whether the patients met respective diagnostic criteria for probable or possible AD [93] or other neurodegenerative dementias. Normal controls (NC) were by definition, within

normal limits on all cognitive tests. All participants gave informed consent to the protocol which was approved by the Research Ethics Board.

Potential participants between ages of 60 and 80 years who were able to walk independently for 15 minutes without any discomfort were screened within six months of their magnetic resonance imaging (MRI) for the following exclusion criteria: for patients that met NINDS-ADRDA criteria for probable AD- an MMSE ≤ 20, and, for both groups- major depression, any history of other neurological disorders, recent hip-fractures, significant arthritis, clinically significant joint deformity, recent hip/knee replacement, sedative medication use, dependence on alcohol and/or neuroleptics drugs, use of assistive devices such as cane/walker and significant neuropathy on examination. Additionally, all patients with AD had to be on a stable dose of one of the three approved cholinesterase inhibitors for inclusion in this study.

3.2.2 Assessments:

Data on history of falls, concomitant medical conditions, cardiovascular risk factors, exercise history and current medications were obtained on all participants, AD patients and NC. Additionally, all participants underwent a physical and neurological examination at the time of gait assessment, including measurement of body-mass index, leg-length, mid-calf girth, blood pressure and resting heart rate. Timed-up-and-go (TUG) test[173], the Unified Parkinson's Disease Rating Scale (UPDRS)[174] and Tinetti gait scale[175] were also scored. Additionally, neuropsychological and neuroimaging data were available to ascertain cognitive and functional and other disease characteristics. As white matter disease has been associated with gait characteristics such as gait speed[71, 73, 76, 176], the presence and severity of white matter disease was scored on the Age-related White Matter Change (ARWMC) scale[177].

3.2.3 Gait apparatus:

3.2.3.1 Over-ground gait parameters

Over-ground spatial and temporal gait parameters were captured on an automated walkway (GAITRite®, CIR Systems, PA) through pressure-activated grid of sensors encapsulated in a carpet measuring 12 x 2 feet prior to the treadmill assessment. The accompanying software (GAITRite Gold, Version 3.2b) reconstructs each traverse across the walkway and automatically computes the spatial and temporal parameters for every traverse. The GAITRite apparatus has been shown to be reliable and consistent in its gait-parameter recording[171, 178]. Participants were asked to walk the length of the 12 foot long walkway at their most comfortable pace as if they were going on a stroll without talking or multitasking. They were also instructed to maintain their gaze at a marked spot placed at the end of the mat level with their head. To discard the acceleration and variability during gait-initiation, participants began their strides 3 feet away from the edge of walkway. Three traverses across the walkway were obtained for each participant. Velocity, cadence, stride length, stride-width and double-support time were utilized for this analysis.

3.2.3.2 Controlled gait parameter

Controlled gait parameters were captured using footswitches (B&L Engineering) placed in the insoles of participant's shoes as they walked on a motorized treadmill **(**Biodex™ RTM400, Biodex Medical Systems, Inc., NY). The use of footswitches for recording temporal gait parameters has been validated and found to be reliable [179]. Foot-switch data was digitized at the rate of 500 samples per second through an analog-to-digital converter. Digitized signals were processed using a user-friendly software (Labview®, National

Instruments, Austin, TX) to measure stride-time, step-timing, swing and stance phases, single- and double-support timing, and gait-variability measures. All participants used a safety-harness (The Biodex Unweighing System®, Biodex Medical Systems, Inc. NY) that was strapped across their chest for safety reasons. Treadmill speed was set to individual comfort level without any inclination to the angle of the treadmill belt. For those unfamiliar with treadmill walking, training was provided initially by allowing walks on the treadmill while holding on to the hand-rails. Subsequently the participant was encouraged to release one hand at a time and walk without holding on to the hand-rails. Participants wore their own footwear with footswitches in place and completed an acclimatization period lasting a minimum of 10 minutes prior to recording their treadmill parameters. This time period was chosen based on other studies that used similar acclimatization time [180]. Participants were instructed to look straight ahead and fix their gaze on a mark placed 3-feet away from the treadmill level with their head and to refrain from talking and fixate on the spot until completion of data capture. Participants walked in a quiet, well-lit room with no visual or auditory distractions for the duration of the data capture. Data was captured for 65 seconds after which the treadmill speed was gradually decreased to zero. The temporal parameters obtained from the treadmill for analysis were cadence, stride-time, double-support time, variability in stride-time and double-support time.

3.2.4 Statistical methodology

Over-ground parameters captured over three traverses on the GAITRite™ mat were averaged to obtain mean velocity, cadence, stride length, stride-width, cycle time and double-support time. Data was summarized as mean ±standard deviation (SD). Depending on the character of the data variable, Student's *t* test and Chi-square tests were used to compare the two groups. Statistical analysis was conducted using SPSS software (Version 11.5, Chicago, Illinois).

3.3 RESULTS

3.3.1 Baseline characteristics

These are highlighted in Table 1. Forty patients with mild stage AD were compared with 27 normal controls (NC). There were no significant differences between the two groups in their age, gender distribution, body-mass index, leg-length, mid-calf girth, waist circumference, blood-pressure and heart rate. As expected, the AD group were significantly more impaired than the NC group on the MMSE (25±3 vs 29±1, $p<0.001$) and the Dementia Rating Scale (119±10 vs 141±2, $p<0.001$). On the TUG, the AD group were significantly slower than the NC group (12±4 vs 9±3, $p=0.001$) but there were no difference in their Tinetti gait scale scores (11±0.6 vs 11.9±0.2, $p=0.1$). The UPDRS score in the mild AD and NC group was statistically significant (7±8 vs 2±4, $p=0.005$). There were no significant difference in AD (18%) and NC (15%) groups on the occurrence of one or more falls in the one-year prior to their study participation. The amount of white matter disease measured on the ARWMC scale showed a higher measure in the AD group but this difference was not statistical significant ($p=0.1$).

3.3.2 Over-ground gait parameters

These are highlighted in Table 2. The AD group walked more slowly ($p<0.001$), with a decreased cadence ($p<0.001$), a longer cycle time ($p=0.002$) and a shorter stride-length ($p<0.001$) than the NC group. The double support time was longer in the AD group than the NC group ($p<0.05$). There was no statistically significant difference in the stride-width between the two groups.

The UPDRS scores was an average of 7 in the AD group, which was significantly higher than that of NC (3±3). Therefore to account for differences in the UPDRS in both groups, the UPDRS score was entered as a covariate in a MANOVA analysis. The statistically significant differences in gait velocity ($F= 17.2$, MS: 4400.5, $p<0.001$) and stride-length ($F=18.1$, MS=4645.9, $p<0.001$) persisted, but no significant differences were observed on the other over-ground gait parameters.

3.3.3 Controlled gait parameters

Thirty-two patients with AD and 20 NC had their gait assessed on the treadmill as well. The results in this sub-sample are highlighted in Table 3. Both groups preferred a slower treadmill-belt speed compared to their over-ground velocity. The preferred speed on the treadmill was significantly slower in the AD group compared to the NC group ($p<0.05$). Enforcing this steady speed through the one-minute duration of walking on the treadmill abolished statistically significant changes in cadence, cycle time and double-support time in the two groups that was noted on over-ground gait.

3.4 DISCUSSION

Key findings of this study are that when sensitively measured on a gait analysis device, over-ground gait-velocity, stride-length, cadence and double-support time are significantly worse in mild AD patients. This sample of AD patients had a higher UPDRS score compared to the NC group consistent with other reports indicating that motor impairment may accompany cognitive decline in early stages of AD[181-184]. After controlling for differences in parkinsonism in the two groups, the differences in gait-velocity and stride-length persisted. Additionally, enforcing a constant speed on a motorized treadmill minimizes any significant differences in temporal gait measures in the two groups. After adjusting for MMSE and Dementia Rating Scale scores in addition to age, the differences in gait did not persist,

suggesting that the degree of cognitive impairment plays a role in gait differences between the groups.

Reports on detailed temporo-spatial parameters of gait in patients with mild AD are limited. Pettersson et al reported a gait velocity of 110±20 cm/sec in their sample of 6 patients with mild AD but compared to our sample they targeted a much younger age group (mean: 58±0.9 years)[135]. In the Goldman et al.[117] study using footswitch data in two stages of AD disease severity based on the CDR scale, very mild AD patients (CDR of 0.5, age: 72 years) were no different in gait velocity from age-matched NC, whereas those with dementia (CDR of 1.0, age:74 years) had a walking speed of 89±20cm/sec which was significantly slower than from those with very mild impairment (108±19 cm/sec) and normal controls (106±19cm/sec)[117]. Nakamura et al.[111] reported significant changes in velocity, stride-length and double-support in moderate and severe stage of AD, but not in their sample of mild stage of AD patients, which may have to do with the sensitivity of apparatus used to capture gait parameters. Studies that have attempted to study gait in mild AD using pragmatic scales such as the Tinetti balance and gait scale [110] or by clinical assessment of gait[118] have not found any evidence of gait slowing, which appears also to be the case in our study. Ceiling effects were seen on the Tinetti gait scale in both groups and therefore, clinically both groups were identical in their gait.

Some sensitive bed-side measures such as the TUG have shown evidence of subtle gait slowing[135] as in the current study, in which significantly longer times for the TUG were observed in our AD group. Moreover, subtle differences in gait became apparent on the more sensitive computerized gait-mat analysis, revealing that over-ground gait-velocity and cadence are reduced in mild stage of AD. The patients with mild AD also had reduced stride-length compared to NC but were identical on their stride-width. Gait velocity correlates strongly with stride-length and cadence and the decrease in stride-length with a trend towards a longer double-support time in our AD sample may be indicative of generalized gait-

slowing rather than changes in spatial parameters. A recent report suggested that patients with amnestic-mild cognitive impairment (MCI), a preclinical state of AD, demonstrate significant decline in cadence[116]. These findings suggest that motor slowing may already be present in the early stages of AD before becoming clinically apparent as the disease progresses to the later stages[5, 34, 110, 111, 113-115].

This study also found that when a steady gait-velocity was enforced on participant's gait on the treadmill, the two groups appeared similar in their cadence. The variability in stride-time and double-support time also appeared to be similar in the two groups under these circumstances. These findings suggest that the treadmill reduced the gait variability in the AD group; possibly due to the constant belt-speed which reduced the temporal degree of freedom and minimized variability in the temporal domain. It is also possible that the treadmill enforced attention to gait by serving as an external cue to maintain a constant step-timing. Of note was the acclimatization period of ten minutes prior to capturing their gait to minimize any learning effects; however, cadence captured on the treadmill cannot be generalized to over-ground cadence even after 15 minutes of continuous walking in unimpaired elderly[24] and therefore within-group differences in gait parameters on and off the treadmill were not investigated. However, the fact that the between-group differences in gait parameters are nullified when on the treadmill is noteworthy. Kinematic studies have shown that under treadmill-walking conditions, gait variability is significantly reduced primarily at the distal lower extremity level[180]. Sensory cueing of gait, by repeated auditory or visual cues, has been shown to improve gait kinematics and decrease variability in patients with Parkinson's Disease and normal elderly[185, 186]. Treadmill may improve gait-stability in these patients by acting as an external pace-maker[185].

Cautious gait, described by Nutt et al.[16], is one that is characterized by mild gait slowing and shortening of stride length with minimal/no difference in the stride-width. However, this is based on clinical judgment and not on specific gait parameters. The term stems from what can be considered as an adaptation to avert falls while walking under conditions that could threaten steady balance[187], such as while walking on an icy pavement, but is also a

commonly observed in gait of patients with arthritis and peripheral neuropathies. O'Keefe et al. characterized gait in three stages of AD and found that a cautious gait was present in 5/21 (24%) patients with a CDR of 1[114]. In our study, patients with mild AD had a shorter stride-length and a slower velocity. Cautious gait is not a consequence of normal aging and is indicative of a fear of falling[187] and therefore, the reduction in stride-length and gait speed in our AD group speaks to the relationship between gait and cognition. Areas such as the prefrontal cortex, that control cognitive functions such as working memory, also play a major role in the execution of gait control, and the deterioration in cognitive functions in AD may also lead to subtle changes in gait control[188].

The reduction in temporal parameters and its variability while walking at a fixed speed on the treadmill further suggested that changes in gait in mild AD may be attributed to temporal characteristics of gait. We did not assess postural sway in our study sample, but postural sway measured over 1-minute of Romberg stance recorded by a gravicorder has been shown to be significantly greater in those with mild stage AD than age-matched controls even when other gait characteristics appear similar. The authors also reported that postural sway increased exponentially with increasing disease severity[111] similar to one other study[114]. Therefore, another possible inference is that the over-ground parameters in this AD sample may reflect underlying mild disequilibrium which corrects itself on the treadmill when a comforted with a safety harness while walking.

These findings may have several clinical implications. Observational studies do report that patients in the early stage of AD fall more frequently and have more serious injuries after falling compared to age-matched healthy population [106, 109]. In a group of community-dwelling older adults (age>75years) according to one study, a decrease in stride-length of 20cm and velocity of 20 cm/s and increase in double-support by 5.5% and doubled the likelihood of a pre-existing fall[162]. Our findings of subtle decrements in gait measures in mild AD (13cm decrease in stride-length and 21cm/sec decrease in velocity and 2.5% increase in double-support time) suggests that quantitative gait assessments should be used routinely as part of routine clinical evaluation to closely monitor subtle changes in gait in patients with

AD time-early in the course of disease may help identify those at risk for falls. Second, there is a limited amount of data on use of treadmill in patients with AD. Treadmill for gait-retraining was studied a sample of 18 older adults (mean age:79 years) with higher-level gait disorders due to underlying cerebrovascular disease[189], but not in AD patients at risk for falls. Further studies focusing on fall risk stratification and appropriate outcome measures in a large sample of AD would be needed to show any effect of treadmill gait retraining. In the mild stage of AD showed comparable gait characteristics to the NC suggesting that treadmill walking with a safety harness may be well tolerated in early stage of AD. Hence, this study suggests that exercise and gait-retraining treadmill programs targeting patients in the mild stage AD might be worthwhile. Third, white matter hyperintensities on MRI have been associated with known cardiovascular risk factors and are commonly seen in older adults. These white matter changes have been associated with gait and balance impairment in normal elderly and specifically with gait-speed in elderly with gait impairment [71, 73]. In our study, the mean score on the ARWMC scale did not differ significantly, suggesting that underlying white matter disease by itself did not contribute critically to the differences in gait parameters between the two groups. Whether white-matter disease represents a "dual-hit" in those with AD cannot be addressed by the current design. The interactions between white matter disease, gait and AD are beyond the scope of our study objectives.

This study has certain limitations. Fluctuations in stride-length and stride-time at any given time are statistically related to several strides prior in the sequence[190]. This fractal property of gait cannot be accounted for by this study design as over-ground gait parameters were captured by averaging multiple traverses on the 12 x 2 feet automated walkway. Secondly, we used a body-weighted support system as a safety-harness ensuring that the system worked without unloading any body-weight. Though the safety harness was not restrictive in anyway, the fact that it may have averted alterations in body sway and other characteristics that influence gait parameters on the treadmill, cannot be denied but not doing so would mean inflicting a risk of fall in out older adult participant.

To summarize, this study found that patients with mild stage AD had significantly different over-ground gait parameters compared to a well-matched group of cognitively normal individuals at their preferred-pace, specifically demonstrating a slower gait-velocity, lower cadence and a shorter stride-length. It also found that when a steady preferred-velocity was enforced on a motorized treadmill, there were no statistically significant differences between the two groups. These findings suggest that subtle changes in gait appear in the early stage of AD and are detectable with sensitive gait analysis measures. Therefore, the incorporation of quantitative assessment of gait even in the early stages of AD is suggested. This study also showed that patients with AD can tolerate walking on the treadmill and that besides the belt-speed on the treadmill, their gait is not different from cognitively normal individuals, suggesting that gait-training may be offered in patients with AD early in the disease course.

Table 1: Baseline characteristics between AD and NC

	AD (n=40)	*NC (n=27)*	***p* value**
Age	74±8	73±8	0.5
Gender (Female %)	55	45	0.2
MMSE [*]	25±3	29±1	<0.0001
DRS score [†]	119±10	141±2	<0.0001
ARWMC score [‡]	8±6	6±5	0.1
Timed-up-and-go (sec)	12±4	9±3	<0.0001
Falls in the previous year	6	4	0.5
UPDRS (AD=35, NC=25) [§]	7±8	2±4	0.005
Tinnetti gait scale score	11±0.6	11.9±0.2	0.1
Body mass Index	25±5	26±5	0.5
Leg length (cm)	91±6	90±7	0.7
Mid-calf diameter (cm)	35±4	37±4	0.6
Systolic BP (mm HG)	127±18	123±29	0.5
Diastolic BP (mm HG)	71±9	74±17	0.3

[*] Minimental-Status Exam

† Dementia Rating Scale Score

‡ Age-related white matter change score

§ Unified Parkinson's Disease Rating Scale

TABLE 2: Over-ground Gait Parameters in AD and NC

	AD(n=40)	*NC(n=27)*	*p value*
Velocity (cm/sec)	99.4±19.2	119.5±14.7	<0.001
Cadence (steps/min)	101.7±9.2	110.9±9.2	<0.001
Stride length (cm)	117.6±18.7	130.3±15.4	0.004
Cycle Time (sec)	1.2±0.1	1.1±0.1	0.002
Stride-width (cm)	9.5±3.4	9.9±3.3	0.6
Double Support time (sec)	0.35±0.2	0.28±0.1	0.03

TABLE 3: Gait Parameters on Motorized Treadmill in AD and NC

	AD(n=32)	*NC(n=20)*	*p value*
Belt speed (cm/sec)	59±19	75±22.3	0.02
Cadence (steps/min)	96.1±12.2	103.2±13.8	0.07
Cycle time (sec)	1.3±0.2	1.2±0.2	0.1
Double-Support time (sec)	0.19±0.08	0.17±0.05	0.4
Coef. variation in cycle-time (SD/mean)*100)	3%	3%	0.4
Coef. variation in double-support (SD/Mean)*100)	10%	8%	0.2

Chapter 4

4 Gait in Relation to Subcortical Hyperintensities Burden in Mild Alzheimer's Disease

ABSTRACT

Background and Purpose: This study compared gait in relation to underlying subcortical hyperintensities (SH) load in patients with mild Alzheimer's Disease (AD) and in healthy normal controls (NC) and explored correlations between SH distribution and gait in each group.

Methods: In 42 mild-AD patients and 33 NC, gait-velocity, stride-length and step-width was captured on an automated walkway within six-months of the MRI scan, which was rated for SH burden using the Age-related White Matter Change scale. Correlations between gait parameters and total and regional distribution (frontal, parieto-occipital, temporal, infratentorial and striate) of SH were explored separately. The AD and NC groups were dichotomized, using a median-cutoff on the total score of SH for each group: AD+ (n=21) and NC + (n=18), denoting high and AD- (n=21) and NC- (n=15), denoting low SH burden respectively.

Results: The AD (74 ± 8 years) and NC (73 ± 8 years) groups were comparable on most demographic characteristics. Total SH score correlated significantly with stride-length and velocity in the AD (r = -0.4, p = 0.01) and NC (r = -0.4, p = 0.02) groups respectively with regional specificity for frontal and basal ganglia regions in both groups. Amongst the four SH-burden based group comparisons, NC- had a significantly superior velocity (127 cm/sec) and stride-length (138 cm) than AD+ and AD- groups but there were no differences in the step-width between these groups..

Conclusion: Poorer gait parameters are associated with higher SH load, specifically in the frontal and basal ganglia regions, in patients with mild AD as well as healthy elderly.

4.1 INTRODUCTION

Subcortical hyperintensities (SH) are high-signal intensity areas seen on FLAIR or proton-density, T2-weighted magnetic resonance imaging (MRI) [41]. They are pathologically related to areas of ischemic injury ranging from alteration in tissue characteristics to demyelination and infarction[57, 191]. In addition to age, SH are associated with known cardiovascular risk factors such as hypertension and diabetes[53], and, therefore, are considered as markers of vascular disease burden in the brain. Epidemiological studies have reported that SH are relatively common in elderly ranging from 27% to 87% [43, 45]. In Alzheimer's Disease (AD), similar prevalence has been reported ranging from 38% to 95% [47, 48]. By disrupting fronto-subcortical circuitry, SH may play a major role in common geriatric syndromes such as falls and mobility impairment [64, 84]. By contributing to gait impairment, SH can further compromise functional ability in AD already affected by cognitive impairment[69].

Gait impairment is not typically seen early in the course of AD, so that, if present during the early stages of cognitive symptoms alternate etiologies of the underlying dementia should be considered[112]. However, recent studies have shown that gait slowing can occur in the early stage of AD, especially on challenging tests of gait and balance such as the Timed-up-and-go task and the figure of '8' walk[117, 119]. Motor slowing leading to reduced gait-speed in the pre-clinical and early stages of AD has been reported by other researchers as well [111, 114-117]. The underlying cause of gait slowing in early AD is not clear.

In the early stages of AD, hypoperfusion in the frontal regions is related to disequilibrium and gait parameters[111]. Specifically, the mean regional cerebral blood flow (rCBF) correlated with postural sway in mild AD (Clinical Dementia Rating (CDR) score of 1) and, together with mean rCBF in frontal regions, correlated with stride-length and postural sway in the moderate stage AD (CDR of 2) [111]. SH can be associated with decreased metabolism and regional cerebral blood flow (rCBF) specifically in the frontal regions[192-194], suggesting that impaired frontal functioning may have an impact on gait in mild AD. Other postulated mechanisms include: [1] interruption in the circuitry between the basal ganglia, cerebellum and its connections with the motor cortex[66], [2] impaired central somatosensory processing[74] and, [3] disruption of long-loop reflexes[64]. The association between gait and balance impairment and SH in community-dwelling elderly has been well studied[69, 71-73, 84]. A few studies in recent years have demonstrated that gait is worse in the presence of SH, but also that performance correlates with total lesion volume[71, 72, 79].

For predicting mobility impairment, Benson et al. found that in a group of community-dwelling elderly (mean age: 79 years, MMSE: 29±0.5), that the presence of frontal periventricular hyperintensities was sensitive (79-93%) but not specific while presence of parieto-occipital hyperintensities was specific (100%) but not sensitive[71]. Bennett et al. [69] showed that in a cohort of AD patients with a wide severity of cognitive impairment (mean age: 70 years, MMSE range of 3 to 26), those with clinically significant gait impairment had a higher periventricular hyperintensities score and white matter lesions. However, it is known that clinically significant gait impairment does not occur until the moderate to severe stages

of AD and therefore the association of gait and SH in a wide range of AD severity may be driven by the gait disorder seen in the later stages of AD.

The primary aim of this study was to explore the association between the total burden of SH in the brain, using a reliable rating scale, and gait parameters, specifically gait-velocity, stride-length and stride-width, in patients with mild AD compared to healthy normal controls (NC). On basis of previous studies associating gait impairment and SH, we hypothesized that in each group those with a higher proportion of SH would have a slower velocity, a shorter stride-length and a wider step-width. Slower gait-velocity, shorter stride-length and wider step-width are associated with gait instability [162], so studying these specific parameters would lay groundwork for future studies to determine whether SH load is an independent risk factor for falls in patients with AD. The secondary objective was to explore the correlation between regional distribution of SH and the gait parameters (gait-velocity, stride-length and step-width). We hypothesized that in both groups, the total SH score and specifically scores for the frontal and basal ganglia regions would correlate with gait velocity and stride-length.

4.2 MATERIALS AND METHOD

4.2.1 Participant population

Participants were recruited from the Sunnybrook Dementia Study, a longitudinal study based in a university cognitive neurology clinic, which prospectively follows patients with cognitive impairment including AD and other dementias and a cohort of age-matched community-dwelling, healthy elderly controls (NC). All consenting participants undergo standardized neuroimaging and neuropsychological assessments annually for up to three years. Patients additionally undergo a thorough diagnostic including clinical history,

neurological and general physical examination and a comprehensive, standardized mental status assessment[172], blood work to rule out secondary causes, and standardized detailed neuropsychological and structural MRI examinations. Clinical data are reviewed independently by two knowledgeable clinicians to determine whether the patients meet diagnostic criteria for probable or possible AD [93] or other neurodegenerative dementias. NC were by definition, within normal limits on all cognitive tests. Participants, or their substitute decision makers, depending on the disease stage at entry, gave informed consent to the protocol which was approved by the Research Ethics Board.

Potential participants between ages of 60 and 80 years who were able to walk independently for 15 minutes without any discomfort were screened within six months of their structural MRI for the following exclusion criteria: MMSE $\leq$ 20 for patients that met NINDS-ADRDA criteria for probable AD (to exclude patients with moderate and severe stage of AD), and for both groups- major depression, any history of other neurological disorders, including overt parkinsonism, overt stroke or cortical infarcts, recent hip-fractures, significant arthritis, clinically significant joint deformity, recent hip/knee replacement, sedative medication use, dependence on alcohol, use of neuroleptics drugs, need for assistive devices to ambulate such as cane/walker and significant neuropathy on examination.

Three cholinesterase inhibitors commonly used for treatment of patients with AD include donepezil, galantamine and rivastigmine[195]. The adverse effects of these drugs are reported to include tremors and rigidity and therefore can worsen parkinsonism[196]. Furthermore, another report suggested that galantamine may improve gait under dual-task conditions in AD[197] probably by its beneficial effects on executive function in AD. However, these drugs can have vagotonic effects and may exacerbate bradycardia and a recent study showed they can be associated with increased rate of syncope, falls, and hip fractures[198-201]. In this study, all patients with AD had to be on a stable dose of one of the three approved cholinesterase inhibitors for inclusion in this study.

4.2.2 Assessments:

Cognitive tests utilized for this report were confined to the MMSE[91] and the Mattis Dementia Rating Scale (MDRS) [202]. Data on history of falls, concomitant medical conditions, cardiovascular risk factors, exercise history and current medications were obtained on all participants, AD patients and NC. Additionally, all participants underwent a physical and neurological examination at the time of gait assessment, including measurement of body-mass index, leg-length, mid-calf girth, blood pressure and resting heart rate. Timed-up-and-go (TUG) test[173], the Unified Parkinson's Disease Rating Scale (UPDRS)[174] and Tinetti gait scale[175] were also scored. Additionally, neuropsychological and neuroimaging data were available to ascertain cognitive and functional and other disease characteristics.

4.2.3 Gait apparatus

Over-ground spatial and temporal gait parameters were captured on an automated walkway (GAITRite®, CIR Systems, PA) through pressure-activated grid of sensors encapsulated in a carpet measuring 12 x 2 feet prior to the treadmill assessment. The accompanying software (GAITRite Gold, Version 3.2b) reconstructs each traverse across the walkway and automatically computes the spatial and temporal parameters for every traverse. The GAITRite apparatus has been shown to be reliable and consistent in its gait-parameter recording[178]. Participants were asked to walk the length of the 12 foot long walkway at their most comfortable pace as if they were going on a stroll without talking or multitasking. They were also instructed to maintain their gaze at a marked spot placed at the end of the mat level with their head. To discard the acceleration and variability during gait-initiation, participants began their strides 3 feet away from the edge of walkway. Three traverses across the walkway were obtained for each participant. Velocity, stride-length and step-width were utilized for this analysis.

4.2.4 MRI

All brain images were acquired using a 1.5 T Signa MR imager (GE Medical systems, Milwaukee, WI). In compliance with recommended criteria for imaging in Vascular Cognitive Impairment, which can include mixed vascular and AD[203], three image sets were acquired in the same imaging session: T1-weighted (axial 3D SPGR with 5ms TE, 35ms TR, 35° flip angle, 1 NEX, 22 x 16.5 cm FOV, 0.859 x 0.859mm in-plane resolution, and 1.2 to 1.4mm slice thickness), proton-density (PD) and T2-weighted images (interleaved axial spin echo, with TEs of 30 and 80 ms, 3s TR, 0.5 NEX, 20 x 20cm FOV, 0.781 x 0.781mm in-plane resolution, and 3mm slice thickness).

4.2.5 SH severity rating

To determine any association of white matter disease with gait characteristics such as gait speed as reported in the literature[69, 71-73, 84], the presence and severity of white matter disease was scored on the Age-related White Matter Change (ARWMC) scale. This is a widely used scale derived by a consensus process with good reliability and validity[177].

The ARWMC scale is a four-point visual rating scale based on the degree of SH in five different regions: (1) the frontal area; (2) the parieto-occipital area; (3) the temporal area; (4) the infratentorial area, which included the brain stem and cerebellum; and (5) the basal ganglia, which included the striatum, globus pallidus, thalamus, internal and external capsules, and insula[177]. The scores in each region are summed to obtain the total ARWMC score for the right and left sides of the brain.

4.2.6 Statistical analysis

Data was assessed for extreme outliers and its distribution was analyzed. Demographic variables between the AD and NC groups were compared using Student's t test and chi-square where applicable. The two groups were further subdivided into four groups according to a median split of the total burden of SH rated on the ARWMC scale for that group. Those that were above the 50^{th} percentile were denoted as AD+ and NC+ and those that equaled or fell below the 50^{th} percentile were referred to as AD- and NC- respectively. ANOVA was used to compare the demographic variables in the four groups. Multivariate analysis of variance (MANOVA) was used to compare velocity, stride-length and step-width in the four groups. Baseline variables that were significantly different in the two groups and had a biologically plausible impact on gait were included as covariates in the MANOVA model. The MANOVA was performed with grouping factor based on the median cut-off of total ARWMC score for the entire group (AD+, AD-, NC+ and NC-). Non-parametric correlations (Spearman) were performed to ascertain the SH correlates of velocity, stride-length and step-width in both groups.

4.3 RESULTS

4.3.1 Demographic differences:

The differences between AD (n=42) and NC (n=33) groups are highlighted in Table 1. AD patients were identical to NC in most baseline characteristics but differed as expected on the MMSE ($p<0.01$) and DRS ($p<0.01$) scores. The AD group had a higher UPDRS score ($p<0.01$) and they took a longer time to complete the TUG test ($p<0.01$).

The ARWMC score showed a trend to a higher total score in the AD group compared to the NC group (p=0.07). Therefore, the median of the total ARWMC score for each group was used so that those above the median were compared with those equal to or below the median. The median total ARWMC score were 7 and 5 for AD and NC respectively. Thus the four groups were AD+ (n=21) and NC + (n=18), denoting high SH load (>50th percentile of total ARWMC) and AD- (n=15) and NC- (n=15) denoting low SH load (≤ 50th percentile of total ARWMC score).

The demographic differences between the four sub-groups segregated on their SH load were obtained using ANOVA and are highlighted in Table 2. There were no statistically significant differences in body morphometrics such as leg-length, BMI and waist circumference. Statistically significant differences between groups were observed in age ($p<0.01$), MMSE($p<0.01$), DRS($p<0.01$), UPDRS score ($p<0.01$)and TUG ($p<0.01$). Post-hoc Tukey's test revealed that the NC- group was significantly younger than NC+ ($p<0.05$) and AD+ and AD-($p<0.01$) groups. The two AD groups had significantly lower MMSE and DRS scores than NC, but there were no statistically significant differences between AD+ and AD- and between NC+ and NC- on these baseline cognitive measures. The AD+ group had significantly higher UPDRS scores than the other three groups ($p<0.01$). The AD+ group also took significantly longer time to complete the TUG as compared to the NC- and NC+ groups. However, there were no statistically significant differences between AD+ and AD- and between NC+ and AD- groups on the TUG test. There was a trend towards a longer time to complete the TUG in the AD- group compared to the NC- group (11.5±3 vs 8.2±3, p=0.05).

4.3.2 Gait differences in sub-groups depending on SH burden

Table 3 outlines the comparison between the four groups on velocity, stride-length and step-width on a MANOVA. There were significant differences in velocity ($F=11$, $p<0.01$) and stride-length ($F=7$, $p<0.01$) but not in step-width amongst NC-, AD-, NC+ and AD+. The Box's *M* statistic, a statistical test for homogeneity of the variance-covariance matrix, was 11 (p=0.92), which indicated that it was safe to proceed with the MANOVA as the matrices did

not differ significantly from each other. The Levene's test of homogeneity, i.e., univariate tests that examined gait-velocity, stride-length and step-width separately, were not significant, indicating that there were no differences in the error variance between groups and that the results of the MANOVA would be valid. The multivariate tests for determining the amount of variance not explained by differences between the four groups based on all the gait variables considered together, revealed a Wilk's lambda (λ) of 0.61 (F=4.2, p<0.01, η^2 = 0.15).

Post-hoc tests were conducted to determine the individual group differences (Figure 1a-d). Tukey's test revealed that gait velocity in the NC- group was significantly faster than that of NC+ (p<0.05), AD- (p<0.01) and AD+ (p<0.001); the AD-, AD+ and NC+ groups were not statistically different in their gait velocities. Stride length in the NC- group was significantly longer than the AD- (p<0.05) and AD+ (p<0.01) groups, but was not statistically different from NC+ group (p =0.1). There were no statistically significant differences in step-width in the four groups.

4.3.3 Gait differences co-varying for baseline differences

Demographic variables such as age, UPDRS score, MMSE, DRS and time to complete the TUG were significantly different between the four groups. Amongst these, age and UPDRS score have direct relationship with gait variables and were therefore, used as covariates in the MANOVA. The TUG is an indirect measure of gait velocity and the MMSE and DRS were measures of cognitive impairment that characterized the AD groups and therefore these were not used as covariates. Co-varying for age alone, mulitivariate tests were significant (λ=0.66, F= 3.3, p=0.001, η^2 = 0.1) with significant differences between-subjects effects in gait velocity (F=4, p<0.001) and stride-length (F=4.3, p=0.007). Co-varying for UPDRS alone, multivariate tests were significant (λ=0.72, F= 2.4, p<0.05, η^2 = 0.1) with significant differences between groups in velocity (F=5.4, p<0.01, η^2 = 0.2). With both age and UPDRS score as covariates in the analysis, the multivariate tests were significant between the four

groups (λ=0.73, F= 2.3, p<0.05, η^2 = 0.1). Between-subject effects revealed that the differences between groups on gait-velocity still persisted (F=5.4, p=0.002, η^2 = 0.21).

4.3.4 Correlation between SH and Gait

Spearman correlation in the whole AD group (AD+ and AD-, n=42) revealed that total ARWMC score significantly correlated with stride-length (r=-0.4, p=0.01) and showed a trend towards significance for gait velocity (r=-0.2, p=0.07). To determine which regional SH-load accounted for this significance, Spearman's correlations were performed between SH scores in the five brain regions and the three gait variables. Stride-length correlated significantly with SH score in the frontal (r=-0.4, p<0.05) and basal ganglia (r=-0.4, p=0.01) regions. Adjusting for age in each group, the statistical significance in correlations between ARWMC score and gait parameters was no longer seen. However, in the entire sample the correlations between stride length and frontal SH (r=-0.2, p=0.05) and between step-width and basal ganglia (r=0.3, p=0.03) reached statistical significance.

In the whole NC group (NC+ and NC-, n=33), total ARWMC score correlated significantly with gait velocity (r=-0.4, p=0.03). Regional SH distribution in the frontal (r=-0.4, p=0.04) and basal ganglia regions (r=-0.4, p=0.03) also correlated with gait-velocity. In addition, SH in the basal ganglia regions also correlated with step-width (r=-0.4, p=0.03).

4.4 DISCUSSION

This study found that within both groups, healthy older adults and patients with mild AD, those with a higher SH scores had a slower gait velocity and a shorter stride-length than their counterparts with a lower SH scores on the ARWMC scale. There was a trend towards a wider step-width in those with greater SH load, but the differences did not attain statistical

significance. Interestingly, post-hoc analysis revealed that velocity in normal controls with a lower SH burden differed significantly from both AD groups as well as from their counterparts with higher SH burden. In fact, the NC group with higher SH load were not significantly different from the two AD group in terms of their gait velocity. Within the AD group there was a trend towards a lower gait velocity and stride length but this did not attain statistical significance. These results show that in this sample of healthy older adults and patients with AD, SH load had a greater impact on gait-velocity and stride-length in normal controls than on patients with mild AD. Substantial work has been done in the last few years on the association of gait and balance impairment with SH in community-dwelling elderly [69, 71-73, 84]. This study differs in that it targeted normal controls and patients with mild AD who had no gait complaints and even on objective gait scales such as the Tinettti both groups were comparable; however, the differences on the time to complete the TUG task do suggest some degree of slowing in the AD group. The results suggest that within this sample of normal older adults with no gait complaints, those with more SH had significant decrements in gait velocity and stride-length and trends towards a wider step-width suggesting that SH may not only play a role in mobility impairment but that the subtle changes in gait parameters can be objectively detected by sophisticated gait assessment devices. These changes may be early indicators of impending mobility impairment given the tendency for SH to increase over time[54]. Further study is needed to see whether these subtle alterations predict falls.

According to previous studies, age-related changes in gait parameters include a decrease in gait velocity and stride-length whereas cadence remains essentially unchanged[19]. While there are numerous factors that contribute to these age-related changes in healthy older adults, the burden of SH may be another factor contributing to these changes as presence and severity of SH are also associated with ageing. The differences in velocity and stride-length in this sample of healthy older adults persisted despite adjusting for age suggests that the gait differences between the two NC groups could be attributed to SH in this analysis. This could mean that in otherwise "normal" brain aging a higher SH load may compromise pathways associated with gait control and adversely interfere with spatial and temporal gait characteristics. In AD, by the time clinical symptoms of the disease are evident, the underlying pathology has already spread beyond the limbic and medial temporal cortices to

involve the frontal and temporo-parietal cortices; hence, the SH-mediated interference with association pathways and cortical sub-cortical connectivity, which is already compromised by the AD process, may be of less clinical significance. Hence, within this sample of mild AD patients, gait parameters were not sufficiently changed, though this might emerge in a large sample with larger range of SH burden.

The UPDRS scores in the AD + group were higher than the AD- group. The score distribution reflected mild bradykinesia possibly attributable to lower-body parkinsonism or vascular parkinsonism described in relation to cerebrovascular disease in the basal ganglia[204]. This AD+ group had a mean total SH score of 14 and showed the slowest gait and shortest stride-length amongst the four groups. However, the differences in these gait parameters attained statistical significance only in comparison to the NC- group. Gait-velocity and stride-length in NC+ group were comparable to the two AD groups, despite differences in the UPDRS scores, implying that SH could directly affect gait. Amongst the three groups with almost similar UPDRS scores (NC-, AD- and NC+, UPDRS score range:1-3), the NC- group significantly differed from the NC+ as well as AD- group, providing further evidence to suggest that the gait differences between healthy older adults and patients with mild AD are independent of bradykinesia (accounted for on the UPDRS score). These results are similar to that of Goldman et al [117] who after carefully excluding those with significant parkinsonism in their sample of mild AD patients, demonstrated that gait velocity was significantly slower than that of healthy older adults.

This study also found that SH load in the frontal and basal ganglia regions correlated with stride-length in AD and gait-velocity in healthy older adults. Statistically significant correlations also emerged between basal ganglia SH load and step-width in healthy older adults. Stride-length and gait velocity are highly inter-correlated variables. In our sample the Spearman r value for the correlation between stride-length and velocity was 0.9 ($p<0.001$). Gait velocity and stride-length are measures of dynamic gait stability. Therefore, the statistically significant correlations between SH load in frontal and basal-ganglia regions and velocity and stride-length in AD and healthy older adults suggests that vascular pathology in

these regions may play an important role in the dynamic stability of gait. Activation of frontal and striate regions while mentally preparing to walk or actually walking has been demonstrated in normal healthy adults using functional imaging techniques such as functional MRI, near-infrared spectroscopic topography and Single Photon Emission Computerized Tomography (SPECT)[7, 12, 13]. Studies have also correlated gait impairment in AD and Parkinson's Disease with impaired cerebral blood flow in the frontal regions on SPECT[111, 205]. SH are associated with decreased metabolism in the frontal regions involving both normal and cognitively impaired individuals[192-194]which could explain our findings that the decrement in gait velocity and stride-length may be associated with the burden of SH in these regions. One other study has reported that elderly with gait impairment had higher burden of SH in frontal regions compared to those without gait impairment [72]. Benson et al. [71] found that in their cohort of elderly participants over 70 years with a MMSE > 24 besides meeting other inclusion criteria, the presence of SH in frontal regions had a sensitivity ranging from 79 to 93% for identifying mobility impairment; of note is that in the current study, SH scores in frontal and basal ganglia region correlated with gait speed and stride-length in the NC and AD group respectively. A decrease in gait speed and stride-length are considered as risk markers for falls in older adults [162].

While this study highlights the possible role that SH may play in gait control of healthy older adults and patients with mild AD, there are several limitations that have to be taken into consideration. Firstly, the sample represented had reasonable range of severity of SH on the ARWMC scale but the mean SH scores of 6 in the healthy older adults and 9 in the AD groups were the mild to moderate range of severity given that the maximum total score on the ARWMC is 30. This is likely because overt strokes or cortical infarcts were exclusionary, likely reducing the upper range of severity of vascular brain disease. Only one participant scored above 20 on the scale related to extensive, incidental periventricular white matter disease. It should be noted that participants were not chosen based on their SH burden; hence, this sample is likely to represent target populations where incidental SH are seen on MRI in 95% of normal elderly and up to 100% of patients with dementia on MRI [206-208]. Secondly, we used a visual rating scale to assess the burden of SH rather than quantitative volumetric measurements of SH, which is technically more demanding and time consuming,

but provide a more accurate volumetric measure of SH burden. However, the rating scales used in this study is well validated and reliable and rating scales of SH burden have been found to correlate well with quantitative volumetric measurement[209]. Thirdly, a larger sample could better delineate differences in gait between patients with mild AD who had higher proportion of SH compared to those with a lower proportion of SH.

4.5 SUMMARY

This study found that in healthy older adults as well as patients with mild AD without mobility impairment on history and examination, the presence of a higher SH burden negatively correlated with gait parameters, detected by sensitive gait parameter detection devices, that are risk markers for gait instability and falls. The significant correlation between velocity and stride-length and the presence of SH in the frontal and basal ganglia regions in both elderly and AD patients is convergent with multi-modal evidence that the fronto-subcortical regions are important for maintenance of gait. Further research looking at associations between SH in these areas and the occurrence of falls in the future in larger samples may help to elucidate the predictive role of SH in fall occurrence.

Table 1: Baseline characteristics of whole sample of patients with mild AD and healthy older adults.

	AD (N=42)	NC (N=33)	*p* value
Age (years)	74±8	73±8	0.52
Gender (female%)	60	47	0.25
BP (mmHG)	128±18/72±10	128±16/76±10	0.8/0.09
MMSE	25±3	29±1	<0.001
Dementia Rating Scale (DRS)	120±11	141±2	<0.001
BMI	25±5	26±5	0.61
Waist circumference (cm)	94±10	90±19	0.37
Leg Length (cm)	91±6	90±7	0.50
UPDRS-motor sub-score	7±7	3±4	0.005
Tinetti gait score	11.6±0.6	12±0.4	0.19
Timed-up-go (sec)	12±4	9±2	<0.001
Total ARWMC score	9±7	6±4	0.2

Table 2: **Differences in the four subgroups based of median ARWMC score**

	NC- (N=18)	AD- (N=21)	NC+ (N=15)	AD+ (N=21)	*F* value	*P*
Age (years)	69±7	71±9	76±7	77±6	5.4	0.002*
Gender (female)	44%	68%	53%	52%	n/a	0.7
MMSE	29±1	24±3	28±1.3	25±2	23.1	<0.001†
Dementia Rating Scale	141±2	117±11	140±2	122±11	41	<0.001‡
Body Mass Index	25±5	25±4	26±4	25±6	0	1.0
Waist circumference	87±22	93±9	95±13	95±12	1	0.5
Leg Length	91±7	93±5	89±7	89±6	.5	0.2
UPDRS	1±3	3±3	3±3	11±9	13.3	<0.001§
Tinetti gait score	12±0	12±1	12±1	12±1	1.4	2.3
Timed-up-go	8±3	11±2	10±1	13±5	7.1	<0.001‖
Total ARWMC score	3±2	3±2	10±3	14±4	73	<0.001#

*: NC-vs NC+ (p=0.03), NC-vs AD+ (p=0.005)

†: NC- vs AD- & AD+ (both $p<0.001$) & NC+ vs AD- ($p<0.001$) & AD+ ($p=0.002$)

‡: NC- vs AD- & AD+ (both $p<0.001$) & NC+ vs AD- & AD+ ($p<0.001$)

§: AD+ vs AD-, NC- (both $p<0.001$) and AD+ vs NC+ ($p=0.001$)

‖: NC- vs AD+ ($p<0.001$) and NC- vs AD- ($p=0.05$)

#: NC+ vs NC-, AD- & AD+ ($p<0.001$) and AD+ vs AD- and NC- (both $p<0.001$)

Table 3: Gait differences in subgroups based on SH load

	NC-	AD-	NC+	AD+	$F_{(3, 74)}$ value	*P*	η^2
Velocity (cm/sec)	127±16	102±17	111±16	96±20	11.1	<0.01*	0.3
Stride-length (cm)	138±17	123±17	124±15	112±18	6.7	<0.01†	0.2
Step-width (cm)	9±3	9±3	11±3	10±4	0.68	0.6	0.03

*: NC- vs AD- & AD+ (both p<0.001); NC- vs NC+ (p=0.04)

†: NC- vs AD- (p=0.04), NC- vs AD+ (p<0.001)

Figure 1: Box-plots of differences in velocity (a), stride-length (b) and step-width (c) in the four groups.

1(a): Velocity

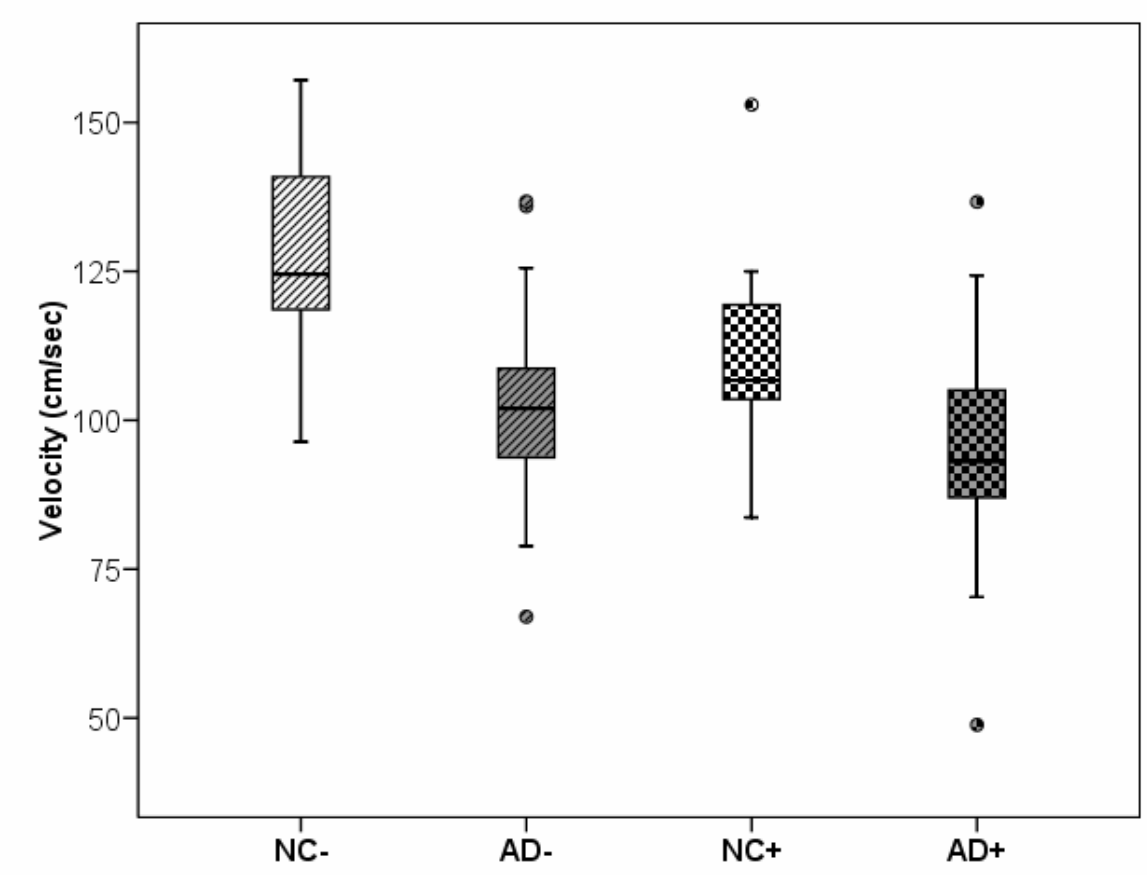


Figure **1(b): Stride-length**

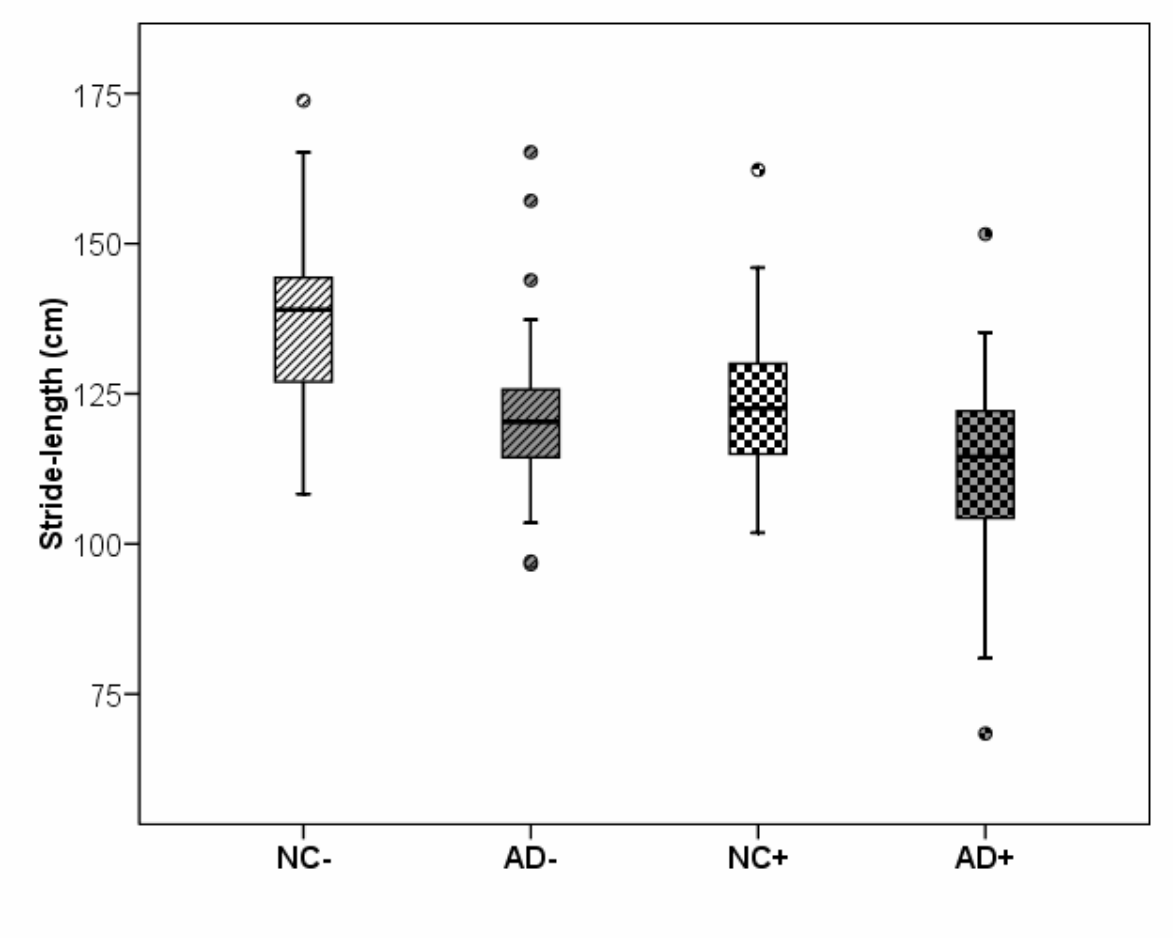
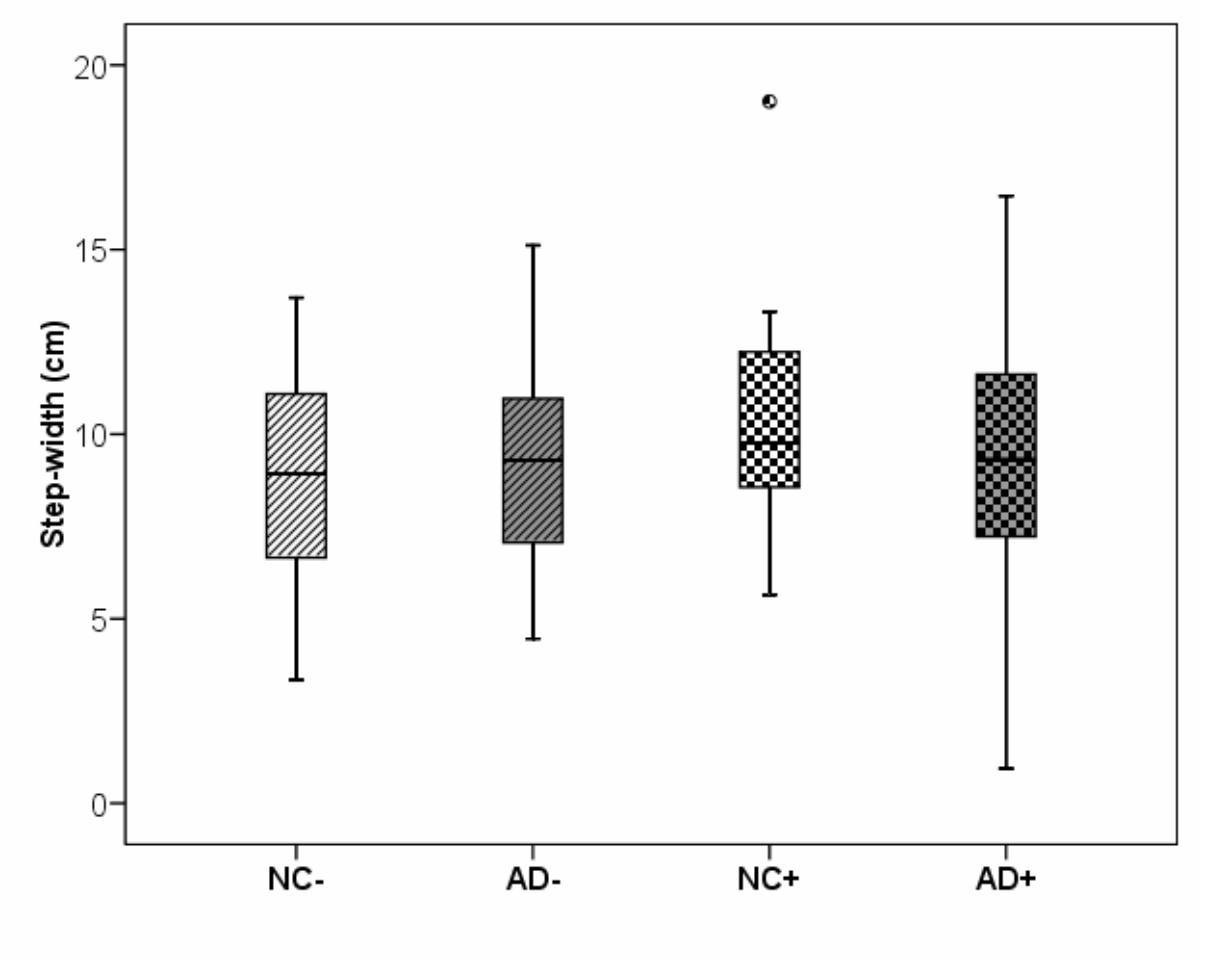


Figure 1(c): Step-width:



Chapter 5

5 Dual-task Effects of Walking and Performing Working-Memory Tasks in Alzheimer's Disease and Healthy Older Adults: Relation to Subcortical Hyperintensities

ABSTRACT:

Background: Little is known of the interaction between concurrent performance of mental functions such as working memory and gait in patients with Alzheimer's disease (AD). Both these functions share common neuronal areas which could be affected by cerebrovascular disease that appears as subcortical hyperintensities (SH) on MRI scans.

Objectives: 1) To explore the costs of working memory performance on cadence (steps/minute) in patients with mild AD compared to normal controls (NC); 2) to examine the costs of walking on working memory performance in the two groups; and 3) to assess whether the overall burden of SH in AD and NC participants influences the costs of dual-tasking within each group.

Methods: MRI scans in patients with AD and NC were rated for SH burden on standardized scales. The AD and NC groups were further subdivided based on their SH load into higher SH (AD+ and NC+) and lower SH (AD- and NC-) groups using a median cutoff SH score. Speed-accuracy tradeoffs (SAT=accuracy/reaction-time x 100) was used as the performance measure on three working memory tasks, x-task (control), 1-back and 2-back, obtained while standing and while walking at a constant velocity on a motorized treadmill. Cadence (steps/minute) was the gait measure obtained on the treadmill as participants walked with and

without performing the above working memory tasks. Costs of dual-tasking on SAT and cadence were compared in the AD and NC groups and then in the four subgroups.

Results: The AD group, compared to the NC group, showed significantly poorer performance on all working memory tasks (for all $p<0.01$). Between the four SH-subgroups, the NC- group alone performed superiorly in all tasks across all conditions. There were no significant differences on the dual task costs on SAT between AD and NC or between AD+, AD-, NC+ and NC- groups. The dual task costs of cadence were significantly higher in the NC group compared to the AD group ($F=11.6$, $p=0.001$, $\eta^2_p=0.21$). When the four groups were compared, there was again a significant effect of dual task costs on cadence ($F=5.3$, $p=0.003$, $\eta^2_p = 0.28$) with the AD+ group consistently revealing a negative dual task cost on cadence for all tasks.

Conclusion: Working memory performance affects cadence when measured at a constant treadmill velocity in both AD patients and healthy elderly. However, AD patients are unable to mount the appropriate response of increasing their cadence while dual tasking. Within the AD group, only those with a higher SH burden (AD+) seem unable to generate the safe adaptation response which increases stability while dual tasking. SH appears to have a negative effect on gait while dual tasking in AD and on working memory performance in the healthy older adults.

5.1 INTRODUCTION

Dual-tasking while walking, that is walking while consecutively performing another task such as talking, has been shown to affect the performance of gait in mixed elderly samples[30-32] and in patients with AD[33-35]. These studies had participants talk while walking, either as a structured cognitive interference task or while being engaged in a casual conversation, and

showed that some patients stop walking while talking while others continued walking, but at the cost of slowing gait velocity and increasing gait variability in velocity, stride-length and/or double-support[30-35]. Experts have suggested that the costs of walking under dual-task conditions are due to competition for attention resources [137], whose neuronal substrates include a large distributed neural network involving frontal and parietal lobes[210].

Dual-task performance is impaired in patients with Alzheimer's Disease (AD) even when two cognitive tasks are performed simultaneously [211, 212]. Evidence suggests that gait relies on executive function abilities and that performance of executive function tasks may interfere with gait performance under dual-task conditions[33, 120-122]. Using a verbal fluency task, Camicioli et al. compared dual-tasking effects in 15 patients with mild AD (MMSE: 21; age: 74 years to that of a group of young and older adults and found that the AD group took significantly longer time to complete a 30 feet walk compared to the other two groups while dual-tasking [35]. Sheridan et al. described increased variability in gait and decreased speed while dual-tasking using a forward digit span task in 28 patients with mild AD[34]. Another study also demonstrated that performance of fluency tasks and digit recall tasks interferes with gait in patients with AD and in healthy elderly[33]. Working memory is an executive function that involves transient maintenance and the concurrent mental manipulation of information in service of a particular task[156]. Experimental data exists to show that working memory tasks can influence gait. For example, in a sample of young adults, counting backwards, which relies on working memory performance, had a greater effect on gait-variability compared to those requiring semantic fluency[141]. Patients with Alzheimer's disease (AD) have impairments in working memory[213], but it is not known whether imposition of a working memory task while walking may adversely affect gait changes in this population.

Subcortical ischemic lesions appear as hyperintense areas in white matter and deep nuclei on T2 and FLAIR sequences on MRI and are often referred to subcortical hyperintensities (SH). SH attributed to arteriosclerosis and other ischemic changes in the brain[57, 191]. SH are extremely common in the elderly with reports suggesting a prevalence as

high as 96%[42]. In AD, similar prevalence has been reported, not significantly different from elderly controls [47, 48, 214, 215]. Some authors reported that SH are more extensive in the AD group [47, 216] but their appearance is similar to that of elderly suggesting that these may be related to age rather than a disease specific process. Clinical manifestation of SH include gait impairment and deficits in executive functioning[64, 84, 206, 217]. Studies suggest that in individuals without dementia the presence of SH affects their attention, speed of processing, visuo-spatial memory, and executive skills[50, 89, 90, 218]. The LADIS study showed a clear association between poorer gait speed and higher SH load on MRI in a sample of over 600 community-dwelling elderly [219]. Other large community studies such as the Cardiovascular Health study demonstrated an association between severity of SH burden and poorer gait speed, stride-length and double-support time in 321 functionally independent older adults [87]. Similar findings have been reported by other studies showing that SH are associated with slower gait speed [71, 73, 76, 176]. The presence of SH in strategic white matter pathways in the brain is hypothesized to interfere with brain connectivity and therefore with single-task performance in executive function and gait [71]. Similarly, disruptions in anterior-posterior connectivity would be expected to interfere with performance under dual-task situations. However, presence of SH has not been taken into account in the current dual-task literature.

Changes in gait during dual-tasking are known to occur when the secondary task necessitates the production of speech. Dault et al. and Yardley et al. suggest that articulation of speech and the rhythmic changes in respiratory cycle while speaking may partly explain to the dual-tasks costs on gait and posture [149, 150]. Therefore, use of non-verbal tasks under dual-task condition can avoid this potential confound. Researchers have also suggested that for two tasks to interfere with each other, the individual tasks must share common neuronal resources, providing a biological basis for competition for the same neuronal substrates[140]. Therefore, one possibility to assess dual-task interference in gait in AD is to use a working memory task that avoids the use articulation in its performance. In addition, gait slowing appears to be a common compensatory mechanism to increase stability of gait[19], and this has been demonstrated in many dual-task studies[30-35]. However, it does not explain why slowing or cessation of gait while dual-asking is associated with falls as demonstrated in one study of 58 residents in a sheltered accommodation, 12 residents stopped walking. Ten of those 12 fell

at least once in the subsequent 6 months of follow-up[30]. It is be possible that if patients with AD were engaged in maintaining their gait velocity while dual-tasking, they may not be able to generate a protective response, making them prone to falls. Therefore, rather than assess standard over-ground gait parameters, we opted to constrain velocity by using a motorized treadmill. This allowed us to examine whether AD patients would make similar compensatory changes as healthy older adults, and whether the burden of SH would adversely affect those changes while dual-tasking.

Treadmill walking, though in theory is mechanically similar to overground walking, in reality is quite different. Studies have found that gait speed, cadence and knee angle on treadmill is different form over ground walking even in unimpaired older adults. [24]. Patient with stroke had faster gait speed, longer stride lengths, and lower cadence over ground than on the treadmill[25]. Habituation on the treadmill in young adults varies up to 1-hour whereas in older adults, even 15 minutes of habituation was not found to equate to overground gait parameters[24, 26].

Hence, to overcome the drawbacks in the dual task literature, we studied the effect of performing a verbal working memory task, on gait parameters in patients with AD, and also investigated any modulating effects of SH on dual-task performance. The specific hypotheses were: 1) performing a working memory task while walking will increase cadence (steps/minute) measured on the treadmill in patients with mild AD and normal controls (NC); 2) walking on the treadmill will slow reaction time and decrease accuracy on working memory task performance; and 3) the overall burden of SH in AD and NC participants will increase costs of dual-tasking.

5.2 METHODS:

5.2.1 Participants:

Participants were recruited from the Sunnybrook Dementia Study, a longitudinal study based in a university cognitive neurology clinic, which prospectively follows patients with cognitive impairment including AD and other dementias and a cohort of age-matched community-dwelling healthy elderly controls (NC). Patients undergo a thorough diagnostic including clinical history, neurological and general physical examination and standardized detailed mental status assessments[172], blood work to rule out secondary causes, standardized neuropsychological and neuroimaging examinations. Clinical data are reviewed independently by two knowledgeable clinicians to determine whether the patients meet respective diagnostic criteria for probable or possible AD [93] or other neurodegenerative dementias. Normal controls (NC) were community volunteers who performed within normal limits on all cognitive tests, were functionally independent in all activities of daily living, had no history of neurological or psychological disorder and were in a stable healthy condition. All participants gave informed consent to the protocol which was approved by the Research Ethics Board.

Potential participants between ages of 60 and 80 years who were able to walk independently for 15 minutes without any discomfort were screened within six months of their magnetic resonance imaging (MRI) for the following exclusion criteria: for patients that met NINDS-ADRDA criteria for probable AD- an MMSE $\leq$ 20, and, for both groups- major depression, any history of other neurological disorders, recent hip-fractures, significant arthritis, clinically significant joint deformity, recent hip/knee replacement, sedative medication use, dependence on alcohol and/or neuroleptics drugs, use of assistive devices such as cane/walker and significant neuropathy on examination. Cognitive tests used for this study to characterize the stage of AD were the Mini-mental Status Examination (MMSE)[91] and the Mattis Dementia Rating Scale (MDRS) [202]. All participants underwent training on the

working memory tasks and those with an accuracy of <70% even after 5 trials of the 2-back working memory task were excluded.

5.2.2 Assessments

Data on history of falls, concomitant medical conditions, cardiovascular risk factors, exercise history and current medications were obtained on all participants, AD patients and NC. Additionally, all participants underwent a physical and neurological examination at the time of gait assessment, including measurement of body-mass index, leg-length, mid-calf girth, blood pressure and resting heart rate. Timed-up-and-go (TUG) test[173], the Unified Parkinson's Disease Rating Scale (UPDRS)[174] and Tinetti gait scale[175] were also scored (see Appendix 1). Additionally, neuropsychological and neuroimaging data were available to ascertain cognitive and functional and other disease characteristics.

5.2.3 MRI

All brain images were acquired using a 1.5 T Signa MR imager (GE Medical systems, Milwaukee, WI). Three image sets were acquired in the same imaging session: T1-weighted (axial 3D SPGR with 5ms TE, 35ms TR, 35° flip angle, 1 NEX, 22 x 16.5 cm FOV, 0.859 x 0.859mm in-plane resolution, and 1.2 to 1.4mm slice thickness), proton-density (PD) and T2-weighted images (interleaved axial spin echo, with TEs of 30 and 80 ms, 3s TR, 0.5 NEX, 20 x 20cm FOV, 0.781 x 0.781mm in-plane resolution, and 3mm slice thickness).

5.2.4 SH severity rating

For this study, the burden of SH was rated using visual rating scales as these are found to be as sensitive in picking out physical and cognitive measures of performance in a clinical setting [220]. The Age-related White Matter Change (ARWMC) scale was used for this purpose, which is consensus-derived four-point scale that assesses severity of SH in five different regions as delineated by Wahlund et al.[177]: (1) the frontal area; (2) the parieto-occipital area; (3) the temporal area; (4) the infratentorial area including the brain stem and cerebellum; and (5) the basal ganglia, which included the striatum, globus pallidus, thalamus, internal and external capsules, and insula. The scores in bilateral regions are summed to obtain the total SH score, which estimates the volumetric burden in both groups.

5.2.5 Gait parameters on motorized treadmill

Controlled gait parameters were captured using footswitches (B&L Engineering) placed in the insoles of participant's shoes as they walked on a motorized treadmill (Biodex™ RTM400, Biodex Medical Systems, Inc., NY). The use of footswitches for recording temporal gait parameters has been validated and found to be reliable [179]. Foot-switch data was digitized at the rate of 500 samples per second through an analog-to-digital converter. Digitized signals were processed using a user-friendly software (Labview®, National Instruments, Austin, TX) to measure cadence, stride-time, step-timing, swing and stance phases, single- and double-support timing, and gait-variability measures. Additionally, digitized video recordings of step-width changes were recorded in all participants for capturing changes in step-width while dual tasking. These gait parameters were captured at a constant velocity on the treadmill that was set to individual comfort level without any inclination to the angle of the treadmill belt. Participants used a safety-harness (The Biodex Unweighing System®, Biodex Medical Systems, Inc. NY) that was strapped across their chest for safety reasons. For those unfamiliar with treadmill walking, training was provided initially by allowing walks on the treadmill while holding on to the hand-rails. Subsequently the participant was encouraged to release one hand at a time and walk without holding on to

the hand-rails. Participants wore their own footwear with footswitches in place and completed an acclimatization period lasting a minimum of 10 minutes prior to recording their treadmill parameters. This time period was chosen based on other studies that used similar acclimatization time [180]. Participants were instructed to look straight ahead and fix their gaze on a mark placed 3-feet away from the treadmill level with their head and to refrain from talking and fixate on the spot until completion of data capture. Participants walked in a quite, well-lit room with no visual or auditory distractions for the duration of the data capture. Data was captured for 65 seconds after which the treadmill speed was gradually decreased to zero. Amongst the several gait variables mentioned above, cadence, i.e., the number of steps per minute, was the gait variable chosen for this analysis as it reflects individual's frequency of stepping in relation to step-length and gait velocity[221]. Besides, the cadence has been shown to be associated with occurrence of falls in older adults[222], it can used in future studies to pragmatically assess relationship between dual-tasking and falls .

5.2.6 Working memory task:

The paradigm was limited to 2-back as the previous studies showed that patients with mild AD were able to perform the 2-back task with ~70% accuracy and these tasks activated the frontal, parietal and thalamus on fMRI in the AD group. [223]. In our pilot studies the patients found the 3-back task too demanding. The working memory task was a variant of the 2-back letter paradigm[160]. Participants were provided detailed instructions and training prior to starting this task. While standing on a treadmill, participants perform the working memory task projected on to a screen placed directly in front of them. They registered their responses by pressing a button held in their preferred hand. Three conditions, 'X' [simple working memory], '1-back' and '2-back' [active working memory load tasks], were presented in random order. All three working memory tasks included as display of continuous stream of letters on the screen in front of them. The display duration was 1500ms and the inter-stimulus interval (ISI) was 2000ms. All the three tasks required participants to maintain information in memory and appropriately register their responses while continuously keeping track of each letter displayed on the monitor.

During the X-condition, participants were instructed to press the button when ever they saw a letter ‘X’ in the continuous stream of letters [Figure 1a]. The two active working memory tasks were based on increasing cognitive load. For the 1-back condition, participants were instructed to press the button whenever a letter same as the one that came just one before it in the sequence [for example (Figure 1b), M-T-T or W-B-B]. For the 2-back task, participants were instructed to press the button whenever the letter was the same as the one that appeared two stimuli prior in the sequence of letters [for example (Figure 1c) U-T-U or B-Q-B]. The letter ‘X’ did not appear in any of the two active working memory tasks. Three to five tasks, each lasting approximately 1 minute, with at least one potential response every 5-6 seconds were administered. Reaction times and task accuracy data were recorded from signals obtained by button-presses.

5.2.7 Study-design

The three cognitive tasks (X-task, 1-back and 2-back) were administered to participants while they were sitting, standing and walking. For purposes of this manuscript we report only the effect of performing working memory tasks on cadence on the treadmill and the costs of walking on working memory task performance compared to that while standing. Data collection was commenced only after sufficient training on the cognitive task while in the seated or standing positions. The task condition including the order of the cognitive task was randomized within and between groups. Each task condition lasted for 1 minute and 3-5 trials were administered. The instructions were repeated after every trial and were the same for both groups (see Appendix 2).

5.2.8 Statistical analysis

Demographic variables between the two groups were compared using Student's t test and chi-square where applicable. To relate the effect of working memory performance on gait parameters to the SH load in the two groups (AD and NC), the median distribution of total SH load was determined for each group and was used as the cut-off. Those that were above the cut-off were denoted as AD+ and NC+ and those that equaled or fell below the cut-off were referred to as AD- and NC- respectively. ANOVA was used to compare the demographic variables in the four groups.

Cadence of regular walking on the treadmill, i.e., walking with gaze fixed on the screen (single task walking), was compared with cadence while dual tasking across three dual-task conditions: the X-task, 1-back task and the 2-back task. To determine the costs on cadence while dual-tasking, a percentage change in cadence on dual-tasking was calculated relative to participant's single-task cadence as done in other such studies[126, 224]:

Dual-task costs of cadence= [(Dual-task cadence–Single-task cadence)/Single-task cadence] x100.

Performance on working memory tasks was determined by combining accuracy and reaction time (RT) into one performance score, the speed-accuracy trade-off (SAT), calculated by (Accuracy/RT)*100. This method has been used in other studies to obtain a composite score of ones performance on cognitive tasks [122]. SAT was calculated for each task during both the standing and walking conditions. Dual-task costs on SAT were measured by the formula: Dual task costs of SAT = (walking SAT- standing SAT) / (standing SAT).

To evaluate dual-task cost effects in AD and NC a repeated measures ANOVA was applied. Differences in dual-task costs were compared using Students t tests for AD vs NC groups. Repeated measures ANOVA was used to compare the dual-task costs for cadence and SAT for the four groups that were obtained after sub-dividing the AD and NC according to their

SH score - those above the median split of the SH score for the respective group were designated as high- SH load subgroups denoted by a '+' (AD+ and NC+) and those at or below the median split were denoted by '-' to indicate lower-SH subgroup (AD- and NC-). The two groups were therefore, subdivided A median split for each group was determined by ANOVA and post-hoc Tukey's least significant difference (LSD) was used to ascertain where these differences occurred during the three dual task conditions. Due to equipment failure, minor differences in the degrees of freedom occurred between the analysis of gait and cognitive data. We considered differences to be statistically significant if the $p \leq 0.05$.

5.3 RESULTS

5.3.1 Baseline characteristics

Patients with AD (n=24) were identical to NC (n=20) in most baseline characteristics (age, gender, BMI, waist circumference, leg-length, mid-calf girth, blood-pressure and heart rate) but differed as expected on the MMSE ($p<0.01$) and DRS ($p<0.01$) scores. The AD group showed a trend towards a higher UPDRS score ($p=0.05$) and had took a significantly longer time to complete the TUG test ($p<0.01$) (**Table 1**) .

The total ARWMC score in the AD group was significantly greater than that of the NC group ($p<0.01$). Therefore, based on the median of the distribution on the total ARWMC score for each group, those above the median were compared with those equal to or below the median. The median total ARWMC score were 7 and 5 for AD and NC respectively **(Figure 1)**. Thus from the two groups, four groups were derived: AD+ and AD- (with cut-off of 7 on the total ARWMC score for the AD group) and NC+ and NC- (with the cut-off of 5 on the total ARWMC score for the NC group).

The demographic differences between the four sub-groups were evaluated using ANOVA and are highlighted in **Table 2**. There were no statistically significant differences in baseline body characteristics such as leg-length, BMI and waist circumference. Statistically significant differences between groups were observed in age ($p<0.01$), MMSE ($p<0.01$), DRS($p<0.01$), UPDRS score ($p<0.01$)and TUG ($p<0.01$). Post-hoc Tukey's test revealed that the NC- group was significantly younger than NC+ ($p<0.05$) and AD+ and AD-($p<0.01$) groups. The two AD groups had significantly lower MMSE and DRS scores than NC but there were no statistically significant differences between AD+ and AD- and between NC+ and NC- on these baseline cognitive measures. The AD+ group had significantly higher UPDRS score than the other three groups ($p<0.01$). The AD+ group also took significantly longer time to complete the TUG as compared to the NC- and NC+ groups. However, there were no statistically significant differences between AD+ and AD- and between NC+ and AD- groups on the TUG test.

There were no differences in the two groups on cadence, cycle time and double-support during the 'walk only' condition though the AD group preferred a slower belt-speed compared to the NC group (60cm/sec vs 74cm/sec, $p=0.02$).

5.3.2 Effect of working memory task performance on cadence

5.3.2.1 Dual-task costs on cadence:

There was a significant effect of dual task costs of cadence between AD and NC groups ($F(2,42)=11.6$, $p=0.001$, $\eta^2_p=0.21$). The dual task costs on cadence were significantly higher in the NC group compared to the AD group [(X task: 4.4±5.0 vs 0.75±5.8 ($p=0.026$); 1-back: 4.9±5.7 vs -0.82±5.2 ($p=0.001$), 2-back: 5±8.7 vs -0.28±4.5 ($p=0.002$) (**Figure 1a**)]. In fact, the AD group showed a decrement in dual task costs on cadence in the 1-back and 2-back

conditions indicating that the mean cadence actually decreased while performing the 1-back and 2-back tasks.

Then the dual-task costs on cadence were compared between four groups using repeated measures ANOVA **(Table 3 and Figure 1b)**. There was a significant effect of dual task costs on cadence in the four groups ($F(3, 41)=5.3$, $p=0.003$, $\eta^2_p = 0.28$). Post hoc tests revealed that the AD+ group showed a significant decline in terms of their mean dual-task costs on cadence compared NC- ($p=0.001$), NC+ ($p=0.004$) and AD- ($p=0.05$) groups **(Figure 2)**.

5.3.3 Effect of Treadmill Walking on Working Memory Task Performance in AD vs NC:

5.3.3.1 Single-task working memory performance:

SAT scores were compared between AD and NC groups and then between the four groups subdivided on their SH load. **Table 4a** highlights the differences in SAT during standing and walking conditions in the AD and NC groups. As depicted, the SAT on all three tasks on both conditions was significantly different in the AD and NC groups. When the same comparisons were carried out between the four groups, as shown in **table 4b**, only the NC- group showed significantly superior performance across all tasks.

5.3.3.2 Dual task costs on Speed-accuracy trade-off (SAT)

Even though the AD group had showed a decrement in dual task costs on SAT compared to the NC group, these differences were not statistically significant group ($F(2, 41)=2.1$, $p=0.153$, $\eta^2_p =0.05$)**(Figure 2a)**. There were no significant differences on the dual task costs

on SAT between the AD+, AD-, NC+ and NC- groups ($F(3, 40)=1.8$, $p=0.162$, $\eta^2_p=0.12$) **(Table 3 and Figure 2b)**. The difference between dual task costs on SAT showed a trend towards statistical significance between the AD+ and NC- groups on the 1-back task ($p=0.06$) and 2-back task ($p=0.057$) but not on the control task. There were no trends towards significance between the AD+, AD- and NC- groups. A large amount of variance was seen in these SAT scores within each group.

5.4 DISCUSSION

This study investigated the effect of performing three working memory tasks of varying complexity on cadence (steps/minute) constrained by a constant velocity on a motorized treadmill in two groups, patients with mild AD and healthy older adults. The effect of increasing SH load on costs of dual tasking was then assessed in these two groups by further segregating them based on the burden of SH depending on the group median cut-off score. To the best of our knowledge, this is the first study that looked at costs of dual-tasking in relation to the burden of microvascular disease in mild stage AD.

In this study, the NC group increased their cadence compared to the AD group during all dual-task conditions. This suggests that NC group decreased their stride-length while maintaining their steady speed on the treadmill in contrast to the AD group. When AD and NC groups were divided based on their SH load and the dual tasks costs were compared in these four groups, only the AD+ group, i.e., those with higher proportion of SH, decreased their dual-task associated cadence indicating that they had to maintain wider strides to keep up with the steady treadmill belt speed. The increase in cadence in NC+, NC- and AD- groups may be considered as a safe compensatory mechanism to maintain dynamic stability during dual-tasking and a decrease in cadence suggests that the AD+ group were unable to make this compensatory strategy. Rather they decreased their cadence, which actually threatens dynamic stability. This suggests that the presence of SH may interfere with the

adaptive responses of the brain to maintain dynamic stability especially in AD. Previous literature consistently shows that gait velocity decreases in order to maintain stability while dual-tasking in older adults and in patients with AD. However, on a treadmill when compensations in gait velocity to maintain dynamic stability is not an option the system is constrained to maintain stability by either increasing double-support time, through decreasing stride-length or increasing the step-width. Increase in double-support and decrease in stride length are considered to be compensatory mechanisms to improve stability in aging [19]. Assuming gait symmetry at all times, the relationship between gait velocity, stride-length and cadence can be captured by the following formula:

Gait velocity= stride-length x Cadence/120. [221]

As gait velocity was unchanged while on the treadmill throughout the experiment, an increase in cadence at a constant velocity would mean a decrease in stride-length. A decrease in stride-length enables more time spent with both feet on the ground (double-support time) and therefore improves stability, which could be a compensatory mechanism to improve stability of gait. Decrease in stride-length is one means of increasing dynamic gait stability while walking akin to maneuvering an ice patch of pavement.

On the cognitive performance measured by SAT, the AD group performed more poorly on all three working memory tasks compared to the NC (Table 4a). When study groups were assessed based on their SH load, there was a considerable overlap in the performance of AD patients with high and lower SH burden suggesting that the presence of increased SH load did not adversely affect the performance on the three working memory tasks in both conditions in AD (Table 4b). In he NC group, there were no statistically significant differences in performance on the standing condition but on the dual task condition, NC-group showed a significantly better performance compared to the NC+ group indicating that SH may adversely affect cognitive performance under more challenging conditions such as dual-tasking. The effect of walking on costs of performance on speed-accuracy tradeoff, an aggregate measure of performance on the working memory tasks, showed no significant effect between AD and NC groups. There were no significant differences between the four groups subdivided on their SH scores; however, differences between AD+ and NC- showed

trends towards significance on the more complex tasks (2-back) suggesting that these differences may hold true in larger samples. These results further suggest that within the NC group, those with higher SH load tend to deteriorate under dual tasks conditions as depicted in Figure 2b. Both the AD+ and NC+ groups show a negative dual task costs on SAT but these differences were not significant. A negative SAT would mean that their dual-task performance was worse than their cognitive task performance while standing.

These results of this study highlight two important features of SH. Firstly, in healthy elderly, the presence of higher SH burden may adversely affect cognitive performance under dual-task condition. Furthermore, the healthy elderly with higher SH load demonstrated a working memory performance similar to both the AD group with and without higher SH load. This suggests that the presence of a high SH burden interferes with working memory performance in healthy elderly. In the AD group, the subgroup with higher SH load had a considerable overlap in performance with those with lower SH score, suggesting that SH may not play a significant role in interfering with working memory in AD. One possible explanation for this could be that by the time AD is clinically apparent, the distribution of disease pathology, neurofibrillary tangles and plaques, has spread outside the medial temporal and enterorhinal cortex to involve the dorsolateral prefrontal and subcortical areas [225], and the presence of SH may not additionally interfere with the afferent connectivity of the frontal cortex as it may be already disrupted by the disease course. Performance of a verbal working memory task and gait rely on common neuronal substrates specifically in the dorsolateral prefrontal cortex, the striatum and parietal cortex and therefore performance of these two tasks simultaneously could have a biological basis for the task interference[7, 14, 158, 226]. The dorsolateral prefrontal cortex plays an important role in the maintenance and manipulation of information in the working memory[227]. The dorsolateral prefrontal cortex also plays a role in adapting gait to environmental conditions through its connections with the supplementary motor areas and basal ganglia[14]. The simultaneous performance of these functions could potentially interfere with patient's ability to execute safe adaptive responses as areas such as the dorsolateral prefrontal cortex may have a double hit, from the disease process of AD as well as the interference in connectivity by SH in these regions. In healthy elderly, the connectivity between cortical areas involved in working memory and gait performance under dual task

conditions may be disrupted by the presence of SH alone and this may explain the lack of significant differences between NC+ and the two AD groups on the working memory performance. Therefore, results of this study suggest that SH burden may play a more important role in processing-speed in healthy cognitively intact adults consistent with other reports[89, 228-231].

Secondly, presence of a high SH load in AD patients adversely affects their walking while dual tasking. Gait in AD, especially under dual-task conditions, relies upon executive functions and the influence of executive functions on gait increases with increasing complexity of the dual-task [34, 108, 232]. Executive function impairment is common to AD even in the early stages of the disease[95, 233, 234]. The areas of the brain that govern executive functions such as the prefrontal and parietal lobes also are the same ones involved in coordination and synchronization of gait[12, 14]. The concomitant performance of the functions supported by these neurons overtax the systems responsible for the performance of the required tasks and in the presence of structural brain damage such as cerebrovascular disease, the dual-task performance may be more attenuated. It appears from our data that the AD participants with higher SH load decreased cadence when dual-tasking, suggesting that impaired executive function may interfere with planning and manipulating gait to maintain stability.

This study made use of the treadmill instead of testing participants on over-ground gait for mainly two reasons. Our pilot studies showed that characterizing changes in gait parameters in mild AD patients while performing a working memory task on the GaitRite mat showed that some patients reduced their speed considerably and some stopped completely while dual-tasking. This obviously did not help in understanding more subtle effects of dual-task costs on gait. Secondly, collecting gait parameters on a short duration traverse (approx. 7 to 10 seconds) on an automated walkway and summarizing the multiple traverses would not be the same as performing a longer trial to obtain reaction time data. Smaller traverses allow for a fewer potentially correct responses. Interpretation of cognitive data over a longer duration would be beneficial and attainable by a treadmill task.

The advantages of the complex dual-task methodology used in this study compared to ones used in other studies are as follows. Use of computerized working memory paradigm allows for capture of accuracy responses as well as reaction time and therefore, processing speed. It is an executive function task whose neuronal substrates overlap with that of gait as mentioned above. The use of non-verbal approach to assess working memory eliminates the direct influence of speech production on gait and also allows its future use in testing patients with speech impairments such as in stroke or primary progressive aphasia. The working memory parameters can be manipulated in the experimental design to increase or decrease the cognitive load of the working memory task using objectively quantifiable measures such as the inter-stimulus interval and display duration of each stimulus.

This study has certain limitations that need to be considered. The subdivision of groups in to those with higher and lower SH burden lead to smaller groups and comparisons between groups, especially the NC+ (n=7), can be viewed as insufficient to ascertain real effects of SH on dual tasking costs. However, we were able to detect a signal even with this small sample suggesting that larger studies with similar protocols are warranted. Secondly, the SH burden was rated on a visual rating scale and not quantified using automated methods; this is generally less sensitive in detecting small differences between groups[235]. Nevertheless, we used a well-validated rating scale (ARWMC scale[177]) which has a larger range of scores than some of the other scales such as the Fazekas scale [47] and is found to be satisfactory in differentiating groups [220, 235]. The use of rating scales and SH rating as a binary variable using the median of the distribution as a cutoff for the group has been utilized in other studies of cognitive impairment [236]. The use of automated SH quantification may have minimized the large overlap in confidence intervals especially within the NC group. Finally, while dual-tasking on the treadmill may not be considered as a "real-world" setting, it does help to underscore the relationship between cognition and involuntary gait changes in a velocity constrained environment.

The results of this study extend the existing knowledge of the interaction between gait and executive function by suggesting that SH can adversely affect dual tasking costs on gait in patients with AD. Prospective studies looking at fall occurrence and its relationship with the adaptive changes in gait while dual-tasking may help understand whether these changes affect stability in a clinically significant manner in the long run. This study also helps to understand the behavioral characteristics of SH. The results suggested a clear signal between SH load and working memory and stepping frequency in healthy older adults and patients with AD. Nevertheless, a closer look at the volume of lesions and their specific locations using automated methods on larger samples may further reveal interesting relationships between lesion-load and its ramifications in the interactions between gait and executive functions.

Table 1: Baseline characteristics of whole sample of patients with mild AD and healthy older adults.

	AD (N=24)	**NC (N=20)**	***p* value**
Age (years)	75±9	72±8	0.16
Gender (female%)	60	47	0.25
BP (mmHG)	130±17/70±9	127±16/74±10	0.5/0.2
MMSE	25±3	29±1	<0.001
Dementia Rating Scale (DRS)	122±10	141±2	<0.001
BMI	25±5	25±5	0.7
Waist circumference (cm)	94±10	88±18	0.17
Leg Length (cm)	92±5	91±7	0.43
UPDRS-motor subscore	6±7	3±4	0.05
Tinetti gait score	12±0.6	12±0.4	0.15
Timed-up-go (sec)	12±3	9±1	<0.01
Total ARWMC score	7.5±7	5.6±4	<0.01

Table 2: Differences in the four subgroups based of median ARWMC score

	NC- **(N=13)**	**AD-** **(N=14)**	**NC+** **(N=7)**	**AD+** **(N=10)**	***F*** **value**	***P***
Age (years)	68±6	72±9	76±5	79±6	5.8	0.002*
Female	19%	36%	19%	26%	n/a	0.7
SBP/DBP	129±18/74±11	134±13/72±8	124±11/75±8	124±20/68±9	1.1/0.9	0.4/0.4
MMSE	29±1	24±3	28±1	26±2	10.4	<0.001†
DRS	141±2	119±11	141±2	126±9	24.2	<0.001‡
BMI	25±5	25±4	25±3	24±8	0.1	0.9
Waist	86±21	93±9	92±10	96±11	1	0.4
Leg Length	90±8	93±4	92±6	92±5	.6	0.6
UPDRS	2±3	3±3	4±4	11±7	9.3	<0.001‖
Tinetti gait score	12±0	12±1	10±1	13±4	0.7	0.6
Timed-up-go	9±2	11±2	10±1	13±4	6.2	0.001§
SH score	3±2	3±2	11±2	14±3	60.2	<0.001#

*: AD+ vs NC- (p=0.001)

†: NC- vs AD- (p<0.001), NC- vs AD + (p<0.05), NC+ vs AD- (p=0.002)

‡: AD- vs NC + and NC- (both $p<0.001$) and AD+ vs NC+ and NC- (both $p<0.01$)

‖: AD+ vs AD- ($p=0.001$), NC- ($p<0.001$), NC+ ($p=0.02$)

§: AD+ vs NC- ($p=0.001$) and AD+ vs NC+ ($p=0.03$)

#: AD+ vs AD-($p<0.001$), NC- ($p<0.001$), NC+ (0.03) and NC+ vs NC- and AD- ($p<0.001$)

Table 3: Dual-task costs on cadence and SAT between four groups:

DUAL TASK COSTS		**NC-**	**AD-**	**NC+**	**AD+**	*F* value	*P*
CADENCE	X-task	4.4±4.5	3.0±5.8	4.3±5.5	-2.5±4.4	4.3	0.01‡
	1-back	5.6±6.3	0.8±4.8	3.6±4.8	-3.3±5.2	5.6	0.003†
	2-back	4.4±9.3	0.3±4.6	6.0±8.2	-1.2±4.6	2.3	0.08¶
SPEED ACCURACY TRADEOFF	X-task	0.4±17	10±41	-0.3±19	0.4±15	0.4	0.7
	1-back	3.2±18	-1.5±25	-11.8±18	-13.6±14	1.6	0.2
	2-back	18±28	-2±38	15±40	-11±33	1.6	0.2

Post-hoc Tukey's:

‡: AD+ vs NC- (p=0.002), AD- (p=0.01), NC+ (p=0.009)

†: AD+ vs NC- (p<0.001), AD- (p=0.06), NC+ (p=0.013)

¶: AD+ vs NC- (p=0.06), AD- (p=0.6), NC+(p=0.04)

Table 4a: Speed-accuracy tradeoff (SAT) [(Accuracy/RT)*100] on performance of three working memory tasks across standing and walking conditions in AD and NC.

Condition	Working Memory task	AD	NC	t	*p* value
STANDING	Control (X)	17.4 ± 0.8	23.1 ± 1.2	-3.978	<0.01
	1-back	15.3 ± 4.1	20 ± 4.8	-3.801	<0.01
	2-back	11.8 ± 3.8	17.1 ± 5.8	-3.820	<0.01
WALKING	Control (X)	17.6 ± 4	22.7 ± 4.6	-4.416	<0.01
	1-back	14 ± 4.1	19.7 ± 4.3	-4.971	<0.01
	2-back	11.1 ± 5	17.8 ± 5.2	-4.656	<0.01

Table 4b: Speed-accuracy tradeoff (SAT) in AD+, AD-, NC+, NC- groups.

Condition	Working Memory task	NC-	AD-	NC+	AD+	F	*p* value
STANDING	Control (X)	24.9±5.1	17.2±4.9	19.6±6.6	17.7±3.3	6.1	0.002†
	1-back	20.9±5	15.1±4	18.6±4.6	15.1±4.6	4.2	0.01‡
	2-back	17.9±6.5	11.4±3.5	13.8±4.7	12.1±4.2	4.4	0.009§
WALKING	Control (X)	24.7±4.7	17.9±4.6	19.6±3.6	17.5±3.6	7.3	<0.001¶
	1-back	21.4±4.3	14.4±3.6	16.6±3.9	13.1±4.8	9.4	<0.001¶
	2-back	20.0±5.5	11.3±5	15.1±2	10.7±5	9.0	<0.001*

†NC- vs AD- ($p<0.001$), NC+ ($p=0.04$), AD+ ($p=0.002$)

‡NC- vs AD- ($p=0.003$) and AD+ ($p=0.007$)

§NC- vs AD- ($p=0.001$) and AD+ ($p=0.008$)

¶NC- vs AD- ($p<0.001$), NC+ ($p=0.02$), AD+ ($p<0.001$)

*NC- vs AD- ($p<0.001$), NC+ ($p=0.04$), AD+ ($p<0.001$)

Figure 1: Costs of performing the control (X), 1-back and 2back tasks while walking on cadence in AD and NC groups (1a) and the four groups based on their SH load (1b)..

Figure 1a:AD vs NC

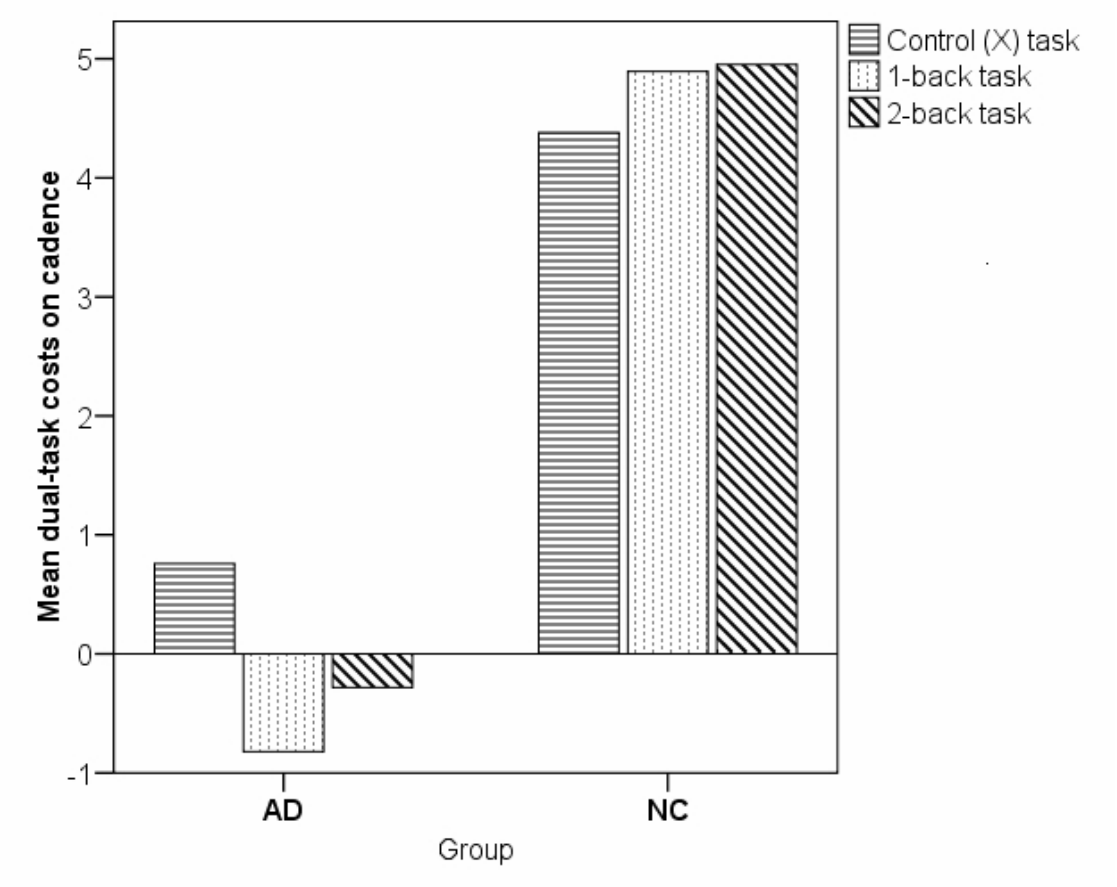


Figure 1b: Four group comparison

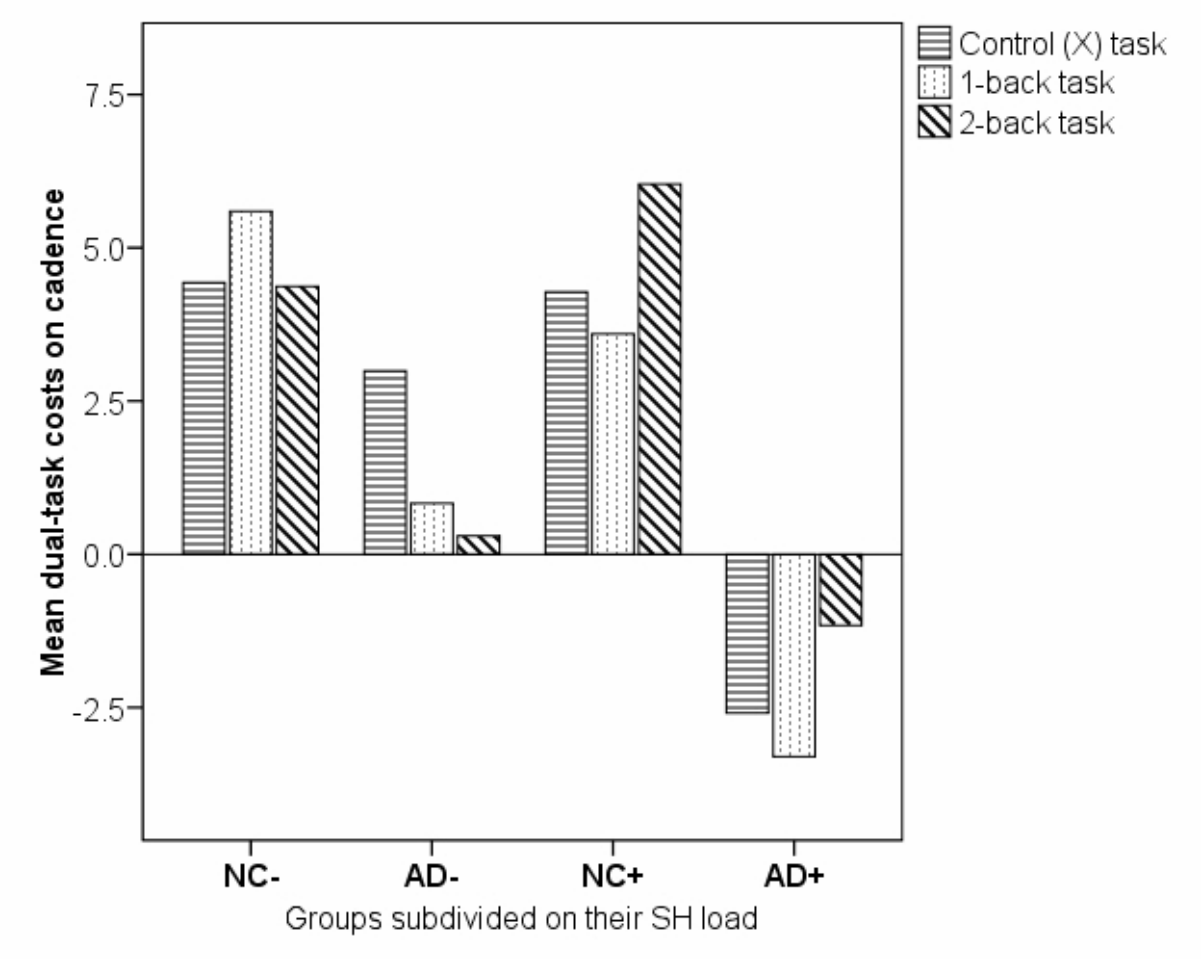


Figure 2: Costs of walking on speed-accuracy tradeoff (SAT) on the control (X), 1-back and 2back tasks in AD and NC groups (2a) and the four groups based on their SH load (2b).

Figure 2(a): AD vs NC:

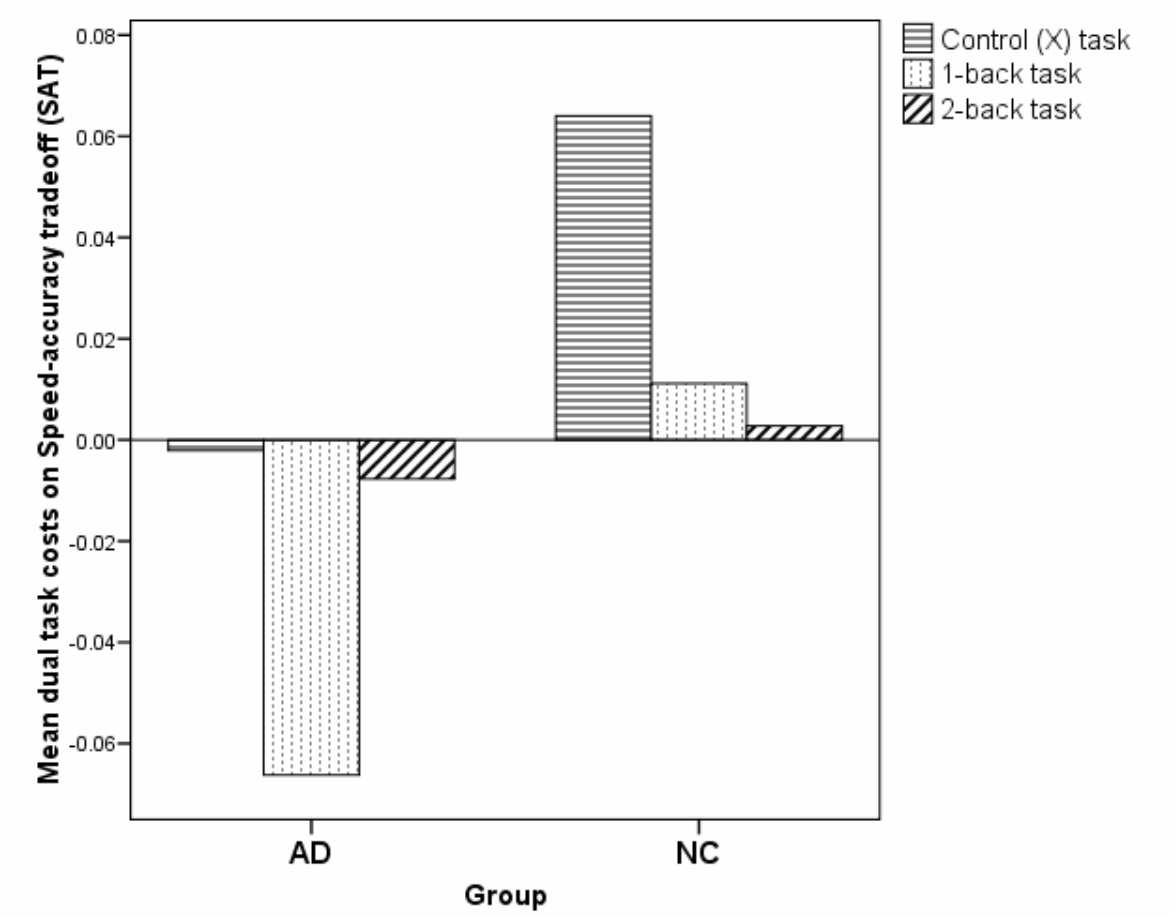
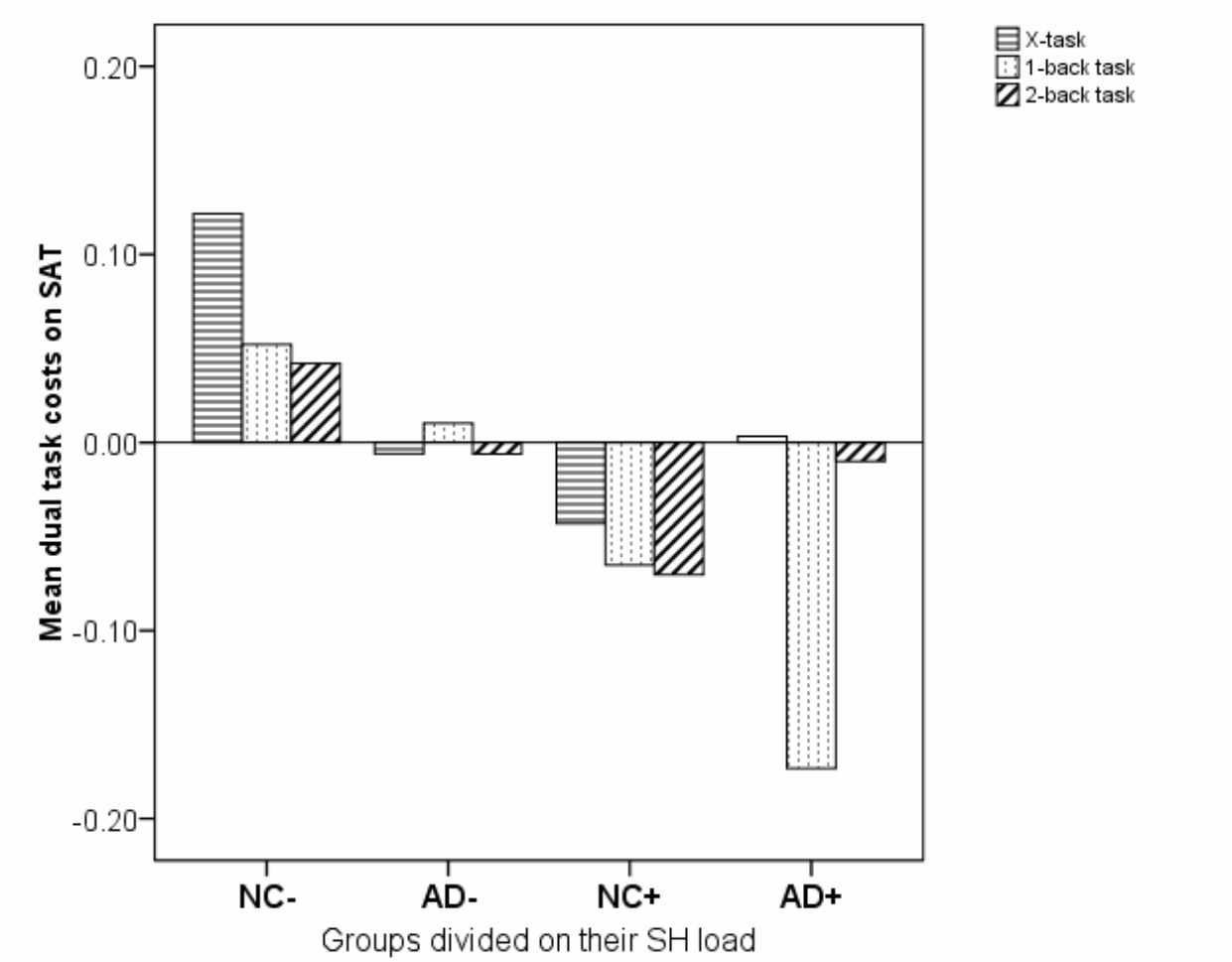


Figure 2(b): Four groups:



Chapter 6

6 Conclusion and discussion

6.1 Experiment #1

In experiment #1, we tested the hypothesis that changes in over-ground gait occur with concomitant performance of spatial-attention and working-memory tasks.. Specifically, young adults reduce their gait speed significantly while performing spatial-attention and working memory tasks while walking. Both groups also showed a significant decrease in stride-length in the two dual-task conditions. As expected, decrease in gait-velocity increased double-support time when dual-tasking in this group. The older adults showed a trend towards decrease in gait velocity and increased double support time but the differences did not attain statistical significance as the sample size was underpowered to show this effect. Furthermore, gait changes on tasks expected to more cognitively demanding such as the working memory task showed a trend towards greater magnitude of changes in gait velocity, stride length and double-support, but this did not attain statistical significance. Overall, the changes in dual-tasking in older adults were not significantly different from the changes in dual-tasking in the young adult group.

These findings are consistent with other studies showing decrements in temporal gait and spatial gait parameters with increase in double-support time in young adults walking while concurrently performing a digit span or a manual dexterity task[128], and increased cadence along with decreased gait speed, while counting, in another sample young and older adults [129]. However, the current study extends previous knowledge by demonstrating that concurrent performance of cognitive activity without elicitation of speech can also influence gait parameters, which is noteworthy as previous studies have also shown that postural

stability may be directly influenced by speech production, such as performing word generation or repetition of digits out loud , or talking while walking[149, 150].

We found that the changes in gait parameters were similar for both working memory and spatial-attention tasks. The magnitude of changes were more marked during the concurrent performance of working memory task but there were no statistical significant differences in costs on gait parameters between the two tasks. The lack of difference may reflect the small sample size and this should be explored in larger samples. The mechanism underlying dual-task interference with gait is not fully understood. Decrease in gait speed on dual tasking has been consistently reported in patients with dementia and stroke [35, 39, 133] and in healthy older adults[122, 134, 145]. Gait slowing associated with dual-tasking is thought to be a compensatory strategy to maintain gait stability, though it is not clear why gait slowing which is associated with more stable gait is also associated with an increase risk of falling in older adults[162]. It is postulated that under dual-task situations, resource sharing of common neuronal areas that sub-serve the individual tasks may lead to "capacity-sharing" and/or "bottle-necking" of common resources, leading to decrements in both tasks [163]. The interference effects for different concurrent motor or cognitive tasks may then depend on whether or not these concurrent processes compete for the same neuronal resources[140]. This may be one reason why some secondary-tasks such as listening have no effect on gait parameters when performed concurrently[124, 127], whereas others such as the ones we used in this study show an interference effect.

Functional MRI studies of working memory and spatial attention tasks have revealed that these tasks evoke a network of activations in multiple frontoparietal regions such as the supplementary motor area, the banks of the intraparietal sulcus, corpus striatum and cerebellar vermis [158]. Functional neuroimaging studies have also suggested that these regions may play an important role in human locomotion[7, 9, 14]. The premotor and prefrontal regions appear to be involved in the maintenance of an individual's walking pace[12], while areas within the parietal lobe provide information about spatial position and relative positions of body parts which can be used to modulate limb movements [164]. Therefore, working memory

and spatial attention may also share possible neuronal resources that control gait speed and other temporal parameters. This may be a possible mechanism for dual-task interference observed in this experiment.

What was suggested by this experiment was that a working memory task may have a greater slowing effect on gait than a spatial attention task. We therefore focused on patient interactions of gait and working memory in the subsequent dual task experiment in patients with mild AD. Before studying such interactions using dual task conditions in AD, however, it was important to first analyze whether the gait characteristics were actually any different in mild AD and healthy older adults. This was accomplished in experiment #2, which compared gait characteristics in mild AD and normal older adults. We also wanted to study whether gait patterns are comparable between the two groups on treadmill walking at constant velocity, to see if there were any diferential group effects on cadence. We also explored any modulatory effects that may relate to presence and severity of SH in both populations.

6.2 Experiment #2

Key findings of experiment #2 were that when sensitively measured on a computerized gait analysis mat, over-ground gait-velocity, stride-length, cadence and double-support time are significantly worse in mild AD patients. This sample of AD patients had a higher Unified Parkinson's Disease Rating Score compared to the NC group consistent with other reports indicating that motor impairment may accompany cognitive decline in early stages of AD[181-184]. None of the patients, however, were thought to have concomitant Parkinson's Disease. Rather we think that a structural assessment of the tone, bradykineasia, gait and balance even in mild AD does reveal subtle changes. After controlling for scores on this in the two groups, the differences in gait-velocity and stride-length persisted. We found that mild parkinsonism was present in a subset of patients with AD and in the NC sample as well. As the UPDRS was done in 33 patients and 30 NC only, the proportion of those with parkinsonism could not be accurately ascertained. The Canadian Study of Health and Aging found that parkinsonism

was present in up to 20% of those with dementia and in 7% with those with mild cognitive impairment.

Reports on detailed temporo-spatial parameters of gait in patients with mild AD are limited. Pettersson et al reported a gait velocity of 110±20 cm/sec in their sample of 6 patients with mild AD but compared to our sample they targeted a much younger age group (mean: 58±0.9 years)[135]. In the Goldman et al.[117] study using footswitch data in two stages of AD disease severity based on the CDR scale, very mild AD patients (CDR of 0.5, age: 72 years) were no different in gait velocity from age-matched NC, whereas those with dementia (CDR of 1.0, age:74 years) had a walking speed of 89±20cm/sec which was significantly slower than on those with very mild impairment (108±19 cm/sec) and normal controls (106±19cm/sec)[117]. Nakamura et al.[111] reported significant changes in velocity, stride-length and double-support in moderate and severe stage of AD, but not in their sample of mild stage of AD patients. This may have to do with the sensitivity of the apparatus they used to capture gait parameters. Studies that have attempted to study gait in mild AD using pragmatic scales such as the Tinetti balance and gait scale [110] or by clinical assessment of gait[118] have not found any evidence of gait slowing, which also appears also to be the case in this experiment as there were no differences observed on gait assessment scales between the AD and NC groups. Ceiling effects were seen on the Tinetti gait scale in both groups and therefore, clinically both groups did not differ on clinical gait scales. This may explain the clinical impression that gait is normal in early stage AD.

Some sensitive bed-side measures such as the TUG have shown evidence of subtle gait slowing[135] as in the current study, in which significantly longer times for the TUG were observed in our AD group. Moreover, subtle differences in gait became apparent on the more sensitive computerized gait-mat analysis, revealing that over-ground gait-velocity and cadence are reduced in mild stage of AD. The patients with mild AD also had reduced stride-length compared to NC, but were similar to NC on their stride-width. Gait velocity correlates strongly with stride-length and cadence. Hence the decrease in stride-length with a trend towards a longer double-support time in our AD sample may be indicative of generalized

gait-slowing rather than changes in spatial parameters. A recent report suggested that patients with amnestic-mild cognitive impairment (MCI), a preclinical state of AD, demonstrate significant decline in cadence[116]. These findings suggest that motor slowing may already be present in the early stages of AD before becoming clinically apparent as the disease progresses to the later stages[5, 34, 110, 111, 113-115].

In experiment #2 we also found that when a steady self-selected gait-velocity was enforced by participant's gait by on the treadmill, the two groups appeared similar in their cadence. The variability in stride-time and double-support time also appeared to be similar in the two groups under these circumstances. These findings suggest that the treadmill reduced the gait variability in the AD group possibly due to the constant belt-speed, which reduced the temporal degree of freedom and minimized variability in the temporal domain. It is also possible that the treadmill enforced attention to gait by serving as an external cue to maintain a constant step-timing. Of note was that we allowed a period of ten minutes prior to capturing gait parameters, to minimize any learning effects. However, cadence captured on the treadmill cannot be generalized to over-ground cadence even after 15 minutes of continuous walking in unimpaired elderly[24]. Time did not permit us to investigate within-group differences in gait parameters on and off the treadmill. However, the fact that the between-group differences in gait parameters are nullified when on the treadmill is noteworthy. Sensory cueing of gait, by repeated auditory or visual cues, has been shown to improve gait kinematics and decrease variability in patients with Parkinson's Disease and normal elderly[185, 186]. Treadmill may improve gait-stability in these patients by acting as an external pace-maker[185].

Cautious gait, described by Nutt et al.[16], is one that is characterized by mild gait slowing and shortening of stride length with minimal/no difference in the stride-width. However, this is based on clinical judgment and not on specific gait parameters. The term stems from what can be considered as an adaptation to avert falling while walking under conditions that could threaten steady balance[187], such as while walking on an icy pavement. This is also commonly observed in the gait of patients with arthritis or peripheral neuropathy. O'Keefe et al., who

characterized gait in three stages of AD, found that found that a cautious gait was present in 5/21 (24%) patients with a CDR of 1[114]. In our study, as a group, patients with mild AD had a shorter stride-length and a slower velocity. Cautious gait is not believed to be just consequence of normal aging. It is indicative of a fear of falling[187] and therefore, the reduction in stride-length and gait speed in our AD group, may suggest a possible relationship between gait and cognition. The prefrontal cortex, which mediates cognitive functions such as working memory, also plays a major role in the execution of gait control, and the deterioration in executive functions even in AD may also lead to subtle changes in gait control[188].

The reduction in temporal parameters and its variability, while walking at a fixed speed on the treadmill, further suggests that changes in gait in mild AD may be attributed primarily to temporal characteristics. We did not assess postural sway in our study sample, but postural sway measured over 1-minute of Romberg stance recorded by a gravicorder has been shown to be significantly greater in those with mild stage AD than age-matched controls, even when other gait characteristics appear similar. The authors of this study also reported that postural sway increased exponentially with increasing disease severity[111], similar to the report by O'Keefe and colleagues[114]. Therefore, another possible inference is that the over-ground parameters in this AD sample may reflect underlying mild disequilibrium, which corrects itself on the treadmill, when the safety harness provides more security on walking.

These findings may have several clinical implications. As stated above, observational studies do report that patients in the early stage of AD fall more frequently and have more serious injuries after falling compared to age-matched healthy population [106, 109]. In a group of community-dwelling older adults (age>75years) according to one study, a decrease in stride-length of 20 cm and of velocity of 20 cm/s, and an increase in double-support by 5.5%, doubled the likelihood of a pre-existing fall[162]. Our findings of subtle decrements in gait measures in mild AD (13cm decrease in stride-length and 21cm/sec decrease in velocity and 2.5% increase in double-support time) suggests that quantitative gait assessments used in routine clinical evaluation of gait in patients with AD early in the course of disease may help

identify those at risk for falls. This could lead to a rehabilitative measure to reduce risk. Second, there is a limited amount of data on use of treadmill in patients with AD. Treadmill for gait-retraining was studied a sample of 18 older adults (mean age:79 years) with higher-level gait disorders due to underlying cerebrovascular disease[189], but not in AD patients at risk for falls. Further studies focusing on fall risk stratification and appropriate outcome measures in a large sample of AD would be needed to show possible benefit of treadmill gait retraining. Our results suggest that treadmill walking with a safety harness may be well tolerated in early stage of AD. Hence, exercise and gait-retraining treadmill programs targeting mild stage AD might be worthwhile. Third, white matter hyperintensities on MRI have been associated with known cardiovascular risk factors and are commonly seen in older adults. These white matter changes have been associated with gait and balance impairment in normal elderly and specifically with gait-speed in elderly with gait impairment [71, 73]. In our study, the mean score on the ARWMC scale did not differ statistically between AD and NC groups, suggesting that underlying white matter disease, by itself, did not contribute critically to the differences in gait parameters between the two groups.

To summarize, experiment #2 found that patients with mild stage AD had significantly different over-ground gait parameters compared to demographically matched group of cognitively normal individuals at their preferred-pace, specifically demonstrating a slower gait-velocity, lower cadence and a shorter stride-length. It also found that when a steady preferred-velocity was enforced on a motorized treadmill, there were no statistically significant differences between the two groups. These findings suggest that subtle changes in gait appear in the early stage of AD and are detectable with sensitive gait analysis measures. Therefore, the incorporation of quantitative assessment of gait even in the early stages of AD may be warranted. This study also showed that patients with AD can tolerate walking on the treadmill and that except for the preferred belt speed their gait did not differ from cognitively normal individuals. However, this analysis did not explain whether the effect of gait slowing in the AD group was attributable to the presence of disease process or whether a secondary pathology such as small-vessel disease, also played a role in the relatively slower over-ground gait in AD patients. Therefore, experiment #3 was conducted that looked to compare gait characteristics in patients with mild AD and healthy elderly, factoring in cerebrovascular

disease, as judged by rating the burden of SH on MRI. To accomplish this based on the median cutoff score on the ARWMC rating scale, the AD and NC groups were subdivided into AD+ and NC+ (higher SH load) and AD- and NC- (lower SH load). Furthermore, experiment #3 explored the possible associations between regional distribution of SH, particularly the frontal and basal ganglia regions, and gait parameters.

6.3 Experiment #3

Key findings in experiment #3 were that within both study groups, healthy older adults and patients with mild AD, those with a higher SH scores had a slower gait velocity and a shorter stride-length than their counterparts with a lower SH scores on the ARWMC scale. There was a trend towards a wider step-width in those with greater SH load, but the differences did not attain statistical significance. Interestingly, post-hoc analysis revealed that gait velocity in normal controls with a lower SH burden differed significantly from both AD groups as well as from their normal counterparts with higher SH burden. In fact, the NC group with higher SH load were not significantly different from the two AD group in terms of their gait velocity. Within the AD group there was a trend towards a lower gait velocity and stride length but this did not attain statistical significance. These results showed that in this sample of healthy older adults and patients with AD, SH load had a greater impact on gait-velocity and stride-length in normal controls than on patients with mild AD. Substantial work has been done in the last few years on the association of gait and balance impairment with SH in community-dwelling elderly [69, 71-73, 84]. This study differs from these studies in that it targeted normal controls and patients with mild AD who had no gait complaints and even on objective gait scales such as the Tinettti both groups were comparable; however, the differences on the time to complete the TUG task do suggest some degree of slowing in the AD group. Within this sample of normal older adults with no gait complaints, these results suggest that those with more SH had significant decrements in gait velocity and stride-length and trends towards a wider step-width. We can conclude that SH may not only play a role in mobility impairment but that the associated subtle changes in gait parameters can be objectively detected by quantitative gait assessment devices.

According to previous studies, age-related changes in gait parameters include a decrease in gait velocity and stride-length whereas cadence remains essentially unchanged[19]. While there are numerous factors that contribute to these age-related changes in healthy older adults, the burden of SH may be another factor contributing to these changes as presence and severity of SH are also associated with aging. The differences in velocity and stride-length in this sample of healthy older adults persisted despite age adjustment, suggesting that the gait differences between the two NC groups may be related to SH in this sample. This could mean that in otherwise "normal" brain aging a higher SH load may compromise pathways associated with gait control and adversely interfere with spatial and temporal gait characteristics. In AD, by the time clinical symptoms of the disease are evident, the underlying pathology has already spread beyond the limbic and medial temporal cortices to involve the frontal and temporo-parietal cortices; hence, the SH-mediated interference with association pathways and cortical sub-cortical connectivity, which is already compromised by the AD process, may be of less clinical significance. Hence, within this sample of mild AD patients, gait parameters were not sufficiently different in the high-SH and low-SH AD groups, though this might emerge in a larger sample or with a larger range of SH burden.

Vascular parkinsonism gets its name from the neuropathological changes associated with a clinical picture including frontal lobe infarcts, basal ganglia infarcts, diffuse cerebral disease, multiple lacunar infarts and subcortical ischaemia[237]. The condition is also referred to as lower body parkinsonism since the symptoms and signs are predominantly in the legs. The gait is wide based, short paced with a slow velocity. The start and turn hesitation is even more common than in Parkinson's disease but can be clinically differentiated from PD. The trunk is upright, facies are preserved and arm swing is preserved. MRI of patients show periventricular hyperintensities and lacunar strokes. Bradykinesia, postural instability and gait difficulties are common. The Unified Parkinson's Disease Rating Scale [UPDRS] scores in the AD + group were higher than the AD- group. The score distribution reflected mild bradykinesia possibly attributable to lower-body parkinsonism or vascular parkinsonism described in relation to cerebrovascular disease in the basal ganglia[204]. This AD+ group had a

mean total SH score of 14 and showed the slowest gait and shortest stride-length amongst the four groups. However, the differences in these gait parameters attained statistical significance only in comparison to the NC- group. Gait-velocity and stride-length in NC+ group were comparable to the two AD groups, despite differences in the UPDRS scores, implying that SH may be affecting gait through another mechanism. Amongst the three groups with almost similar UPDRS scores (NC-, AD- and NC+, UPDRS score range:1-3), the NC- group significantly differed from the NC+ as well as AD- group, providing further evidence that the gait differences between healthy older adults and patients with mild AD are not just related to bradykinesia (accounted for on the UPDRS score). These results are similar to that of Goldman et al [117] who after carefully excluding those with significant parkinsonism in their sample of mild AD patients, demonstrated that gait velocity was significantly slower than in healthy older adults.

Experiment #3 also found that SH load in the frontal and basal ganglia regions correlated with stride-length in AD and gait-velocity in healthy older adults. Statistically significant correlations also emerged between basal ganglia SH load and step-width in healthy older adults. Therefore, the statistically significant correlations between SH load in frontal and basal-ganglia regions and velocity and stride-length in AD and healthy older adults suggests that vascular pathology in these regions may play an important role in the dynamic stability of gait. Activation of frontal and striate regions are associated with mental imagery of walking on near-infrared spectroscopic topography and with the uptake of contrast while walking prior to Single Photon Emission Computerized Tomography (SPECT)[7, 12, 13]. Studies have also correlated gait impairment in AD and Parkinson's Disease with impaired cerebral blood flow in the frontal regions on SPECT[111, 205]. SH are associated with decreased metabolism in the frontal regions involving both normal and cognitively impaired individuals[192-194]. This observation could explain our findings that a decrement in gait velocity and stride-length are associated with the burden of SH in these regions. One other study has reported that elderly with gait impairment had higher burden of SH in frontal regions compared to those without gait impairment [72]. Benson et al. [71] found that in their cohort of elderly participants over 70 years with a MMSE > 24 the presence of SH in frontal regions had a sensitivity ranging from 79 to 93% for identifying mobility impairment. Of

note is that in the current study, SH scores in frontal and basal ganglia region correlated with gait speed and stride-length in the NC and AD group respectively suggesting that these brain regions are involved in gait control.

In the previous experiments, this study showed that working memory affects gait parameters in young and old adults, that gait is slower in mild AD patients and that normal elderly with higher SH load are indistinguishable from patients with AD. In the final experiment#4, a main objective of this thesis was to study the costs of dual tasking on gait and working memory performance in mild AD patients compared to healthy elderly, and to evaluate whether the presence of a higher SH load negatively affected these costs of dual tasking.

6.4 Experiment #4

Experiment #4, thus, investigated the effect of performing three working memory tasks of varying complexity on cadence (steps/minute) constrained by a constant velocity on a motorized treadmill in a subset of the two groups, patients with mild AD and healthy older adults who participated in experiment #2 and #3. The effect of increasing SH load on costs of dual tasking was also assessed in these two groups by sub-grouping them into them on the burden of SH, using the median cut-off score for each group. To the best of our knowledge, this is the first study that looked at costs of dual-tasking in relation to the burden of small vessel disease in mild stage AD.

The results in experiment #4 showed that the NC group manifested an increase in dual task costs on cadence compared to the AD group on all three working memory tasks, indicating that the NC group increased their cadence to maintain their stability while dual-tasking. When AD and NC groups were divided based on their SH load and the dual tasks costs were compared in these four groups, only the AD+ group, i.e., those with higher proportion of SH,

demonstrated negative dual task costs on cadence (i.e., a decrease in cadence). The increase in cadence in NC+, NC- and AD- groups can be considered as a safe compensatory mechanism to maintain dynamic stability during dual-tasking and a decrease in cadence suggests that the AD+ group were unable to mount this compensatory strategy and in fact decreased their cadence. This suggests that the addition of significant SH load in AD, may interfere with the adaptive responses of the body to maintain dynamic stability. A possible explanation for why a decrease in cadence while dual tasking can be considered a maladaptive response is as follows. Previous literature consistently shows that gait velocity decreases in order to maintain stability while dual-tasking in older adults and in patients with AD. However, on a treadmill at fixed speed, when compensations in gait velocity to maintain dynamic stability is not an option, the system is constrained to maintain stability by either increasing double-support time, decreasing stride-length or increasing the step-width. Increase in double-support and decrease in stride length are considered to be compensatory mechanisms to improve stability in aging [19]. Assuming gait symmetry at all times, the relationship between gait velocity, stride-length and cadence can be captured by the following formula:

Gait velocity= stride-length x Cadence/120. [221]

As gait velocity was unchanged while on the treadmill through the experimental conditions, an increase in cadence at a constant velocity would mean a decrease in stride-length. A decrease in stride-length enables more time spent with both feet on the ground (double-support time) and therefore improves stability. This would be a compensatory mechanism to improve stability of gait such as one experiences while trying to maintain a constant velocity while maneuvering an icy patch of pavement. For some reason, this adaptation, presumably relying on prefrontal cortices, was not available to AD subjects with higher SH burden, suggesting that the presence of higher amount of small vessel disease could be implicated.

On the cognitive performance measured by speed-accuracy tradeoff (SAT), an aggregate measure of performance on the working memory tasks, the AD group performed more poorly on all three working memory tasks compared to the NC. When study groups were assessed based on their SH load, there was a considerable overlap in the performance of AD patients

with high and lower SH burden suggesting that the presence of increased SH load did not worsen the performance on the three working memory tasks in both conditions in AD, perhaps because AD itself produced a floor effect. However, in the NC group there was a considerable divergence in the performance between those with higher and lower SH load especially in the walking conditions suggesting that SH may interfere with cognitive performance under more challenging conditions. The effect of walking on costs of performance on SAT, however, showed no significant difference between AD and NC groups as a whole nor were there any significant differences between the four groups subdivided on their SH scores. Differences between AD+ and NC- did nevertheless show trends towards significance on the more complex tasks (2-back) suggesting that significant differences may emerge in a larger sample. These results suggest that within the group of NC, those with higher SH load tend to show a deterioration of performance under dual tasks conditions as depicted in Figure 2b. Both the AD+ and NC+ groups show a negative dual task costs on SAT but these differences were not significant, suggesting that significant degree of SH diminished the performance level to approach that of AD subjects.

These results at least two important clinical features of SH pertinent to the objectives of this study. Firstly, in healthy elderly, the presence of higher SH burden may adversely affect cognitive performance under single-task conditions but not necessarily under dual-task conditions. Furthermore, the healthy elderly with higher SH load demonstrated a cognitive performance similar to both the AD group with and without higher SH load. This suggests that the presence of a high SH burden interferes with working memory performance in healthy elderly. In the AD group, the subgroup with higher SH load had a considerable overlap in performance with those with the lower SH scores, suggesting that SH may not interfere as significantly with processing-speed in AD patients whose performance is directly affected by AD. One possible explanation for this could be that by the time AD is clinically apparent, the distribution of disease pathology, neurofibrillary tangles and plaques, has spread outside the association cortices in the bein medial temporo-parietal areas and enterorhinal cortex to involve the frontal – subcortical and subcortical areas [225], The presence of SH may not additionally interfere with the connectivity of the fronto-parietal or fronto-subcortical network, as it may be already disrupted by the Alzheimer pathology.

Performance of a verbal working memory task and gait rely on common neuronal substrates specifically in the dorsolateral prefrontal cortex, the corpus striatum and parietal cortex and therefore performance of these two tasks simultaneously could have a biological basis for the task interference[7, 14, 158, 226]. The dorsolateral prefrontal cortex plays an important role in the maintenance and manipulation of information in the working memory[227]. The dorsolateral prefrontal cortex also plays a role in adapting gait to environmental conditions through its connections with the supplementary motor areas and basal ganglia[14]. The simultaneous performance of these functions could potentially interfere with patient's ability to execute safe adaptive responses as areas such as the dorsolateral prefrontal cortex may have a double hit, from the disease process of AD as well as the interference in connectivity by SH in these regions. In healthy elderly, the connectivity between cortical areas involved in working memory and gait performance under dual task conditions may be interrupted by the presence of SH alone and this may explain the lack of significant differences between NC+ and the two AD groups on the cognitive performance. Therefore, results of this study suggest that SH burden may play a more important role in processing-speed in healthy cognitively intact adults consistent with other reports[89, 228-231].

Secondly, dual-tasking effects on gait are more pronounced in the subgroup of AD patients with higher SH load, compared to those with lower SH. AD+ patients showed a drop in cadence compared to the other three groups suggesting that higher SH load adversely affects compensatory adaptations in AD patients who are walking while dual tasking. Gait in AD, especially under dual-task conditions, relies upon executive functions and the association between executive functions and gait increases with increasing complexity of the dual-task [34, 108, 232]. Executive function impairment is common to AD in the early stages of the disease[95, 233, 234]. The areas of the brain that govern executive functions such as the prefrontal and parietal lobes also are the same ones involved in coordination and synchronization of gait[12, 14]. The concomitant performance of the functions supported by these neurons may overtax the systems responsible for the performance of the required tasks, and in the presence of structural brain damage caused by cerebrovascular disease, the dual-task capability may be more attenuated. It appears from our data that the AD participants with higher SH load were

maladaptive, adopting a decrease in cadence with dual-tasking, implying poor executive control on planning and modulating gait.

This study made use of the treadmill instead of testing participants on over-ground walking for mainly two reasons. Our pilot studies that characterized changes in gait parameters in mild AD patients during a working memory task on the GaitRite mat showed that some AD patients reduced their speed considerably and others stopped walking completely while dual-tasking, This did not help understanding dual-task costs on gait, other than to imply that there was an obvious cost. If reduction in gait speed to improve dynamic stability is an effective strategy to prevent falls this does not explain why a decrease in gait speed is a marker for increased risk of falls [162]. It was hypothesized that maintaining a constant speed on the treadmill, would therefore, prevent this adaptation. By maintaining a steady velocity, other gait stabilizing responses such as increasing double-support time and step-width would be utilized. It was expected that this would be at a cost manifest as deterioration in the performance on working memory parameters- accuracy and reaction time. In addition, collecting gait parameters on a short duration traverse (approx. 7 to 10 seconds) on an automated walkway, and summarizing multiple traverses on that walkway would not be the same as performing a longer trial to obtain reaction time data. Smaller traverses allow less opportunity to correct responses, so that allowing the cognitive task to be performed over a longer period should be more interpretable.

The advantages of the complex dual-task methodology used in this study compared to ones used in other studies are as follows. The computerized working memory paradigm allowed us to capture accuracy responses as well as reaction time, and therefore, processing speed and speed accuracy tradeoffs. Working memory is an executive function task whose neuronal substrates overlap with that of gait as mentioned above. The use of non-verbal approach to assess working memory eliminated the direct influence of speech production on gait and also allows future use in testing patients with speech impairments such as in stroke or primary progressive aphasia. Furthermore, working memory parameters can be manipulated in the experimental design to increase or decrease the cognitive load of the working memory task

using objectively quantifiable measures such as the inter-stimulus interval and display duration of each stimulus.

The results of this study extend existing knowledge of the interactions between gait and executive function by suggesting that SH can adversely affect dual tasking costs on gait in patients with AD and on working memory performance while walking in NC. Prospective studies looking at fall occurrence and its relationship with the adaptive changes in gait while dual-tasking may help understand whether these changes affect stability in the long run. This study also helps to understand the behavioral correlates of SH including gait as a cognitive frontally-controlled task. The results suggested a clear relationship between SH load and processing speed and stepping frequency in healthy older adults and patients with AD. Nevertheless, a closer look at the volume of lesions and their specific locations using automated methods on larger samples may further elucidate interesting relationships between lesion-load and location, and gait as well as dual task capacities.

6.5 Summary

In summary, this work advances current knowledge on the interfering of spatial-attention and working memory tasks on gait performance in healthy adults. It adds new data to demonstrate that over-ground cadence, velocity and stride-length in patients with mild AD is less than that of cognitively normal healthy, but that when a steady velocity is enforced their gait characteristics comparable to those of healthy elderly. Presence of a higher SH burden negatively influences gait in healthy elderly making their gait characteristics no different from that of patients with AD. Working memory also interferes with gait even when a steady velocity is enforced on a treadmill in healthy elderly and patients with mild AD but patients with AD show maladaptive responses. When those with higher SH burden are compared to those with lower SH burden, only the subgroup of AD patients with higher SH show maladaptive responses to dual tasking in the velocity-constrained environment. Presence of

SH in healthy elderly affects their performance on working memory tasks but not on the costs of dual tasking.

Chapter 7

7 Limitations

There are certain general limitations to this thesis and a few specific ones pertaining to each experiment as discussed below. Common to all experiments, was that the differences could be better explained had we had larger sample sizes. Diagnosis of AD was made by two experienced clinicians using clinical data including history, physical exam, functional, mental status examination, neuropsychological and detailed neuroimaging investigations, which were used in conjunction with established diagnostic criteria for AD. However, the gold standard for the diagnosis of AD is on histopathology only and hence a confirmatory diagnosis of AD cannot be made in those with AD in this study. The capture of gait signals using footswitches was cumbersome and on two occasions participants were requested to return for collection of some of the data as footswitch signal were not interpretable. Patients with Lewy body dementia have a higher rate of multiple falls than patients with AD[105]. Albeit the presentation of patients with LBD is characteristically different from AD, overlapping pathologies can complicate the phenotype and clinical progression. Even though clinical diagnosis of AD was performed by experienced behavioral neurologist and clinicians, the presence of coexisting LBD pathology cannot be ruled out.

Experiment specific limitations are as follows. In experiment#1, which sought to explore changes in gait with concurrent performance of spatial attention and working memory tasks, the advantage of using an automated walkway to enable accurate and easy capture of gait parameters was compromised by the relatively short length of the walkway (12 feet). The experiment therefore did not allow for the capture of continuous gait parameters beyond the duration required to complete a single traverse. To mitigate this drawback we averaged gait parameters over 5 traverses for each condition. Secondly, there was a significant main effect of dual-task condition on gait parameters in the two groups but the effect sizes (denoted by partial eta squared values (η_P^2)) for the main effects were small (in range of 0.1 to 0.2). The small effect size indicates that the changes in gait parameters using these concomitant tasks would likely be too subtle to be noticed by the naked eye and was only picked up on sensitive

automated gait assessment systems used in this study. Effect sizes are not usually reported in dual-task gait studies in healthy individuals and comparisons with those targeting gait-impaired populations cannot be made.

Fractals represent information contained in a unit of a larger continuous recording of data obtained temporally from an irregularly and rhythmically occurring source such as heart beats, breathing patterns and gait parameters. Fractal scaling analytical techniques have found that these measures could be better predictors of falling as well as disability than the predictive value of gait variability[185]. In experiment #2, which compared over-ground and treadmill gait parameters in mild AD and healthy older adults, had similar limitations of short length of walkway. Particularly, the fractal property of gait could not be accounted for by this study design which means that fluctuations in stride-length and stride-time at any given time are statistically related to several strides prior in the sequence[190]. Secondly, while measuring gait parameters on the treadmill, we used a body-weighted support system as a safety-harness ensuring that the system worked without unloading any body-weight. Though the safety harness was not restrictive in anyway, the fact that it may have averted alterations in body sway and other characteristics that influence gait parameters on the treadmill, cannot be denied but not doing so would mean inflicting a risk of fall in out older adult participant.

In experiment #3, there are several limitations that have to be taken into consideration. Firstly, the sample represented had reasonable range of severity of SH on the ARWMC scale but the mean SH scores of 6 in the healthy older adults and 9 in the AD groups were the mild to moderate range of severity given that the maximum total score on the ARWMC is 30. This is likely because overt strokes or cortical infarcts were exclusionary, likely reducing the upper range of severity of vascular brain disease. Only one participant scored above 20 on the scale related to extensive, incidental periventricular white matter disease. It should be noted that participants were not chosen based on their SH burden; hence, this sample is likely to represent target populations where incidental SH are seen on MRI in 95% of normal elderly and up to 100% of patients with dementia on MRI [206-208]. Secondly, we used a visual rating scale to assess the burden of SH rather than quantitative volumetric measurements of

SH, which is technically more demanding and time consuming, but provide a more accurate volumetric measure of SH burden. However, the rating scales used in this study is well validated and reliable and rating scales of SH burden have been found to correlate well with quantitative volumetric measurement[209]. Thirdly, a larger sample could better delineate differences in gait between patients with mild AD who had higher proportion of SH compared to those with a lower proportion of SH.

In experiment #4, the subdivision of groups in to those with higher and lower SH burden lead to smaller groups and comparisons between groups, especially the NC+ (n=7), can be viewed as insufficient to ascertain real effects of SH on dual tasking costs. However, we were able to detect a signal even with this small sample suggesting that larger studies with similar protocols are warranted. Secondly, the SH burden was rated on a visual rating scale and not quantified using automated methods and are generally less sensitive in detecting small differences between groups[235]. Nevertheless, we used a well-validated rating scale (ARWMC scale[177]) which has a larger range of scores than some of the other scales such as the Fazekas scale [47] and is found to be satisfactory in differentiating groups [220, 235]. The use of rating scales and SH rating as a binary variable using the median of the distribution as a cutoff for the group has been utilized in other studies of cognitive impairment [236]. The use of automated SH quantification may have minimized the large overlap in confidence intervals especially within the NC group. Finally, while dual-tasking on the treadmill may not be considered as a "real-world" setting, it does help to underscore the relationship between cognition and involuntary gait changes in a velocity constrained environment.

Chapter 8

8 Future Directions:

These experiments bear interesting results in the laboratory setting in selected population of patients with mild AD and healthy elderly. A bench-to-bedside application of these findings would be one future direction to explore association between outcome variables in this thesis such as gait parameters, dual task costs, SH distribution and other clinical variables known to affect quality of life in AD such as occurrence of falls, loss of functional abilities, use of gait assistive devices, behavioral and cognitive decline, stroke, etc. Our lab has collected data on falls in this sample upon their completion of this study protocol. It would be a question worthy of exploration whether changes in gait on dual-tasking can predict occurrence of future falls. Some studies have found that certain gait parameters including variability in gait during dual tasking can differentiate fallers from non-fallers [238, 239] [147]. Beauchet et al. found that in a sample of 187 older adults living in a senior community, slowing of gait while concurrently counting backwards did not predict occurrence of first fall[240] but an faster backward count while walking compared to single-task counting was significantly associated with falls[241]. However, they found that a reduced speed in both single and dual task conditions (walking and counting backwards) was associated with recurrent falls (>2 falls)[242], which is not surprising as reduced gait speed is a predictor of falls in community dwelling elderly as well as nursing home dwelling populations[162, 243]. There are no studies that have looked at the association between gait changes under constant velocity during dual tasking and occurrence of falls in real world situations where certain older adults may be compelled to maintain a fast velocity even while multitasking.

In this thesis, the characterization of SH on MRI was done using visual rating scales such as the ARWMC scale. It would be important to obtain quantification of SH on MRI and utilize this data on lesion volumetry to better explain the findings in this study such as associations between regional volume distribute of SH and gait changes, cognitive performance, dual-task costs on gait and working memory performance.

One of our findings was that elderly with higher SH burden subtle changes in gait compared to their counterparts with lesser SH load. Longitudinal follow up of quantitative gait analysis and cognitive changes in this population of healthy adults with higher SH load may help to understand why gait changes predict cognitive decline in older adults with dementia[244, 245].

We also found that patients with mild AD have a slower gait than healthy older adults with less SH burden. Assessing gait and dual tasking costs in relation with cognitive changes in mild cognitive impairment, a preclinical phase that can progress to AD, may help to identify those patients who develop AD.

A recent report suggested that galantamine, one of the three approved cholinesterase inhibitors for the treatment of AD, not only has benefits on cognitive and behavioural decline in AD but also walking performance under dual task conditions[197]. As all our patients were on stable dose of one of the three cholinesterase inhibitors there may be differential effect of these drugs on walking ability, working memory performance and dual task costs, which would be another line worthy of investigation.

We have shown that executive function task, such as working memory, had a greater effect on inducing gait changes compared to spatial attention tasks as reported in experiment #1. Not reported in this thesis is the analysis of data collected in a subset of these participants on dual tasking on the treadmill when involved in more complex executive function tasks. We collected dual tasking cognitive and walking data on the treadmill when participants were engaged in performing 2-back task with shorter ISI and stimulus display interval. Also, data was collected in a subset while engaged in performing Luria motor sequences to ascertain the effect of such a motor executive function task on walking. Analysis and interpretation of this data will be one of the immediate next steps.

We also captured digitized video recordings of step width while single and dual tasking on the treadmill, which will require interpretation and analysis. Changes in step-width while dual tasking will help understand changes in lateral stability of gait while dual tasking and is another analysis that is worthy of future study. .

Results of experiment #2 also showed that patients with mild AD can adapt to the using a treadmill with little training and tolerate the use of treadmill even without prior experience on it. Therefore, regular walking on the treadmill can be encouraged in this population as results of a recent study showed that moderate exercise in people with memory complaints had a significant effect in delaying cognitive decline in these people[246]. Treadmill walking may help in understanding dual-task changes, gait variability, and at the same time provides means of assessing gait in loading and unloading of weight with appropriate use of harness.

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Appendices

8.1 Appendix 1: Case report form

THE DUAL-TASKING GAIT STUDY

Case Report Form

DEMOGRAPHY:

- Participant's Initials:
  _____

- Date of Birth (dd/mm/yy): _____/_____/_____

- Age: _____

- Sex: Male □ Female □

- Date of Consent (dd/mm/yy): _____

- Participant Database ID#: _____

- Gaitrite ID#: _____

- GAIT STUDY Date (dd/mm/yy): _____/_____/_____

INCLUSION CRITERIA

	YES	NO
Is the participant between 55 and 85 years of age?	□	□
Is the participant enrolled in the CIHR study?	□	□
Can the participant walk independently for at least 15 minutes?	□	□
Has the participant had an MRI in the last six months?	□	□
If 'NO', is a MRI scheduled in the next six months?	□	□
If the participant is a patient, does he/she meet NINDS criteria for AD?	□	□
If the participant is a patient with AD, is his/her MMSE ≥ 21	□	□
If the participant is a patient with AD, is his/her DRS ≥ 100	□	□

EXCLUSION CRITERIA

Does the participant have any neurological disorder affecting his/her gait?	□	□
Does the participant have any significant visual problems?	□	□
Does the participant have any significant hearing impairment?	□	□
Have you ever been diagnosed with dyslexia/reading impairment?	□	□
Does the participant have history of the following:		
1. Hip fractures in the last year	□	□
2. Hip/knee replacements in the last year	□	□

3. Congestive heart failure, active coronary artery disease	□	□
4. Severe peripheral arterial disease	□	□
5. Significant arthritis	□	□
6. Joint deformity	□	□
7. Sedative medication use, psychostimulants	□	□
8. Alcohol dependence	□	□

Is the participant able to perform the working memory tasks (≥70% accuracy) □ □

HISTORY:

1. Has the participant had any falls to the ground in the last one year?: YES □ NO □

(Fall is considered to have occurred when the person had inadvertently come to rest on the ground OR a lower level that is not caused by loss of consciousness)

If yes, please specify:

- number of falls to the ground in the past 12 months _____
- place of occurrence _____
- approximate dates of the falls (mm/yy)_____
- approximate time of falls_____
- duration of lie on the ground or lower level in minutes_____
- Was assistance required to regain posture, if so, how_____
- the extent of injury associated with the fall/s _____
- circumstances that led to the fall/s (e.g. loss of consciousness, dizziness, tripping, ice, etc.) _____

2. Does the participant have any past history of extremity or vertebral fractures?YES□ NO□

If yes, please specify: _____

3. Does the participant have any of the following conditions?: **If yes, please specify**:

i. upper or lower gastrointestinal dysfunction: YES □ NO □ _____
ii. endocrine dysfunction: YES □ NO □ _____
iii. musculoskeletal dysfunction: YES □ NO □ _____
iv. ischemic heart disease/myocardial infarction: YES □ NO □_____
v. hypertension, hyperlipidemia, stroke:YES □ NO □ _____
vi. psychiatric condition including depression:YES □ NO □_____
vii. urinary incontinence: YES □ NO □ _____
viii. claudication / rest pain: YES □ NO □ _____

ix. remote history of head trauma: YES □ NO □

4. Does the participant exercise regularly? YES □ NO □

Details including frequency: _____

Have you been on a treadmill before?_____

5. Does the participant have any fear of falling (Please ask,

"Are you afraid of falling?" Any response that is affirmative

is considered "fearful") YES □ NO □

6. Has the participant been on any medications including herbals, OTC, alternative methods:YES □ NO □

If yes, please specify name and date of onset:	start date	end date	(dd/mmm/yyyy)
1._____	__/___/__	__/___/_	
2._____	__/___/___	__/___/_	
3._____	__/___/___	__/___/_	
4._____	__/___/___	__/___/_	
5._____	__/___/___	__/___/_	
6. _____	__/___/___	__/___/_	
7. _____	__/___/___	__/___/_	

7. Please note any other significant past medical history: _____

PHYSICAL EXAMINATION:

1. Height (ft' in"): _____
2. Weight (lb): _____
3. Body Mass Index: _____
4. Waist circumference: _____cm
5. (i) Leg Length Measurement (ASIS-med. malleolus) R:_____ L :_____

   (ii) Leg circumference (mid-calf): R: _____ L:_____
6. Visual Acuity: R: _____ L: _____
7. Hearing : R: _____ L: _____
8. Timed one-leg stand (sec): R:_____ L:_____
9. **Blood pressure (after sitting for at least 5 minutes):** _____mm HG
10. **Heart rate (resting)**: _____

Neurological examination (lower extremities):

Motor Examination: Bulk: _____

Tone: (Right leg) _____ (Left leg) _____

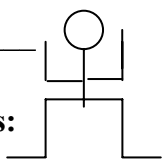
Strength	i/psoas	abd	Add	quad	ham	d-flex	p-flex	Toe ext
Right								
Left								

Abnormal Movements: Tremor _____ Myoclonus _____ Other

Sensory Examination: Vibration _____ Position _____

Co-ordination: Finger nose: R ____ L ____ Heel shin: R ____ L ____

Rapid alternating movements: R _____ L _____ **Reflexes:**



Stance and Stability (on pullback): _____

Tandem: _____Romberg: _____Plantar Response:_____

SPECIAL TESTS:

1. **MMSE** Score (most recent score): _____

   Date of MMSE (dd/mm/yy): _____/_____/_____
2. Timed-Up-and-Go test (**TUG**) (secs): _____
3. **UPDRS** Score: Motor subscore:_____
4. **Tinetti** Assessment Tool: **Gait** score :____/12 Balance Score:___/16

   TOTAL:___/28
5. **Overground speed (captured on Gaitrite):**
   - Traverse #1: _____
   - Traverse #2: _____
   - Traverse #3: _____
   - Traverse #4: _____
   - **Mean velocity on Gatirite**: _____
6. **Treadmill velocity**: _____ (adjusted to participant comfort)
7. **Camera calibration** (distance between heels while standing and camera lens): ____ cms
8. **Luria motor sequences:**
   - **Single task: _____ errors in _____ sequences**
   - **Dual-task: _____errors in _____sequences**

Time: _____seconds

Procedure log:

Time	**Event**	**File name**	**comment**	**ACTION**

8.2 Appendix 2: Procedural record: dual-tasking gait study

[I] GAIT LAB SET- UP (performed one hour prior to participant's scheduled arrival):

1 □. Ensure the following **equipment** is available and working efficiently

- i □. Cart with laptop for displaying the stimuli
- ii □. Gait-Rite mat and its assigned Gait-rite laptop (if not in gait lab, check in A455)
- iii □. Main computer (desktop) for data collection
- iv □. Footswitches for right and left foot (located in the blue translucent box on the top shelf in Gait lab).
- v □. Hand held button (located on the shelf near the main computer monitor).
- vi □. Digital video camera (located in cabinet in A455, key in Valerie's desk drawer)
- vii □. Mini-DV tapes for the video camera
- viii □. LCD projector (located in cabinet in A455, key in Valerie's desk drawer).
- ix □. Treadmill with safety harness.
- x □. Stopwatch for TUG (hanging on the shelves in the gait lab).

2 □. **Sanitize** the footswitches and hand held button with disinfectant wipes

3 □. Perform the following **connections**:

a □. Connections to the power box, interface box and cart laptop:

- i □. Look for the power box (bluish grey box located on the shelf next to main computer monitor) that supplies the interface box: Connect the red (+ve) and black (-ve) wires, which are in turn connected to the interface box via grey and black wires, to the respective inputs on the power box by threading the wires

through the hole in the input sockets and screw the knobs clockwise over them to secure the connection.

ii □. Connect the right and left footswitches (marked W-5) to correspondingly marked inputs located on the on the open end of the grey wire.

iii □. Track the wire from port#12 of the interface box and connect this cord marked 'AP ACCEL' to the back of cart laptop at the DAC0 port. To do this, unscrew the cord marked DAO that is usually connected to the multiple DAC0 connections on the cart laptop and connect the cord marked AP ACCEL that you tracked from the interface box.

iv □. Ensure that the hand-held button is connected to the black and white cylindrical box that connects to the interface box at location 15 and +5 volt slot.

v □. Turn the main power supply on (on left side of the wall as you enter the gait lab).

b □. **Connect the Gait rite** to the computer:

i □. Unroll the Gait-rite mat across the wooden platform.

ii □. Track the grey wire that comes out of the sensor on the right-side end of Gait rite and connect it to the assigned Gait-rite laptop via a USB connection.

c □. **Connect the LCD** projector:

i □. Position the projector to adequately display the stimuli on the wall in front of the treadmill

ii □. Connect the projector to the cart laptop that displays the stimuli.

4 □. Perform the following steps to **start the system**:

a □. Switch on the bluish-grey coloured **power box**.

b □. Start the **main computer**

i □. Login: 'administrator'. Password: 'winnt'

ii □. Open 'main_collection' program on desktop

iii □. Exit the screen that appears initially by clicking on the 'run continuously' button

iv □. You will see a screen titled ‘File directory for data storage’. Under ‘Look in’ select the folder where data will be saved. To do this, go to D:\data\neelesh and create a new folder for the participant using the following format: LastnameFirstinitial_ddmmmyyyy and hit enter. Open this folder that you just created. Ensuring that this folder is open, click on ‘Select Cur Dir’ button that appears below the ‘Open’ and ‘Cancel’ buttons. The ‘File directory for data storage’ screen will disappear.

v □. On the ‘selecting AD channels’ screen, ensure that the red buttons adjacent to the ‘AD in’ channels are turned on (green) for the following: #8 (L foot), #9 (R foot), #12 (DAC0 from cart laptop) and #15 (Trigger from RT button).

vi □. Highlight the number in the ‘Time(s)’ column and enter “70” to set it to 70 seconds. Ensure that the sampling frequency (‘Rate(Hz)’) is set to 500 Hz and the ‘Starting trial#” is set to 1. Double-click ‘Press Ok when done’. This will bring you back to the first screen that appeared when you started the ‘main_collection’ program.

c □. Turn on the **Gait-rite assigned laptop**:

i □. Open ‘control GAITrite’

ii □. User-ID: ‘student’

iii □. Create a new profile for the participant by clicking ‘New Patient’ and entering the particulars (name, DOB, age, gender). Click ‘Save’.

d □. Turn on the **cart laptop** assigned to display stimuli

i □. Password: “richard0”

ii □. Create a new folder for the participant in the following location - C:\Data\neelesh. Use the following format: ddmmyyyy_[CIHR ID#].

iii □. Open ‘vWM_neelesh’ on desktop

iv □. Click the white arrow to reach the C::\Data\neelesh folder that contains the letter files for the stimuli

v □. Open the vWM_neelesh screen and select the appropriate stimulus file from the 'letter_files'. Click 'OK' to exit the screen

vi □. Minimize screen

e □. **Video camera set-up**

i □. Set up the camera with the tape behind the treadmill on top of the blue box

ii □. Measure the distance from midway of the treadmill to the front of camera and record on the video.

5 □. Test drive the whole system

a □. On the cart laptop:

i □. Scroll up to enter the information on the display screen:

1. Subject identifier: [CIHR ID #]
2. Task identifier: control/1b/2b
3. Trial identifier: 1/2/3
4. Duration of the trial: 60sec
5. Display duration (ms): ensure it is set at 2000ms
6. Gap duration (ms): ensure it is set at 1500ms

ii □. Scroll down enough so that only the centre green button and the manual trigger buttons are seen.

b □. On the main computer click 'Manual trigger'

c □. ASAP, on the cart laptop, click the manual trigger button to start the trial. This will run for the duration of the trial with the parameters as set above

d □. Once complete, the green button will appear on the cart laptop. On the main computer, the screen will change to show the four channels: top-most channel displays the responses captured by pressing the hand held button, the next channel displays waves each representing one stimulus, the following two display the footswitch capture.

e □. On the main computer, enter the 'post trial comment' the following format: CIHRID#_ddmmyyyy_condition(sitting/standing/dualtask)_task(control/1back/2back)_trial (1-5). Click the pink button 'Accept comment'. This pink button and the comment will disappear leaving the 'Manual trigger' ready for the second trial. You will also see that the 'Waiting to collect#' has changed to the successive number

f □. Repeat steps 5a to 5e ensuring the identifying details are appropriately changed and the tasks and trials are run in succession.

6 □. **Set up for baseline measurements**:

a □. Open the CRF on the laptop or obtain a copy for recording information

b □. For TUG: Place a standard arm chair on one end of the platform at the '3m' mark and look for the black tape marked at a distance of 3m (~10 feet) from the edge of the chair.

c □. Obtain a Tinnetti Assessment tool with gait and balance score sheets

d □. Obtain a UPDRS

e □. Obtain the Hachinski Ischemic Scale

[II] EXPERIMENT PROCEDURES (timed upon participant's arrival):

Time 0 to 10 minutes: Consent forms

1 □. **Greet** participant and **thank** him/her for their role and escort them to gait lab. Briefly go through the protocol and answer questions if any. Obtain **informed consent** and ensure that consent forms are signed and dated. Ensure that **page #1 and #2** of the CRF is completed.

2 □. Time 10 to 25 minutes: Baseline measures

3 □. **Perform the baseline measures** and record on **page#3** of CRF

a □. Height, weight and BMI

b □. Waist circumference at level of umbilicus

c □. Right and left Leg length: distance from anterior superior iliac spine to medial malleolus

d □. Right and left Mid-calf circumference: circumference at the mid leg-level.

e □. Record heart rate, BP, and test for hearing and visual acuity

f □. Record brief neuro exam

4 □. Perform and record on **page #4** of CRF

a □. Record most recent **MMSE** score

b □. Record Timed-up and Go Test: (see instructions for performing the **TUG**).

i □. Inform participant of sequence and outcome: *"When I say go, you are requested to stand up from the chair, walk to the mark on the floor, turn around, walk back to the chair and sit down. I will be timing you using the stopwatch. Are you ready?"*

ii □. Participant starts with their back against the chair, their arms resting on the arm rests.

iii □. Use a cue: *"Ready, set, go"*.

c □. Record **UPDRS**

d □. **Tinetti** Assessment tool: Record gait score and balance score (see instructions)

e □. Record **Hachinski Ischemic Score**

5 □. **Record regular paced gait parameters**:

a □. Ask the participant to stand on **one end of the GaitRite**.

b □. Speak clearly and slowly: indicating the intension and sequence of subsequent events to the participant. *"Now I will ask you to start walking looking straight across at a central point on the opposite wall. Keep walking on the mat until you reach the other side. Walk at your normal pace as though you are out on a stroll. Once you have crossed the other end of the mat, please do not walk back, instead I will ask you to keep standing until I instruct you to begin walking."*

c □. Clinck 'New test' under the respective participant name

d □. On the screen click 'start walk'. The computer will initialize and within a few seconds, a message 'begin walking' will appear.

e □. Only when this message appears, instruct the participant *"Begin walking"*.

f □. Once the participant is on the other side, the computer will automatically process the footsteps for that traverse. If it does not process automatically, click 'Done' for manual processing.

g □. Click 'Save'.

h □. **Record the velocity** (cm/sec) for **each** of the traverse.

i □. Record parameters for at least three traverses across the walkway.

j □. Make a note of the **average velocity** across the three traverses. **Convert it to km/hour** for adjusting it on the treadmill (multiply cm/sec by 0.036 for km/hour). Record on the CRF.

6 □. Time 25 to 45 minutes: Working Memory task practice:

7 □. Inform participant: *"Now let's practice the three computer tasks"*

a □. Have participant sit on a chair in front of the cart laptop screen with button in hand

b □. Set the paradigm for **starting the control task**. Speak clearly and slowly: *"Let's start with the first computer task. This green dot that you see on the centre of the screen will disappear as soon as I start this trial. The green dot will be replaced by a series of letters appearing one after the other at 1-2 second intervals. The letters will appear randomly and are not in any particular order. For this particular task, I will ask you to press the button as soon as you see the letter "X". The letters will continue to appear for one minute. Please do not press the button at any other time unless the letter displayed is an 'X'. Do you have any questions?"*

c □. Ask participant to repeat the instructions to **ensure that they understand**.

d □. Start the recording on the main computer

e □. "*Ready, set, go"* and start the trial.

f □. The trial and the recording will end after 60 seconds.

g □. Record the comment in the main computer and click 'Accept comment' as instructed above

h □. Once completed scroll down to make a note of their performance

i □. Re-set the paradigm for **starting the control task**.

j □. *"Now let's practice another trial of the same task. I will ask you to press the button whenever you see the letter 'X'. Do not press the button at any other time unless the letter is an 'X'".*

k □. Start the recording on the main computer

l □. "*Ready, set, go"* and start the trial.

m □. The trial and the recording will end after 60 seconds.

n □. Record the comment in the main computer and click 'Accept comment' as instructed above

o □. Once completed scroll down to make a note of their performance

p □. Re-set the paradigm for **starting the control task**.

q □. *"Now let's practice another trial of the same task. I will ask you to press the button whenever you see the letter 'X'. Do not press the button at any other time unless the letter is an 'X'".*

r □. Start the recording on the main computer

s □. "*Ready, set, go"* and start the trial.

t □. The trial and the recording will end after 60 seconds.

u □. Record the comment in the main computer and click 'Accept comment' as instructed above

v □. Set the paradigm for **starting the 1-back task**. Speak clearly and slowly:

"Good. Now we will go on to do the next task. Just as before, when I start the task, the green dot will be replaced by a series of letters appearing one after the other. Unlike the previous task, you will not see the letter 'X'. For this particular task, I will ask you to press the button whenever you see a letter which is the same as the one that appears just one prior to it in the sequence. In other words, whenever you see a letter repeated one after the other, back to back, press the button as quickly as you can. Please do not press the button at any other time unless the letter is repeated one after the other. Do you have any questions? If not, are you ready to start?"

w □. Ask participant to repeat the instructions to **ensure that they understand**.

x □. Start the recording on the main computer

y □. "*Ready, set, go"* and start the trial.

z □. The trial and the recording will end after 60 seconds.

aa □. Record the comment in the main computer and click 'Accept comment' as instructed above

bb □. Once completed scroll down to make a note of their performance

cc □. Re-set the paradigm for **starting the 1-back task**.

dd □. *"Well done. Now we will repeat this task once again and perform the task exactly as you did by pressing the button as soon as you see a letter repeated one after the other."*

ee □. Start the recording on the main computer

ff □. "*Ready, set, go"* and start the trial.

gg □. The trial and the recording will end after 60 seconds.

hh □. Record the comment in the main computer and click 'Accept comment' as instructed above

ii □. Once completed scroll down to make a note of their performance

jj □. Re-set the paradigm for **starting the 1-back task**.

kk □. *"Well done. Now we will repeat this task once again and perform the task exactly as you did by pressing the button as soon as you see a letter repeated one after the other."*

ll □. Start the recording on the main computer

mm □. "*Ready, set, go"* and start the trial.

nn □. The trial and the recording will end after 60 seconds.

oo □. Record the comment in the main computer and click 'Accept comment' as instructed above

pp □. Once completed scroll down to make a note of their performance

qq □. Set the paradigm for **starting the 2-back task**.

rr □. Speak clearly and slowly: *"Now we will go on to do the last of the three computer tasks. Just as before, when I start the task, the green dot will be replaced by a series of letters appearing one after the other. Unlike the previous task, please DO NOT (re-iterate "not") press the button whenever you see a letter back to back. Instead, for this trial I will ask you to press the button when you see a letter that is the same as the one that appeared, NOT one before, but two letters prior in the sequence. In other words, whenever you see a letter repeated after a different letter appears in between you will press the button and please do so as quickly as you can. Please do not press the button at any other time unless the letter is repeated with one different letter in the middle. The trial will only last for a minute. Do you have any questions?."*

ss □. Use a paper and pencil to illustrate the task if necessary. Ask participant to repeat the instructions to **ensure that they understand.**

tt □. "*Ready, set, go"* and start the trial.

uu □. The trial and the recording will end after 60 seconds.

vv □. Record the comment in the main computer and click 'Accept comment' as instructed above

ww □. Once completed scroll down to make a note of their performance

xx □. Re-set the paradigm for **starting the 2-back task**.

yy □. "*Now let's practice another trial of the same task. I will ask you to press the button when you see a letter that is the same as the one that appeared, NOT one before, but two letters prior in the sequence. In other words, whenever you see a letter repeated after a different letter appears in between you will press the button. Do not press the button at any other time unless the letter is repeated after a different letter in between. The trial will only last for a minute. If at anytime you wish to stop walking during the trial please feel free to inform me immediately and I will bring the treadmill to a halt. Do you have any questions?*"

zz □. "*Ready, set, go"* and start the trial.

aaa □.The trial and the recording will end after 60 seconds.

bbb □. Record the comment in the main computer and click 'Accept comment' as instructed above

ccc □.Once completed scroll down to make a note of their performance

ddd □. Re-set the paradigm for **starting the 2-back task**.

eee □."*Now let's practice another trial of the same task. I will ask you to press the button when you see a letter that is the same as the one that appeared, NOT one before, but two letters prior in the sequence. In other words, whenever you see a letter repeated after a different letter appears in between you will press the button. Do not press the button at any other time unless the letter is repeated after a different letter in between. The trial will only last for a minute. If at anytime you wish to stop walking during the trial please feel free to inform me immediately and I will bring the treadmill to a halt. Do you have any questions?***.**"

fff □. Regularly encourage the participant as deemed appropriate. *"Excellent! Now we are done with the practice sessions, I will ask you to do the same three tasks again while on the treadmill."*

Walking on the treadmill: Practice first then record

Time 45 to 60 minutes: Treadmill walking practice

8 □. **Getting ready for the treadmill**:

a □. **Footswitches**:

i □. When participant is seated comfortably, request that he/she remove their shoes.

ii □. Insert the right and left footswitches in respective shoes ensuring that the wires come out from the medial border.

iii □. Have participants wear them on and adjust them as long as they fit snuggly and are not too tight (If footwear is too tight, the footswitches will not capture foot timing).

iv □. Ensure that the wires are taped to the socks or trousers with an enough lag in them so as to avoid tripping over them or preventing free movement of ankles.

b □. **Safety harness:**

i □. Assist the participant in getting the safety harness on.

ii □. Fasten the Velcro straps on the trunk.

iii □. Adjust the length of the thigh straps to allow unrestricted movement of the safety harness

iv □. Fasten the Velcro straps for each thigh.

v □. Have the participant **stand on the treadmill**.

vi □. Hook the safety harness to its assembly and adjust the length of the belts to avoid any restrain in movement.

c □. **Connect the respective footswitches** to the grey wire.

d □. To **ensure that the wires do not get in the way**, fasten the grey wires over the safety harness or trouser's belt loop and loop the loose end over the hook on the ceiling.

e □. Have the participant hold the button device in their dominant hand. Loop its wires such that they do not come in way of arm, leg or body movement.

f □. Turn on the **LCD projector** and display the central mark on the screen via the cart laptop.

9 □. **Practicing treadmill walking**:

a □. Turn the treadmill power on.

b □. Record the gait on the main computer as directed above.

c □. Instruct the participant to begin walking as you gradually increase the treadmill velocity to reach that which you recorded in **Step II.5.h**.

d □. Start the stopwatch after target velocity is reached.

e □. Have the participant walk for at least six minutes.

f □. Ask participant whether he/she would require more time on the treadmill.

g □. Gradually decrease speed to zero after informing your intension of ending this practice session.

h □. Discontinue recording.

Time 45 to 60 minutes: Treadmill walking practice

10 □. Record single task treadmill walk

a □. Turn the treadmill power on.

b □. Record the gait on the main computer as directed above.

c □. Instruct the participant to begin walking as you gradually increase the treadmill velocity to reach that which you recorded in **Step II.5.h**.

d □. Start the stopwatch after target velocity is reached.

e □. Have the participant walk for at least six minutes.

f □. Ask participant whether he/she would require more time on the treadmill.

g □. Gradually decrease speed to zero after informing your intension of ending this practice session.

h □. Discontinue recording.

X- CONTROL TASK while standing and then while

Single-tasking: X-control only

11 □. Working memory tasking while **standing - CONTROL TASK**.

a □. On the cart laptop, set the paradigm for **starting the control task**.

b □. Have participant **stand on the treadmill** with the button, footswitches and harness in place.

c □. Repeat the instructions for this task. *"Now I am going to ask you to perform the second computer task. When I start the task, the centre mark will be replaced by a series of letters appearing one after the other. For this particular task, I will ask you to press the button whenever you see the letter 'X'. Do not press the button at any other time unless the letter is an 'X'. The trial will only last for a minute. Before we start collecting the data I will give you a few practice trials. Do you have any questions?"*

d □. Ask participant to repeat the instructions to **ensure that they understand**.

e □. *"Now let's practice a few trials."*

f □. Start the control paradigm on the cart laptop.

g □. Once completed scroll down to obtain the # of correct hits.

h □. If satisfactory (accuracy greater than 70% and less than 2 incorrect hits) go to item #n.

i □. "*Now let's practice another trial of the same task. I will ask you to press the button whenever you see the letter 'X'. Do not press the button at any other time unless the letter is an 'X'."*

j □. Start the control paradigm on the cart laptop.

k □. Once completed scroll down to obtain the # of correct hits.

l □. If satisfactory (accuracy greater than 70% and less than 2 incorrect hits) go to item#n.

m □. If not satisfactory, repeat item #i.

n □. Get ready to start the control task on the cart laptop

o □. "*Now let's record this trial. I will ask you to continue the press the button whenever you see the letter 'X'. Do not press the button at any other time unless the letter is an 'X'."*

p □. Start the recording on the main computer

q □. "*Ready, set, go"* and start the trial.

r □. The trial and the recording will end after 60 seconds.

s □. Record the comment in the main computer and click 'Accept comment' as instructed above

t □. Once completed, say, *"Well done. Now we will do the same thing. Perform the task exactly as you did by pressing the button as soon as you see the letter 'X'."*

u □. Start the recording on the main computer

v □. "*Ready, set, go"* and start the trial.

w □. The trial and the recording will end after 60 seconds.

x □. Record the comment in the main computer and click 'Accept comment' as instructed above.

y □. Once completed, say, *"Well done. Now we will do the same thing. Perform the task exactly as you did by pressing the button as soon as you see the same letter repeated right after it appears."*

z □. Start the recording on the main computer.

aa □. *"Ready, set, go"* and start the trial.

bb □. The trial and the recording will end after 60 seconds.

cc □. Record the comment in the main computer and click 'Accept comment' as instructed above.

Dual-tasking: X-control + walk

12 □. Working memory tasking while **walking - CONTROL TASK**.

a □. Inform participant: *"Now I will ask you to perform the same task while walking on the treadmill. I will first start the treadmill and when you have reached your regular strolling speed I will start the computer task. "*

b □. Repeat the instructions for this task: *"Just as before, I will ask you to press the button whenever you see the letter 'X'. Do not press the button at any other time unless the letter is an 'X'. Now let's have some practice trials. If at anytime you wish to stop walking during the trial please feel free to inform me immediately and I will bring the treadmill to a halt. Do you have any questions?"*

c □. Ask participant to repeat the instructions to ensure that they understand.

d □. Start the **treadmill to desired speed** (recorded in **Step II.5.h**).

e □. On the cart laptop, set the paradigm for starting the 1-back task.

f □. *"Okay, let's start with the practice trials."*

g □. Start the control paradigm on the cart laptop.

h □. Once completed, inform the participant your intension to stop the treadmill.

Stop the treadmill

i □. On the cart laptop, scroll down the page to obtain their performance summary.

j □. If satisfactory (accuracy greater than 70% and less than 2 incorrect hits), skip item# k – p.

k □. "*Now let's practice another trial of the same task. I will ask you to press the button whenever you see the letter 'X'. Do not press the button at any other time unless the letter is an 'X'."*

l □. Start the control paradigm on the cart laptop. It will run on for 1 minute

m □. Once completed scroll down to obtain the # of correct hits.

n □. If satisfactory (accuracy greater than 70% and less than 2 incorrect hits), skip item# k – p.

o □. If not satisfactory, go to item # k.

p □. "*Now let's record this trial. Once again, I will start the treadmill firs. When you have reached the steady speed if walking on the treadmill, I will start he computer task. I will ask you to continue to perform the task as you did by pressing the button whenever you see the letter 'X'. Do not press the button at any other time unless the letter is an 'X'. Do you have any questions?"*

q □. Get ready to start the control task on the cart laptop

r □. Start recording on the main computer.

s □. *"Ready, set, go"* and start the trial.

t □. Recording of the trial will end after 60 seconds.

u □. Record the comment in the main computer and click 'Accept comment' as instructed above

v □. "*Now let's record another trial. Once again, I will start the treadmill first. When you have reached the steady speed I will start he computer task. I will ask you to continue to perform the task as you did by pressing the button whenever you see the letter 'X'. Do not press the button at any other time unless the letter is an 'X'. Do you have any questions?"*

w □. Get ready to start the control task on the cart laptop

x □. Start recording on the main computer.

y □. *"Ready, set, go"* and start the trial.

z □. Recording of the trial will end after 60 seconds.

aa □. Record the comment in the main computer and click 'Accept comment' as instructed above

bb □. "*Now let's record one final trial. Once again, I will start the treadmill first. When you have reached the steady speed I will start he computer task. I will ask you to continue to perform the task as you did by pressing the button whenever you see the letter 'X'. Do not press the button at any other time unless the letter is an 'X'. Do you have any questions?"*

cc □. Get ready to start the control task on the cart laptop

dd □. Start recording on the main computer.

ee □. *"Ready, set, go"* and start the trial.

ff □. Recording of the trial will end after 60 seconds.

gg □. Record the comment in the main computer and click ‘Accept comment’ as instructed above.

1-BACK TASK while standing and then while walking

Single-tasking: 1-back only

13 □. Working memory tasking while **standing - 1-BACK TASK**.

a □. On the cart laptop, set the paradigm for **starting the 1-back task**.

b □. Have participant **stand on the treadmill** with the button, footswitches and harness in place.

c □. Repeat the instructions for this task. *"Now I am going to ask you to perform the second computer task. Just as before, when I start the task, the centre mark will be replaced by a series of letters appearing one after the other. Unlike the previous task, you will not see a 'X'. For this particular task, I will ask you to press the button whenever you see a letter which is the same as the one that appeared just prior in the sequence. In other words, whenever you see the same letter repeated back to back, press the button as fast as you can. Do not press the button at any other time unless the letter appears back to back. The trial will only last for a minute. Before we start collecting the data I will give you a few practice trials. Do you have any questions?"*

d □. Ask participant to repeat the instructions to **ensure that they understand**.

e □. *"Now let's practice a few trials."*

f □. Start the 1-back paradigm on the cart laptop.

g □. Once completed scroll down to obtain the # of correct hits.

h □. If satisfactory (accuracy greater than 70% and less than 2 incorrect hits) go to item #n.

i □. "*Now let's practice another trial of the same task. I will ask you to press the button whenever you see a letter which is the same as the one that appeared just prior in the sequence. In other words, whenever you see the same letter*

repeated back to back, press the button as fast as you can. Do not press the button at any other time unless the letter appears back to back."

j □. Start the 1-back paradigm on the cart laptop.

k □. Once completed scroll down to obtain the # of correct hits.

l □. If satisfactory (accuracy greater than 70% and less than 2 incorrect hits) go to item#n.

m □. If not satisfactory, repeat item #i.

n □. Get ready to start the 1-back task on the cart laptop

o □. "*Now let's record this trial. I will ask you to continue the press the button whenever you see a letter which is the same as the one that appeared just prior in the sequence. In other words, whenever you see the same letter repeated back to back, press the button as fast as you can. Do not press the button at any other time unless the letters appears back to back. Do you have any questions?"*

p □. Start the recording on the main computer

q □. "*Ready, set, go"* and start the trial.

r □. The trial and the recording will end after 60 seconds.

s □. Record the comment in the main computer and click 'Accept comment' as instructed above

t □. Once completed, say, *"Well done. Now we will do the same thing. Perform the task exactly as you did by pressing the button as soon as you see the same letter repeated right after it appears."*

u □. Start the recording on the main computer

v □. "*Ready, set, go"* and start the trial.

w □. The trial and the recording will end after 60 seconds.

x □. Record the comment in the main computer and click 'Accept comment' as instructed above.

y □. Once completed, say, *"Well done. Now we will do the same thing. Perform the task exactly as you did by pressing the button as soon as you see the same letter repeated right after it appears."*

z □. Start the recording on the main computer.

aa □. *Ready, set, go"* and start the trial.

bb □. The trial and the recording will end after 60 seconds.

cc □. Record the comment in the main computer and click ‘Accept comment’ as instructed above.

Dual-tasking: 1-back + walk

14 □. Working memory tasking while **walking - 1-BACK TASK**.

a □. Inform participant: *"Now I will ask you to perform the same task while walking on the treadmill. I will first start the treadmill and when you have reached your regular strolling speed I will start the computer task. "*

b □. Repeat the instructions for this task: *"Just as before, I will ask you to press the button whenever you see a letter which is the same as the one that appeared just prior in the sequence. In other words, whenever you see the same letter repeated back to back, press the button as fast as you can. Do not press the button at any other time unless the letter appears back to back. Now let's have some practice trials. If at anytime you wish to stop walking during the trial please feel free to inform me immediately and I will bring the treadmill to a halt. Do you have any questions?"*

c □. Ask participant to repeat the instructions to ensure that they understand.

d □. Start the **treadmill to desired speed** (recorded in **Step II.5.h**).

e □. On the cart laptop, set the paradigm for starting the 1-back task.

f □. *"Okay, let's start with the practice trials."*

g □. Start the 1-back paradigm on the cart laptop.

h □. Once completed, inform the participant your intension to stop the treadmill.

Stop the treadmill

i □. On the cart laptop, scroll down the page to obtain their performance summary.

j □. If satisfactory (accuracy greater than 70% and less than 2 incorrect hits), skip item# k – p.

k □. "*Now let's practice another trial of the same task. I will ask you to press the button whenever you see a letter which is the same as the one that appeared just prior in the sequence. In other words, whenever you see the same letter repeated back to back, press the button as fast as you can. Do not press the button at any other time unless the letter appears back to back."*

l □. Start the 1-back paradigm on the cart laptop. It will run on for 1 minute

m □. Once completed scroll down to obtain the # of correct hits.

n □. If satisfactory (accuracy greater than 70% and less than 2 incorrect hits), skip item# k – p.

o □. If not satisfactory, go to item # k.

p □. "*Now let's record this trial. Once again, I will start the treadmill first when you have reached the steady speed I will start he computer task. I will ask you to continue to perform the task as you did by pressing the button whenever you see a letter which is the same as the one that appeared just prior in the sequence. In other words, whenever you see the same letter repeated back to back, press the button as fast as you can. Do not press the button at any other time unless the letter appears back to back. Do you have any questions?"*

q □. Get ready to start the 1-back task on the cart laptop

r □. Start recording on the main computer.

s □. *"Ready, set, go"* and start the trial.

t □. Recording of the trial will end after 60 seconds.

u □. Record the comment in the main computer and click 'Accept comment' as instructed above

v □. "*Now let's record another trial. Once again, I will start the treadmill first. When you have reached the steady speed I will start he computer task. I will ask you to continue to perform the task as you did by pressing the button whenever you see a letter which is the same as the one that appeared just prior in the sequence. In other words, whenever you see the same letter repeated back to back, press the button as fast as you can. Do not press the button at any other time unless the letter appears back to back. Do you have any questions?"*

w □. Get ready to start the 1-back task on the cart laptop

x □. Start recording on the main computer.

y □. *"Ready, set, go"* and start the trial.

z □. Recording of the trial will end after 60 seconds.

aa □. Record the comment in the main computer and click ‘Accept comment’ as instructed above

bb □. “*Now let’s record another trial. Once again, I will start the treadmill first. When you have reached the steady speed I will start he computer task. I will ask you to continue to perform the task as you did by pressing the button whenever you see a letter which is the same as the one that appeared just prior in the sequence. In other words, whenever you see the same letter repeated back to back, press the button as fast as you can. Do not press the button at any other time unless the letter appears back to back. Do you have any questions? ”*

cc □. Get ready to start the 1-back task on the cart laptop

dd □. Start recording on the main computer.

ee □. *“Ready, set, go”* and start the trial.

ff □. Recording of the trial will end after 60 seconds.

gg □. Record the comment in the main computer and click ‘Accept comment’ as instructed above.

2-BACK TASK while standing and then while walking

Single-tasking: 2-back

15 □. Working memory tasking while **standing -2-BACK TASK**.

a □. On the cart laptop, set the paradigm for **starting the 2-back task**.

b □. Have participant **stand on the treadmill** with the button, footswitches and harness in place.

c □. Repeat the instructions for this task. *"Now I am going to ask you to perform the final computer task. Just as before, when I start the task, the green dot will be replaced by a series of letters appearing one after the other. This time, I will ask you to press the button when you see a letter that is the same as the one that appeared, NOT one before, but two letters prior in the sequence. In other words, whenever you see a letter repeated after a different letter appears in between you will press the button. Please do not press the button at any other time unless the letter is repeated with one different letter in the middle. The trial will only last for a minute. Do you have any questions?"*

d □. Ask participant to repeat the instructions to **ensure that they understand**.

e □. *"Now let's practice a few trials. Ready, set, go."*

f □. Start the 2-back paradigm on the cart laptop.

g □. Once completed scroll down to obtain the # of correct hits.

h □. If satisfactory (accuracy greater than 70% and less than 2 incorrect hits), skip item # i to m.

i □. "*Now let's practice another trial of the same task. I will ask you to press the button whenever you see a letter which is the same as the one that appeared,*

NOT one before, but two letters prior in the sequence. In other words, whenever you see a letter repeated after a different letter appears in between you will press the button. Do not press the button at any other time unless the letter appears back to back."

j □. *"Ready, set, go"*

k □. Start the 2-back paradigm on the cart laptop.

l □. Once completed scroll down to obtain the performance summary.

m □. If satisfactory (accuracy greater than 70% and less than 2 incorrect hits) go to item#n.

n □. If not satisfactory, repeat item #i.

o □. Get ready to start the 2-back task on the cart laptop

p □. "*Now let's record this trial. I will ask you to continue the press the button whenever you see a letter which is the same as the one that appeared, NOT one before, but two letters prior in the sequence. In other words, whenever you see a letter repeated after a different letter appears in between you will press the button. Do not press the button at any other time unless the letter is repeated after a different letter appears in between."*

q □. Start the recording on the main computer

r □. "*Ready, set, go"* and start the trial.

s □. The trial and the recording will end after 60 seconds.

t □. Record the comment in the main computer and click 'Accept comment' as instructed above

u □. Once completed, say, *"Well done. Now we will do the same thing. Perform the task exactly as you did by pressing the button as soon as you see the same letter repeated after a different letter appears in between you will press the button."*

v □. Start the recording on the main computer

w □. "*Ready, set, go"* and start the trial.

x □. The trial and the recording will end after 60 seconds.

y □. Record the comment in the main computer and click 'Accept comment' as instructed above.

z □. Once completed, say, *"Well done. Now we will do the same thing. Perform the task exactly as you did by pressing the button as soon as you see the same letter repeated after a different letter appears in between you will press the button."*

aa □. Start the recording on the main computer.

bb □. *Ready, set, go"* and start the trial.

cc □. The trial and the recording will end after 60 seconds.

dd □. Record the comment in the main computer and click 'Accept comment' as instructed above.

Dual-tasking: 2-back + walk

16 □. Working memory tasking while **walking - 2-BACK TASK**.

a □. Inform participant: *"Now I will ask you to perform the same task while walking on the treadmill. I will first start the treadmill and when you have reached your regular strolling speed I will start the computer task. "*

b □. Repeat the instructions for this task: *"Just as before, when I start the task, the centre mark will be replaced by a series of letters appearing one after the other. This time, I will ask you to press the button when you see a letter that is the same as the one that appeared, NOT one before, but two letters prior in the sequence. In other words, whenever you see a letter repeated after a different letter appears in between you will press the button. Do not press the button at any other time unless the letter is repeated after a different letter appears in between. The trial will only last for a minute. If at anytime you wish to stop walking during the trial please feel free to inform me immediately and I will bring the treadmill to a halt. Do you have any questions?"*

c □. Ask participant to repeat the instructions to ensure that they understand.

d □. Start the **treadmill to desired speed** (recorded in **Step II.5.h**).

e □. On the cart laptop, set the paradigm for starting the 2-back task.

f □. *"Okay, let's start with the practice trials."*

g □. Start the 2-back paradigm on the cart laptop.

h □. Once completed, inform the participant your intension to stop the treadmill.

Stop the treadmill

i □. On the cart laptop, scroll down the page to obtain their performance summary.

j □. If satisfactory (accuracy greater than 70% and less than 2 incorrect hits), skip item# k – p.

k □. "*Now let's practice another trial of the same task. I will ask you to press the button when you see a letter that is the same as the one that appeared, NOT one before, but two letters prior in the sequence. In other words, whenever you see a letter repeated after a different letter appears in between you will press the button. Do not press the button at any other time unless the letter is repeated after a different letter in between. The trial will only last for a minute. If at anytime you wish to stop walking during the trial please feel free to inform me immediately and I will bring the treadmill to a halt. Do you have any questions?"*

l □. Start the 2-back paradigm on the cart laptop.

m □. Once completed scroll down to obtain the performance summary.

n □. If satisfactory (accuracy greater than 70% and less than 2 incorrect hits), go to item# p.

o □. If not satisfactory, go to item # k.

p □. "*Now let's record this trial. Once again, I will start the treadmill first when you have reached the steady speed I will start the computer task. I will ask you to press the button when you see a letter that is the same as the one that appeared, NOT one before, but two letters prior in the sequence. In other words, whenever you see a letter repeated after a different letter appears in between you will press the button. Do not press the button at any other time unless the letter repeated after a different letter appears in between. The trial will only last for a minute. If at anytime you wish to stop walking during the trial please feel free to inform me immediately and I will bring the treadmill to a halt. Do you have any questions?"*

q □. Get ready to start the 2-back task on the cart laptop

r □. Start recording on the main computer.

s □. *"Ready, set, go"* and start the trial.

t □. Recording of the trial will end after 60 seconds.

u □. Record the comment in the main computer and click 'Accept comment' as instructed above

v □. "*Now let's record another trial. Once again, I will start the treadmill first when you have reached the steady speed I will start the computer task. I will*

ask you to press the button when you see a letter that is the same as the one that appeared, NOT one before, but two letters prior in the sequence. In other words, whenever you see a letter repeated after a different letter appears in between you will press the button. Do not press the button at any other time unless the letter repeated after a different letter appears in between. The trial will only last for a minute. If at anytime you wish to stop walking during the trial please feel free to inform me immediately and I will bring the treadmill to a halt. Do you have any questions?"

w □. Get ready to start the 2-back task on the cart laptop

x □. Start recording on the main computer.

y □. *"Ready, set, go"* and start the trial.

z □. Recording of the trial will end after 60 seconds.

aa □. Record the comment in the main computer and click 'Accept comment' as instructed above

bb □. "*Now let's record one more final trial. Once again, I will start the treadmill first when you have reached the steady speed I will start the computer task. I will ask you to press the button when you see a letter that is the same as the one that appeared, NOT one before, but two letters prior in the sequence. In other words, whenever you see a letter repeated after a different letter appears in between you will press the button. Do not press the button at any other time unless the letter repeated after a different letter appears in between. The trial will only last for a minute. If at anytime you wish to stop walking during the trial please feel free to inform me immediately and I will bring the treadmill to a halt. Do you have any questions?"*

cc □. Get ready to start the 2-back task on the cart laptop

dd □. Start recording on the main computer.

ee □. *"Ready, set, go"* and start the trial.

ff □. Recording of the trial will end after 60 seconds.

gg □. Record the comment in the main computer and click 'Accept comment' as instructed above.

End of study

17 □. Commend the participant's involvement in research and thank them for their time and patience

18 □. Unfasten the Velcro straps of the safety harness starting with the thighs first and then proceeding to the vest.

19 □. With the grey wire and its connections to the footswitches held in your hand, assist the participant in descending from the treadmill.

20 □. While the participant is seated in a chair disconnect the footswitches and remove the grey wire if looped on the participant

21 □. Remove footswitches from the shoes and sanitize them upon removal

22 □. Disconnect the footswitches from the grey wire.

23 □. Coil the loose wires and return it to its prior location

24 □. Disconnect the computers and return to their respective locations.

25 □. Return the equipment to its location

26 □. Ensure all data is collected and appropriately stored

27 □. Log-off turn off the computers.