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PhD in Engineering

Development of Neural Engineering Methods for the Objective Assessment of Cognitive Processing based on Gait Data: An Analysis of a Truly Nationally Representative Cohort of Older Adults

A dissertation submitted to the University of Dublin for the degree of

Doctor of Philosophy

by

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Isabelle Killane

06th July 2015

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ABSTRACT

Knowledge of the brain substrates and neural networks at play during gait are not well understood. However, strong associations between gait and cognitive function have been found in literature. Examining this relationship further may allow inferences to be drawn through investigating the contributions of specific elements of cognitive function to gait. This thesis outlines the role that cognitive function has been found to play in gait performance in older adults and early stage cognitive impairment. Gait speed has been examined in detail due to its association with survival[2] and activities of daily living[3]. A large portion of this thesis examines a nationally representative population (n=8504, age (range, mean(SD)): 50-91 yrs, 63.14(10.21)) employing the Irish Longitudinal Study on Ageing (TILDA). Two studies employing young healthy participants were examined also. Various systems were employed to record gait performance (pressure sensing mats, electromyography, a motion sensor system) and cognitive function (neuropsychological and computerised assessment tests, electroencephalography, dual task paradigms). The contribution of executive function, attention, short term memory and processing speed to gait speed and gait variability (stride time variability) were examined. It was found that many factors affect gait performance, with age, the affect of task and global cognition being specifically highlighted. Various cognitive function elements were required for all gait tasks in older adults, however when examining younger adults the relationship was task dependent. Greater sustained attention, processing speed and short term memory were specifically highlighted to contribute to faster gait speed in older adults. More complex gait tasks were found to require additional elements of cognitive function specific to the task performed, mostly recruiting additional executive resources. A novel aspect of this thesis are findings that pinpoint specific gait speed differences for specific cognitive performance scores. This was achieved due to the large number of participants and broad range of health characteristics available from the TILDA dataset to allow adjustments be made. In addition, significant correlations between specific gait speeds and executive function scores were found which were proposed as points of transition from automatic to a more consciously controlled gait. Attention, as measured by sustained attention, dual task paradigms or a novel auditory evoked potential electroencephalography experiment, was found to play a significant role in gait performance in older adults. However, gait speed was found to be a poor biomarker for global cognitive function and executive function due to its complex relationship with age and the good health prevalent in this population. The results

of this thesis furthers our understanding of the associations between cognitive function and gait in healthy older adults, and strengthen the hypothesis of the pre-frontal cortex involvement in complex gait tasks. The results of the studies described in this thesis add to the knowledge gained on the neural linkages and connectivities, specifically probing bidirectional links between executive and motor activity, and dual task theories. These results are clinically relevant as they have formed a baseline for motor-cognitive health in individuals from fifty years old from which pathology may be judged. These results may inform clinical practice as enhancement of both cognitive function and gait performance may increase quality of life and reduce adverse events experienced by older adults.

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GLOSSARY

Bottle Neck Theory	Attentional resources are limited and this affects processing of information such that the second task is delayed until the processor is free from the first task
Cadence	The number of steps taken in a given time, the usual unit being steps per minute
Capacity Sharing Theory	Attentional resources have a limited capacity when processing two tasks simultaneously resulting in the deterioration in task performance in one or more of the tasks. This theory assumes that it is possible to voluntarily allocate attentional capacity to a specific task.
Cognitive Flexibility	Ability to shift between two concepts, tasks or response rules
Divided attention	Simultaneously attending to two tasks.
Executive Function	Executive function refers to higher neurologic processes, such as planning, attention, decision making, cognitive flexibility, working memory, error utilisation, inhibition and abstract thinking and are needed to carry out activities of daily living.
Gait	The manner or style of walking. Walking is a method of locomotion involving the use of the two legs, alternately, to provide both support and propulsion with at least one foot being in contact with the ground at all times.
Gait Cycle	The time interval between two successive occurences of one of the repetitive events of walking.
Gait Speed	The distancce covered by the whole body in a given time [cm/s] or [m/s]

Inhibition	Ability to over-ride habits in order to choose a correct solution that is more complex and requires more effort
Short Term Memory	Ability to hold and manipulate information over a small amount of time. Immediate recall can be categorised as working memory under executive function. Delayed recall can assesses the encoding process: free and cued recall, recognition memory, in additionn to semantic and autobiographical memory and learning.
Multiple Resource Theory	Information processing requires a number of resources. If two simultaneously performed tasks do not share a common resource there will be no interference in performance.
Salutogenesis	The generation and maintenance of health
Selective attention	Maintenance of attention despite competing stimuli and/or distractors.
Speed of processing	Time to complete task.
Sustained attention	Maintenance of attention over time.

ABBREVIATIONS

TILDA	The Irish Longitudinal Study on Ageing
MMSE	Mini Mental State Examination
MOCA	Montreal Cognitive Assessment
CTT	Color Trails Test
CoV	Coefficient of Variation
MRI	Magnetic Resonance Imaging
MCI	Mild Cognitive Impairment

PUBLICATIONS

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CHAPTER 1: Literature Review

Spectacular advances in medicine, science and technology have allowed the global population of people sixty years and older to double since 1980. This population is forecast to reach two billion by the year 2050. Along with these benefits come challenges. Most notably, maintaining a high quality of living for a growing older population while preserving efficient and effective health service infrastructures with good fiscal economics.

Sensorimotor and cognitive changes occur during normal ageing and are quantitatively different to cognitive impairments in pathology such as in Alzheimer's disease. Researchers have differing opinion on exact cognitive changes during ageing, however most agree that impairments include a decline in learning of new information and a decline in delayed recall[4]. These changes are typical of normal ageing, however not all individuals experience such changes in which case the individual is referred to as ageing successfully or optimally. The reasons behind one individual successfully ageing and another experiencing more severe changes is not fully understood. In addition, motor and cognitive changes occur in pathology such as Alzheimer's disease. The prevalence of Alzheimer's disease doubles every five years from 65 to 95 years of age [5] so is becoming increasingly prevalent with the ageing of the global population. This emphasises the need to further explain health, in addition to pathogenesis, longitudinally prior to the possible initiation of age-related disorders or decline. Further understanding of how health is generated and maintained during ageing, specifically brain health, would be clinically beneficial in order to diagnose transitions to pathology. The clinical assessment of health may form a baseline on which normal ageing and pathology could be compared. The aim of this thesis was to investigate the links between gait and cognitive function during ageing employing neural engineering methods.

A large proportion of this thesis investigates associations between gait and cognitive function within The Irish Longitudinal Study of Ageing (TILDA) dataset[i]. TILDA is a nationally representative sample of residents of Ireland fifty years and older. The Irish population is one of the youngest

[i] http://www.tilda.ie/.

populations in Europe with a median age of 35.4 years (2013 WHO). TILDA has a mean age of 61 years. Genetically the Irish population is regarded as a population with a relatively homogenous genetic background [6]. The TILDA dataset has gained from this homogeneity in terms of less complex data collection and interpretation of results compared to larger less homogeneous populations. In addition, many studies exploring gait and cognitive associations have employed much smaller participant numbers with smaller age ranges than TILDA (n= 8174, 50-91 years). Given that this association has not been asked of such a large dataset previously, we envisage that novel findings will be the highly beneficial outcome from the studies described in this thesis.

The literature review described in this chapter provides a comprehensive overview of the research linking gait and cognitive function. In addition, gait and specific cognitive disturbances characteristic to impaired cognitive function are discussed. Methods employed to measure cognitive function and cognitive impairment through gait, and the main findings acquired with these measures are presented in detail. Firstly, the conventional measures of cognitive examination and gait assessment including: neuropsychological assessments, neuroimaging and kinematic analysis are described, followed by a depiction of the new, innovative measures of cognitive function and gait interactions including gait analysis, ambulatory Electroencephalography (EEG) and intervention trials. The explicit thesis objectives are detailed at the end of the chapter.

1.1. Normal Ageing

Sensorimotor and cognitive changes occur during typical or normal ageing and are quantitatively different to cognitive impairments in pathology such as the amnesic syndrome in Alzheimer's disease. During normal ageing sensorimotor changes include: reduction in gait speed, reduced integrity in distal muscles, reflexes, and vibratory sensibility. In addition, loss of other modalities such as pain and proprioception are common. Researchers have differing opinion on exact cognitive changes during ageing, however most agree that impairments include a decline in learning of new information and a decline in delayed recall[4]. These changes are typical of normal ageing, however not all individuals experience such changes in which case the individual is referred to as ageing successfully or optimally. The reasons behind one individual successfully ageing and another experiencing more severe changes is not fully

understood. Further research is required to explain health, in addition to pathogenesis, longitudinally both prior to the possible initiation of age-related decline or disorders and during each stage of the ageing process.

1.2. Models of Ageing

There are many models of ageing, two of which are: the senesence model and the life span model. The senesence model and the life span model both have inherent perspectives and follow different definitions of normal ageing. The senesence model includes two phases of life: growth and ageing. Growth includes a physical growth and differentiation, culminating in maturity. An ageing phase follows resulting in a loss of functional capacity and adaptability, or senescing. The life-span model includes developments from conception to death including growth, development and ageing. In this model maturation continues from physical growth until death and changes occur throughout maturation.

The senesence model treats and diagnoses age related changes, whereas a stages of life approach is more appropriate for the life span model[7]. The senscence model can equate disease to ageing, as pathology also includes loss of functional capacity and adaptability.

Within the studies described in this thesis both the senesence and life span model have been embraced allowing the inclusion of interventions for normal ageing (senesence model) with a perspective that normal ageing includes changes, distinct from that of a condition (life span model).

1.3. Changes During Ageing

1.3.1.Neurological and Cognitive Changes with Age

Ageing changes higher neurological areas both functionally and structurally with variable degrees of change in cortical structure, functional activity and cognitive function. Feli et al [8] suggested that most brain structures do not follow a simple path throughout adult life and that their accelerated decline in very old age is not a norm of healthy brain ageing.

However, structural changes such as an increased number of white matter hyperintensities has been found with ageing [9, 10]. Functional brain networks have a reduced efficiency with age, however decline in brain function with age has been shown to be slow [11]. Reduced inter-regional connectivity occurs during ageing both in short range connections (within frontal, parietal and occipital lobes) and long range connections (of fronto-parietal and fronto-occipital). Additionally, global networks become more segregated[12]. In particular, the frontal lobes of the brain have been shown to be susceptible to age related changes[13, 14] with a reduction in white frontal cortex volume found in some studies[13]. These changes require compensatory strategies in the ageing brain to maintain performance but are dependent on specific individual traits such as cognitive reserve. One such compensatory strategy employed by older adults is the recruitment of different neurological regions when compared with younger individuals. In particular, literature has shown a greater recruitment of prefrontal regions and a decreased activation of posterior regions in older adults [15-17].

Through neuroimaging studies (functional Magnetic Resonance Imaging (fMRI)) [16, 18, 19] less efficient use of the occipital lobe has been shown in older adults when compared with younger adults. As a consequence frontal lobe resources were shown to be recruited to a greater degree in older adults, especially during more complex tasks. This is thought to result in transitions from automatic to more voluntary processes to maintain performance[20]. When attending to a task O'Connell et al [21] has shown a frontal shift in electroencephalographic (EEG) scalp activation in older adults when compared with their younger counterparts. These findings seems to be in agreement with other studies [16] which have also shown this frontal shift, termed PASA or Posterior Anterior Shift in Ageing.

Neuropsychological assessments have allowed insight into the behavioural perspective of ageing. Performance on different tests of cognitive function varies with age. Salthouse et al [22] discussed the crystallised abilities, such as vocabulary and general informaton as tending to stabilise, or occasionally increase, with age and the fluid abilities, such as memory, reasoning, forming new associations and problem solving as tending to decrease with age. Specifically it has been reported that changes in speed of processing and

executive function, required for effective, goal orientated actions and attentional control [23], are the main mediators of age related cognitive decline.

1.3.2.Mobility and Gait Changes with Age

Locomotion occurs as a result of a complex system of processes and interactions which are, as of yet, not fully understood. In a healthy person locomotion engages the motor cortex, cerebellum, basal ganglia, and involves feedback to the proprioceptive, visual, and vestibular sensors producing precise motor commands and resultant co-ordinated muscle firing and limb movements. Gait and postural control is important for good quality of life and loss of mobility is a significant fear among older adults. Furthermore, mobility impairment increases with age to 14% in those over 75 years and 50% in those over 85 years[9]. In addition, disorders of gait are increasingly linked to poor outcomes, such as increased risk of institutionalization and death [24]. Interactions and influences that result in a correct or disordered gait are not fully understood. However, disorders of gait have been shown to increase with age, neurological disease and frailty level.

Kinematic parameters change with age. Centre of pressure and centre of mass which influence balance have been found[25] to be significantly different in older and younger participants during level walking and obstacle crossing. In addition, the introduction of gait adaptations and rapid locomotor adjustments, such as reducing gait speed, are more common with age [26]. Older adults are also at a higher risk of experiencing loss of balance or instability and falls compared with their younger counterparts. Those with a higher risk of falling have a more conservative gait pattern with smaller temporo-spatial gait parameters and increased variability in step timing compared with those with a lower risk of falling. Literature has shown that those with slower gait speed, shorter step length, narrower stride width and larger variability in step length or step time have a higher risk of falling[27]. This result was found when comparing differences in gait between hospital admittants who had fallen, those who had not fallen and active older adults. Concluding that these differences in gait reflect reduced automaticity of gait.

Other important factors in order to maintain gait and balance include being able to maintain a stable visual field when walking. Menz et al[28, 29] found that those who found it difficult to control trunk and head motion were at higher risk of falling when compared to those with control. This was seen through changes in harmonic ratios in vertical and anterior-posterior directions especially when walking on irregular surfaces.

1.3.3. Factors Affecting Gait and Cognitive Impairment with Age

Increasing age, lower educational attainment, poorer health status, poorer sensory abilities, less physical and cognitive exercise, greater scores on depressive scales and existence of personality, mood and anxiety disorders have been linked to poorer mobility and poorer cognitive function in older adults. In addition, neurobiological factors such as greater build up of white matter hyperintensities[9] in the brain, in addition to genetics have also been linked to poorer mobility and poorer cognitive function. Multi-faceted factors such as residual attention reserve, awareness of limitations and recognition of hazards also influence gait and cognitive function in older adults. Balance and psychological factors such as loss of balance and fear of falling have been specifically shown to affect gait. In addition, hypothesised major determinants between age and cognitive function are childhood cognitive ability, and neurobiology[22]. Level of educational attainment, health status and sensory ability have been found to influence the relationship between age and cognitive function. However, they are not primary causes as cognitive function changes with age within different education, health status and sensory ability groups.

Educational Attainment

Level of educational attainment has a strong positive correlation with cognitive function and contributes to the relationship between age and certain measures of cognitive function[22] in cross sectional analysis. Wiederholt et al [30] has also found age, gender and education to affect neuropsychological assessment test scores.

Health Status

Specific and cumulative impairments affect gait and cognitive function individually. In addition, impairment due to disease or disorder may also affect the relationship between gait and cognitive function. Health conditions such as cardiovascular disorders [31], respiratory disease [32] and vitamin deficiency[33] have been associated with measures of cognition. In addition, prevalence of these conditions all increase with age and may contribute to the relationship between age and cognitive function. Cardiovascular disorders such as hypertension, cardiac disease [34] and respiratory disease such as asthma, chronic lung disease[35] have been found to affect gait also.

Sensory Ability

Sensory ability and multisensory integration has been associated with gait and cognitive function, in addition to the age-cognitive function relationship [22, 36]. This can be explained by the existence of deficits in registration of information which are required to complete a task (e.g.: motor or cognitive task) in those with sensory impairment. Awareness of limitations, recognition of hazards and residual attention reserve also affects gait and cognitive function in older adults. These are multi-faceted factors but are affected themselves by sensory ability.

Physical and Cognitive Training

In addition to age and height, the amount of lower extremity muscle has been found to affect gait speed [37]. Furthermore, those who participate in more physical training are more likely to have higher cognitive function and less likely to have dementia[38]. In addition, cognitive training has been shown to correlate with the cross sectional age-cognitive function relationship [39].

Rosendahl et al[40] investigated the effect of high intensity physical training routines on older adults and found a high intensity physical training program had positive long-term effects on physical function in older adults who were not independent, as assessed by theactivities of daily living score. Specifically, at 6 months the physical training group had a significantly greater improvement than the control group in balance (the Berk Balance

Scale (p=0.05)), self-selected gait speed (p=0.009) and lower limb strength (p=0.03) (FOPANU dataset, Sweden[ii]).

While investigating motor planning using high density EEG, Berchicci et al (2013)[41](n=130, age:15-86 years) found that physical training improved motor response times in older adults. In addition, Berchicci et al found that middle-aged adults who participated in moderate-to-high levels of physical training had improved planning/execution of responses and showed no signs of prefrontal hyperactivity during motor planning. Berchicci et al concluded that physical activity counteracts neural over-activity in older adults by improving executive function.

Winchester et al[42] found that participants who engaged in walking for more than two hours a week had a significant improvement in their global cognition (Mini-Mental State Examination test scores) compared with those who walked less and sedentary participants.

Depressive Symptoms

Depression has been shown to influence both mobility and cognitive function in older adults. In literature, depression is often measured using the Center for Epidemiologic Studies Depression (CES-D) scale [43] which is a short self-report scale designed to measure depressive symptoms in the general population. The items of the scale are symptoms associated with depression. CES-D scale is commonly used and despite its popularity, several recent investigations have called into question the robustness and suitability of the commonly used 4-factor 20-item CES-D model [44].

White Matter Hyperintensities

Literature has shown loss of myelin integrity, as measured by increased number of white matter hyperintensities, to be a potential mediator of age-related cognitive decline.

[ii] Residents of nine residential care facilities: n=191, mean age 84.7±6.5yrs, 139 female, MMSE >10, 68% severely cognitive or physical impaired.

Reduction of the myelin sheath around axons can slow neural signal transmission, which may affect communication across neural networks and temporal coding. This may result in desynchronisation of impulses and functional disconnections.

Research suggests that accumulation of white matter hyperintensity has a greater effect on mobility than cognitive function in older adults. Speed of processing is affected, but it does not result in global cognitive decline, however, deterioration in mobility occurs both cross sectionally and longitudinally[10]. Damage to peri-ventricular white matter, the site of temporal sensory integration, especially visuo-spatial inputs nesessary for mobility and efficient organisation of effective motor action, may explain this.

Genetics

The apolipoprotein E (APOE) gene is known to influence brain disease, as it is a risk factor for Alzheimer's disease [45] and cardiovascular disease. Chang et al (2014) [46] found that the APOE allele interacts with age to modify the rate of cognitive decline and brain changes in participants with Alzheimer's disease at twelve month follow up (n=227, fMRI and neuropsychological assessments). The APOE allele has also been associated with gait. More specifically, it has been associated with a faster decline in motor function in older adults, with a decline in gait speed (Einstein Aging study [47]) and a reduction in physical function. However, some studies contradict this with no association found with risk of disability, loss of mobility or frailty.

Holtzer et al (2010) [48] also investigated associations between the Catecol-0-methyltransferase (COMT) gene, gait and executive control in ageing. The COMT gene facilitates dopamine degradation and is expressed primarily in the cortex and striatum. Dopamine neurotransmission has been shown to be important for regulation of executive and attentional functions [49] which in turn have been associated with gait performance in non-demented adults [50]. Holtzer et al reported associations between polymorphism in COMT ($Val^{158}Met$) and faster gait speed, in addition to better attention and executive function.

Childhood Cognitive Function

Childhood cognitive function has been found to be correlated with cognitive ability in old age at aged sixty seven[51], seventy seven, seventy nine [52] and ninety[53] years of age respectively. In addition childhood cognitive function correlates with decline in memory and speed of processing from forty three to fifty three years of age[54].

Neurobiology

The neurobiology of an individual is a factor found to specifically affect cognitive function. Preliminary research has linked gait and specific neurobiological factors. However, future research should investigate if this relationship is independent of cognitive function. Behaviour is an important factor to consider in cognitive ageing. Little is know about the neurobiology of cognitive ageing, however physiological factors, such as molecular biology and gene expression[55, 56], change with age. Further progress in this area would increase understanding of the neural substrates of cognitive function in addition to the causal factors and determinants of cognitive ageing or impairment.

The measurement of neural activity, quantifying global brain volumes, regional brain volumes and neurotransmitter receptor sites is achievable. It is more difficult to measure the possible specific causal factors at play such as neuron death, synapse or vascular integrity or shrinking neurons, in addition to the reduction in the number of support cells or neurotransmitter quantity and effectiveness[57].

Dopamine, a neurotransmitter thought to modulate the frontal lobes of the brain, is suspected to have a particularly important role in cognitive function decline during ageing [58] and a change in dopamine receptor sites have been found to be associated with age and different cognitive domains.

1.4. Cognitive Impairment

Impairment in cognitive function exists in mild to progressively more severe forms, generally termed in literature mild cognitive impairment (MCI), cognitive impairment (CI) and dementia

respectively. Dementia is a chronic illness that arises from a combination of genetic, environmental and behavioural factors, with many adverse influences on social and physical activities and quality of life [59]. Normal daily functioning and independence is greatly affected in dementia, but affected to a lesser degree in CI and MCI. In addition, individuals with MCI have an increased risk of falling and postural sway[60].

The term neurocognitive disorder (NCD) has been included in the recently published Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM 5[61] (see Appendix 1), with the proposed aim of encapsulating different levels of cognitive impairment. Within the manual a neurocognitive disorder is defined as a complex syndrome characterized by global and irreversible cognitive decline that is severe enough to affect daily activities. It includes major neurocognitive disorders and, a new diagnosis termed "mild neurocognitive disorders". Major neurocognitive disorder was previously termed dementia. Mild neurocognitive disorder is a new diagnosis for less severe, earlier stage cognitive impairments which is comparable to the term mild cognitive impairment (MCI) referred to in literature. Controversially, mild neurocognitive disorder has a broad definition: a cognitive impairment that requires compensatory strategies and accommodations to help maintain independence and perform activities of daily living and goes beyond normal cognitive deficits of ageing.

1.4.1.Epidemiology, Pathophysiology and Etiology

Dementia is a syndrome in which there is deterioration in cognitive function which affects behaviour and the ability to perform everyday activities. Dementia affects older people. It is not a normal part of ageing, and it is a major cause of disability and dependency. Globally, over thirty five million people have been diagnosed with dementia, with over seven million new cases every year. Dementia is projected to double in numbers every twenty years, to over sixty five million in 2030 and over one hundred and fifteen million by 2050. It is estimated that two to eight percent of the general population aged over sixty years have dementia (WHO 2012).

Epidemiology

Dementia affects memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgement. In dementia, cognitive impairment is usually accompanied by, and occasionally preceded by, deterioration in emotional control, social behaviour or motivation. Lack of awareness and understanding of dementia can result in stigmatising patients which may be a barrier to diagnosis and care. In addition, caregivers, family and societies may be affected physically, psychologically, socially and/or economically. There is currently no cure for dementia and no treatment to slow down disease progress. Up until recently there had been no diagnosis, no symptom assessment or appropriate treatment guide for early stage dementia. Further understanding of diagnostic criteria and potential therapies are needed. Earlier diagnoses would improve quality of life of patients by optimising their physical and cognitive health. In addition, quality of life may be improved by providing information and support to caregivers and patients and by diagnosis and treatment of any accompanying physical illnesses, behavioural and psychological symptoms.

Pathophysiology

There are three stages to the signs and symptoms of dementia: early, middle and late stage. The early stage has a gradual onset with symptoms such as forgetfulness, losing track of time and becoming lost in familiar places. Recently the term mild neurocognitive disorder has been given to diagnose this stage. Diagnosis in this stage is thought to increase the effectiveness of interventions with more treatments available to potentially prevent or reduce disease progression. During the middle stage everyday activities are further restricted which increases awareness of the signs and symptoms of the disorder to the individual, caregivers and health professionals. Symptoms include becoming forgetful of recent events and people's names, becoming lost at home, having increasing difficulty with communication, needing help with personal care, experiencing behaviour changes, including wandering and repeated questioning. During the late stage of dementia individuals are dependent and inactive and have severe memory disturbances and obvious physical signs and symptoms. Symptoms include: becoming unaware of time and

place, having difficulty recognizing relatives and friends, having an increasing need for assisted self-care, having difficulty walking, experiencing behaviour changes that may escalate including aggression.

Etiology

Dementia is caused by a variety of diseases and injuries that primarily or secondarily affect the brain. Dementia etiology subtypes are as follows:

- Mild or major vascular neurocognitive disorder (vascular dementia)
- Mild or major neurocognitive disorder due to Alzheimer's disease, frontotemporal neurocognitive disorder, Lewy bodies, Parkinson's disease, traumatic brain injury, HIV infection, Huntington's disease, Prion disease, substance/medication, another medical condition and multiple etiologies[61].

Sixty to seventy percent of dementia cases are thought to be caused by Alzheimer's Disease (WHO 2012). However, boundaries between different subtypes are indistinct and composite subtypes co-exist. Dementia, especially in the mild to moderate stages, has distinct behavioural features, namely depression and psychotic symptoms such as paranoia, other delusions and visual hallucinations. Depression is common in the early stages of dementia aswell as other mood disorder symptoms such as anxiety, elation and apathy. Other behavioural symptoms include wandering, disinhibition, hyperphagia, hoarding and sleep distrubances (insommnia, hypersomnia, circadian rhythm disturbances). Disruptive motor or vocal activity due to agitation, confusion and frustration are common in later stages of dementia.

Older populations have been found to have a high risk of being affected by the following etiology subtypes: mild or major vascular neurocognitive disorder (vascular dementia) and mild or major neurocognitive disorder due to Alzheimer's disease, Lewy bodies and Parkinson's disease. In addition, the term "neurocognitive disorder of ageing" will be used within section 1.4 of this thesis for those dementia etiologies.

1.4.2.Risk Factors

Risk factors of neurocognitive disorders of ageing vary by etiology subtype. For all neurocognitive disorders of ageing the biggest risk factor is age, due to an increased risk of neurodegeneration and cerebrovascular disease with age. Many risk and protective factors have been found for cognitive impairment and dementia. Specifically, Hendrie et al [22, 62] found fifty two risk or protective factors included in a review of ninety six journal papers from large cohort studies that longitudinally tracked participants predominantly of sixty five years and older. Major risk factors included: Age, hypertension, diabetes, stroke or transient ischemic attacks, presence of infarcts or white matter lesions from brain imaging, low mood and higher body mass index ratings. The most consistently reported protective factors included: better baseline cognitive function, higher educational attainment, higher socioeconomic status, emotional support, better lung capacity, more physical exercise, moderate alcohol use and use of vitamin supplements. Some studies have found being female a risk factor, possibly due to a longer life expectancy. Age, culture, occupation, education and living arrangements have been found to affect the awareness of cognitive symptoms and effectiveness of diagnoses. For instance, Alzheimer's disease is rarely diagnosed before sixty years of age but prevalence increases sharply after this.

1.4.3.Disease Course

The disease course of neurocognitive disorders of ageing vary with etiology subtype. Neurocognitive disorders of ageing due to neurodegenerative diseases may have cerebral cortex, basal ganglia, thalamus, and subcortical white matter pathology and are marked by a slow, deceptive onset and a gradual disease progression. Those with Alzheimer's disease have been shown to have subcortical and cortical lewy bodies associated with plaques and tangles [63]. Often the sequence of onset of cognitive deficits and associated features help to distinguish between diseases. Neurocognitive disorders of ageing occur in conjunction with an increased risk of developing age related disorders such as medical conditions, frailty, sensory deficits and with increasing possible sources of neurocognitive decline. This adds to the complexities of diagnosis and subtype differentiation. In addition,

during normal ageing modest cognitive deficits can occur, making it important to differentiate between these deficits of normal ageing and the more severe cognitve deficits in mild neurocognitive disorders of ageing.

1.4.3.1. Motor impairments

Gait disorders are common in Dementia, even at the earliest Mild Cognitive Impairment stage[64] where there is an increase risk of falling and postural sway[60]. Waite et al (1996) [65] recognised specific gait abnormalities in neurodegenerative disease and dementia subtypes. Many participants experience a high level gait disorder, or gait apraxia, in conjunction with cognitive impairment due to the many sites of pathology; cerebral cortex, basal ganglia, thalamus, and subcortical white matter. Literature has hypothesised that these gait disorders are probably due to changes in higher levels of motor control resulting from cortical lesions which impair the primary motor cortex and in turn impair motor control[66].

Pathology in the cortical-basal ganglia-thalamocortical loop, an area which produces movements and postural synergies that are adapted to environmental constraints, multi-sensory inputs and personal desires, is of particular interest[67]. Tanaka et al (1990) hypothesised two specific diagnostic criteria for these gait disorders: (i) ataxia (impaired tandem gait and balance) and (ii) slowing (reduction of speed, step length and arm swing). Elble et al[67] has also proposed a set of diagnostic criteria for high level gait disorders but specifically arising from cortical-basal ganglia-thalamocortical loop pathology. Four core clinical features were specified as corresponding to the physiology of the cortical-basal ganglia-thalamocortical loop: (i) inappropriate limb movements, postural synergies and interaction with the environment (ii) qualitatively variable performance influenced by environment and emotion (iii) hesitation and freezing (iv) absent or inappropriate rescue reactions.

Impairments in both the propulsion component of gait, such as a reduction in gait speed[68, 69] and stability components of gait, such as an increase in stride time variability[70] have been found in participants with Mild Cognitive Impairment and Alzheimer's disease. Wittwer et al (2010)[64] have quantified this decline in gait performance over one year as a reduction of 8.5% and 19.6% in gait speed and stride

length respectively, in addition to an increase of 5.6% and 1.1% in double support and stride length variability respectively. Gait impairments have been found to occur to a greater extent in complex gait tasks which involve dual tasking compared with simple gait tasks. In addition, Muir et al (2012)[71] found a significant reduction in gait speed, an increase in stride time and stride time variability in individuals with Alzheimer's disease when compared to those with Mild Cognitive Impairment during complex gait tasks, but not during simple gait tasks. Many studies [68, 69, 72] have suggested that this impairment occurs due to the addition of an attention task affecting performance on a gait task

Annweiler et al (2013)[66] found both cortical volume and neurochemistry of the primary motor cortex to be associated with gait performance in both simple and complex gait tasks in participants with Mild Cognitive Impairment. Results found those with impaired gait performance in complex gait tasks, as measured by slow gait speed, were over two times more likely to have smaller cortical volume than those who performed well. In addition, larger cortical volumes correlated with smaller stride time variability during simple gait tasks. Annweiler et al also found that participants who had major gait disturbances during complex gait tasks were sixty three percent more likely to exhibit abnormal metabolite ratios in the primary motor cortex. Concluding that in individuals with MCI stride time variability was sensitive to neuronal function and gait speed was sensitive to inflammatory damage and volumetric change.

1.4.3.2. Other Risk Factors

Behaviour is an important factor to consider in cognitive and motor ageing. Behavioural factors, such as lifestyle, influence neural processes[73-75]and should be taken into account. In addition, mood symptoms, especially depression, are common and seen as a significant feature in the earliest stages of mild neurocognitive disorders.

1.4.4.Symptoms and Diagnosis

Diagnostic features of major and mild neurocognitive disorders are impairment on a spectrum of cognitive and functional abilities. Diagnostic criteria for a neurocognitive disorder (see Appendix 1) include an acquired cognitive decline in one or more cognitive domains and the presence of cognitive decline which must be based on both a concern and objective evidence. It could be (i) a concern that the individual, a clinican or a knowledable informant has about cognitive function in addition to (ii) a poorer than expected performance or a decline from baseline performance on an objective assessment such as a neuropsychological assessment.

At the mild neurocognitive level, likely concerns are tasks taking longer, being more difficult or requiring compensatory actions whereas in major neurocognitive disorder cognitive deficits progress to a stage where the individual has concern about not being able to complete tasks without assistance.

The standard measure of a neurocognitive disorder is the performance on a neuropsychological assessment based on normative values for appropriate age, education and cultural background groups. A positive assessment result would be two or more standard deviations below the normative value for a major neurocognitive disorder and between one and two standard deviations for mild neurocognitive disorder (as per DSM 5).

1.5. Methods to Detect and Monitor Gait, Brain Function and Cognitive Function

1.5.1.Measuring Gait

Gait can be measured using pressure sensing mats, accelerometers and gyroscopes or systems which integrate several different measurement devices. Accelerometers have also been used to assess falls risk such as in the Narayanan et al study[76] and to assess head movement during gait[28]. Estimates for the potential risk of falling, balance and

motor impairment have also been measured using the Berg Balance Test (BBT), Unified Parkinson's Disease Rating Scale (UPDRS Motor), Activities Specific Balance Confidence (ABC), number of falls per year and the Dynamic Gait Index (DGI).

1.5.1.1. Gait Analysis: Measures, Recording and Neural Origins

Gait analysis employs kinematics, a branch of mechanics concerned with motion of objects, and applies it to human locomotion. Human locomotion needed for everyday activities is a complex process requiring two opposing actions: propulsion and balance. Walking is defined as a method of locomotion involving the use of the two legs, alternately, to provide both support and propulsion with at least one foot being in contact with the ground at all times [77]. Gait is the manner or style of walking and involves simultaneous collective interactions between the brain, spinal cord, peripheral nerves, mucles, bones and joints. Awareness of destination and the ability to appropriately control limb movements and navigate complex environments influence gait also.

Gait Measures

Gait is described through the gait cycle. The gait cycle is defined as the time interval between two successive occurences of one of the repetitive events of walking. For example, the time between two heel strikes of the right foot. The gait cycle has general descriptors or components such as major events, phases and side of movement and more specific temporal, spatial and temporo-spatial parameters. In addition, proportions or percentages that each measure occupies in one gait cycle can also be calculated and used as a measure of gait.

Generally, the description of the gait cycle extends from heel strike to heel strike of the right leg, where heel strike is defined as contact of the heel to the ground.. The left foot will go through the same sequence as the right foot but displaced by half a cycle. The major events of the gait cycle are: inital heel contact, opposite toe off, heel rise, opposite initial contact, toe off, feet adjacent and tibia vertical.

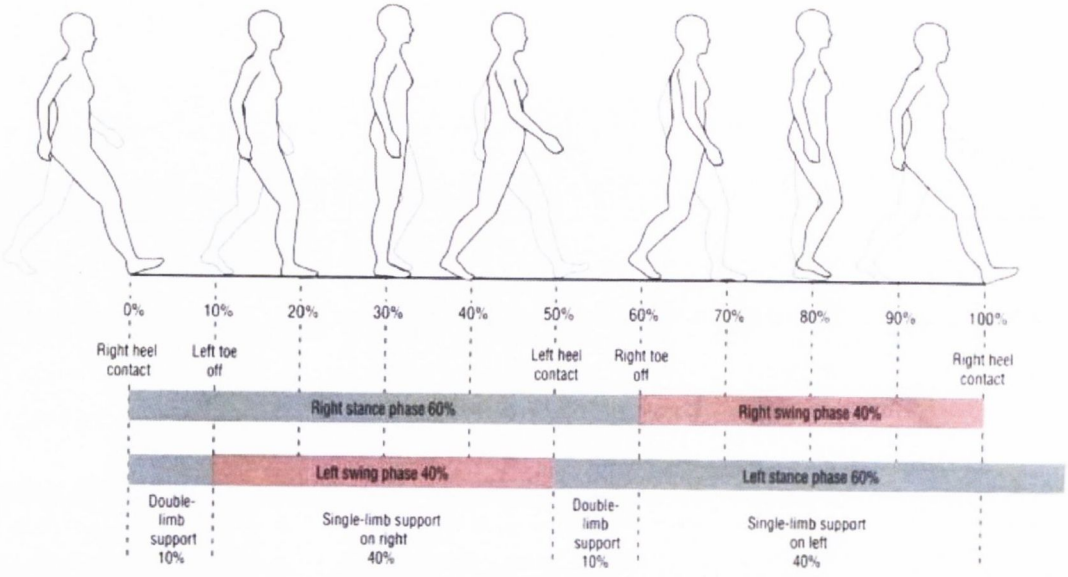

Figure 1: The Gait Cycle [iii]

The gait cycle can also be categorised as either in stance (foot on the ground) or swing (foot off the ground), and single support (one foot touching the ground) or double support (two feet touching the ground). The gait cycle usually comprises of sixty percent stance phase and forty percent swing phase. However, the ratio of stance to swing phase in the gait cycle is dependent on gait speed. A faster gait speed will increase the amount of time in swing phase and reduce the time in stance phase due to a reduced time in double support.

Gait Cycle Parameters

Similar to other physiological recording systems during gait analysis temporal, spatial and temporo-spatial parameters can be recorded. The parameters measure a specific event during an individual's gait or are proposed to measure different physiological processes at play during the locomotor process.

Temporal gait parameters exist such as swing, stance, stride, step, single support and double support times. Spatial gait parameters exist such as stride and step

[iii] http://media.lanecc.edu/

lengths and medio-lateral, anterior-posterior or vertical sway or deflection lengths. Temporo-spatial gait parameters exist such as gait speed and gait velocity. In addition, parameters can be described by variation about their mean value, such as stride time variation in standardised (coefficient of variation) or non-standardised (standard deviation) terms. Standard units are seconds for temporal gait parameters, metres or centimeters for spatial gait parameters and the units of the respective components, such as metres per second [m/s], for temporo-spatial parameters.

1.5.1.2. Specific Analysis: Use of Gait in Diagnosis and Testing

Five factors describing variance in gait have been found in healthy older adults: Rhythm, Phase, Variability, Pace and Base Support (Hollman et al)[78]. The Rhythm domain is characterised by cadence and temporal parameters such as stride time. The Phase domain includes specific gait cycle events such as swing, stance, single support and double support phases. The Variability domain includes gait cycle and step variability parameters. The Pace domain is characterised by parameters including gait speed, step length and stride length. The Base domain is characterised by step width and step width variabilty[78]. This factor analysis employed a comprehensive list of 23 gait parameters recorded from an electronic walkway (GaitRite system). However, Verghese et al [79] employed a smaller number of gait parameters when characterising gait in dementia and found three factors that describe variances in gait: Pace (gait speed and length), Rhythm (cadence, swing time and stance time) and Variability (stride length). Lord et al [80] investigated healthy older adults and found similar factors to Hollman et al. Lord et al also employed principal component analysis to extract the relative contribution of each factor to variance in gait finding: Pace (22.5%), Rhythm (19.3%), Variability (15.1%), Asymmetry (14.5%) and Postural Control (8.0%).

Specifically, within the Pace domain gait speed is reported to describe an individual's general health and is useful in comparing task performance. In addition, within the Variability domain gait variability and temporal aspects of gait are reported to

describe neurological processes such as function of the cortical-basal ganglia-thalamocortical loop. In addition, recent studies employing ambulatory monitoring have shown that patterns of gait are also of interest, with more complex gait patterns associated with healthy ageing [81].

Gait Speed

Gait speed is a robust predictor of mortality [2, 82, 83]. Gait speed has been measured, both cross sectionally and londitudinally, over different gait conditions and measured with differing experimental systems. Slower gait speed is associated with multiple falls [84-86], survival rate [2] [2, 87], poor activities of daily living [3] and gait and balance disruptions. This has added impetus to calls to introduce slow gait speed as a standard clinical measure or "vital sign" in geriatric assessment[82] [88], termed Bradypedia.

Gait speed changes during pathology, but also during normal ageing with changes in physical strength and joint integrity. However, this is also thought to be a manifestation of changes in higher neurologic areas of movement control which occur as we age. This affect also occurs with pathology and has been shown to decline more aggressively such that individuals with mild cognitive impairment have been shown to have a slower gait speed and a higher risk of falling than healthy age matched controls [89].

Gait speed varies with gait task and differences in gait speed across different gait tasks are also of interest. During a fast paced gait task both a slower baseline gait speed and a decline in gait speed over time has been found to predict mortality[iv][83]. This corresponded to a 0.009 m/s faster decline in gait speed between those 908 participants who died (-0.021 m/s) and those who survived (-0.031 m/s). Annual decline in fast gait speed was categorised as normal if less than 0.04 m/s, small if between 0.04 and 0.08 m/s , and over 0.08 m/s as a substantial decline. The small and substantial declines in fast gait speed were associated with a 1.2-fold and a 1.4- fold greater risk of mortality.

iv n=4,016, age: 65-85 yrs, 5 follow up sessions over 12 year period

Gait speed has also been associated with cardiovascular risk factors[34, 90-92]. However, associations between gait speed and mortality still remain after adjusting for cardiovascular risk factor. Some hypothesise that gait speed decline may be due to underlying cardiovascular conditions. Others hypothesise that declines in gait speed may be an early indicator of loss of muscle strength[37], sarcopenia[93] or frailty[94] which predict mortality.

Ryberg et al[v] [95] found a correlation between corpus collosum atrophy and gait speed ($p<0.01$) and motor performance ($p<0.05$) in older adults. In addition, a reduction in total corpus collosum area was associated with gait difficulty ($p<0.05$).

Gait Variability

Gait variability is an indicator of stability that increases with reducing gait speed[96], more complex gait tasks[72, 97] and pathology such as Alzheimer's disease[70], Parkinson's Disease[98, 99] and Stroke[100]. In a much cited journal paper Gabell and Nayak(1984)[101] described increased gait variability as an indicator of pathology and not a normal characteristic of ageing. Further advances in analysis however have shown changes in gait variability with age[102].

It has also been suggested that gait variability is a more discriminative measure of gait performance than standard spatio-temporal gait measures. Hausdorff et al[103] reported greater stride time variability, but not mean stride time, to be increased in individuals with Parkinson's disease who fall. Hausdorff et al also suggests that gait variability provides insight into the neural control of locomotion[104]. A view that was strengthened with findings such as stride time variability reducing with levodopa medication, a medication which is assimilated into the movement regulating dopamine neurotransmitter[103]. Hollman et al [78] has also found all domains of gait (Pace, Rhythm, Phase, Base of Support) except for the Variability domain, which is

[v] Ryberg et al investigated global cognition (MMSE), fMRI, balance lower extremity strength longitudinal data over 5yrs (n=639, 312 female, 74.2±5.1 yrs, MMSE=27.4±2.4) and gait measures with 5 follow up sessions over 12 year period (n=4,016, age: 65-85 yrs).

composed of gait variability measures, to be statistically significantly affected by age or gender.

1.5.1.3. Factors Affecting Motor Activity

It is important to investigate the role of the many processes that contribute both directly or indirectly to the gait process. For instance results may be affected by sensory ability, sensory processing and multi sensory integration, in addition to motor and central nervous system responses. Any change in physiological processes can directly affect gait such as increasing age or presence of injury, surgery, polypharmacy and chronic disease.

The age related reduction in or slowing of some sensory, physical and neural processing abilities have been associated with a slower gait speed and a reduced step length [105], in addition to an increase in postural sway and support times. Many of these changes are due to compensatory factors which allow us to maintain balance and prevent occurence of falls.

Visual, auditory, vestibular and proprioceptive processing ability and integration of these multiple sensory inputs are needed for navigating environments. In addition, good stability requires good strength, control of muscles and joints aswell as appropriate footwear. Furthermore, medication use and presence of disease can affect processes required for gait and balance. The ability to control attention has been thought to influence gait performance[106]. Links between gait and executive function have also been investigated[23]. However, a recent review has explored the role of the central nervous system in gait and posture including neurobiological factors and other cognitive functions[107].This area of literature is discussed in detail in Section 1.6.

1.5.2.Cognitive Function Measures

Neuropsychological assessment tests are commonly used to assess global cognition in addition to specific cognitive domains or cognitive processes. The following paragraphs

describe common clinically employed neuropsychological assessment tests including: global cognition, executive function, visual reasoning and short term memory. In addition, some novel neuropsychological tests cited in recent literature are also described: sustained attention and processing speed.

1.5.2.1. Cognitive Function Assessed by Neuropsychological Test Scores

Global Cognition

The Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MOCA) provide a general overview of cognitive function, termed global cognition. MOCA and MMSE are standard clinical assessment test for global cognitive function. In older adults, both MOCA and MMSE have a very high sensitivity for the detection of Alzheimer's disease[108]; 100% and 78% respectively. Both MOCA and MMSE have a very high specificity for the detection of Mild Cognitive Impairment (MCI) in older adults; 100% and 87% respectively, however, MOCA has a higher sensitivity than MMSE [108, 109]; 90% compared with 18% respectively. These sensitivities and specificities were based on a cutoff score of 26 for both MOCA and MMSE employed to indicate MCI and Alzheimer's Disease. Both global cognitive assessment tests, MOCA and MMSE, are required for the clinical assessment of global cognition. MOCA has a higher executive component and participants in general find it more difficult to complete. However, those with severe cognitive impariment may find MOCA too difficult to complete. MMSE is often administered before MOCA to gauge cognitive function and MOCA may be admisitered subsequently if participants score well.

In the literature, an MMSE cutoff score of 26 has been employed to indicate MCI [108, 110] and a cut-off score of 25 to indicate severe cognitive impairment. In literature a MOCA score of 26 or above is typically considered normal [108], a score of less than 26 employed to indicate MCI [108, 110]. However, some studies[111, 112] have argued that a lower MOCA cutoff of less than 24 is more appropriate to indicate MCI after findings indicated greater specificity (96%) while

maintaining a high sensitivity (95%) when employing this cutoff. Similarly, O'Bryant et al (2013)[113] recommends an MMSE cutoff score of below 27 for those with high educational attainment, finding a high sensitivity (89%) and specificity (91%) with this cutoff.

Limitations of MMSE are its reduced sensitivity to mild cognitive impairment and executive impairments, its reliance on language and lack of non-verbal cognitive function included in the assessment [114], in addition to its limited instructions on administration and interpretation[115]. In addition, MOCA has been found to have less of a ceiling effect and stronger associations with functional decline than MMSE[116].

The Mini-Mental State Examination (MMSE)

The Mini-Mental State Examination (MMSE) [117] is often employed to screen for cognitive impairment in older adults. The MMSE consist of a variety of questions. It has a maximum score of 30 points, and can be administered in 5-10 minutes. It assesses orientation to time and place, attention, memory and ability to follow commands. The MMSE provides a quick quantitative assessment of an individual's cognitive state. Although the MMSE was designed for use with hospitalised patients [117], the scale has attained widespread use clinically and in research concerned with primary care [118-120] and community dwelling individuals [121].

The MMSE assesses: Orientation to time and place, registration, memory, attention and concentration, praxis, constructional and language capacity. Orientation to time is assessed by asking the participant to state the season, the date, the day of the week and the month. Orientation to place is tested by asking the participant to state what state, county, city or town, building, floor, and address they are in. Immediate registration is tested by asking the participant to repeat a word list of three common objects. Concentration or attention and calculation are tested by asking the participant to subtract seven from one hundred, and seven from the

result, and so on for five computations ('Serial sevens' task). Alternatively, the participant is asked to spell the word 'world' backwards. Delayed recall is tested by asking the participant to recall the word list of three objects named in the immediate registration task. Language is assessed by asking the participant to name two common objects, repeat a phrase ('no ifs, ands or buts'), follow a three step command, read and obey a single command, write a sentence and copy a drawing of a two pentagon design [117].

The score is calculated from the total number of correct answers. The maximum score for the MMSE is 30 points. The correct interpretation of the results is critical and can only be based on the correct administration of the test. This includes asking the question clearly and unambiguously. There is considerable anecdotal evidence that delivery is poor and that underestimates the level of cognitive impairment in the participant being tested [114].

The Montreal Cognitive Impairment

The Montreal Cognitive Assessment[122] (MOCA) is a brief screening tool for Mild Cognitive Impairment (MCI) [108]. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations and orientation. Time to administer the MOCA is approximately ten minutes. The total possible score is 30 points.

MOCA tests visuo-spatial ability and executive function by asking the participant to complete an alternating trail making task and by copying a drawing of a cube. Visuo-constructional skills are tested with a task requiring the participant to draw a clock showing the time ten past eleven. Verbal memory is assessed by the animal naming test where the participant is asked to name three animals. Short term memory is assessed by the immediate memory task where the participant is asked to

repeat five words in two trials. Delayed memory is tested by administration of delayed recall of the five words used during the test of immediate memory task. If the participant cannot recall any of the five words, a category cue is presented. If the participant still cannot remember, a multiple choice cue is given. Attention is tested by administration of a forward and backward digit span, a vigilance and a serial sevens tasks. During the forward digit span task the participant is asked to repeat five numbers in the same order as they were recited by the test administrator. The participant is requested to repeat in reverse order the set of three numbers during the backward digit span task. Language is assessed by asking the participant to repeat two sentences articulated by the test administrator. Verbal fluency is assessed by the verbal fluency task where the participant is instructed to name as many words as he/she can think of that begin with the letter F in one minute. Abstraction is assessed by presenting the participant with three pairs of words and asking what these words have in common. Orientation to time is assessed by asking the participant to state the current date, month and year. Orientation to place is tested by asking the participant in what place and city he/she is currently located.

The total score is calculated as a sum of the scores from all tasks. There are twenty five subscores which add to give eleven domains scores which add to give one total score. After completion of the test, the test administrator enters individual item subscores underneath each test: trail making, cube drawing, clock drawing (numbers, contours and hands), animal naming (rhino, camel and lion), forward digit span, backward digit span, vigilance, serial sevens, sentence repitition, verbal fluency, abstraction, delayed recall, date, month, year, day, place and city orientation. Subscores are added to give eleven Domain scores: Visuo-spatial executive, Naming, Memory (no points), Attention (3 subscores), Language (2 subscores), Abstraction, Delayed Recall, Orientation. Domain scores and the total score are entered in a column on the right hand side of the test sheet. One point is added for individuals that have 12 years or

fewer of formal education. The possible maximum is 30 points. The MOCA is becoming more popular as an assessment of cognitive function [123, 124]. The utility of MOCA domain scores at predicting conversion from mild cognitive impairment to Alzheimer's disease have also been recently explored in literature[125].

Executive Function

Executive function refers to higher neurological processes, such as attention, mental flexibility and abstract thinking [23], which use and modify information from many cortical systems and are needed to carry out activities of daily living. Declines in executive function are thought to be due to functional and structural declines in: the frontal cortex, the subcortex and the vascular system [126-128]. Neuroimaging studies (fMRI) have shown executive function, as measured with the Trail Making Task (TMT), to be primarily sensitive to frontal region function in the left hemisphere with left middle and superior temporal gyrus activity found also. Executive function performance can be broken down into specific components; one being cognitive flexibility which has been shown to be sensitive to left sided dorsolateral and medial frontal activity [129] (as measured with TMT difference (ΔTMT). Executive function can be measured with many neuropsychological assessment tests such as the Stroop task, the Frontal Assessment Battery (FAB) and trail tests (Color Trail Test (CTT), Trail Making Task (TMT).

The Color Trails Test (CTT)

The Color Trails Test™ (CTT) [130, 131] is an objective, fast test of executive function involving selective attention, mental flexibility and visuo-spatial skills. It consists of two parts; Part 1 involves connecting numbers in ascending order with a pencil as quickly as possible, and Part 2 additionally requires alternating between vivid pink and yellow numbers that are perceptible to colour-blind individuals[130]. Both parts are timed giving two measures: CTT1 (Part 1) and CTT2 (Part 2). The difference in time between CTT1 and CTT2 , delta CTT (ΔCTT) [132] is also used as a

measure of executive function. The Color Trail Test (ΔCTT) has been shown to remove cultural and language bias [130]. ΔCTT requires cognitive flexibility and adjusts for differences in upper extremity motor speed and visual scanning[128].

The Trail Making Test (TMT)

The Trail Making Test is similar to the Color Trails Test. However, in Part 2 of the trail making task (TMT2) participants are asked to alternate between letters and numbers: A-1-B-2-C-3 etc. Measures similar to the CTT measures are employed in the Trail Making Task: TMT1, TMT2 and ΔTMT.

Visual Reasoning

Visual Reasoning is also a component of executive function. Visual reasoning can be assessed with the Visual Reasoning task from the Revised Cambridge Examination for Mental Disorders of the Elderly (CAMDEX-R)[133]. This test consists of three boxes with objects inside and one empty box. The participants are asked to identify the missing object to complete the pattern from a list of six options (six sequences).

Sustained Attention

Sustained Attention is a fundamental executive function for achieving goals over a period of time[134]. The Sustained Attention to Response Task (SART) [135] is widely used in research as a behavioural measure of sustained attention failures.

The Sustained Attention to Response Task (SART)

This test involves key presses to frequently visually presented non-targets, but with the requirement to withhold motor responses to occasional targets. The stimuli are presented one by one with at least two non-targets between targets. In the studies described in the following chapters the stimuli were presented in

random order. The capacity to withhold responses to some but not all instances of the no-go target is interpreted as reflecting lapsing attentional control over the response [136]. SART coefficient of variation is a measure used to assess sustained attention. It is the mean variation in reaction time, across the task, to all stimuli except for the digit '3'. The mean reaction times, number of commission errors (key press for targets) and number of omission errors (missing key press for non-target) may also be measured for this test.

Speed of Processing

There are many types of processing speeds that can be measured. This thesis will focus on cognitive and motor processing speeds. In literature processing speed may be assessed by the finger tapping test[137] and a Choice Reaction Time (CRT) Test.

Choice Reaction Time Test (CRT)

The Choice Reaction Time test (CRT)[138] involves a yes/no stimulus appearing on the screen in front of participants. Participants are asked to respond by releasing a button and pressing a corresponding yes/no button (100 repetitions). Total speed of processing is measured as the time taken from release of the button to pressing the yes/no button. Speed of processing can be further divided into cognitive and motor speed of processing. The cognitive reaction time measures cognitive speed of processing and is the time taken to release the button in response to the stimulus. The motor reaction time measures motor speed of processing and is the time taken to press the yes/no button after releasing the button.

Short Term Memory

Short term memory can be measured by an Immediate and Delayed Word Recall Test. This test is similar to the short term memory test in the Montreal Cognitive Assessment (MOCA), however usually there are ten words to be recalled. Participants are asked to repeat ten words in two trials in the immediate recall

test. Delayed memory is tested by administration of delayed recall of the ten words used during test of immediate memory. If the participant cannot recall any of the ten words, a category cue is presented. If the participant still cannot remember, a multiple choice cue is given.

Neuroimaing studies have found associations between short term memory and characteristics of brain ageing (resting state fMRI) [12]. In addition, the medial temporal and prefrontal regions have been found to have an important role in age-related memory decline (fMRI) [139]. Poorer memory performance has been associated with more localised information processing [12]. However, many factors moderate brain ageing and ageing is not exclusively associated with memory decline due to compensatory mechanisms [139].

1.5.2.2. Variations, Reliability and Limitations

Physical factors, demographic factors, test anxiety, fatigue, depression, dysphasia, psychosocial stressors, pain, physical illness and medication such as psychotropic medications among others can affect performance on neuropsychological tests.

Age, education and gender and sometimes race, ethnicity or social class can affect performance on neuropsychological assessments. Sensory processes such as vision and hearing decline with age and some pathology, so test stimuli must be designed to be appropriate for the cohort being assessed. It is important that test material can be clearly seen by participants and that the administrator would consult with the participant to ensure instructions are heard and understood. If appropriate, participants should be asked to wear aids such as glasses and hearing devices.

Test anxiety also affects performance on neuropsychological tests. Participants may not be used to being tested, especially in older cohorts where many only have primary education. Participants who feel their mental capacity declining may also be anxious and fearful of what the test will reveal and the implications of this. In addition, a lack of test anxiety or lack of effort or motivation may also affect test performance, such as if the participant does not value the test being administered.

Test fatigue can also affect performance and can occur sooner in older than in younger participants due to a decline in stamina. For this reason shorter test batteries are recommended when assessing older participants. In addition, administrators need to be vigilant to the signs of test fatigue.

Individual differences in neuropsychological scores increase dramaticially with age. It is normal for a wider variability in neuropsychological test measures in older participants when compared with younger participants. In addition, ceiling and floor effects are more likely in older participants than younger participants.

The definitions of normality or cut off scores for normal cognitive function (eg: MMSE of 23 or 26) are often limited to those between sixty or sixty five years of age to eighty five years of age. However, in many countries the very-old (over eighty five years) are the most rapidly growing segment of the population. In addition, normative values for the middle aged and healthy young-old (under 70 years) are needed as they could be employed as a baseline for health in these age groups on which pathology could be judged.

1.5.3.Cognitive Function Measured through Neuroimaging and Electrophysiology

Neuropsychological assessment tests are standard clinical assessment of cognitive function, however they are subjective in nature. Many factors affect test outcomes including the administrator, the language ability of the participant/administrator and the participant's level of education, fatigue, perception of test, anxiety or sensory impairments that they may have. Measures of cognitive function, cognitive domains or cognitive processes which are more direct and objective would be clinically beneficial and may aid in finding pre-clinical biomarkers for cognitive impairment.

1.5.3.1. Attention Measured Through Electroencephalography

Information derived from electroencephalography (EEG), such as P300 event related potentials (ERPs), can be employed as a measure of cognitive function specifically reflecting attention and context updating[140]. P300s are considered a measure of

cortical activity when processing complex information and are assessed by means of its two main components: amplitude and latency. Reduction in amplitude or increase in latency can indicate cognitive decline or cognitive load.

The P300 has been one of the most extensively investigated human electrophysiological markers [21]. Hypothesised neural substrates of the P300 are widely distributed frontotemporoparietal networks indexing attentional systems [141]. The P300 has two components: P3a and P3b which are thought to reflect different neurological functions. P3b is elicited 300 to 600 milliseconds after the appearance of a rare target stimulus which occurs in a stream of frequent distractor stimuli. P3a is thought to reflect top down allocation of attentional resources required to evaluate the stimulus. P3a is proposed to reflect stimulus driven bottom up attention orientating [142-145]. The P300 P3b Event Related Potential (ERP) is a measure employed in Study 6 to assess attention.

The P300 has been shown to be sensitive to normal ageing and age related pathology [146, 147] including dementia [148, 149]. P300 amplitude and latency has been correlated with neuropsychological test scores during ageing [150]. Specifically, poorer P300 performance has been associated with lower executive function task scores[151].

Some studies have acquired functional Magnetic Resonance Imaging (fMRI) in addition to EEG and so were able to infer about brain topography, structure and function. O'Connell et al (2012) [21] found an age related anterior shift in the P300 scalp location toward the pre-frontal cortex. This anterior shift corresponded to a reduced amplitude and a greater latency in older adults when compared with younger individuals. O'Connell et al concluded that this suggests an increased reliance on pre-frontal resources to support the processing of the target and the distractor stimuli. It may also indicate a reduced habituation to the task or suggest that a compensatory process is at play.

1.5.3.2. Variations, Reliability and Limitations

Electroencephalography (EEG) is acquired by recording cortical activity by placing electrodes on the scalp. EEG traces cortical neural activity with fine grained temporal accuracy in the order of milliseconds. Limitations of EEG are that only limited inference can be drawn regarding underlying generators. FMRI provides sophisticated structural and functional neural imaging, however the haemodynamic response from which the fMRI signal is generated is very slow in comparison to the neural activity recorded by EEG and so fMRI is said to have limited temporal resolution. Many of the hypotheses posed by the studies described in this thesis are temporal in nature and require such this fine grained temporal accuracy.

1.6. Gait and Cognitive Function

The link between gait and cognitive function and impairment is being increasingly recognised [152]. However, the locomotor system is a complex one which is not fully understood. Further understanding of the relationship between gait and cognitive function would have far reaching clinical benefits as it would allow insight into gait and higher level neurological control and thus further our understanding of neurodegeneration and its link to motor function and disorder.

While reviewing mobility limitations in community dwelling individuals, Rosso et al [107] found them to be common and hazardous but understudied, especially in regard to their link with the central nervous system. In addition, Rosso et al found literature lacking in clearly defined pathophysiology, clinical terminology and effective treatments. They concluded that findings from basic, clinical and epidemiology studies suggest the central nervous system is an important contributor to mobility limitations in normal ageing.

Studies have also shown a relationship between gait speed, a general health indicator, and survival. In addition, the specific relationship between gait speed and cognitive function may be a useful proxy for health and physical functioning as gait speed and cognitive function both depend on several organ systems. Gait speed and cognitive function have also both been shown to have accelerated decline before death. One hypothesis is that both gait and cognitive function represent two aspects of the same process but exhibited indirectly through

differing modes. This indicates that different physiological functions exhibit faster decline, or a terminal decline and terminal drop [153], in the years before death. Research into the terminal decline in cognitive function has suggested that this occurs regardless of pre-morbid cognitive level [154, 155]. This shows that gait control and cognitive function are complex brain processes.

1.6.1. Reserve

The term reserve has been proposed to account for the differences in degree of pathology and its clinical manifestation. Katzman et al (1993) classified reserve into passive and active modes.

Brain reserve is thought of as a passive process with a specific brain reserve or threshold. Brain reserve can be defined as individual differences in the brain itself that allow some individuals to cope with brain pathology better than others. Brain reserve capacity is derived from characteristics such as cortical volume, number of neurons, number of synapses and brain anatomy influenced by life experiences causing neurogenesis, angiogenesis, resistance to cell death and neuroplasticity enhancement. It is assumed that brain reserve capacity has a fixed critical threshold after which clinical or functional impairments emerge. This also assumes that there is a specific threshold below which functional impairment will occur for all individuals [156, 157]

Cognitive reserve is thought of as an active process based on more efficient utilization of brain networks or enhanced ability to recruit alternative brain networks as needed. It can be defined as individual differences in how tasks are processed which allow some individuals to cope with brain pathology better than others. Cognitive reserve can be sub-divided again into neural reserve and neural compensation. Neural reserve is the difference in brain network efficiencies, capacity and flexibility that affect task performance. Greater efficiency means less resources utilised to perform a task which may aid in coping with impairments inflicted by brain pathology. Neural compensation is the difference in ability to compensate for disruptions in standard brain networks (caused by brain pathology) by employing alternative brain structures or networks not normally used in healthy intact brains to maintain or improve performance [156, 157].

1.6.1.1. Cognitive Reserve

Ageing is not exclusively associated with decline and moderating factors such as cognitive reserve play an important role. It has been shown that some older adults employ neural compensation mechanisms to cope with brain decline by shifting to alternate brain resources that can compensate for any existing deficits [139]. In addition, strategies employed by individuals to manage neurodegeneration are of particular interest to gerontological research. For example, the efficient use of existing cognitive processes or the recruitment of alternative processes to respond to task demands successfully [157] when brain impairments exist. Cognitive reserve has been proposed as an important factor that modifies the impact of brain pathology on cognitive function [158]. Reserve has been found to modify rates of conversion from MCI to Dementia and longitudinal executive function decline. Similar to other pathologies, those with low reserve have been found to have a stronger link between brain pathology and cognitive decline than those with high reserve [158]. Those with higher cognitive reserve use their cognitive resources more effectively than those with less cognitive reserve while maintaining task performance. Cognitive reserve has been found to be more important a factor than cortical volume with an inverse relationship between brain structure, brain function and cognitive reserve in health and pathology [159]. Healthy adults have larger brain volumes and reduced neural activity during cognitive processes in high cognitive reserve groups compared with low cognitive reserve groups. Those with impaired cognitive function (MCI or Alzheimer's disease) have smaller brain volumes (both MCI and Alzheimer's groups) and greater brain activation (Alzheimer's group only) in high cognitive reserve groups compared with low cognitive reserve groups. Indicating those with a higher cognitive reserve in health with a higher cognitive reserve have a more effective use of cerebral networks in health and when cognitively impaired a more advanced neuropathology exists butan active compensatory mechanism occurs.

Daselaar et al investigated cognitive reserve and memory deficits and suggested that many factors moderate brain ageing and memory decline. Concluding that ageing is not exclusively associated with decline due to compensatory mechanisms such as

cognitive reserve [139]. Holtzer et al [160] investigated the effect of cognitive domains on gait and cognitive reserve. Holtzer et al found those with higher cognitive reserve, as measured with the Weschler Adult Intellgience Scale (WAS) III vocabulary test, to have greater protective effects of executive function and memory against gait speed decline in ageing (n=731, 80.5 years (5.4)).

1.6.2.The Dual Task Theories

Multitasking plays an important role in our daily activities and dual task paradigms, where two tasks are performed simultaneously, are used to create more ecologically valid experimental environments. Recent literature has measured divided attention employing the dual tasking paradigm. A dual task pardigm involves participants being asked to perform two tasks simultaneously to probe attentional capacity. The paradigm is thought to divide the participant's attention between the two tasks. Dual task measures have been found to correlate with activities of daily living [161]. In addition, the effect of the dual task on gait performance (e.g.: gait speed) increases progressively from health to more severe cognitive impairment, such as from MCI to Alzheimer's Disease [71, 89, 129, 162, 163]. Therefore, more complex walking tasks using a dual task paradigm may be more beneficial than a simple walking task for clinical purposes. However, neural correlates of dual task processing remain unclear [164] but theories exist such as the bottleneck, central resource capacity and multiple resource theories [165]. In addition, further investigation of different dual task paradigms is needed to evaluate any sensitivities and specificities to specific impairments or deficits.

In gait and posture studies dual gait tasks often consists of a gait and a cognitive task [50, 86, 166]. However, motor or fast walking tasks have also been employed [83, 167, 168]. Cognitive tasks commonly employed are serial subtraction tasks [86], reciting alternate letters of the alphabet [50] and the auditory Stroop task [166]. Motor tasks are less common, however tasks including carrying objects and spontaneous speech [166] have been employed. Obstacle avoidance tasks have also been employed [169] in some studies to assess spatial abilities. Although not a dual task paradigm, fast walking tasks where

participants are asked to walk as fast as they can are also employed to bring the participant to a point of stress.

Strategies and self-selected or administrator guided priorities of task are also important in dual task paradigms. Literature has termed a "posture first" strategy as a priority employed to maintain good balance. Posture first is indicated by a greater reduction in the additional task (i.e.: the cognitive task in a dual gait cognitive task) and a good performance in the gait task. Some studies have shown that those with cognitive impairments are less likely to employ a posture first strategy [129, 170] which may explain the higher risk of imbalance or falls in these cohorts. Most studies assume that the gait task is prioritized as a primary task and the additional task given less priority, however this may not be the case. The slowing of gait speed or slowing of cognitive response time during a dual task can be seen as the "cost" of the addition of a dual task or the "interference" effect that performing the task has on the gait task. Recently there has been increased interest in the effect of task on gait. However, to the author's knowledge after extensive searching, all studies have shown a reduced gait speed in dual tasks compared with single tasks in older adults.

Automaticity of Gait

In addition to their role in cognitive function, the frontal lobes of the brain also play a role in mobility changes with age [171]. Functional changes such as declines in executive function and gait disturbances together with age related structural changes and neuropathology[172], cause increased recruitment and activation of frontal lobe resources [20, 128, 173]. This increased activation and recruitment causes stress on the frontal lobes [20, 171] which may manifest in an individual's gait [72], such as a decrease in gait speed. It is thought that there exists a certain point where a transition from an automatic to a more self-aware gait starts to occur [23, 174]. As a consequence executive function is thought to contribute to disruptions of gait and balance and be a good predictor of falls [106]. Furthermore, this age related activation difference is thought to increase as a function of task difficulty and with cognitive impairment [175]. This is particularly seen during dual task paradigms [20] and is measured as a difference (dual

task difference) or a percentage difference (dual task cost) in gait performance from a simple to a dual gait task.

1.6.3. Bidirectional Influence between impaired cognitive function and gait in ageing

Scherder et al (2007) [176, 177] reported subtle gait disturbances in ageing and dementia indicating that gait should no longer be considered a simple automatic process but should be treated as a higher level of cognitive functioning. Many studies [163, 178, 179] have indicated that cognitive decline leads to gait disorders, however other studies[180] argue that gait impairments occur prior to cognitive impairment. This apparent contradiction does however illustrate the bidirectional link between impaired cognitive function and gait which may differ in health and pathology.

Other studies have reported links between gait and cognitive function without discussing directionality. Verlinden et al [181]investigated gait and cognitive function in the general population (n=1232, 66.3 years (11.5)) and described it as a distinct pattern of association with a close but complicated relationship which may unravel the broad spectrum of effects of brain ageing. Beauchet et al (2008) [163] suggested that higher control of motor function involves cognitive function to generate complex motor responses that have been adapted to multiple sensory inputs and environmental constraints. Beauchet et al concluded that the primary motor cortex supports global motor control messages which may be generated in response to afferent information accumulated and integrated from many systems [182, 183].

1.6.4.Neural Imaging of Cognitive function during movement

Concurrent imaging of brain and body dynamics has traditionally been restricted by brain imaging constraints. Most experimentation that has been carried out in this area has involved non-human participants. The idea of recording neural activity during normal daily activities such as fully ambulatory walking is complex due to contamination from movement artifact. In addition, walking is possibly the most complex multi-sensory process and gaining meaning from any neurophysiological recordings that are acquired is

difficult. However, there has been limited literature showing imaging of human movement to be possible. A review of the literature found some studies involving motor tasks such as shooting, driving, finger tapping and golf-putting but the experimental protocol for these studies was generally very restrictive, with muscle activity extremely limited and movement kept to a minimum. In addition, recording human electro-cortical brain dynamics directly non-invasively during normal daily activities would have far-reaching clinical benefits. However, this is a complex process and advances are required in our understanding and measurement of neural processes involved in complex physical movement.

1.6.4.1. Electroencephalography Recordings During Movement

Cognition can be measured, in isolation to motor activity, using the differences in amplitude and latency between electrophysiological signals, where a reduction in amplitude or latency can indicate cognitive impairment or cognitive load. The recording of this neural activity during motion has several precedents. Mainly, these efforts have dealt with controlled motion on exercise machines (treadmills, exercise bicycles) due to the restrictions of the EEG equipment [184-188].

However, the idea of recording neural activity during normal daily activities such as full ambulatory walking has few precedents because EEG signals are considered too susceptible to contamination to allow for neurophysiological recordings to be interpreted[188]. Current technology allows neurophysiological recordings to be taken in only extremely controlled clinical environments. It is unknown to what extent clinical neurophysiological recordings, obtained in highly constrained clinical EEG environments, represent the neural activity in ecological environments and to what extent cognitive function varies during performance of a specific motor task. EEG is the best suited for use in ambulatory applications due to the excellent temporal resolution, compared with most neuroimaging methods, and with the advancement in portability of recording devices. Individual EEG studies are also less expensive to perform than alternative methods such as fMRI or PET. Further developments in signal processing methodology allowing investigation of resultant degradation of

signal quality may allow this to be assessed further. However, EEG signal degeneration in ecological recording environments results from electrical interference, uncontrolled temperature and humidity, in addition to lapses in attention due to increased distraction. Movement-related signal degeneration results from electromyographic activity, electrode movement, perspiration and increased electrooculographic activity due to the need for participants to look for obstacles. It would be beneficial to record EEG in more ecologically valid experimental environments. Measures could be elicted by responses to standard auditory and visual stimuli in the form of discrimination tasks in different environmental conditions. Further developments are needed in the recording and processing of such neural activity.

1.6.5.Neuropsychological Assessments and Gait Analysis

Global cognition has been shown to predict longitudinal gait speed decline[189]. However, there is limited knowledge on the specific contributions of each cognitive domain to gait performance at baseline in healthy older adults.

During simple gait tasks, some studies have found short term memory and executive function to play the biggest part[189], other studies also including attention[190] and global cognition[191]. However, few studies have evaluated cognitive contributions needed during the more ecologically valid dual gait tasks. Those that have, reported executive function and short term memory[165], in addition to composite speed/executive/attention scores to be influencial on gait speed[50].

1.6.5.1. Global Cognition

Burrachio et al [192] has found an acceleration of gait speed decline up to twelve years before Mild Cognitive Impairment. In addition, Burrachio et al found the Pace gait domain (gait speed and stride length) to be the only factor associated with cognitive decline when also investigating Rhythm and Variability gait domains. Other studies however have found declines in global cognition to be associated with Rhythm, Pace and Variability gait domains[193] in initially non-demented individuals.

Greater gait performance deficits, as measured by gait speed reduction from simple to more complex gait tasks, are also associated with poorer global cognition scores [129].

Theill et al (2012)[129] assessed gait and cognitive performance during a complex cognitive-gait task and found participants with impaired cognitionhad significantly slower gait performance, but not poorer cognitive performance.. Theill et al suggesting this result indicates prioritisation of the cognitive task over the gait task for those with poorer global cognition.

Taniguchi et al [180][vi] investigated cognitive decline in a population of Japanese older adults over a four year period by examining gait speed in terms of its two component parts: step length and step frequency. From gait speed, step length and step frequency, step length was found to be the most predictive of cognitive decline (3 point reduction in MMSE) and an independent predictor after controlling for confounders[vii]. Specifically, in the lowest terile of step length, men (during maximum walking task) and women (during normal walking task) were 4.42 and 5.76 times respectively more likely to develop cognitive decline as those in the highest tertiles. They concluded that step length may be a better predictor than overall gait speed of cognitive decline.

Deshpande et al [168] analysed global cognition, as measured with MMSE score[viii], and gait parameters during usual and fast walking alone and also during a cognitive task[ix] at three and six year follow up (n=660, 74.6±4.5yrs age, 54% female, community dwelling, InCHIANTI Study). Participants with cognitive impairment walked at a slower gait speed and received less education, more depressive symptoms, worse visual acuity than those with a higher global cognition (adjusting for age and gender). Longitudinally, gait speed in all three gait conditions predicted cognitive performance[x]. In the fully adjusted model[xi] only fast gait speed was a significant

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[vi] n=666, mean age = 75.5±4.4 yrs, 59.3% women, median follow up = 2.7 yrs

[vii] Age, years of education, study site, living arrangements, hyperlipidemia, red blood cell, total cholesterol, creatinine, albumin, MMSE score and follow up year.

[viii] MMSE score < 24: Cognitively Impaired (n=134). MMSE score reduction of 3 points or more over three years: Severe Cognitive Decline

[ix] Reciting animal names that began with a particular letter

x after adjusting for baseline MMSE score

independent predictor of cognitive accelerated decline over 3 years. They concluded that fast walking is more demanding on the locomotor system, thus imposing a higher conscious control, than a more automatic slow walking. In addition, good performance during fast walking is closely related to conservation of cortical function integrity and is a measure which changes in participants with lower global cognition.

1.6.5.1.1. Gait and Specific Elements of Cognitive Function

Literature has found links between cognitive function and kinematic parameters of gait [20, 194]. Certain associations between specific elements of cognitive function and specific gait parameters have provided insight into organisation, regulation, interactions and stability of the locomotor system [102, 104]. Specifically, literature suggests a strong link longitudinally and cross sectionally between gait parameters (gait speed, gait variability, temporal gait parameters) and cognitive function utilising neuropsychological assessment test (short term memory, processing speed, executive function and attention [195]. These relationships are examined in detail below.

Short Term Memory

Short term memory is thought to be one of the first cognitive elements to be affected by ageing, however not all studies have employed comprehensive neuropsychological assessments. Hausdorff et al has hypothesised that the prefrontal cortex also plays a role in short term memory[89]. In healthy older adults poorer short term memory, in addition to poorer performance on other neuropsychological tests[23, 50, 86, 165, 189, 191], have been associated with slow gait speed during simple single gait tasks [189, 191] and during more complex dual gait tasks[165] [86]. However, other studies have not found short term memory to be an independent contributor to slower gait speed[190], finding processing speed to be a larger contributor during single gait tasks.

[xi] adjusted for baseline MMSE, age, sex, BMI, years of formal education, depressive symptoms and visual acuity.

Processing Speed

In the general population, cognitive processing speed has been associated with the Rhythm gait domain and motor processing speed associated with the Tandem gait domain[181]. Processing speed has been isolated as a main contributor to gait speed in healthy individuals and those with pathology[196]. Karli et al[197] found individual's with greater processing speed, as measured with faster reaction times, to have higher activation volumes in motor and visual cortices.

Executive Function

Poorer executive function [128, 173, 198] has been associated with slow gait speed[191], slower performance on motor tasks [199][xii], gait disruptions [78, 79, 193] and falls prediction [106, 200-202]. Executive function and attention have also been associated with the Pace gait domain [78, 181]. Many studies examining participants with dementia have found poor executive function, increased falls risk and declines in gait speed [203]. Impaired executive function has also been found to be associated with more serious falling patterns [204]. In addition, in community dwelling older women executive function may be a possible mediator between age and the onset of and progression of declines in physical function [205]. Bolandzadeh et al (2014) [206] has also found the impact of white matter hyperintensities on gait speed is mediated by executive function ability. This has increased calls to consider; those with poor executive function as a target population for fall prevention and executive function as a factor mediating improvements in fall prevention interventions[204].

Cross sectionally, poorer executive function, as measured by the Trail Making Task (TMT), has been associated with slower gait speed during single gait tasks [50] [207] (n=186 Einstein Aging Study, n=493), with a relative decrease in gait speed (DTE, dual task effect) and slower gait speed during dual gait tasks [128, 169]

[xii] Timed Up and Go (TUG)

(n=77, n=926 InCHIANTI study). In addition, longitudinally a decrease in executive function (TMT performance) has been correlated with a reduction in gait speed during single gait tasks[128] [103]. Both Ble et al [128] and Coppin et al[169] employed the delta Trail Making Task (ΔTMT) measure and gait speed was measured during single and dual task walking[169]. However, little research exists on the associations between gait and other measures of executive function which do not have cultural or language influences such as the Color Trails Test (CTT) [127].

For certain walking tasks the percentage decline in gait speed has been found to change with executive function. Gait speed statistically significantly differed walking around an obstacle for those with a low versus high executive function, concluding that the association between executive function and gait speed is task dependent. In addition, this was found to be dependent on the degree of locomotion, the sensory adaptations required and the demand on executive control.

Executive function has been found to be specifically associated with dual task gait performance. Persad et al (2008) [208] found executive function to be specifically associated with slower dual task gait performance during different dual gait tasks in older adults with cognitive impairment (Healthy Controls = 12, MCI = 24, Alzheimer's disease = 12). However, significant associations between gait speed and; memory, visual attention and visual spatial skills were not found.

Other studies investigated relative contributions from specific elements of executive function to gait performance. Holtzer et al (2013) [209] investigated non-demented older adults with particular emphasis on dual tasking and defined executive function key components to be: processing speed, conflict resolution and intra-individual variability. Holtzer et al found that only intra-individual variability predicted performance differences in gait speed in both single and dual gait tasks. Further investigating of the differences in executive function contributions to gait over the duration of a task, such as in Holtzer et al's measure, may probe aspects of automaticity of gait.

Attention

Attention is seen to play a central role in gait and locomotion[210]. Woolacott et al[106] reviewed research on the relationship between attention and the control of posture. Findings show the main areas of interest to be the frequent use of the dual task paradigm and the contribution of attention to instability in participants of all ages. Concluding; that complexity and type of dual task is important. In addition, the dual task paradigm is relevant for assessment of effect of disease, and in helping predict falls and instability in patients. Attention is a subgroup of executive function and importantly can be crudely divided out according to function including; divided, sustained, focused and alternating. However, most gait and posture studies focus on divided attention.

Divided Attention

Srygley et al (2009)[211] investigated divided attention as assessed by the dual task effect during a complex dual cognitive gait task. Findings show that even young healthy adults demonstrate a reduced cognitive performance when performing a sufficiently complex gait task. Some studies also show the effect of the dual gait task has been found to be dependent on task with dual task decrements in executive tasks (stroop task) but not for motor tasks[166] (spontaneous speech task). Other gait parameters such as stride time variability and gait symmetry have been shown to be affected by the addition of a task while walking in older adults but not younger adults[166].

During dual cognitive gait tasks, Woolacott et al[106] found a slowing of cognitive response time to a cognitive task and a slowing of gait speed. Dual task decrements in gait speed have been found to be greater in those who walk more slowly than those who walked faster at baseline[166]. Cross sectionally, De Bruin et al[167] investigated a single cognitive[xiii] task, a single gait task and a dual gait

[xiii] Tap (test for attentional performance) and MMSE

tasks[xiv] and found stride time to be associated with divided attention during the gait task at normal gait speed and stride time, stride length and gait speed to be associated with divided attention during a fast walking task[xv] (n = 62, community dwelling older adults, mean age 72.5±5.9 yrs). In addition, De Bruin et al found a high relative dual task cost during the fast walking task. They concluded that improving divided attention may translate to better performance on complex walking tasks.

In addition to findings showing a reduction in gait speed [212] and an increase in gait variability[64, 70] with Alzheimer's Disease, dual task paradigms are also useful experimentally when investigating pathologic cohorts. Hausdorff et al[213] finding a "profound effect of attention on gait" in individuals with Parkinson's disease.

Hausdorff et al[165] found that the everyday activity of walking while performing a task was dependent on multiple factors including a consistent gait pattern and executive function. The addition of a dual task (Dual Task Difference (DTD)) decreased gait speed and swing time but increased swing time variability. DTD in gait performance was correlated with the ability to perform the single walk and cognitive function. The effect was found to be dependent on the dual task, the gait feature studied and the cognitive domain. In addition, higher swing time variability from single to dual task was correlated with lower executive function, mobility and affect (e.g.: depressive symptoms) and gait speed difference or dual task gait speed was correlated with single task gait speed but not with mobility or cognitive tests.

Sustained attention

Sustained attention or alertness refers to the ability to maintain attention to a task over a period of time[214]. Sustained attention has been linked to higher risk of falls and frailty but has not been investigated in relation to gait.

[xiv] Normal & Fast walking recorded on a pressure sensing mat (GaitRite)
[xv] Dual task cost or DTC was calculated from the difference between the dual and single tasks.

Sustained attention performance and variability has been found by O'Halloran et al [134, 215] to correlate with pre-frailty and frailty in older adults within a longitudinal ageing study, (the TILDA dataset: n=4317, IQR = 55-68years) after adjusting for confounders[xvi]. The index of frailty was defined as individuals who had a low gait speed, a low grip strength, unintentional weight loss, self-reported exhaustion and low physical activity. However, this study is particularly relevant as gait speed has been shown to be a major determinant of frailty within this population[216]. Sustained attention was measured using response time mean and variability during the SART test. In the over sixty five year age group mean response time was associated with frailty and variability in response time associated with pre-frailty. In the fifty to sixty four year age group both response time mean and variability were associated with pre-frailty.

Previous research by O'Halloran et al [217] also found links between retrospective falls, fear of falling and poor sustained attention (SART response time variability). This research further strengthens the relationship between attention and gait and balance in older adults.

1.6.6.Proposed Clinical Assessment Tests

Verghese et al (2012)[218] validated a novel cognitive risk assessment that included motor function which the author calls "motor signs" and terms the test Motoric Cognitive Risk (MCR). The MCR was posed as an assessment for individuals at high risk of developing dementia. The MCR was defined as the presence of cognitive complaints and slow gait (one standard deviation below age and gender specific gait speed means) in nondemented individuals. They found MCR to be statistically significantly associated with risk of dementia or vascular dementia after adjusting for covariates (age, gender and education). Verghese et al also found a diagnostic overlap with Mild Cognitive Impairment subtypes.

[xvi] Cognitive processing speed, executive function, chronic conditions, medications, age and gender.

Clinically relevant gait changes have also been investigated. Brach et al (2010) [219] have suggested clinically relevant gait variability to be 0.01 seconds for stance time variability and swing time variability, and 0.25 centimetres for step length variability.

In addition, several studies have indicated gait speed changes during a gait task with a self-selected pace that are thought to be clinically relevant: a gait speed of faster than 1.0 metres per second[220] [221] or 0.8 metres per second [222] suggesting healthier ageing, slower than 0.6 metres per second[220] suggest increased likelihood of poor health and function. In addition, predicted life expectancy at median age and sex was found to occur at a gait speed of 0.8 metres per second with faster gait speed predicting life expectancy beyond the median: over 1.0 metres per second indicating better than average life expectancy, above 1.2 metres per second suggesting exceptional life expectancy [82].

Other studies also show a fast paced gait task to have clinical utility in predicting overall health. During a fast paced gait task both a slower baseline gait speed and a decline in gait speed have been found to predict mortality[xvii][83]. The small (between 0.04 and 0.08 m/s) and substantial (over 0.08 m/s) declines in fast gait speed were associated with a 1.2-fold and a 1.4- fold greater risk of mortality.

1.6.7.Interventions

Cognitive functions that have been associated with gait performance have been shown to be enhanced with training in older adults. Enhancing specific elements of cognitive function may aid in enhancing gait performance. Enhancement of both cognitive function and gait performance may increase quality of life and reduce adverse events experienced by older adults.

The purpose of any motor-cognitive intervention is usually to expose participants to stressful environments frequently in order to increase their capacity for these stressful environments during normal daily activities. The intervention could be in the form of a single motor or cognitive task or a dual task. The exact process which increases performance due to some training or intervention is unknown [202, 223]. One hypothesis

[xvii] n=4,016, age: 65-85 yrs, 5 follow up sessions over 12 year period

is that the participant's threshold for transitioning from an automatic process to a more voluntary process has increased. This may be due to, for instance, a habit being formed or a skill being learnt during the training sessions [224, 225]. This habit or skill may allow the task to be performed with greater ease thereby increasing cognitive reserve. This however will differ across participants. Some participants will require very simple interventions, such as instructions of: "stop talking while walking" [226]. Other participants will be able to perform multi-tasking more proficiently or without increased risk of adverse effects such as falling. Recently published research by Kearney et al[204] has recommended executive function training during interventions after finding executive dysfunction to be a factor affecting intervention success in older adults with dementia.

1.6.8.Gait Disorder and Cognitive Function

Ageing and pathology changes higher neurological areas of movement control, in particular the cortical-basal ganglia-thalamocortical loop, which produce movements and postural synergies. Cross sectionally, Herman et al[227] found gait variability statistically significantly increased in those with high level gait disorders[xviii] compared to healthy controls and it was also found that gait variability in those with gait apraxia was statistically significantly associated with Geriatric Depression Scale and fear of falling (n=53, 78yrs, 68% female). However, it was not found to be associated with age, gender, MMSE, muscle strength, no of co-morbidities or balance. Gait variability was calculated using detrended fractal dynamics on gait parameters taken from a ten meter and 2 minute walk while the participants were wearing force sensitive insoles. In addition, a measure of unsteadiness was correlated with a group of participants that walk with fear not attributed to falling (frequency of falls questionnaire) indicating a possible neurological problem, specifically a timing problem. Herman et al hypothesised that gait changes in older adults who walk with fear are likely a marker of underlying pathology.

Falling is the most severe gait disorder resulting in a complete failure of balance with severe consequences. Global cognition, as measured by MMSE, has been associated with an increased risk of falls in patients with a history of falls [228]. Springer et al [229] studied

[xviii] Defined as those who had a gait disorder with no obvious cause

performance during single and dual task conditions in healthy older adults (including fallers and non-fallers) and younger adults with similar memory scores. Springer et al found performing a dual gait tasks reduced the gait speed of all three groups but the swing time variability only increased in older adults who fell. This variability in swing time variability was correlated with executive function.

1.6.9.Gait and Neurological Function

Some literature has viewed gait as a window to neurological function, in particular neurological timing. Random or irregular fractal properties of gait dynamics have been linked to changes in the central nervous system, in particular in the internal timing mechanism. Hausdorff et al[230] investigated the fractal properties of gait dynamics in participants who were young, ageing or had Huntington's Disease. They found gait variability to be a good measure of fall risk in community dwelling older adults. Findings show that stride-to-stride variability statistically significantly predicted falls and correlated with multiple factors such as strength, balance, gait velocity, functional status and mental health. Hausdorff et al hypothesised that these fluctuations in temporal gait parameter intervals are altered by changes in neurological function associated with ageing and certain neurological diseases. Measuring the degree to which one stride interval is correlated to the previous and subsequent stride intervals over different time scales they found significantly less correlation (more randomness) in ageing and those participants with disease (Huntington's disease) compared with younger and control participants. This measure was also correlated with the degree of functional impairment in the participants with Huntington Disease.

Monterro-Odasso et al [231] also commented on this apparent randomness of gait pattern in disease states while investigating participants with Mild Cognitive Impairment. Monterro-Odasso et al measured performance on a single cognitive task, a single gait task and a dual gait tasks[xix] cross sectionally (n=11, mean age 76.65±7.3 yrs). The mean gait speed was found to decrease statistically significantly with dual task and a high relative stride time was found for preferred gait speeds. They hypothesised that an altered gait

[xix] Counting backwards

pattern may be a type of gait "arrhythmia", similar to that described by Hausdorff et al[104] as randomness, and may correlate with other health outcomes.

Furthermore, gait can improve in both ageing and Parkinson's disease with certain rhythmic tasks such as walking to a metronome or a rhythmical listening task. It is hypothesised that a re-setting of the participant's internal clock through rhythmic auditory stimulus results in an improved stepping rhythm of gait. This assumes a higher neurological control of gait.

1.7. Conclusions

In conclusion, several research questions emerge out of this literature review. Many of the studies to date have focused on cohorts with pathology. However, research is lacking into the cognitive contributions to gait performance in the general population. Further understanding of this contribution would form a baseline on which pathology could be judged. In addition, those studies that have investigated healthy older adults use small number of participants and have not included specific cognitive domains or cognitive processes comprehensively. Given the representative nature of the TILDA dataset, validation of gait parameters (gait speed, gait variability) during different walking tasks over a larger age range would allow the gait of those from mid-life to very-old age be assessed more objectively. Differences in speed of processing, short term memory, in addition to executive function and attention have been found to contribute to the gait-cognitive function relationship. However, neuropsychological assessments are multideterminate in nature and including a comprehensive list of neuropsychological tests may parse apart specific cognitive function elements at play during gait in this population. In addition, knowledge is lacking into how this cognitive function contribution changes with differing gait tasks. Clinical assessment would benefit from further understanding of the independent contribution of each specific element of cognitive function to healthy motor and cognitive function. Further research in these areas would contribute to the understanding of health and transitions to cognitive impairment or incipient pathology across different age groups.

In addition, it is important to consider the gait task administered, the protocol employed, the prioritisation given and the gait parameters assesssed when choosing an experiment. Gait speed has been shown to be sensitive to general health. Temporal gait parameters, in particular their variability measures, have been shown to be associated with neurological impairments and possibly incipient cognitive impairment. Executive function and dual gait tasks are important components to include in assessments of healthy older adults also.

Therefore, I hypothesise that by investigating the cognitive contribution, in particular the contribution of exectutive function, attention and global cognition, to gait performance that these areas of research will be advanced. This hypothesis will be tested by the examination and investigation of the following research questions.

1.8. Research Questions

A. **Are there links between specific behavioural test scores and gait parameters?**

Correlations between participant variability on neuropsychological test scores and gait speed were investigated. Firstly, the relative contributions of elements of cognitive function (processing speed, short term memory, executive function, sustained attention, verbal fluency and visual reasoning) to gait speed in a nationally representative population of adults over 50 years old was examined in Study 4. Study 4 aimed to reduce bias caused by the multi-determinate nature of neuropsychological assessment tests by including a comprehensive list of these tests and examining their independent contribution to gait performance (gait speed) in a step-wise manner. This is achieved in part due to the large dataset (n=8507) examined.

Secondly, the robustness of this gait-cognitive function relationship was examined by exploring this relationship in a more commonly clinically employed assessment test: the Montreal Cognitive Assessment (MOCA). Gait speed was examined as a predictor of global measures of cognitive function in Study 2. In addition, the relative

contributions of elements (domains, subscores) of the MOCA test to gait speed were examined in a nationally representative population of adults over 50 years old in Study 5.

B. **Are there links between specific executive function test scores and gait performance?**

Given the link between gait performance and executive function found in literature the between-participant variability in executive function test scores (Color Trails Test, CTT) and correlations with gait speed were examined in Study 3.

C. **Higher Control of Gait**

Study 3 probes this executive function-gait relationship further by examining correlations between executive function test scores and gait speed decrements in three gait tasks in a nationally representative population. Study 3 also extends findings from literature [23, 174] exposing potential specific transition points from an automatic gait to a more consciously controlled gait during three gait tasks.

D. **Dual Task changes in gait parameters: The effect of gait task**

Previous studies have found gait performance to change with gait task. Gait performance during a simple gait task and two complex gait tasks were investigated and compared throughout the research described in this thesis. Study 4 examines this area in detail where variability in cognitive contributions to gait speed between-participant and within-participants were investigated in the three gait tasks. .

E. **Division of attention: What is the link between different measures of attention and gait variability during different gait tasks?**

Study 4 and Study 7 investigated between-participant variability in attention, a cognitive element highlighted in literature as important. Study 4 and Study 7

examined sustained attention test scores and divided attention measures and their correlations with gait performance (gait speed and gait variability) in older adults. Motivated by research questions probing what information other gait performance measures hold. Study 8 investigated variability between-participants in sustained attention test scores (SART scores) and gait variability in young adults.

F. **Higher Control of Gait: What variability is present in time series generated from gait parameters via non-linear analysis?**

Literature has highlighted gait variability as an important gait performance measure to assess when examining cognitive function. In addition, research questions emerged during previous studies (Study 1- Study 8) probing if different methods could be employed to generate more descriptive gait measures, in particular gait variability measures such as were employed in heart rate variability research. Motivated by this study 8 explored between participant and within-participant variability employing a dynamic series approach to generate stride time variability measures. This allowed links between the rhythmicity of the locomotor system and cognitive function in healthy young females to be examined

G. **What is the effect of age and cognitive decline on variability of gait parameters?**

Research is lacking into the effects of covariates, such as age, on the gait-cognitive function relationship in a cohort with a large age range. In addition, little is known about how this gait-cognitive function relationship changes with cognitive function group: from healthy cognition, mild cognitive impairment and dementia. Interactions between age and elements of cognitive function and its affect on gait speed were investigated across simple and complex dual gait tasks. This research question was examined in Study 1, Study 2 and Study 4. Study 5 specifically investigated interactions between global cognition and cognitive domains (as measured by domains assessed in the MOCA test) and its affect on gait speed across simple and complex dual gait tasks.

H. **What are the neurophysiological measures of cognitive function in ambulatory monitoring?**

Concurrent acquisition of gait and cognitive function measures in ecologically valid environments would be highly beneficial. It would allow further exploration of cognitive and kinematic changes prior to adverse events such as falls. It would also allow examination of changes in attention during different simple and complex tasks. Study 6 examined the quality of an ambulatory EEG signal during different movement tasks.

I. **Are the results clinically useful in the diagnosis of Mild Cognitive Impairment?**

Finding an objective biomarker for prodromal cognitive impairment would be clinically beneficial as more treatment options are available during earlier stages of the disease. Study 2 explored if gait could be employed as a biomarker for cognitive impairment.

J. **What contribution do these experimental results make to our understanding of the locomotor system?**

Previously, gait was thought to be an automatic process but more recently it is thought that a critical point exists when even healthy individuals require some conscious control over their gait. This research question was explored throughout the studies described in this thesis.

K. **What is the within-participant and between-participant distribution of gait performance measures and cognitive function performance measures in a nationally representative population? What factors affect this performance?**

As discussed previously in the literature review, TILDA is a novel dataset which has a large number of participants, ranging in age from mid-life to very-old age. The representative nature of the dataset allows for research outcomes to be clinically informative. The distribution of gait and cognitive function measures were explored throughout the studies described in this thesis.

1.9. Research Focus

a. Gait Performance and Cognitive Function in a Nationally Representative Population:

Many of the studies to date that have investigated gait and cognitive function have based findings on small participant numbers. Cross sectional data from a large cohort of older healthy adults from the The Irish Longitudinal Study on Aging (TILDA) dataset, a recently collected sample of the Irish population, was employed to investigate gait performance and cognitive function.

b. Ambulatory Monitoring:

Employing a novel EEG experimentation set up to investigate attention during mild exercise in young healthy adults. The electroencephalography (EEG) method used was deemed to be the best imaging method due to its superior time resolution and the portability of the acquisition systems.

c. Gait Variability and Attention

Employing a motion analysis system to assess gait variability and a computerised cognitive function assessment to assess sustained attention in young healthy females. Investigating continuous gait data and continuous cognitive data employing a novel analysis method.

The studies described in this thesis aimed to probe the research areas found to be lacking in literature. Many studies described in this thesis investigated the The Irish Longitudinal Study on Ageing (TILDA) dataset, a nationally representative population of adults fifty years and older. Although nationally representative of community dwelling adults over fifty years of age, the TILDA dataset is a relatively healthy sample. Thereby, when examining TILDA we were exploring the many possible combinations of healthy ageing and any possible transitions from these healthy states. Specifically, studies described in this thesis which employed the TILDA dataset investigated variations between participant's gait performance and global cognition or elements of cognitive function such as executive function, attention and global cognition. Different measures of

attention were explored (divided attention and sustained attention) acquired through different methods. Gait performance was assessed by employing gait cycle time, stride time variability, gait speed or a derivative of gait speed. Correlations between specific scores on cognitive function assessment tests and gait performance during simple and complex gait tasks were examined. Higher control of gait and automaticity of gait were explored by investigating points of transition from an automatic to a more consciously controlled gait. The relative contribution of different cognitive measures to gait performance was also investigated. This was examined in order to find independent predictors of gait performance. The effect of covariates, global cognition and task on variance in gait performance was explored. The efficacy of gait as an biomarker for impaired cognitive function was explored by examining correlations between cognitive function and gait performance during different gait tasks. A positive result (good efficacy) would support the introduction of a gait task to assess cognitive function in clinical practice. In addition, the specific values found(executive function-gait speed points of transitions) were evaluated as diagnostic tests for changes in executive function.

Two studies described in this thesis employed young healthy adults and investigated associations between attention and gait performance. This was examined by evoking task switching to divide attention and employing different tasks with varying complexity. Sustained attention was also investigated and its associations with gait variability in healthy young females and older adults. Higher control of gait was also investigated by examining what variability was present in time series gait data generated from gait tasks employing dynamic analysis and linking the rhythmicity of locomotor system to cognition in healthy young females. In addition, it was investigated if neuropsychological measures of cognitive function could be acquired during ambulation.

Finally, the research question: What contribution do these experimental results make to our understanding of the locomotor system?, was examined throughout the studies described in this thesis. The spectrum of gait and cognitive function performance, in addition to any interactions, across a nationally representative population with a wider age range and a larger number of participants than previously explored were examined. Any outcomes of this research will strengthen our understanding of health, in particular in community dwelling adults over fifty years of age.

CHAPTER 2: General Methods

Given these research questions one needs to consider what methods are available to us. Firstly, the research questions need to be investigated in a larger cohort than previously examined and there is a requirement for data to be acquired with previously validated commercially available methods. Secondly, in order to probe the research questions fully the relationship between gait and attention needs to be explored. Finally, further validation is required on methods employed to investigate the relationship between gait and cognitive function, such as recording cognition through neuroimaging during movement. Investigation of the research questions posed employing these methods would allow conclusions be drawn. Study procedures including descriptions of participant characteristics, gait and cognitive measures recorded and the analysis methods employed are described below.

2.1. An Introduction to The Irish Longitudinal Study on Ageing (TILDA)

The Irish Longitudinal Study on Ageing (TILDA) is a longitudinal study charting detailed social, economic and health circumstances utilising both survey interviews and biological measurements of a sample of 8507 community dwelling persons aged fifty years and over. The target population for the TILDA survey was the population of persons aged fifty or over living in residential addresses in the Republic of Ireland, and their spouses or partners of any age. TILDA recruited a stratified clustered sample of 8178 adult's representative of the community dwelling Irish Population aged fifty years and older. Younger spouses and partners were also invited to participate, thereby including those under fifty years of age in the dataset, primarily to aid with the collection of information on family and financial circumstances. The planned duration of TILDA is ten years, however all data included in this thesis are based on the cross sectional data from the first wave of TILDA. This included data from all 8507 TILDA respondents (from 6282 households) of who 8178 were over fifty years of age.

The studies within this thesis examine the first wave of the TILDA dataset. Data collection in TILDA comprised of a computer-assisted personal interview, a self-completion questionnaire and a health centre assessment[232]. Participants were only excluded from the study if they were unable to perform the face-to-face interview. All participants underwent the extensive face-to-face computer-assisted interview, were left the self-completion questionnaire to complete and return and were invited to a health assessment either at a dedicated centre or in the home[233]. The overall response rate to the study was 62.0% which corresponded to 5037(61.6%) agreeing to attend the health assessment and a high proportion returning the self-completion questionnaire. Most gait and neuropsychological data analysed in the studies described within this thesis were collected at the health centre assessments. Inclusion criteria for analysis employed in this thesis were valid gait and neuropsychological data, making a maximum of 5037 participants eligible (51% women, 62.0(8.5) mean (SD) age). Other data employed (comorbidities, covariates etc) were collected at interview or through the questionnaire. Participants who attended the health assessment had different personal characteristics than the general population; for example they were more likely to be from urban locations, healthier and younger. In order to remove this bias, and to represent the Irish population, weights were created and applied to statistical analysis, see Section 2.6.1: Statistical Analysis and Interpretion.

The target population of the TILDA study included all members of the population of Ireland who were fifty years or older and who live in the community. To generate the TILDA sample all postal addresses in Ireland were assigned to one of 3155 geographic clusters, and a sample of 640 of these clusters was selected, stratified by socio-economical group and geography to maintain a population representative of individuals aged fifty and over in each cluster. A response rate of 62% equated to a total of 8178 interviews conducted with respondents belonging to 6282 households from October 2009 through to February 2011.

There were three parts to the data collection of social, economic and health circumstances: a computer-assisted personal interview, a self-completion questionnaire and a health centre assessment[232].

During the TILDA face-to-face Computer Assisted Interview (CAPI) each participant was asked about: social circumstances, health and healthcare, employment and lifelong learning, planning for retirement expectations, sources of income, assets and transport. Specifically in

the health and healthcare section each participant was asked about diagnoses such as; cardiovascular disease, mobility disorders, neurological disorders and mental health, in addition to self-reported physical and mental health (including memory, hearing, vision, physical activity and other health behaviours). More sensitive questions were included in the self-completion questionnaire on social connectedness, loneliness, perceived stress, stressful life events, anxiety, worry, quality of life, ageing perceptions and alcohol consumption.

The health assessment comprised of a battery of health assessments where neuropsychological, cardiovascular, gait, balance, sensory, strength, bone density and macular degeneration measures were collected. All health assessment measures were collected in one of two dedicated health assessment centres in similar environments by trained medical personnel. The neurpsychological and gait assessments included during the TILDA health assessment are of most interest to the studies described in this thesis, however some information is also included from the TILDA interview and questionnaire when calculating adjustments (e.g.; comorbidity variable) for analysis.

Ethical approval was obtained from Trinity College Dublin Research Ethics Committee. All participants provided personal written informed consent, thereby excluding those with severe cognitive impairment. The study design and data collected were described previously [127, 233]. Further information can be found on the cohort profile [233], the design report[234] and initial findings[235] of The Irish Longitudinal Study on Ageing at www.tilda.ie.

2.1.1.Gait Measures

During the TILDA gait assessment participants completed a walk under simple single gait task condition in addition to two complex dual gait task conditions. Gait speed, stride time, step time and gait variability were the gait performance parameters investigated.

2.1.1.1. Gait Assessment Test

During the TILDA health assessment participants performed a gait assessment. Participants were asked to complete three walks in total: a single gait task and two dual gait task. The two dual task were a dual motor gait task and a dual cognitive gait task.

The dual motor gait task involved walking while carrying a plastic glass filled one inch from the top with water. The dual cognitive gait task involved walking while reciting alternate letters of the alphabet (A, C, E, etc.). Instructions given to participants were to: "walk at your normal pace and, as you walk, recite alternate letters of the alphabet out loud" for the cognitive gait task, and "walk at your normal pace and, as you walk, carry this glass of water", a glass filled one inch from the top with water, for the motor gait task. While seated, participants were given a practice alternate letters trial.

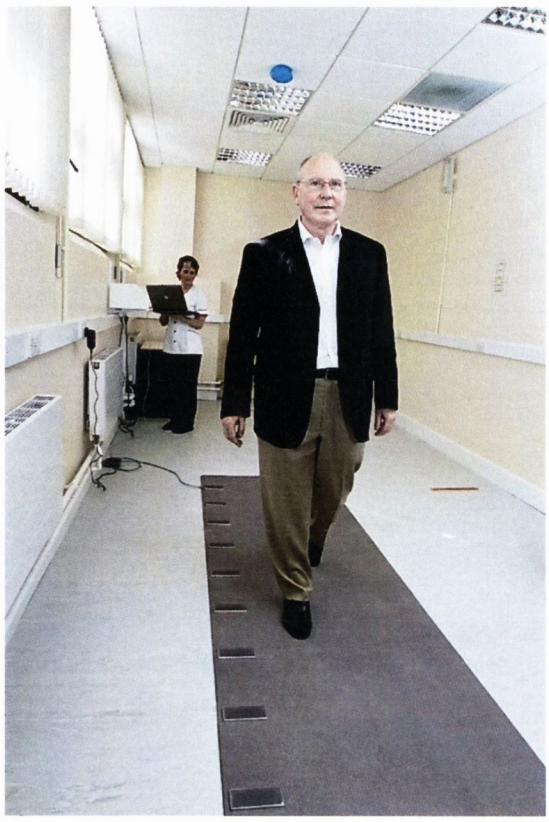


Figure 2: A TILDA participant performing the gait assessment test.

Gait parameters were recorded during all three gait tasks. Participants were asked to wear normal walking shoes and to walk at a self-selected pace. The gait tasks began 2.5 metres before the start of the walkway and continued for 2 metres past the end of the walkway to facilitate acceleration, deceleration and turning. Two passes of the mat were recorded for each task at a self-selected comfortable pace and an average gait parameter was calculated from the two passes.

2.1.1.2. Pressure Sensing Mat

A 4.88m walkway from the Gait Rite System Incorporated, CIR, USA [236] was employed in the TiLDA gait assessment to acquire gait measurements of TILDA participant who attended the TILDA health assessment.

The GAITRite System is an electronic walkway. The system is composed of pressure activated sensors that are embedded in the walkway which have the ability to measure temporal and spatial (two dimensional geometric position) parameters. The system's GAITRite Platinum Interface Module calculates inferred parameters such as gait speed and relationships between spatial and temporal events by applying common physics and math formulas. The total walkway is 4.88 metres long, 0.9 metres wide and 3.2 millimetres in depth. The system has 1.27 [cm] spatial resolution and 1 sample temporal accuracy. The walkway is composed of anti-slip vinyl (outer top), open cell neoprene rubber (outer bottom) and uncoated polyesters (inner).

Each sensors encapsulated within the walkway has an active area of 61 centimetres square and contains 2,304 sensors arranged in a 48 by 48 grid pattern. The sensors are activated when pressure is exerted by the participant's feet as they ambulate across the walkway. The system records the geometry of pressure exerted by the foot and the relative arrangement between footfalls in two dimensional space.

The system identifies each footprint by grouping sensors and employing proprietory algorithms. The footprint is then divided into a quadrilateral that encloses the footprint, the heel area, the mid area, the toe area, the centroid and the geometric center of each area.

The following gait parameters recorded by the GaitRite system were included in this thesis: gait speed, cycle time, step time, stride length and step length during all three gait tasks (single, dual cognitive and dual motor gait tasks). Measures of disturbed gait were identified by the GaitRite system in addition to those noted by test administrators.

Gait measure definitions vary from study to study which may affect results. The gait measure definitions used by the GaitRite system to calculate gait parameters are as follows.

- Gait speed is the distance travelled divided by the ambulation time. Where ambulation time is the time elapsed between first contact of the first and last footfalls.

- Cycle Time is the time elapsed from first contact of one foot to first contact of the same foot and includes the stance and swing phase of both legs.
- Step Time is the time elapsed from first contact of one foot to first contact of the opposite foot.
- Stride length is the distance on the line of progression between the heel points of two consecutive footprints of the same foot (left to left, right to right).
- Step Length is the distance along the length of the walkway from the heel center of the current footprint to the heel center of the previous footprint on the opposite foot.
- Mean and standard deviaitons of footfall measured events are calculated at the footfall level. Mean, standard deviations and coefficient of variance of gait cycle events are calculated using summary data where standard deviation is the population standard deviation. The Population Standard Deviation is the square root of the sums of variances from the mean divided by n-1:

$$Population\ Standard\ Deviation, s = \frac{1}{n-1}\sqrt{\sum_{i=1}^{n}(xi - \overline{x)}}$$

$$Population\ Coefficient\ of\ Variation = \frac{S}{\bar{X}} * 100$$

- Disturbed Gait: Gait during any gait task included distrubances such as pauses, short steps and stepping backwards.

Step and stride measures of the right side of the body were investigated. Body side differences for all measures were examined for statistical differences.

Participants were asked to walk at a self-selected pace. Gait speed for the single gait task and both dual gait tasks calculated by the Gait Rite system were employed. Temporal and spatial parameters (step time, stride time, step length and stride length) calculated by the Gait Rite system and variables derived from gait speed: Dual Task Difference and Dual Task effect, were also employed.

2.1.2.Cognitive Function Measures

The TILDA neuropsychological assessment tests were employed to assess cognitive function. Global cognition and elements of cognitive function (short term memory, processing speed, executive function, verbal fluency, sustained attention and visual reasoning) were assessed by seven assessment tests during a forty minute neuropsychological assessment as part of the TILDA health assessment. Most neuropsychological tests measured more than one cognitive element, but each task is classified according to its main cognitive element below.

2.1.2.1. Measures of Global Cognition

The Montreal Cognitive Assessment (MOCA) and The Mini Mental State Examination (MMSE) assessed global cognition. MOCA and MMSE are two types of 0 to 30-point cognitive screening test. A cut-off test score of 26 in MMSE is commonly used as a "normal" or healthy cognitive function, an MMSE score of below 24 as severe cognitive impairment and under 26 in MOCA for Mild Cognitive Impairment (MCI). Both tests take about 10 minute for the participant and the clinician to complete and the total score is a measure of global cognition which is the sum of the following tests:

Figure 3: Experimental set up for the TILDA Neuropsychological assessment

- Short Term Memory (noun learning & recall)

- Visuospatial Abilities (draw Clock, Cube)
- Executive Function (language fluency, abstraction)
- Attention (sustained attention task)
- Concentration (subtraction task)
- Working Memory (forward and back digit task)
- Language (naming, sentences, fluency)
- Orientation (time & place)

MOCA in addition includes tests to measure visuospatial function and executive function (Trail Making Task (TMT)). MOCA and MMSE assessment test have been included in Appendix 2 and Appendix 3 respectively.

The Montreal Cognitive assessment (MOCA), a test of global cognition, has also been shown to have a good sensitivity to detecting MCI[109]. MMSE has been shown to be affected by education, however for MOCA years of education can be allowed for by the addition of a point onto the test score if the participant has less than 12years of education. Nasreddine et al[109] found MOCA to be more sensitive at detecting cognitive impairment than MMSE in older adults with a 90% sensitivity for MOCA as opposed to 18% for MMSE for MCI (using a test score cut off of 26). In addition, Nasreddine et al found 100% sensitivity for MOCA as opposed to 78% for MMSE for detecting Alzheimer's disease. Both tests were found to have very high specificity of 100% (MMSE) and 87% (MOCA) at detecting Alzheimer's disease.

It is interesting to note that Monterro-Odasso et al found that a presence of MCI did not preclude performance of dual task, however they defined a MOCA score of 26 or lower as mildly cognitively impaired and excluded these participants from the study.

Paul et al conducted a neuroimaging study on the MOCA task[109]. Although overall MOCA score did not significantly correlate with any of the neuroimaging indices assessed, it was found that MOCA did correlate with a more extensive cognitive test, RBANS and MOCA sub-scores (visuospatial/executive, attention and learning) were found to correlate with one neuroimaging index used (Whole Brain Volume (WBV)).

Further detail on MOCA and MMSE is described in Chapter 1: Literature review.

MMSE and MOCA are measure of global cognition, however the cognitive abilities that make up global cognition may also be assessed individually by means of other neuropsychological tests such as sustained attention (SART), visual memory and executive function (CAMDEX), speed of processing (choice reaction time test), visual attention and task switching (Trail Making Task (TMT)). The neuropsychological tests employed within the studies described in this thesis are discussed below:

2.1.2.2. Measures of Short Term Memory

Short term memory was assessed using a ten word recall test which requires immediate and delayed recall.

2.1.2.3. Measures of Processing Speed

Processing speed was measured using mean cognitive reaction time from the Choice Reaction Time test (CRT)[138]. A yes/no stimulus appeared on the screen and participants responded by releasing a button and pressing a corresponding yes/no button (100 repetitions). Cognitive reaction time was the time taken to release the button in response to the stimulus.

In Study 1 the choice reaction time test measured speed of processing. Differences between response times in the first half of the test compared with the second half of the test were calculated to assess if any practice effect ensued which can be an indicator of healthy cognitive function.

$$\Delta CRT = \frac{CRT\ First\ 50\ Response\ Times - CRT\ Second\ 50\ Response\ Times}{CRT\ First\ 50\ Response\ Times}$$

Response time can be further broken up into cognitive and response time. Cognitive reaction time is the time taken to release the button in response to the stimulus. Motor response time is the time taken to press the yes/no button after the button is released.

2.1.2.4. Measures of Executive Function

The Color Trail Test (CTT) was used as an alternative to the Trail-Making Task (number and letter), employed by Coppin et al[169], to assess executive function as it removes cultural and language bias[130].

Study 1, Study 2 and Study 5 employ the Color Trials test (CTT) to assess exectutive function. However, visual reasoning, verbal fluency, divided attention and sustained attention measures employed in the studies described in this thesis are also considered elements of executive function.

The Colour Trial Test was developed to have the same sensitivity and specificity as the standard TMT but to be free from possible language or cultural bias influences. The CTT is deemed more suitable for cross cultural and special needs contexts as it retains the psychometric properties of the standard TMT therefore can be compared with the standard TMT but substitute English letters for colour.

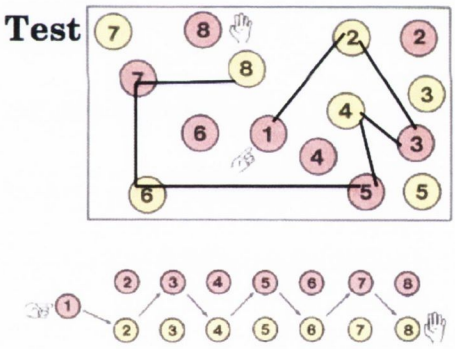


Figure 4: Instructions for completion of part 2 of The Color Trails Test

The CTT [130, 131] is a standard test thought to measure frontal lobe function. The CTT is an objective, fast test of executive function which was initially developed by the US Army, as an individual battery test for its capacity to be a measure of selective attention, mental flexibility and visuo-spatial skills.

The CTT is comprised of two trials – Part 1 and Part 2. Part 1 involves connecting numbers in ascending order with a pencil as quickly as possible, and Part 2 additionally requires alternating between vivid pink and yellow numbers that are perceptible to colour-blind individuals[130], see Figure 4. Both parts are timed. The

difference score is the time taken to complete Part 2 minus Part 1, or ΔCTT, [132] and it has been employed as a measure of executive function. ΔCTT requires cognitive flexibility and adjusts for differences in upper extremity motor speed and visual scanning[128].

We calculated ΔCTT as follows:

$$\Delta CTT = Time\ to\ Complete\ CTT\ Part\ 2 - Time\ to\ Complete\ CTT\ Part\ 1$$

Performance on the CTT is seen as a sensitive indicator to neurological impairment. Part 1 is thought to measure visual search and motor speed and Part 2, a dual cognitive-cognitive task, thought to measure higher level cognitive skills such as cognitive flexibility. Time to completion of part 1 or 2 is a commonly reported performance index. The difference score has been shown to be a better indicator of executive function than part 2 alone as it removes the speed element from the test evaluation thus eliminating the examiner's reaction time and participant correction time. CTT has been shown to be sensitive to cerebral dysfunction as it probes both motor speed and attention. ΔCTT can also be seen as a cognitive-cognitive dual task cost and thus a measure of cognitive flexibility.

Little has been reported on categorising CTT scores, however Coppin et al categorised ΔTMT group divisions into low (>156s), intermediate (70-156 s) and good (< 70 s) executive function. Other ΔTMT group divisions have been used such as less than 78, between 78 and 187 and greater than 187 seconds for good, intermediate and poor executive function respectively.

2.1.2.5. Measures of Visual Reasoning

Visual reasoning was assessed using the Revised Cambridge Examination for Mental Disorders of the Elderly (CAMDEX-R)[133] Visual Reasoning Task which requires visuoperceptual/spatial and some executive function ability was assessed by performance on a pattern sequence task. Three boxes were presented with objects inside and one empty box. Participants were asked to identify the missing object to complete the pattern from a list of six options.

2.1.2.6. Measures of Verbal Fluency

Verbal fluency was assessed using the MOCA Letter Fluency Task which requires language, in addition to some memory and executive function ability, and involves listing as many words as possible beginning with "F" in one minute[108].

2.1.2.7. Measures of Attention

Sustained attention, divided attention and attentional capacity were assessed. The method employed to acquire a measure of sustained attention is described below. Divided attention and attentional capacity were acquired through gait analysis methods in both the dual motor and dual cognitive gait tasks employed during the TILDA gait assessment is described in Section 2.4: Dual Task Paradigms. No specific measures of selective or focused attention were collected in the TILDA dataset.

Sustained Attention

For all studies described in this thesis (including Study 8) the fixed sustained attention response task (SART) was the task employed to assess sustained attention.

During the SART assessment test repeated digits were presented sequentially from '1' through to '9' on a screen directly in front of the participant. This block of sequential digits was run 23 times one after the other (207 digits), 800ms Inter Stimulus Intervals (ISI). Participants were asked to press a button for every digit presented 'except for the digit '3'. (i.e.: press on '1', '2', '4', '5', '6','7', '8' and '9').

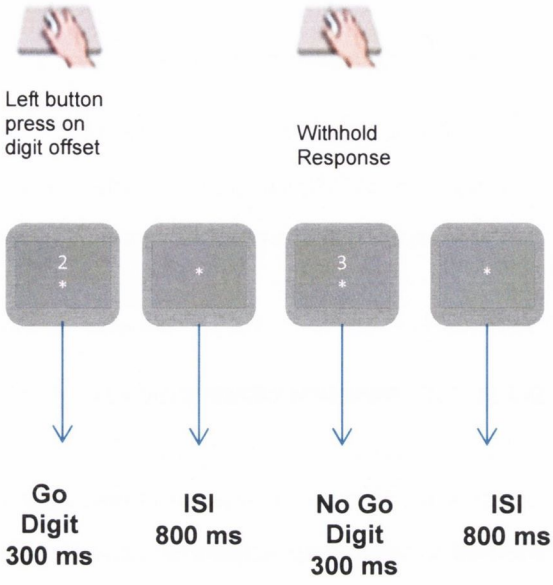


Figure 5: Sustained Attention to Response Task (SART) Experimental Paradigm

SART coefficient of variation is the mean variation in reaction time, across the task, to all stimuli except for digit '3' and is employed as the measure of sustained attention[237]. Additionally mean and standard deviation of the average response time to each digit, mean total errors of commission and mean total errors of omission were explored.

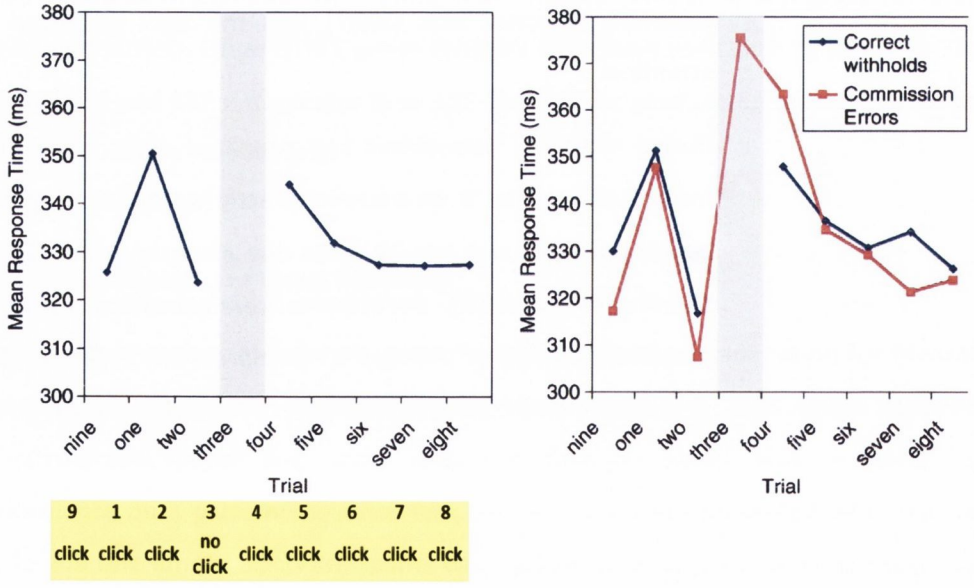


Figure 6: Sustained Attention to Response Task (SART) mean response time variation with and without errors of commission [1]

Response time units are in milliseconds. Greater SART Reaction Time Variation and greater SART Error of Commission are indicative of poorer sustained attention. These variables are of interest as they measure stages of attentional disengagement [214]: response time variation (Stage 1), anticipations (Stage 2), and omissions (Stage 3) assessed here as SART response time coefficient of variation (Stage 1), errors of omission (Stage 3) and anticipations which may be included in errors of omission and also in errors of commission.

A major advantage to employing the Sustained Attention to Reponse task is that it can be computer administered. In addition, research has shown that sustained attention as measured by SART has a neural basis [1] where monitoring and maintaining performance against attentional drift, as well as response inhibition roles have been found to be active during the SART task. Specifically fMRI studies have shown a significant activation in the pre-frontal cortex [238].

2.1.3.Decriptive Measures

Age, gender, body mass index, educational attainment and depression descriptive measures were employed to describe the population. In addition, to address the research questions posed and gain a true understanding of the relationship between gait and cognitive function analysis method outcomes were adjusted for these factors.

The Centre for Epidemiological Studies Depression scale (CES-D) was used to measure depression symptoms in participants. The CES-D is a short test designed to measure depressive symptoms in the general population.

2.1.4.Comorbidity Measures

During the TILDA face-to-face interview each participant was asked about diagnoses such as cardiovascular disease, mobility disorders, neurological disorders and mental health and self-reported physical and mental health including memory, hearing, vision, physical

activity and other health behaviors. Specifically each participant was asked about the number of chronic diseases their doctor had told them they currently have or previously had from the following list: heart attack, heart failure, angina, hypertension (self-report), high cholesterol (self-report), stroke, diabetes, cataracts, lung disease, asthma, arthritis, osteoporosis, cancer, Parkinson's disease, peptic ulcer and hip fracture.

2.2. Methods to Measure Attention during Movement

A small pilot study was undertaken to measure attention during mild exercise. This pilot study took place at laboratories within The Trinity Centre for Bioengineering and The Physiological Department both at Trinity College, University of Dublin and The Physiotherapy Department, St James's University Hospital, Dublin.

Participants completed a movement and a cognitive assessment (n=7 (4 female), 22-32 years). Ethical approval was obtained from Trinity College Dublin Research Ethics Committee. All participants provided personal written informed consent.

Electroencephalography (EEG) was used in Study 6 to measure neural activity during mild exercise.

2.2.1.The Kinematic Measures

2.2.1.1. Electromyocardiography

In Study 6 gait activity was acquired employing electromyography (EMG) to record activity of the lateral and medial right soleus muscle. The EMG recordings were acquired along with the EEG recordings with a Biosemi data acquisition system[239]

2.2.2.Cognitive Measures

2.2.2.1. Electroencephalography Measures

Electroencephalography (EEG) was used in Study 6 to measure neural activity during mild exercise. As part of the electroencephalography recording process potential

differences were recorded to determine the underlying neural activity with high temporal precision (sampling rates > 512Hz), but low spatial precision (a common setup employs 128 electrodes, which has a 6 – 8 cm^3 spatial resolution[240] compared with other neuroimaging methods such as functional Magnetic Resonance Imaging (fMRI)[xx]. Furthermore EEG was used during this study as it is smaller and more portable than other imaging systems and can be battery powered and self-contained, and so was suitable for mounting on motion platforms, allowing for controlled motion while recording neural activity.

During EEG recording the skull and skin act as spatial filters for the signal and so the underlying neural activity is highly attenuated therefore a high level of amplification is needed to detect the signal, which is in the range of 20 – 40 μV. Due to this amplification, other unwanted signals contaminate the recorded EEG signal such as electrooculogram (EOG) activity from eye blinks electromyogram (EMG) activity, due to movement. These artifacts can be a particular issue in motion-based research.

However, EEG recording during performance of a cognitive task can directly and quantitatively measure cognitive function such as the P300. The P300 event related potentials (ERPs) are considered a measure of cortical activity when processing complex information and are assessed by means of its two main components: amplitude and latency. Reduction in amplitude or increase in latency can indicate cognitive decline or cognitive load.

2.2.2.2. Methods

Electrophysiological (EEG, EOG, EMG) recordings were taken for 7 healthy participants (aged 22 – 32 yrs, 4 female) while presented with an auditory oddball task. Data was recorded in different experimental conditions increasing in magnitude of movement. A control, a static (seated) and a dynamic (fixed cycling) experimental condition were investigated. Recordings were also taken for two participants during treadmill walking. Both cycling and walking occurred at a self-selected comfortable pace for the duration of the recording.

[xx] fMRI: temporal precision (sampling rates < 1Hz), spatial precision (2 – 3mm typical).

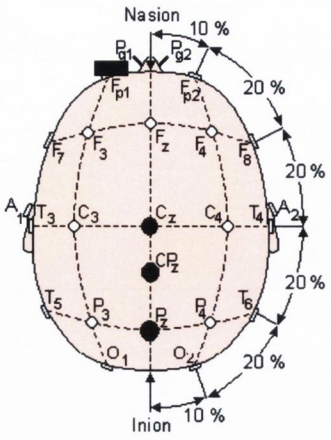


Figure 7: The 10-20 EEG electrode placement system[144] and position of Cz, CPz, Pz and Fp1 (facial EMG)

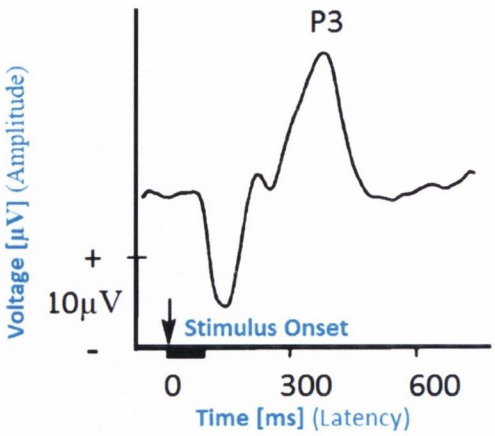


Figure 8: The auditory P300 Component – an o measure of cognitive function. P300 occurs approx 300 [ms] after onset of stimulus[145]

2.2.2.2.1. The Auditory Paradigm

The auditory oddball task lasted seven minutes and required participants to react to target stimuli (oddball probability of 0.2, 41 target stimuli) which occurred in a stream of more frequent non-target stimuli (probability 0.8)[241]. Target and non-target events (1000 Hz and 500 Hz tones respectively) each presented for a duration of 60ms in a pseudo-random fashion, were performed using Presentation® software, Version 0.70 [242]. Participants were asked to respond by a button press immediately after hearing the target stimulus and were instructed not to react upon hearing the non-target stimuli. Each experiment consisted of four, seven-minute long blocks of the auditory oddball task.

2.2.2.2.2. Electrode Placement

A Biosemi[239] data acquisition system was used to record information from eight electrodes (5 EEG, 1 EOG, 2 EMG electrodes plus a reference mastoid). Two electromyographic (EMG) electrodes which were placed on the lateral and medial

right soleus muscle on the calf which has been shown to be active once per gait cycle. EMG data was digitised at a sampling rate of 1024Hz.

EEG activity was recorded from three midline electrode sites at the vertex of the head (Cz, CPz and Pz according to the 10-20 system[243, 244]) using an elastic electrode cap[239], see Figure 7. EOG and facial EMG (Fp1 in Figure 7) were recorded from above and below the left eye. Data were referenced to the left mastoid. Data were sampled at 512 Hz for control, static and cycling experiments and 1024Hz for the treadmill experiment due to EMG recording restrictions.

2.2.3.Procedure

Control, Static, Bicycle and Treadmill Experimental Conditions

Participants were asked to keep a steady pace on all exercise trials and to move their upper body as little as possible. The trials were conducted in the Neural Engineering laboratory, the Department of Physiology and the Department of Physiotherapy (St James' Hospital), all affiliated to Trinity College Dublin.

The control experiment, to provide a basis for comparison, followed standard clinical practice whereby participants were instructed to sit in a dark room, with feet flat on the ground without moving for the duration of the experiment except to click the mouse button and to refrain from blinking as much as possible.

A static experiment followed the same protocol as the control experiment, except it was performed in an illuminated environment. This was underaken in order to ascertain the effect of illumination on recordings so as to allow comparison with cycling and treadmill experiments, which needed to be performed in illuminated environments. All other experimental conditions were the same as the control experiment.

The third experimental condition included a motor task by way of a light intensity cycling exercise performed on a stationary exercise bicycle. The intensity of the exercise was chosen to be light so as to reduce perspiration and maintain a steady body temperature and heart rate. Participants were asked to sit upright, with minimal upper body movement and to maintain a steady cycling speed throughout the trials.

The final experiment included a walking task performed on a treadmill. The treadmill allowed the speed and direction of the light intensity walking exercise to be maintained constant throughout experimentation. Participants were asked to maintain a steady walking speed and to try to curtail their vertical motion while walking and minimize sway of arms and body during the gait cycle. Treadmill speed was selected such that gait cycle frequency was not in phase with stimulus presentation.

Participants began the motor task a few minutes before the cognitive task began, both to familiarize themselves with the procedure and to allow skin impedances to reach a steady-state level[245].

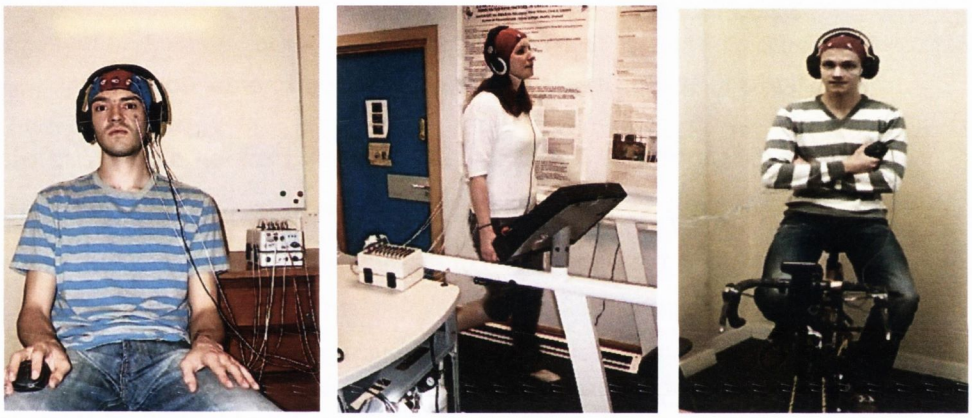


Figure 9: Static, Cycling and Treadmill Experimental Conditions

2.3. Methods to Measure Gait Variability and Sustained Attention

Measure of gait variability and sustained attention were acquired at laboratories in The Physiotherapy Department, St James's University Hospital, Dublin. This involved collaborative efforts from the Trinity Centre for Bioengineering, The Physiotherapy Department, St James's University Hospital and The Technology for Independent Living Study, Intel Corporation. The main aim of the study was the validation of a novel system to record gait by undertaking a comparison with a standard gait acquisition system (CODAmotion). This study investigated gait parameters acquired from this standard validated system and a cognitive function parameters.

Participants completed a gait and a cognitive assessment assessment (n=12, 26.10±4.43 years, height; 164.39±1.91 [cm], weight; 62.93±9.83 [kg], leg length; 75.58±3.83 [cm]). Ethical approval was obtained from Trinity College Dublin Research Ethics Committee. All participants provided personal written informed consent.

2.3.1.Procedure

Measures of gait variability and sustained attention were acquired.

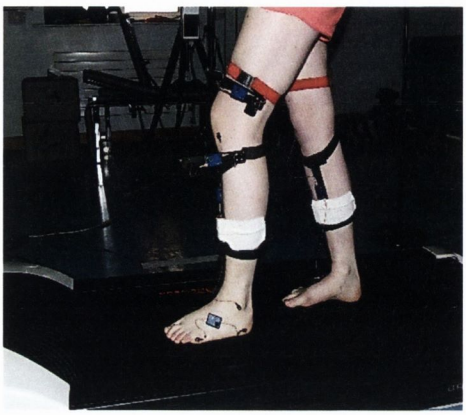
2.3.2.Gait Measures

Gait variability was assessed by stride time standard deviation.

2.3.2.1. Gait Assessment Test

Stride time standard deviation was the measure employed to assess gait variability acquired with a CODAmotion system (Charnwood Dynamics, England) as per Figure 10. Stride time variability was acquired from 12 healthy female adults while they performed three gait tasks on a treadmill. Gait speed was kept constant at 3.5 km/hr.

One simple single gait tasks and two complex gait tasks were investigated: serial seven substraction task while walking, reaching while walking as per Figure 11 and Figure 12.



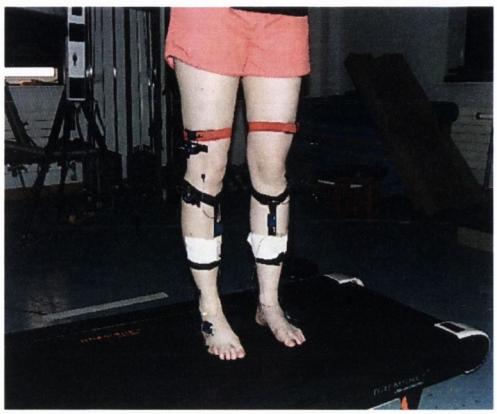


Figure 10: Placement of markers

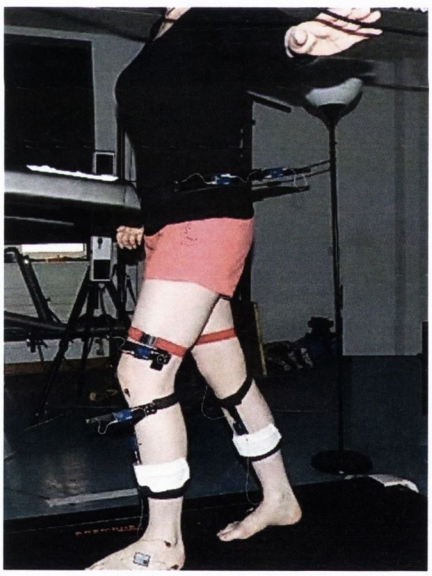


Figure 11: Participant during the Reach dual gait task

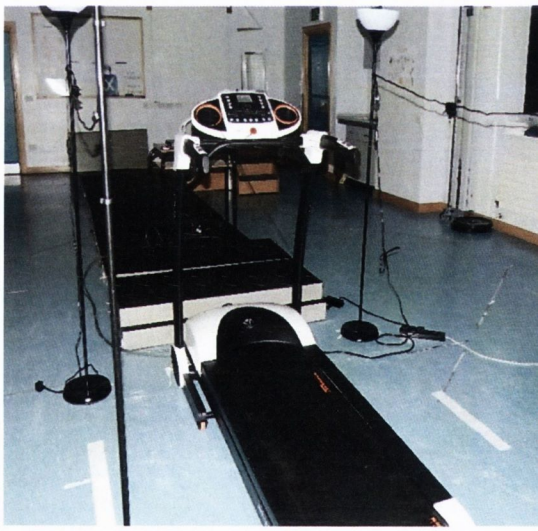


Figure 12: Experimental set-up for the Reach dual gait task

2.3.3.Cognitive Measures

The neuropsychological assessment included a sustained attention assessment test. The sustained attention response task (SART) was the task employed to assess sustained attention[237]. The SART protocol and experimental conditions were replicated to be as similar as possible to the protocol and experimental set up employed by Study 1, Study 4 and Study 7 to aid in comparison of datasets. Standard SART masures were recorded as follows: mean, standard deviation and coefficient of variation of the response time to each digit, mean total errors of commission (pressing on '3') and mean total errors of omission (not pressing button on '1', '2', '4', '5', '6','7', '8' or '9'.

2.4. The Dual Task Paradigm

Woolacott et al[106] defined attention as the information processing capacity of an individual which is limited for any individual and a certain portion of its capacity taken up when performing any task. It follows then that if two tasks are performed together (dual tasking) and they require more than the total capacity of an individual the performance on either or both tasks deteriorates. Dual tasking is seen as a more ecologically valid environmental set up than performing one task alone Dual tasking refers to performing any two tasks simultaneously but motor-cognitive, motor-motor and cognitive-cognitive dual tasks were the only combinations employed in the studies described in this thesis.

A dual task can be used to examine the attentional demands of a postural task and to examine the effects of, for instance, performing an attentionally demanding cognitive task on the control of posture. During the dual task paradigms employed by the studies described in this thesis a motor (walking) and a cognitive or motor task are performed simultaneously. This is a common dual task paradigm for many postural research studies, and postural control is assumed to be the primary task. Dual tasking is usually thought of in this manner where it is employed (i) to examine effects of performing an attentionally demanding cognitive task on the control of posture but it may also be employed (ii) to examine the attentional demands of a postural task inferred by the changes in the secondary cognitive task. This is dependent on

what emphasis the participant puts on each task 9priority of task) and creating a composite measure taking into account both possibilities seems a beneficial exercise.

In Study 3 and Study 4 Dual Task Difference (DTD) or Dual Task Effect (DTE) were employed. A Dual Task Effect or Interference Effect was calculated where a reduction in gait speed from a single to a dual task would create a negative value. The greater the negative value the greater the "cost" of the secondary task (cognitive or motor) to the primary gait task (interference effect).

Dual task difference was defined as the difference between single and dual gait tasks in cm/s:

$$Dual\ Task\ Difference\ [cm/\ s] = Single\ Task\ Gait\ Speed\ [cm/\ s] - Dual\ Task\ Gait\ Speed\ [cm/\ s]$$

Dual Task Effect or Cost was defined as the percentage difference in gait speed between the single and the dual gait task standardised over the single task performance:

$$Dual\ Task\ Effect\ [\%] = \frac{Single\ Task\ Gait\ Speed\ [cm\ /s] - Dual\ Task\ Gait\ Speed\ [cm\ /s] * 100}{Single\ Task\ Gait\ Speed\ [cm\ /s]}$$

Cognitive-cognitive dual tasking is also used to measure cognitive flexibilty. For instance where a participant is asked to follow a colour and number sequence simultaneously, such as in the Trail Making Trial B or the Color Trail Test Part 2.

There is one single task paradigm and two dual task paradigms included in the gait assessment in Study 1-5 and Study 7: one dual motor gait task and one dual cognitive gait task. The motor dual task involved walking while carrying a plastic glass filled one inch from the top with water. The cognitive dual task involved walking while reciting alternate letters of the alphabet (A, C, E, etc.). In Study 3 Dual Task Effect was calculated as above for each individual for each dual task. In Study 4 Dual Task Difference is employed to calculate effect of task.

There are two single task paradigms and two dual task paradigms included in Study 6: Measures of Attention during Movement. The single cognitive task paradigm consist of a

seated auditory task both in a dark room and then in an illuminated room. The dual task paradigm consist of 2 dual cognitve-motors tasks: treadmill walking + auditory task, cycling + auditory task. Within the auditory task there are attentional and motor (button press) components.

There is one single task paradigm and two dual task paradigms included in Study 8. The single task paradigm consist of a gait task involving walking on a treadmill. The dual task paradigm consist of 2 dual cognitive-motor tasks: treadmill walking + reaching task, treadmill walking + serial sevens task.

2.5. Analysis Methods

2.5.1.Effect of Task

The effect of a gait task employing differences in single and dual task paradigms was investigated throughout the studies described in this thesis in a number of ways. Firstly, this was investigated by investigating gait speed values across the gait task and their relative statistical outcomes. In addition, the effect of an additional task on gait speed was also investigated using the single gait task as a baseline value.. Finally, in Study 4 effect of task was investigated by including dual task difference as a dependent variable in regression analysis. The outcome of the regression analysis quantifies the effect of the addition of the dual task on gait performance. This can then be compared against regression outcomes for gait speed. Any resultant outcomes are specific to that dual task in question.

2.5.2.Gait Analysis Methods

2.5.2.1. Standard Gait Analysis Methods

Saggital Plane Bilateral Symmetry

In individuals with a correct gait pattern the gait parameters will have a bilateral symmetry about the saggital plane. A measure from either side of the saggital plane of

the body (left or right side) can be employed if there is no significant difference between the two sides. Stride time variability for the right side of the body was employed for both Study 7 after employing this method to validate differences.

Measures of Gait Variability

Gait variability can be assessed employing standard deviation or coefficient of variation measures. The standard deviation should be employed to describe gait variability if it is not correlated with the mean gait measure, for instance: stride time standard deviation is employed if it is not correlated with stride time. Where standard deviation is correlated with the mean gait measure, the coefficient of variation should be employed to describe gait variability. In Study 8 stride time standard deviation was the measure employed to assess gait variability. In Study 7 stride time coefficient of variation was the measure employed to describe gait variability as stride time standard deviation correlated with stride time for this study.

Validity of Gait Variability

Gait variability is a measure of the dispersion of a particular gait parameter about the mean. There is conflicting opinion on the number of strides required for validity of gait variability measures. Many studies that have employed the GaitRite electronic walkway to record gait variability [72, 219, 246-252] have employed a similar experimental set up and protocol to the TILDA gait assessment. However, recent recommendations by Galna et al include the use of a continuous walkway recording thirty steps or more[246].

In addition, those with movement disorder, such as are present in individuals with Parkinson's disease or Stroke, have a large amount of variability habitually within their gait. When examining gait variability in community dwelling individuals it is recommended to exclude gait data for these participants with irregular or larger amount of gait variability.

These recommendations were followed in Study 7 which examined stride time variability excluding participants with Parkinson's disease, Stroke and those with less than 8 steps per walking condition from analysis.

2.5.2.2. Analysis of data from pressure sensing mats

Study 1-5 and Study 7 explored gait parameters calculated employing standard gait processing methods to examine the footfall of all participants during each gait tasks. Specifically, the results explored gait speed in all three gait tasks, in addition Study 1 explored temporal and spatial stride and step measures and Study 7 explored gait variability employing stride time standard deviation calculated as above during the single gait task.

2.5.2.3. Analysis of data from motion analysis systems

In study 8 stride time standard deviation was derived from the angular acceleration of the left and right knee.

2.5.2.4. Analysis of data from electromyography

In Study 6 markers of muscle activity and inactivity were employed to calculate muscle activity from EMG data taking a threshold of greater than 200μV and 500ms after the last stimulus. In addition, data analysis including standard signal processing methods that were employed to remove movement artefact and are described in Section 2.5.3.5.

2.5.2.5. Dynamic Analysis Methods

The complexity of locomotion, which involves both planning and execution, suggests that identifying any temporal correlation requires the investigation of a time series

over a large number of consecutive samples. Little is known about the long-range correlations of locomotion, however potentially important information may be held in the neural and biomechanical mechanisms generating these correlations [253, 254]. In particular the non-linear aspects of such time series data has been shown to hold clinically relevant information such as a marker for risk of falling when investigating stride to stride intervals [104, 254]. This suggests the potential of such analysis to highlight prodromal impaired neurological function such as incipient cognitive impairment.

Many methods have been employed to time series gait data[255] such as fractal dynamics[256, 257] [258] [104]. In addition, in the area of cardiovascular research many studies have shown temporal correlations of heart rate dynamics employing the Poincare method[259-261] [253, 254]. These cardiovascular studies suggest that measures calculated employing the Poincare method explicitly describe specific physiological functions. However, only a few studies have investigated the Poincare method in relation to gait [259] (minimum foot clearance).

Poincare Method

Study 8 explores variations in temporal gait parameters (stride time variability) employing the Poincare method. The Poincare method is a geometric representation of a time series in a cartesian plane[259]. The Poincare Method involves generating a plot of each interval (eg: stride time) against the subsequent interval (eg: stride time + 1). Measures employed are: SD1, SD2 and their ratio (SD1/SD2).

SD1, a measure of short term variability, and SD2, a measure of long term variability, can be calculated from the width and the length of the Poincare plot respectively. SD1 is described in Study 8 as a measure of short term variability, however it is more accurately defined as the variation over a single stride. Study 8 also described SD2 as a measure of long term variability, however it is more accurately defined as a measure of both the long and the short tern variability over a complete dataset.

Study 8 examines two Poincare measures: SD1 and SD2. Concatinated datasets were investigated to allow more data points be included in analysis. In Study 8 this analysis was completed in Matlab [MathWorks, Cambridge] employing equations as per Brennan et al[260] as follows:

$$SD1 = \sqrt{\frac{1}{2} Var\,(ST_n - ST_{n+1})}$$

$$SD2 = \sqrt{\frac{1}{2} Var\,(ST_n + ST_{n+1})}$$

2.6.1.Cognitive Analysis Methods

2.6.3.1. Generation of Categorical Variables

In order to compare cognitive performance across populations many of the studies in this thesis employed categorical division of neuropsychological assessment tests.

Study 1 divides the TILDA population into categories according to the standard global cognition assessment tests:. Poor, Intermediate and Good MOCA groups were defined as those with <24, 24 and 25 and >25 MOCA total scores respectively. Poor and Good MMSE groups were defined as those with <23 and >26 MMSE total scores respectively.

Study 4 and Study 5 define global cognition categories by employing similar neuropsychological categories as Study 1 above for MMSE and MOCA.

Study 7 and Study 8 define poor and good sustained and divided attention as those who perform above and below the median. Study 2 and Study 7 include categorical variables in multiple linear regression models as per 2.4.1 Methods: Statistical Analysis. Categories employed in Study 1, Study 2 and Study 3 are described below.

2.6.3.2. MOCA Domain and Subscore Categorisation

In Study 5 some MOCA subscores and MOCA Domains have varying numbers of scoring systems.

The twenty five MOCA Subscores have varying numbers of scoring systems. Study 5 investigated the relative contribution of MOCA Subscores to gait speed in two ways in order to reduce any effect the different scoring systems, and thereby different variances of scores, had on regression outcomes. Firstly, by investigating MOCA Subscores in their raw format and then by exploring MOCA Subscores using dichotomous categories. Dichotomous categories were generated for the five MOCA Subscores that had different scoring systems based on those participants below and above the tenth percentile for that MOCA Subscore.

The eight MOCA Domains have varying numbers of scoring systems. Study 5 investigated the interactions between each MOCA Domain and MOCA Group to gait speed by exploring interactions between eight dichotomous MOCA Domains and three MOCA Groups. Dichotomous categories were generated for the eight MOCA Domains by dividing participants into two groups partioning at the fiftieth percentile for that MOCA Domain where allowable.

2.6.3.3. Executive Function Categorisation

In Study 3 participants were classified according to their ΔCTT score. Three categories are employed: executive function Tertile, Decile and Division categories.

Executive function divisions were based on findings by Ackermann et al [262]: poor (less than 5^{th} percentile), intermediate (5^{th}-50^{th} percentile), Good (greater than 50^{th} percentile). All analysis was carried out by STATA 12 employing the "egen" functionality.

ΔCTT was employed to investigate the following:

- The executive function spectrum within the TILDA population
- How executive function related to gait speed and Dual Task Effect in all gait tasks
- Where the effect of executive function begins to occur in order to pinpoint transitions from automatic gait.

2.6.3.4. Categorising Healthy Cognitive and Gait Cohorts

In Study 2 the TILDA population was categorised into a Healthy Cognitive function Group and a Healthy Gait Group

The Healthy Gait Group excluded participants with the following:

- An MMSE of less than 28.
- Alphabet problems during the alternate letter dual cognitive gait task.
- A disturbed walk during either dual gait tasks
- Walking aid users
- Any activity difficulties (as defined by the activities of living measure employed in TILDA)
- Poor vision or less
- Arthritis, Osteoporosis, hip fracture and hip or knee pain
- Memory impairments, Alzheimer's Disease, Dementia, Stroke and Parkinson's Disease.

Note: All participants with alphabet problems during the alternate letter dual cognitive gait task had an MMSE score of under 28 and so were excluded.

2.6.3.5. Signal Processing of Cortical Activity

A measure of attention acquired through electroencephalography was employed. Cortical activity was recorded on the scalp and P300 event related potentials (ERPs) were calculated as a measure of cognitive activity, specifically reflecting attention and context updating[140].

Data analysis included standard signal processing methods to achieve a clear ERP and P300 waveform: filtering (high pass (1Hz), notch (47-53Hz) and low pass (95Hz)), referencing, data epoching and epoch averaging. Filtering removed baseline drift, powerline noise and EMG activity from the signal respectively. Trials were rejected employing: Epoching included automatic epoch rejection (600 ms post stimulus) and visual inspection of electrooculography activity (EOG) and activity of the electrode positioned near the participant's eye (Fp1 channel).

P300s, which are considered a measure of cortical activity when processing complex information, were assessed by peak P300 amplitude and latency values which were taken as the maximum value of average P300 peaks. P300s were averaged for all participants for each electrode position and peak amplitude and latency investigated.

2.6. Methods to Measure Links between Gait and Cognitive Function

2.6.1.Statistical Methods and Interpretation

All statistical analysis carried out in this thesis employed either STATA 12 [StataCorp LP, USA] [263]or SPSS [264]. Study 1 through to Study 5 and Study 7 which investigated the TILDA dataset employed STATA 12 as this has increased functionality over SPSS to answer epidemiological research questions that were posed when investigating the TILDA population. In particular STATA has beneficial post regression functionality such as the "estadd", "beta" and "margins" functions which were employed in Study 3, Study 4 and Study 5 to calculate relative values for multiple variables in a regression analysis. The regression outcomes can also be adjusted for covariates and statistical weights can be included in regression models in order for the outcomes to represent a population. Furthermore, STATA has the functionality to calculate interactions with covariates such as age (Study 4) and global cognition group (Study 5). SPSS was employed in Study 6 and Study 8 when smaller cohorts (n = 12 (Study 6), n = 15 (Study 8) were investigated.

Study 1 through to Study 5 and Study 7 assessed the effect of neuropsychological test scores on gait performance by employing descriptive statistics and linear regression

models. Analysis in many of these studies followed a three step process for each of the three gait tasks. Firstly, the effect of neuropsychological test performance on gait performance was examined individually. Secondly, this relationship was examined controlling for covariates such as comorbidities. Finally, some studies (Study 4 and Study 5) also examined the independent effect of each neuropsychological assessment test score on gait performance while also controlling for covariates.

Results from Study 2 to Study 5 and Study 7 are population representative, (see Section 2.6 for further details). Results from Study 1, Study 6 and Study 8 did not weight or adjust and so are not population representative but based on the participants who completed the gait or neuropsychological assessment test in question.

The study described in Study 5 employed descriptive statistics and linear regression models to assess the effect of global cognition test scores on gait speed for both dual tasks. This was undertaken in order to parse apart contributions to gait speed from different MOCA Domains and Subscores. Specifically, MOCA total score, eight MOCA Domains and twenty five MOCA Subscores were investigated. Four regression models were investgated: Model 1, Model 2, Model 3 and Model 4. All models employing multiple linear regression analyses constructed to predict the contribution of MOCA to gait speed for both dual gait tasks. Model 1 investigated MOCA total score contribution, Model 2 investigated the relative contribution of MOCA Domains, Model 3 investigated the relative contribution of MOCA Subscores and Model 4 explored the relative correlations between gait performance and MOCA Group-MOCA Domains interactions.

Regression

Ordinary linear regression analysis was employed throughout the studies described in this thesis. A linear regression expresses the dependency of one variable (the response, outcome or dependent variable) on one or more other variables (predictors, regressors or independent variables)[265]. For a linear regression to be valid the association should be linear, the residuals should be normally distributed and the variation of the residuals should be independent (homoscedasticity).

Simple and complex linear regression analysis was undertaken. In order to satisfy linear regression assumpions the gait variables were assigned as the dependent variables and the cognitive variables were assigned as the predictor variables. The simple regression analysis that was employed was univariate linear regression which involves only one outcome and one predictor. The complex regression analyses that were employed were multiple linear regression with one outcome and more than one predictor. Covariates and comorbidities were also included in the multiple linear regression models in order for outcomes to be adjusted for the covariates or comorbidities included in the model. Predictors included in both simple and complex regression analyses may be continuous variables or categorical variables such as a dichotomous variable gender and the trichotomous variable educational attainment for example.

Regression model outcomes include a p-value and an R-squared value for the regression model, in addition to regression coefficients and p-values for each predictor. For the overall regression model to be significant the p-value of the F test must be less than 0.05 for a ninety five percent significance. This was the case for all regression models employed in the studies described in this thesis. The variability of the outcome that is accounted for in all the predictors in the regression model is expressed by the R-squared value. A regression coefficient is calculated for each predictor in the regression model. Each regression coefficient indicates the amount of change expected in the outcome for a one-unit change in the predictor, given all other variables in the regression model are held constant. This change in the predictor may be an increase or a decrease with a minus indicating a decrease. An increase would indicate a positive relationship between outcomes and predictor and a decrease would indicate a negative relationship between outcomes and predictor. In this thesis the regression coefficient refers to the amount of change expected in gait performance for a one unit change in cognitive performance. Standardised regression coefficient (Beta coefficients) can be calculated in the statistical software package STATA using the beta function. Standardised regression coefficient or Beta coefficients can be employed to compare the relative strengths of the various predictors in the regression model. The standardised regression coefficients are a form of z-score (see Section 2.5.3.3 for details). They follow the same format as regression

coefficients, however the units of measurementse differ with the beta coefficients indicating a one standard deviation change in cognitive performance for a certain standard deviation change (according to beta value) in the predicted gait performance.

To ensure the data in Study 2 to Study 5 and Study 7 were nationally representative; all analyses were weighted to age, sex and education of the Quarterly National Household Survey (2010) and by health status and socio-demographic factors to adjust for potential selection bias among those who attended the TILDA health assessment centre.

In Study 4, four regression models were investgated: Model 1, Model 2, Model 3 and Model 4. All models employed multiple linear regression analyses and were constructed to predict the contribution of MOCA to gait speed for both dual gait tasks

Regression models were also adjusted for age, gender, body mass index or height, educational attainment, depression and in Study 3 were also additionally adjusted for physical factors which affect gait speed: self-rated vision, number of chronic diseases and activities difficulties, presence of Parkinson's Disease, arthritis, osteoporosis, hip or knee pain, or hip fracture and use of a walking aid. Study 4 additionally adjusted for a "Comorbidity" variable which included factors affecting gait and cognitive function, see Covariates section.

In order to reduce variability in results due to age, gender and height inclusion criteria for Study 8 was restricted to females aged 20-35 years who were 160-166 cm in height.

Interactions

The phenomenon of the affect of cognitive function on gait performance being different for different age groups for example is called an interaction or effect modification. STATA software interaction functionality e.g.: MOCA#AGE, can determine the effect of an interaction between two variables on the dependent variables. It calculates this by comparing the observed and predicted values of the dependent variables after running a regression analysis.

Study 4 examines the effect of interactions between eight age groups and each element of cognitive function on gait speed for each gait task.

Study 5 examined the effect of interactions between three global cognition groups (Poor, Intermediate and Good with MOCA scores of <24, 24 and 25 nd >25 respectively) and each MOCA Domain on gait speed for each gait task.

Covariates

Three types of covariates are adjusted for in the studies described in this thesis. Firstly, age, gender, body mass index (BMI), educational attainment and depression are adjusted for in Study 3, Study 4, Study 5 and Study 7. Secondly, in additon to adjusting for these covariates Study 3 adjusts for factors found to affect gait. Finally, in addition to adjusting for age, gender, body mass index (BMI), educational attainment and depression, Study 4 and Study 5 adjust for factors affect gait and cognitive function (termed in these studies as "comorbidity").

This Comorbidity derived variables includes those taking more than five medications (polypharmacy) and those who responded "yes" to the question "Has a doctor ever told you that you have?" when asked about: cardiovascular disorders, memory impairments, arthritis, osteoporosis, parkinson's disease, cancer, chronic lung disease or asthma, as well as those who self reported poor vision, hip or wrist fracture, hip or knee pain, or walking aid use. Comorbidity also included the number of comorbidities a participant experienced. Participant characteristics included in this derived variable are described in Study 5.

Participants with serious memory impairments, dementia, Alzheimer's Disease, Stroke, Parkinson's Disease were excluded from the Healthy Cognitive Group in Study 2. This data was collected in the TILDA CAPI questionnaire and included participants who responded "yes" to the question "Has a doctor ever told you that you have?" when asked about: serious memory impairments, dementia, organic brain syndrome, senility, Alzheimer's Disease, Stroke and Parkinson's Disease as Study 2. Appendix 4 describes the generation of this healthy cohort.

Multiple Comparison Correction

Study 4 additionally adjusts for multiple comparisons testing in Model 2 and Model 3. The rational for multiple testing corrections is that if a lot of hypotheses are indiscriminantly tested then false positive will be encountered. The hypothesis of Study 5 relates to the effect of elements of cognitive function on gait speed across three gait tasks after adjusting for other factors. Therefore, p-values from this analysis (Model 3) should only be participant to the correction and so a threshold p-value was set and applied only to the multivariate models (Study 5: Model 3). P values for each of the seven neuropsychological tests on each walking task from Model 3 were entered into the STATA multproc program in accordance with literature by Newson et al (2003)[266].

The outcome of the STATA multproc program calculated a revised critical value of 0.011 for positive associations with seven cognitive tests at q=0.05 (using Stata multproc procedure[266]). Predicted changes in gait speed and Dual Task Difference were calculated for each neuropsychological test utilising standardized beta coefficients.

2.6.3.1. Z-Scores

Z-scores were employed in Study 2 of this thesis to explore if gait speed could predict cognitive impairment. Cognitive Impairment was defined in three ways:

1. As measured by those with memory impairments in the TILDA dataset.
2. As measured by those in the Poor MOCA category
3. As measured by an abnormal MOCA Zscore

A z-score is a variable that has been rescaled to have a mean of zero and a standard deviation of one. The zscore indicates the deviation from the mean of the population in number of standard deviations similar to the standardised beta coefficients. Employing z-scores in Study 2 analysis ensured all variables contributed evenly to the scale when items were added together allowing clear interpretation of outcomes. A z-score is usually calculated by subtracting the population mean from the individual mean and dividing this difference by the population standard deviation. However, in

Study 3 age matched controls were investigated as age has been found to influence both cogntion and gait performance.

$$Z - score = \frac{(Individual\ Mean - Population\ Mean)}{Population\ Standard\ Deviation} = \frac{(x - X)}{\sigma}$$

The population mean and standard deviation was taken as the mean and standard deviation of TILDA participants excluding those with missing gait or MOCA data. Participants were categorised into seven age bands: 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80+ years. For each age group, control groups for gait and cognitive performance were calculated: Healthy Gait Group and Healthy Cognitive Group (as per Methods section 2.5.3.4). Age-adjusted z-scores were calculated by substracting the mean age matched zscore for controls from the mean for each participant and dividing this by the age matched standard deviation as follows:

$$MOCA\ Zscore = \frac{Participant\ MOCA\ test\ score - Age\ matched\ Mean\ Control\ MOCA\ test\ score}{Age\ matched\ Control\ MOCA\ test\ score\ Standard\ deviation}$$

$$Gait\ Zscore = \frac{Participant\ Mean\ Gait\ Speed - Age\ matched\ Control\ Mean\ Gait\ Speed}{Age\ matched\ Control\ Gait\ Speed\ Standard\ Deviation}$$

$$Composite\ Gait\ Zscore = \frac{Motor\ Gait\ Zscore + Cognitive\ Gait\ Zscore}{2}$$

Gait Z-scores included a Motor Gait Z-score, a Cognitive Gait Zscore and a Composite Gait Zscore. Motor Gait Zscores and Cognitive Gait Zscores were calculated as per the Gait zscore equation above taking gait speed during the dual motor gait task and dual cogntiive gait task respectively. A zscore taking account of performance on both the dual motor gait task and the dual cognitive gait task was explored. This was termed the Composite Gait Zscores and was calculated from an average of the Motor Gait Zscore and the Cognitive Gait Zscore.

A normal cut-off of 2.5 standard deviations below the relevant age-related control group mean was defined. In addition a less conservative cutoff of 1.5 standard

deviaitons, as defined in DSM 5 for Mild Cognitive Impairment has also been suggested.

2.6.3.2. Sensitivity, Specificity and Predictive Value Calculation

In Study 2 a simple statistical test was undertaken to assess how good "poor gait speed" and "large Dual Task Effect" were at diagnosing executive function impairment as per Altman et al[267]. The gait task was the diagnostic test. Poor gait speed or large Dual Task Effect indicated a positive diagnosis of executive function impairment and values greater than a specified gait speed value indicated a negative diagnosis of executive function impairment.

Executive function impairment was measured by the poor executive function division (5^{th} percentile) as described in Section 2.5.3.3: Executive Function Categorisation). Poor gait speed and large dual task effect was defined as per points found to be significant in regression analysis. Predictive values were generated for the diagnostic test employing sensitivity and specificity values. True positive and true negative results were calculated. True positive results were calculated as the proportion of participants with poor gait who were correctly "diagnosed" by the diagnostic test as having executive function impairment. True negative results were calculated as the proportion of participants with healthy gait who were correctly "diagnosed" by the diagnostic test as having healthy executive function. Sensitivity was calculated as the proportion of true positives that were correctly identified by the gait assessment test. Specificity was calculated as the proportion of true negatives that were correctly identified by the gait assessment test.

$$Sensitivity = Proportion\ of\ true\ positives\ correctly\ identified\ by\ the\ test$$

$$= \frac{number\ of\ participants\ with\ abnormal\ test\ results}{number\ of\ participants\ that\ are\ impaired}$$

$$Specificity = Proportion\ of\ true\ negatives\ correctly\ identified\ by\ the\ test$$

$$= \frac{number\ of\ participants\ with\ normal\ test\ result}{number\ of\ participants\ with\ no\ impairment}$$

Predictive values were also assessed for the gait assessment test. Positive predictive values (PPV) and negative predictive values (NPV) of the gait assessment test were calculated. Positive predictive values were calculated as the proportion of participants with positive results who are correctly diagnosed. Negative predictive value was calculated as the proportion of participants with negative results who were correct diagnosed. Adjusted PPV and NPV were also calculated as they adjust for the prevalence of the impairment in the population.

$$\boldsymbol{Positive\ Predictive\ Value, PPV}$$
$$= Proportion\ of\ participants\ with\ a\ positive\ test\ result\ correctly\ diagnosed$$
$$= \frac{Number\ of\ participants\ with\ abnormal\ test\ result\ that\ have\ impairment}{Number\ of\ participants\ with\ abnormal\ test\ result}$$

$$\boldsymbol{Negative\ Predictive\ Value, NPV}$$
$$= Proportion\ of\ participants\ with\ a\ negative\ test\ result\ correctly\ diagnosed$$
$$= \frac{Number\ of\ participants\ with\ normal\ test\ result\ with\ no\ impairment}{Number\ of\ participants\ with\ normal\ test\ result}$$

$$\boldsymbol{Adjusted\ Positive\ Predictive\ Value} = \boldsymbol{PPV\ adjusted\ for\ prevalence\ in\ population}$$
$$= Sensitivity * Prevalence + ((1 - specificity) * (1 - prevalence) * specificity * (1 - prevalemce))$$

$$\boldsymbol{Adjusted\ Negative\ Predictive\ Value} = \boldsymbol{NPV\ adjusted\ for\ prevalence\ in\ pop}ulation$$
$$= ((1 - Sensitivty) * Prevalence) + (Specificity * (1 - Prevalemce))$$

2.6. Appropriate Methods to examine the relationship between gait and cognitive function

In general, regression models are appropriate at assessing the relationship between gait and cognitive function due to the fact that adjustment for covariates is possible when employing this method. In addition, throughout the studies described in this thesis which employ regression analysis methods differences in gait performance can be expressed in terms of standard deviations of cognitive function performance. This is of benefit as it allows for comparison of gait and cognitive measures with other studies. In addition, it allows forthe comparison with previously defined thresholds found in literature such as fast gait speed values linked to increased likelihood of survival and successful aging.

2.6. Conclusion

One of the main conclusions arising from this Chapter is that the GaitRite pressure sensing mat is a good choice for recording gait parameters as it is more automated than other kinematic systems. It allows participants to walk with no restrictions for 7 metres without the time restraint of fitting equipment or the burden of the equipment attached to clothing. The GaitRite pressure sensing mat has high accuracy for routine gait parameter measurement and little post assessment processing. This was beneficial to ensure that data was recorded in the same manner while minimising the time taken to set up the gait assessment given the large number of participants being assessed in TILDA. In addition, GaitRite has been employed in previous studies and so comparison of results with other studies is less complicated.

The CODAmotion system is a good choice when investigating recording gait variability due to its higher sensitivity. However, the CODAmotion system is restricted as it only has a smaller measurement area. In order to obtain enough subsequent strides the test procedure would require participants to walk on a treadmill. However, this will require participants to walk at a constant speed.

Additional conclusions pertaining to cognitive measurement systems are as follows:

EEG is a good choice when measuring neural responses during movement due to high temporal resolution. There are many choices when assessing cognitive function with neuropsychological assessment tests. Many of the neuropsychological assessment tests

described in this chapter are employed as standard clinical assessment tests and have been validated and so researched to a greater extent than others. In addition, each neuropsychological test has its own specific advantage and limitation.

Given these methods we are now able to focus on the research questions posed.

CHAPTER 3: Study 1 - Variation In Cognitive Function And Motor Performance in a Nationally Representative Population

The aim of the study described in this chapter was to assess gait and cognitive performance across The Irish Longitudinal Study on Ageing (TILDA), a nationally representative population of people over fifty years of age. Based on knowledge gained in Chapter 2: Literature Review gait measures: gait speed and temporal gait variability, in addition to cognitive measures: global cognition, executive function and attention were found to be of particular interest to the relationship between gait and cognition. Cognitive and gait performance was assessed by exploring mean values and variation from mean in these gait and cognitive measures. The TILDA study is a novel dataset as it includes over eight thousand participants from 50-91 years of age. Performance on all assessment tests was compared across single and dual gait task paradigms. It was hypothesized that performance in gait assessment tests and cognitive function tasks within this cohort represent physiological states. In particular, differences in these gait or cognitive performances represent different physiological states and those who perform poorly in gait or cognitive function tasks may be experiencing early age related changes or more sinister prodromal pathology such as mild cognitive impairment.

Outcomes of this study contributed in part to the following conference presentation:

I. Killane, O. Donoghue, G. Savva, H. Cronin, R.A. Kenny, R.B. Reilly (June 29-July 03 2014): "Contributions of the Montreal Cognitive Assessment (MOCA) to Dual Task Gait Performance". The ISPGR and GMF (The Joint World Congress of the International Society of Posture & Gait Research, Gait and Mental Function), Vancouver, Canada.

3.1. Introduction

This study summarises behavioural, physiological and personal characteristics within the TILDA dataset. Each gait and cognitive variable included within the TILDA dataset was

examined. Raw variable scores were examined for any missing values and new variables were derived accordingly omitting missing values where appropriate.

Examining variations in cognitive and motor performance in a population sample which spans in age from fifty to ninety one years, a broader range than explored in previous large cohort studies is clinically informative. In addition, further understanding of the relationship between cognitive and motor performance within this dataset, as well as the affect of age, gender and educational attainment is needed. Executive function [169, 204, 207, 268] and attention [23, 106, 269-271] have been highlighted in literature as elements of cognitive function of particular interest.

In addition to a summary of a broad range of gait and cognitive function measures the study described in this chapter probes the relationship between global cognition and gait speed using cross sectional data. Global cognition test scores were divided into categories according to test score performance. A comparison was then undertaken in order to investigate if there was a difference in gait performance between participants with different cognitive performance. In addition, observed differences and correlations were examined between participant's cognitive and motor performance.

3.2. Methods

3.2.1. Study Design

This study investigated baseline cross sectional data from The Irish Longitudinal study on Ageing (TILDA). Differences in gait and cognitive function performance across the TILDA dataset were examined. Further detail of the study procedure can be found in Chapter 2: General Methods.

Data collection in the TILDA study comprised of three parts: a computer-assisted personal interview, a self-completion questionnaire and a health assessment. Participant characteristics detailed in this chapter were recorded during the computer-assisted personal interview. All neuropsychological and gait measure described in this chapter were assessed during the TILDA health centre assessment[232].

3.2.2.Measures

The study used baseline cross sectional data (n = 8504, 56% women, age = 63.14(10.21) yrs) from the TILDA dataset with no exclusion criteria. This study examined performance on global cognitive (including MOCA subscores), processing speed, short term memory (immediate and delayed recall), executive function, sustained attention, visual reasoning and verbal fluency assessment tests that were administered during the TILDA neuropsychological assessment. This study also examined gait parameters that were recorded with a GaitRite pressure sensing mat in the TILDA gait assessment. The single and dual task gait speed, stride time and step time means, standard deviations and coefficients of variation values calculated by the GaitRite™ system were the measures of gait performance employed. The gait parameter definitions used within this study are listed in Chapter 2: General Methods.

Global Cognition was assessed using both the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MOCA). An MMSE score less than 24 was employed to indicate severe cognitive impairment[272] and a score of less than 26 in MOCA to indicate Mild Cognitive Impairment[108, 110]. A MOCA score of 24 and 25 was also investigated as some studies [111, 112] have argued that a lower MOCA cutoff is more appropriate to indicate Mild Cognitive Impairment.

3.2.3. Analysis

Mean values for participant characteristics in addition to gait and cognitive measures were examined for all partipants in the TILDA dataset, for those over fifty years of age and for those attending the health assessment (Table 1- Table 4). Distribution of gait and cognitive measures within these cohorts were also investigated. All other tables or figures in this study describe data from TILDA participants that there was gait and neuropsychological data available for. Results were not weighted or adjusted.

Gait speed has been calculated in categories according to those suggested by Studenski et al[82]: Gait speed less than 60 cm/s, Gait speed between 100 cm/s and 120 cm/s and Gait speed over 120 cm/s.

Effect of gait task was investigated by examining gait speed differences over the single gait task and both dual gait tasks. In addition, dual task difference and dual task effect were investigated. Effect of gender and age on gait speed for each gait task was also examined.

Descriptive statistics were employed to assess correlations between differences in gait speed for all three gait tasks across global cognition categories.

3.3. Results

A summary of participant characteristics, gait measures and neuropsychological test scores from the first wave of TILDA can be found in Table 1, 2, 3 and 4. Table 1: Column 2 details participant characteristics for the complete dataset of 8504 TILDA participants. Table 1: Column 3 excludes the 329 participants in the TILDA dataset who were younger than fifty years of age leaving 8175 participants fifty years and over. Table 1: Column 4 details 5034 participants who attended the health assessment which gives a 61% health assessment attendance rate from the complete TILDA dataset. All stride and step values are for the right side of the body as no significant differences were found with the left hand side. Table 4 displays MOCA subscore values.

Analysis carried out in this study are based on those 5034 participants who agreed to attend the health centre assessment (51% women, 61.95(8.47) mean (SD) age). However, in subsequent studies results have been weighted to represent community dwelling Irish residents of fifty years and over.

4910 participants over fifty years of age completed the gait assessment as part of the TILDA health assessment. Results from Table 2 show a fast gait speed: Gait speed (mean (SD)) for the single gait task was 135.70 (20.62) cm/s, 111.51 (26.31) cm/s for the cognitive gait task and 133.30 (21.01) cm/s for the dual motor gait task. Effect of gait task was found to a significant with gait speed statistically significantly different for all gait tasks: single gait task compared against both dual gait tasks in addition to the dual gait tasks compared against each other

(paired t-test, $p < 0.05$). Distribution of gait speed in this population can be seen in Figure 13. The addition of a cognitive task reduced gait speed by 24.3 [cm/s] (18.25%) and a motor task reduced gait speed by 2.57 [cm/s] (1.87%). Age and gender were also observed to affect gait speed linearly as seen in Figure 14.

Results from Table 3 show a high global cognition (mean (SD)) with a MMSE test score of 28.59 (1.9) and a MOCA test score of 25.2 (3.3). 100 participants were found to have an MMSE score of below 24, indicating severe cognitive impairment. 1,203 and 1031 participants were found to have a MOCA of under 24 and 26 respectively, indicating mild cognitive impairment. Figure 15 and Figure 16 show distribution of global cognition within this population.

In Figure 17 gait speed was found to change linearly with MMSE score. However, MOCA test scores have a less linear relationship with gait.

Table 1 Participant Characteristics for all TILDA Participant (n=8504), for Participants over Fifty years (n=8175) and for TILDA Participants over fifty years who attended a health assessment (n = 5034)

Characteristic	All Participants	Participants 50yrs +	Attended Health Assessment
Number of Participants, n	8504	8175	5034
Gender: Female, n (%)	4724 (56)	4431(54)	2728(51)
Age, mean(SD) [years]	63.14(10.21)	63.83(9.78)	61.95(8.47)
Height, mean(SD) [m]	165.76(9.18)	165.81(9.27)	166.19(9.15)
Weight, mean(SD) [kg]	78..97(16.39)	79.06(16.33)	79.16(16.30)
Body Mass Index, mean(SD) [Kg/m^2]	28.66(5.11)	28.68(5.07)	28.57(4.94)
Educational Attainment			
Primary	2521	2504	1102
Secondary	3431	3263	2104
Tertiary	2548	2404	1826
Depression,			
CES-D, Mean (SD)	4.66(4.14)	4.69(4.15)	4.41(4.03)
n≤16 (%)	5975(98%)	5727(97%)	4912(98%)
Falls in last year			
None	6862	6590	4028
One	1033	997	659
Two+	607	586	345

Reported above are characteristics, means and standard deviations for Depression (Center for Epidemiologic Studies Depression Scale (CES-D) with percentage within healthy normal score), Number of fallers (numbers of participants who fell in the last 12 months (self reported).

Table 2: Gait Speed Outcomes as measured by the GaitRite Pressure Sensing mat for all TILDA Participant (n=8504), for Participants over Fifty years (n=8175) and for Tilda Participants over fifty years who attended a health assessment (n = 5034)

Gait Measures, mean(SD) [cm/s]	All Participants	Participants 50yrs +	Attended Health Assessment
Single Gait Task			
Gait Speed	136.2(20.64)	135.67(20.62)	135.70(20.62)
n: <60[cm/s]	10	10	10
n: >100[cm/s]	787	767	767
n: >120[cm/s]	4168	3952	3951
Stride Time	1.05(0.10)	1.05(0.10)	1.05(0.10)
Stride Time Std Dev	0.018(0.013)	0.018(0.013)	0.018(0.013)
Stride Time CoV	1.72(1.11)	1.72(1.13)	1.72(1.13)
Stride Length	141.41(17.62)	141.19(17.76)	141.19(17.76)
Stride Length Std Dev	2.668(1.701)	2.675(1.708)	2.675(1.707)
Step Time	0.53(0.05)	0.52(0.05)	0.52(0.05)
Step Time Std Dev	0.0127(0.009)	0.0128(0.009)	0.0128(0.009)
Step Time CoV	2.43(1.55)	2.43(1.56)	2.43(1.56)
Step length	70.81(8.91)	70.71(8.98)	70.71(8.98)
Step Length Std Dev	1.777(1.110)	1.78(1.12)	1.78(1.12)
Cognitive Dual Gait Task			
Gait Speed	112.18(26.36)	111.50(26.31)	111.51(26.31)
n: <60[cm/s]	173	171	171
n: >100[cm/s]	1510	1456	1456
n: >120[cm/s]	2054	1902	1902
Dual Task Difference	24.13(18.70)	24.30(18.80)	24.30(18.80)
Dual Task Effect [%]	-18.26(13.79)	-18.23(13.79)	-18.25(13.79)
Letters Attempted [n]	0.27(84.70)	-0.06(86.69)	-0.06(86.69)
Letters Correct [n]	-1.12(84.58)	-1.46(86.57)	-1.46(86.58)
Stride Time	1.24(0.31)	1.25(0.31)	1.25(0.31)

Stride Time Std Dev	0.063(0.119)	0.064(0.120)	0.638(0.120)
Stride Time Cov	4.30(5.22)	4.35(5.29)	4.35(5.29)
Stride Length	133.69(21.05)	133.49(21.22)	133.49(21.22)
Stride Length Std Dev	4.195(3.595)	4.23(3.57)	4.23(3.57)
Step Time	0.62(0.17)	0.62(0.17)	0.62(0.17)
Step Time Std Dev	0.044(0.283)	0.045(0.289)	0.045(0.290)
Step Time Cov	5.42(8.07)	5.49(8.21)	5.49(8.21)
Step length	66.92(10.65)	66.82(10.74)	66.82(10.74)
Step Length Std Dev	2.772(2.373)	2.799(2.400)	2.799(2.400)
Dual Motor Gait Task Task			
Gait Speed			133.30(21.01)
n: <60[cm/s]	133.82(21.06)	133.30(21.01)	10
n: >100[cm/s]	10	10	852
n: >120[cm/s]	872	852	3758
Dual Task Difference	3974	3759	2.57(8.25)
[cm/s]	2.54(8.26)	2.57(8.25)	-1.87(6.31)
Dual Task Effect [%]	-1.87(6.3)	-1.87(6.31)	1.05(0.10)
Stride Time	1.05(0.10)	1.05(0.10)	0.0178(0.012)
Stride Time Std Dev	0.018(0.012)	0.018(0.012)	1.68(1.03)
Stride Time CoV	1.67(1.02)	1.68(1.03)	138.72(17.72)
Stride Length	138.93(17.59)	138.72(17.71)	2.520(1.467)
Stride Length Std Dev	2.51(1.46)	2.520(1.467)	0.52(0.05)
Step Time	0.52(0.05)	0.52(0.05)	0.012(0.008)
Step Time Std Dev	0.012(0.008)	0.012(0.008)	2.36(1.45)
Step Time CoV	2.35(1.44)	2.36(1.45)	69.30(8.94)
Step length	69.40(8.87)	69.30(8.94)	1.6556(0.870)
Step Length Std Dev	1.65(0.86)	1.656(0.870)	

Reported above are characteristics, means, standard deviations (SD) and coefficient of variations (Cov).

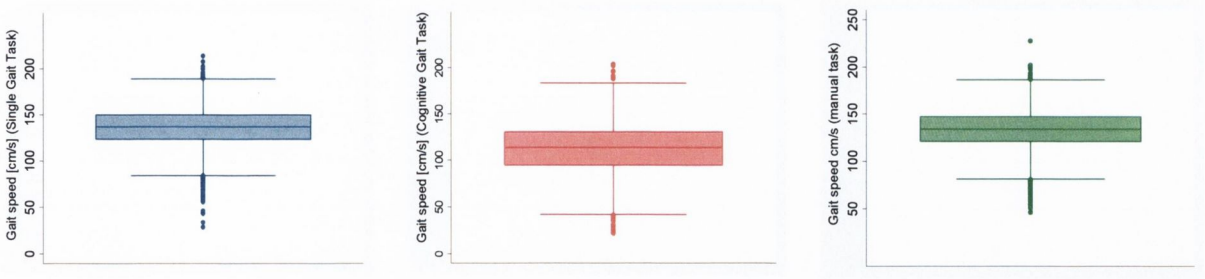


Figure13: Distribution of Gait Speed in the TILDA Dataset for the single gait task (right), the dual cognitive gait task (centre) and the dual motor gait task (left)

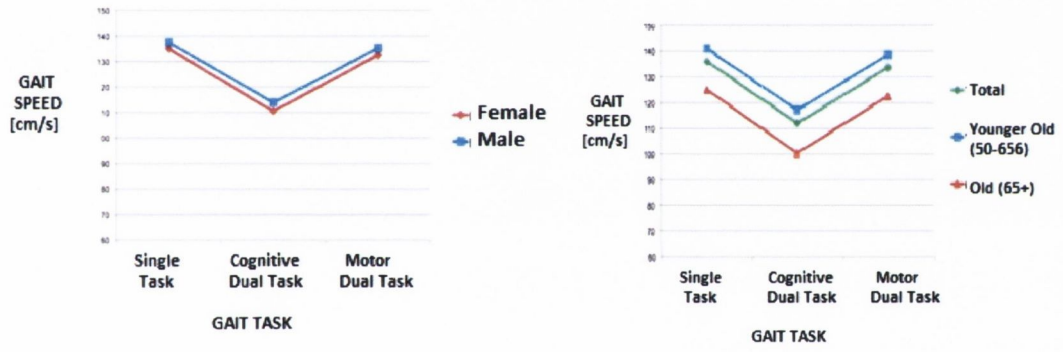


Figure 14: Gait Speed by Gender for Single Gait Task and Cognitive and Motor Dual Gait Tasks; Red (Female), Blue (Male) (Left). Gait Speed by Age for Single Gait Task and Cognitive and Motor Dual Gait Tasks; Red (over 65 years old), Blue (50-65 years old) and Green (total) (Right)

Table 3: Performance on Neuropsychological Tests for all TILDA Participant (n=8504), for Participants over Fifty years (n=8175) and for TILDA Participants over fifty years who attended a health assessment (n = 5034)

Neuropsychological Measures, mean(SD), IQR	All Participants	Participants 50yrs +	Attended Health Assessment
Global Cognition			
MMSE	28.32(2.21), 28-30	28.29(2.23), 28-30	28.59(1.88), 28-30
MOCA	24.75(3.76), 23-27	24.68(3.78), 23-27	25.19(3.30), 23-28
Short Term Memory			
Immediate Recall [n]	5.71(1.74), 5-7	5.68(1.74), 5-7	5.97(1.61), 5-7
Delayed Recall [n]	5.92(2.35), 4-8	5.87(2.35), 4-8	6.27(2.24), 5-8
Processing Speed			
Total CRT Response Time [ms]	842.15(330.49), 670.42-897.6	846.16(323.7), 674.43-901.8	814.20(282.61), 666.65-876.53
Total CRT Cognitive Response Time	518.72(167.42), 435.21-556.94	520.24(165.34), 436.41-559.37	509.35(148.17), 433.79-551.54
Total CRT Motor Response Time	278.89(156.27), 192.63-319.32	280.70(151.48), 194.34-322.53	264.86(133.47), 188.95-304.16
Delta CRT Response Time	26.05(194.21), (-4.75) - 61.95	24.95(189.85), (-4.48)-62.47	23.00(179.55), (-4.39)-59.83
Executive Function [s]			
CTT 1	57.83(29.99), 38.97-67.5	58.62(30.25), 39.53-68.5	55.36(25.59), 38.80-64.69
CTT 2	112.61(44.96), 81.81-132.16	113.93(45.25), 82.84-133.66	108.72(39.58), 81.22-126.6
Delta CTT	56.05(29.59), 36.16-69.87	56.63(29.89), 36.5-70.72	54.05(27.25), 35.34-67.47
Sustained Attention	382.55(100.44), 305.21-447.26	383.73(100.24), 306.36-448.35	379.12(99.00), 302.91-440.46
SART Response Time	31.88(16.49), 19.85-40.04	32.06(16.53), 19.91-40.56	30.6(16.02), 19.27-37.82

SART Response Time CoV [%]	4.21(4.25), 1-6	4.28(4.29), 1-6	3.86(3.93), 1-5
SART Errors of Commission	8.28(11.32), 1-11	8.45(11.47), 1-11	7.12(9.61), 1-9
SART Errors of Omission			
Visual Reasoning, [n]	3.04(1.36), 2-4	3.01(1.36), 2-4	3.14(1.33), 2-4
Verbal Fluency, [n]	11.78(5.15), 8-15	11.71(5.15), 8-15	12.21(5.05), 9-15

Reported above are neuropsychological test score means, standard deviations (SD) and interquartile ranges (IQR) for Mini mental state examination (MMSE), Montreal Cognitive Assessment (MOCA), Choice Reaction Time (CRT), Difference between the first and second 50 cognitive response times in the CRT (delta CRT (ΔCRT)), Color Trail Test one (CTT1) and Color Trail Test two (CTT2) and difference in time to complete CTT1 and CTT2 (delta CTT (ΔCTT)), Coefficient of response time variation (CoV) in the Sustained attention response task (SART).

Table 4: Distribution of MOCA Subscores from the TILDA Health Assessment.

n = 4560	MOCA SUBSCORE [Range]												
	VISUoSPATIAL/EXECUTIVE					NAMING			MEMORY	ATTENTION			
Statistic	**Trail [0-1]**	**Cube [0-1]**	**Contour [0-1]**	**Numbers [0-1]**	**Hands [0-1]**	**Lion [0-1]**	**Rhino [0-1]**	**Camel [1]**	**Memory Trial #2 [0-5]**	**Forward [0-1]**	**Backward [0-1]**	**Letters [0-1]**	**Serial Sevens [0-3]**
mean	.842	.559	.994	.921	.799	.941	.687	1	4.929	.956	.866	.947	2.732
sd	.365	.497	.077	.269	.401	.235	.464	0	.301	.204	.341	.224	.629
min	0	0	0	0	0	0	0	1	1	0	0	0	0
max	1	1	1	1	1	1	1	1	5	1	1	1	3
IQR	1, 1	0, 1	1, 1	1, 1	1, 1	1, 1	0, 1	1, 1	5, 5	1, 1	1, 1	1, 1	3, 3

n = 4560	**MOCA SUBSCORE [Range] Cont'd**											
	LANGUAGE			ABSTRACTION		MEMORY	ORIENTATION					
Statistic	**Repeat [0-2]**	**Fluency [0-1]**	**Word # [0-31]**	**Sim1 [0-1]**	**Sim2 [0-1]**	**Recall [0-5]**	**Date [0-1]**	**Month [0-1]**	**Year [0-1]**	**Day [0-1]**	**Place [0-1]**	**City [0-1]**
mean	1.586	.626	12.205	.811	.782	2.93	.968	.994	.996	.986	.986	.999
sd	0.602	.484	5.040	.392	.413	1.526	.177	.075	.059	.118	.118	.036

min	0	0	0	0	0	0	0	0	0	0	0	0
max	2	1	31	1	1	5	1	1	1	1	1	1
IQR	1, 2	0, 1	9, 15	1, 1	1, 1	2, 4	1, 1	1, 1	1, 1	1, 1	1, 1	1, 1

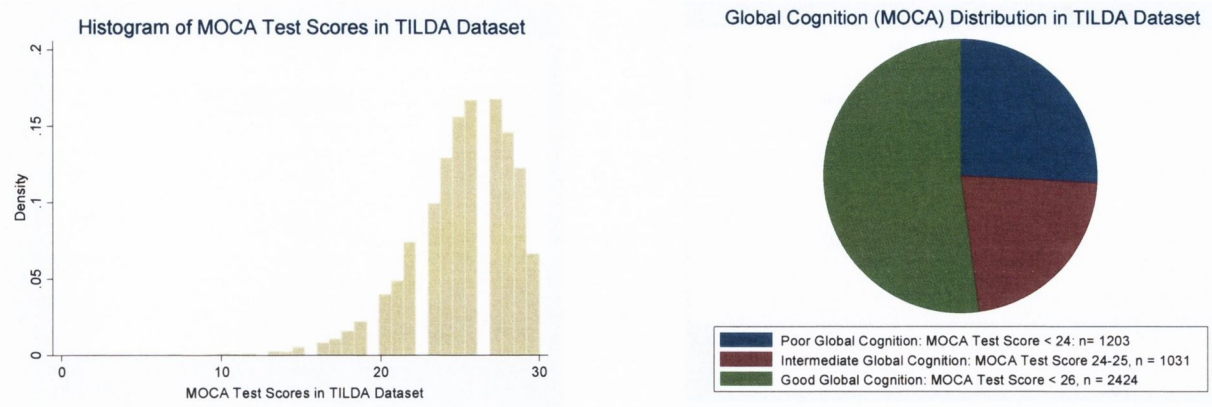


Figure 15: Histogram and Pie chart of MOCA distribution in the TILDA dataset

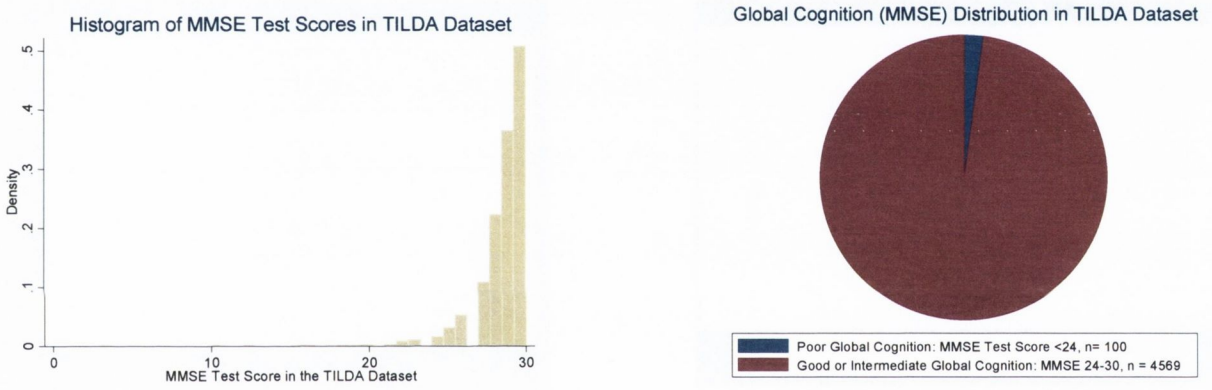


Figure 16: Histogram and Pie chart of MMSE distribution in the TILDA datset

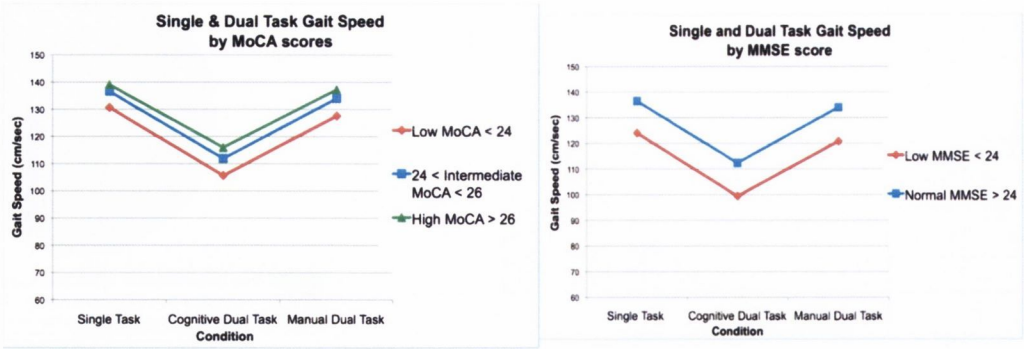


Figure 17: Gait Speed by Global Cognition for Single Gait Task and Cognitive and Motor Dual Gait Tasks. MOCA score (right): Red (cognitively Impaired), Blue (at risk of mild cognitive impairment) and green (cognitively healthy) (Left). MMSE scores (right): Blue (cognitively healthy), Red (cognitively impaired)

3.4. Discussion

The results of this study confirm the hypothesis of this study that gait and neuropsychological outcomes measures in the TILDA dataset explain the physiological state of this population. That is the TILDA population were observed to be as per expected for this cohort compared with literature indicating a relatively healthy cohort. Participants walked fast with low variability and had good global cognition. In addition, the gait task performed during the gait assessment statistically significantly affected the self-selected gait speed at which the participant walked. Gait speed was observed to be affected by age and gender as well as global cognition performance. The very good global cognition performance seen in the dataset resulted in a skewed distribution. Gait parameters were found to be more broadly distributed and so are more appropriate regression model dependents. Gait speed may be a good gait measure to investigate in future studies as it has been shown to be an important factor affecting those at risk of falling and of mortality[2]. It is therefore more appropriate to use an alternative parameter, such as gait speed, as the dependent and neuropsychological parameters as the predictors in the regression models. Participant characteristics were observed to differ for the participants attending the health assessment compared with participants included in the entire TILDA dataset. This indicated that in order for the outcomes of the subsequent studies to be

representative of a population any analyses must be weighted. Concluding that, raw data requires sophisticated analysis in order for its employment clinically or in research. The results of this study may be employed as a baseline to assess unadjusted gait and cognitive function in adults over fifty years of age.

3.5. Conclusions

Results of this study are representative of those 5034 TILDA participants who attended the health assessment over fifty years of age. Subsequent studies should employ multiple linear regression which has the functionality to adjust and weight outcomes. Previous studies employing the TILDA dataset[232] have shown that those who attended the health assessment were younger, with higher educational attainment, greater mobility and lived closer to the health assessment centres. The results of this study were observed to be in agreement with these findings on age and education. Functionality within multiple linear regression models that allow to weight for characterisitcs such as age, education and geography should be employed in subsequent studies. This would allow outcomes of the regression models that employ the TILDA dataset to be representative of a community dwelling population of over fifty years old. Furthermore, results from the study described in this chapter show gait parameters, are more appropriate regression model dependents than cognitive measures such as MOCA test scores.

CHAPTER 4: Study 2 - Gait Speed a Biomarker for Cognitive Impairment?

Study 1 found gait performance to differ across global cognition categories. In addition, literature suggests that gait performance may be a good biomarker for cognitive impairment. The study described in this chapter explored the efficacy of employing poor gait performance as a biomarker for cognitive impairment. This study employed standardised gait and cognitive scores (zscores) to assess the efficacy of gait zscore at highlighting those with poor MOCA performance and memory impairments. In addition, this study explored correlations between gait performance and global cognition categories employing regression analysis.

4.1. Introduction

Recent literature has expressed the view that elements of gait performance, such as gait speed or stride time variability, may be possible biomarkers for incipient cognitive decline [70, 82] as per Chapter 2: Literature review. Specifically, Burrachio et al [192] found an acceleration of gait speed decline up to twelve years before Mild Cognitive Impairment. Burrachio et al also found pace (gait speed and stride length) to be the only factor associated with cognitive decline when also investigating rhythm and variability factors. It would be clinically beneficial for a biomarker to be found for Mild Cognitive Impairment, thereby aiding in diagnosing prodromal Alzheimer's disease[273].

A biomarker is a specific term with particular stipulations for its use [274-276] and further research is needed in order to employ this term with confidence in gait and cognitive function research. The term biomarker, or biological biomarker, refers to a broad subcategory of medical signs that are objective indications of a medical state that can be observed from outside the patient[277]. The National Institute of Health (NIH) Biomarkers Definitions Working Group have defined a biomarker

as: "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention". A biomarker must be sensitive enough to detect most positive cases at an early stage, but specific enough not to detect other pathologies. In addition, biomarkers must have a strong predictive value. Furthermore, the NIH Biomarker Definitions Working Group state that for a biomarker to be useful as a screening method; the test must be inexpensive, non-invasive and simple to apply and should ideally be related to the fundamental pathology[274].

Gait performance tests, in particular the gait speed test, facilitate the inexpensive, non-invasive and simple to apply criteria stipulated for a biomarker. However, the sensitivity and specificity of a gait speed test at assessing global cognition or MCI has not been fully evaluated. The study described in this chapter investigates the efficacy of a gait speed test at being a biomarker for cognitive impairment by employing the TILDA population. Gait speed zscores were calculated to assess the efficacy of gait speed during dual gait tasks as a biomarker for cognitive impairment. In order to calculate zscores a control dataset (healthy older adults) had to be formed.

4.2. Methods

4.2.1. Study Design

This study used baseline cross sectional data (n = 8504, 56% women, age = 63.14(10.21) yrs) from The Irish Longitudinal study on Ageing (TiLDA). Inclusions criteria for this study were complete gait speed and MOCA data, making 4368 TILDA participants eligible (55% women, 62.4(8.2) mean (SD) age, MOCA, MMSE). Further detail of the study procedure can be found in Chapter 2: General Methods.

Data collection in the TILDA study comprised of three parts: a computer-assisted personal interview, a self-completion questionnaire and a health assessment. Participant characteristics detailed in this study were recorded during the computer-assisted personal interview. All neuropsychological and gait measure described in this study were assessed during the TILDA health centre assessment[232].

4.2.2. Gait and Cognitive Function Measures

A 4.88m walkway recorded average gait speed during two dual gait tasks: motor and cognitive. Global cognition was assessed by the MOCA and MMSE assessment tests during the TILDA neuropsychological assessment. Memory impairment data was collected in the TILDA CAPI questionnaire and included participants who responded "yes" to the question "Has a doctor ever told you that you have?" when asked about: serious memory impairments, dementia, organic brain syndrome, senility or Alzheimer's Disease.

4.2.3. Analyses

MOCA was categorised into Poor, Intermediate and Good global cognition categories based on cutoff scores of 0-23, 24-25 and 26-30 respectively as defined in Chapter 1: Literature review and calculated as discussed in Chapter 2: General Methods: Generation of a Categorical Variable. Briefly, the healthy control gait group excluded participants with alphabet problems during the alternate letter dual cognitive gait task, a disturbed walk during either dual gait tasks, those who use a walking aid, had any activity difficulties, poor vision or less, arthritis, osteoporosis, hip fracture, hip or knee pain, memory impairments, Alzheimer's Disease, Dementia, Stroke and Parkinson's Disease. The healthy control cognitive group excluded excluded participants with an MMSE of less than 28 and those with serious memory impairments, Alzheimer's Disease, Dementia, Stroke and Parkinson's Disease. In addition, a subcohort of those in the TILDA dataset who had memory impairments was formed.

For Model 1, age adjusted Gait Zscores and MOCA Zscores were derived for the TILDA dataset (see Section 2.5.3.4: Zscores) and employing gait control groups of the population (see Chapter 2: General Methods: 3.2.2.4). Motor Gait Zscores, Cognitive Gait Zscore and Composite Gait Zscores were employed as measures of gait performance where poor gait speed defined poor gait performance. Composite Gait Zscores were calculated from the average of the Motor Gait Zscore and the Cognitive Gait Zscore. Individuals in the memory impaired subcohort, in the Poor MOCA category and in the abnormal MOCA Zscore category were employed as the Cognitive

Impairment group. Univariate linear regression was employed to assess if differences in Composite Gait Zscores were correlated with differences in MOCA Zscores.

Gait Zscores were assessed over the three cognitive categories to investigate if poor gait speed is a biomarker, as assessed with a zscore threshold value, for cognitive impairment. The three cognitive categories were: (i) those in the memory impaired subcohort (ii) those in the poor MOCA category and (iii) those with an abnormal MOCA Zscore. A Gait zscore of less than -2.5 was employed as an abnormal test result.

In addition, Model 2 examined multiple linear regression was employed to investigate if differences in gait performance was correlated with global cognition categories (Poor, Intermediate and Good) while adjusting for age, gender, body mass index, educational attainment and depression. Gait performance was assessed as gait speed during the single gait task and the dual cognitive or dual motor gait tasks, in addition to dual task effect during both dual gait tasks.

4.3. Results

A Motor Gait Zscore, a Cognitive Gait Zscore and a Composite (motor-cognitive gait task) Gait Zscore were calculated. The correlation between MMSE and MOCA was moderate ($r\ (5132) = 0.56$, $p<0.0001$). Linear regression found Composite Gait Zscores to statistically significantly increase ($p<0.05$) with increasing Cognitive Zscores as can be seen in Figure 18.

When evaluating gait zscores as biomarkers for cognitive impairment (Model 1) employing a zscore of less than -2.5 results show the following: Composite Gait Zscore recorded abnormal tests for 7.7% (n=1) of the memory impaired subcohort and 1.5% (n=16), 1.3% (n=13), 0.9% (n=22) of the Poor, Intermediate and Good MOCA categories respectively and 3.1% (n=7) of the abnormal MOCA zscore cohort. Cognitive Gait Zscore recorded abnormal tests for none of the memory impaired subcohort, 1.2% (n=13), 1.8% (n=18) and 1.8% (n=41) of the Poor, Intermediate and Good MOCA categories respectively and 1.8% (n=4) of the abnormal MOCA zscore cohort. Motor Gait Zscore recorded abnormal tests for 7.7% (n=1) of the memory impaired subcohort, 2.8% (n=29), 1.6% (n=16) and 1.3% (n=30) of the Poor, Intermediate and Good MOCA categories respectively and 4.8% (n=11) of

the abnormal MOCA zscore cohort. This result can be seen in Figure 19 which shows Gait Zscore distribution over MOCA test scores for each individual. However, when examining group differences as can be seen in Figure 20 (boxplot) and Figure 21 (mean zscores) lower gait zscores show a trend towards abnormality for the memory impaired cohort and progressively less abnormal scores in MOCA 0-23, 24-25 and 26-30 categories.

Multiple Linear regression (Model 2) found participants with Intermediate (24 and 25) and Good (26-30) MOCA test scores to have significantly different gait speed for both dual gait tasks when compared with those with Poor MOCA test scores (<24), see Table 5 and Figure 22 and Figure 23. For the single gait task, gait speed was only significantly different when comparing Poor MOCA test scores to Intermediate MOCA tests scores. Both cognitive and motor dual task effects were significantly different for those with Poor MOCA test scores compared to those with Good MOCA test scores.

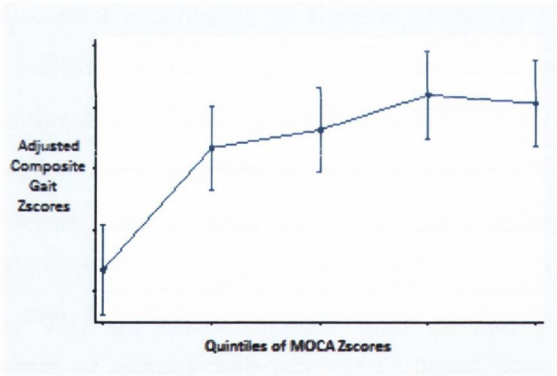


Figure 18: Predicted Composite Gait Zscores across Quintiles of Cognitive Zscores.

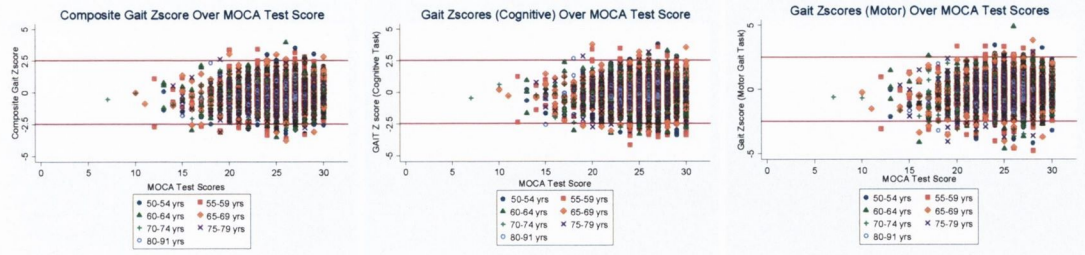


Figure 3: Gait Zscores over MOCA test scores (n= 4380) (i) Composite Gait Zscore (left) , (ii) Gait zscore (Cognitive Gait Task) (centre) (iii) Gait zscore (Motor Gait Task) (right)

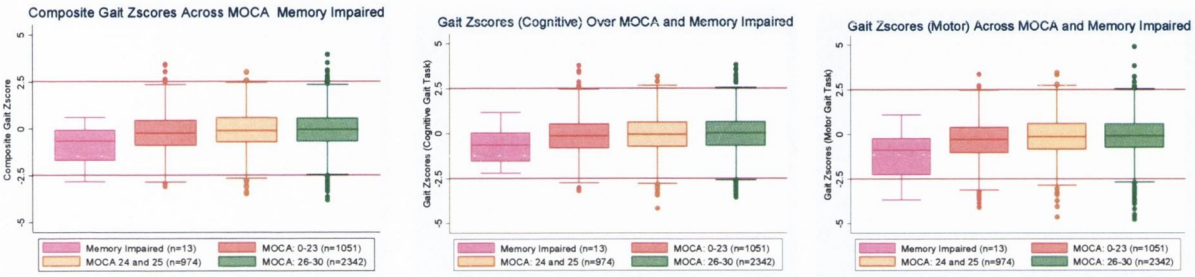


Figure 20: Gait Zscores against Memory Impaired Sub-cohort and MOCA categories (n=4380) for (i) Composite Gait Zscore (top left) (ii) Gait Zscore (cognitive Task) (top right) (iii) Gait Zscore (Motor Gait Task) (bottom).

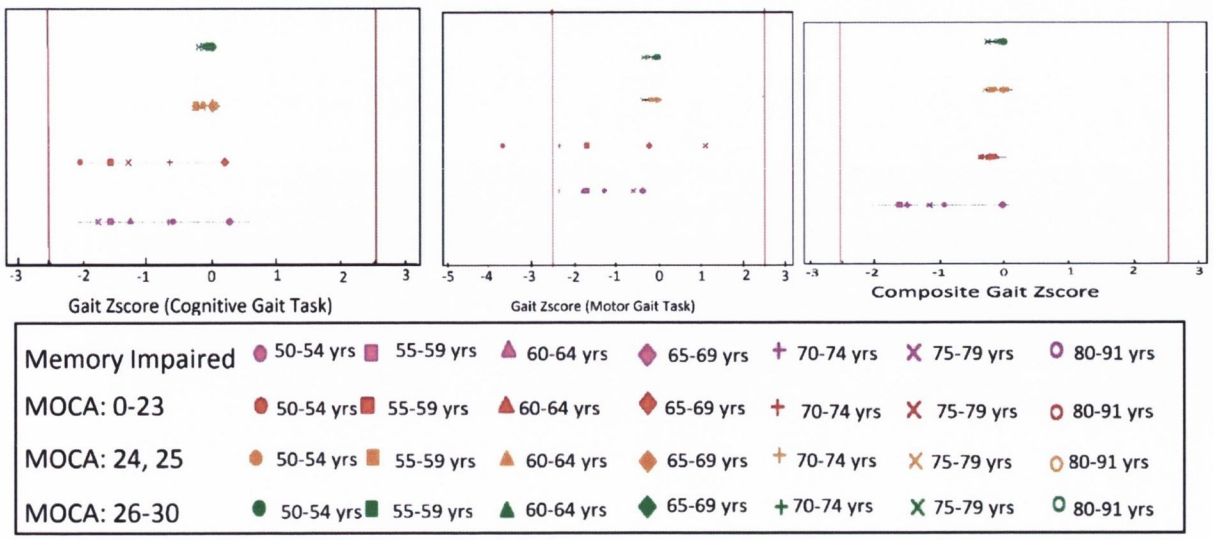


Figure 21: Mean Gait Zscores across memory impaired subcohort and MOCA categories

Table 5: Correlations between Gait Performance (Gait speed or Dual Task Effect) and MOCA category (Model 2) adjusted for gender, body mass index, educational attainment and depression

	Poor MOCA	Intermediate MOCA	Good MOCA
	p	p	p
Single Gait Task	-	0.009	0.183
Cognitive Gait Task	-	0.025	<0.0001
Motor Gait Task	-	0.001	<0.0001
Cognitive Dual Task Effect	-	0.539	<0.0001
Motor Dual Task Effect	-	0.093	<0.0001

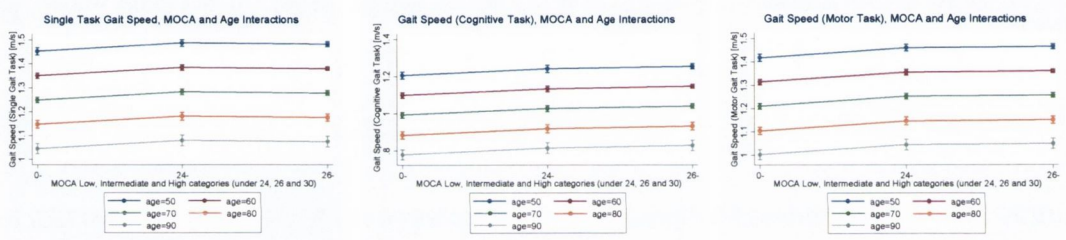


Figure 22: Model 2 Interaction between MOCA categories, Age group and Gait Speed during the (i) Single Task (ii) Dual Cognitive Gait Task (iii) Dual Motor Gait Task. Post Regression Linear Predictive Margins with 95% Confidence Intervals adjusted for gender, body mass index, educational attainment and depression.

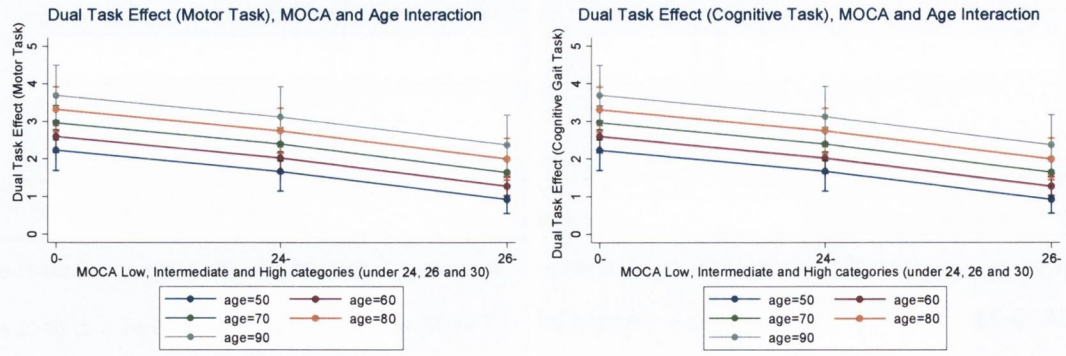


Figure 23: Interaction between MOCA categories, Age group and Dual Task Effect during the (i) Dual Cognitive Gait Task (ii) Dual Motor Gait Task. Post Regression Linear Predictive Margins with 95% Confidence Intervals adjusted for gender, body mass index, educational attainment and depression

4.4. Discusssion

This study investigated the efficacy of gait speed as a biomarker for cognitive impairment by employing zscore measures. Poor gait speed was found to be a poor biomarker for cognitive impairment both as assessed with diagnosis of memory impairment and as assessed with MOCA categories. However, when employing regression analysis to assess the correlations between Composite Gait Zscores and Cognitive Zscores, those with greater Gait Zscores had statistically significantly greater Cognitive Zscores. In addition, regression analysis employing covariate adjustments found that those with poorer global cognition (MOCA score < 24) had statistically significantly slower gait speed and a greater Dual Task Effect than those with better global cognition.

The predictive values of a test in clinical practice depend critically on the prevalence of the impairment in the participants being tested[278]. Compared to gait and cognitive performance in literature the TILDA population is a highly functioning population of community dwelling adults over fifty years of age. Without further diagnosis it is unclear whether all those participants with a MOCA test score of under 26 are mildly cognitively impaired. Predictive values were only based on MOCA test scores; perhaps if additional markers of cognitive impairment were included the gait assessment task would have gained a higher predictive value.

Furthermore, when Cognitive Zscores are taken into account they are significantly correlated with Composite Gait Zscores. Cognitive Zscores are calculated employing a healthy cohort with MMSE test score of over 28. Perhaps categorising Good global cognition with a higher MOCA cut off score would have been a more appropriate method of differentiating the TILDA population and may have gained more successful predictive values. In addition, perhaps employing a lower standard deviation to highlight abnormal zscores may yield a higher predictive value, for instance DSM5 recommends a 1-2 standard deviation difference to indicate those with Mild Cognitive Impairment (mild neurocognitive disorder).

In addition in order to calculate an appropriate zscore a healthy control cohort has to be generated. Possibly this process was not successful due to a "healthy" cohort being exceptionally difficult to define in a community dwelling older population who may have poor global cognitive scores but who may be compensating for these with other processes

or strategies. One particular strategy that may be used is prioritising gait speed over the secondary dual task which would not be seen in the gait speed measure employed. This is a limitation of this study and including errors in the secondary dual task should be included in future studies. In addition, literature does state that gait speed may be a more general marker of health and gait parameters that have been associated with more specific elements of cognitive impairment such as dual task effect or gait variability may gain higher predictive values.

Finally, age in particular has a large effect on gait performance in this population and future studies should adjust for this along with other covariates such as gender, height, depression and education found to affect the relationship between gait and cognitive function in Study 1 and in literature. In conclusion, gait speed during any gait task was not found to be a biomarker for cognitive impairment as measured by a MOCA score under 24 or a diagnosis of memory impairment. Further research should include adjustment for covariates or employ more sensitive standard deviation cut offs.

4.5. Key Points

- Age adjusted gait zscores during dual gait tasks are not effective biomarkers for cognitive Impairment in this population.
- Age is too strong a covariate to adjust out in zscore analysis. Adjusting for age in regression analysis seems to be a more subtle method.
- However, when employing regression analysis and adjusting for covariates those who have higher global cognition were found to walk faster during simple and complex gait tasks.

CHAPTER 5: Study 3 - Automaticity of Gait: Investigating Gait Speed across the Executive Function Spectrum in a Nationally Representative Population

Study 2 found associations between gait and global cognition. However, probing contributions from specific elements of cognitive function would be beneficial. It has been reported in literature that there is a certain attentional capacity for each individual and this can be stressed during a complex dual task. Literature also reports that executive function is significantly associated with gait performance and automaticity of gait is a significant factor in gait performance and gait task effect. Probing attentional capacity changes in an ageing cohort with differing cognitive, executive and attentional capacities and investigating the differences in dual cognitive gait task performance would be very interesting. This study hypothesised that poor executive function will be significantly correlated with slower gait speed and higher Dual Task Effect for all gait tasks. Secondly, it was hypothesised that the executive function/gait performance change point would indicate a transition from automatic to self-aware gait.

It is suspected that executive function contributes to disruptions of gait and balance, however a detailed understanding of this relationship has not yet been exposed. In addition, it has been suggested that executive function impairments as shown through performance of complex gait tasks may be an indication of incipient Mild Cognitive Impairment. Understanding the relationship between gait performance, gait task and executive function would have far reaching clinical benefits. A major advantage of the study described in this chapter is the large cohort size and the fact that the cohort is nationally representative of people over fifty years of age. Studies to date have based findings on small participant numbers or larger cohorts of adults older than those employed in this study. The study described in this chapter probes the relationship between gait speed and executive function using dual tasking and the Color Trail Test using cross sectional data from the TILDA dataset. Gait speed has been chosen as a gait parameter of interest as it has been shown to be an important factor affecting those at risk of falling and of mortality.

The aim of this study was to explore associations between variation in executive function performance and simple and complex gait task performance in a nationally representative population.

A conference proceeding has been derived from research in this chapter.

I. Killane, C. Brennan, G. Savva, O. Donoghue, H. Cronin, R. A. Kenny, R. B. Reilly (24-29th June 2012). Comparisons between Simple and Complex Gait Tasks across different Executive Function Groups and Tertiles - Cross Sectional Data from The Irish Longitudinal Study on Ageing (TILDA). Presentation ID 79201. Joint World Congress of ISPGR (International Society of Posture and Gait Research) and GMF (Gait and Mental Function), Trondheim, Norway.

5.1. Introduction

The Introduction of gait speed as a standard clinical measure in geriatric assessment has gained interest due to its association with multiple falls [84], survival rate [2] and activities of daily living [3]. In addition, age related functional changes, such as impaired executive function, [128, 173] have been associated with slow gait speed[191], gait disruptions [78, 79] and fall prediction [106, 201, 202]. Further understanding of the relationship between gait task, gait speed and executive function in a population representative of community dwelling adults over fifty years of age would contribute to understanding healthy motor-cognitive processes. In addition, increasing our understanding of any sub-clinical changes that exist in gait or underlying neurocognitive pathology manifested in poor motor function would inform clinical assessment.

Executive function refers to higher neurological processes, such as a decline in attention, mental flexibility and abstract thinking[23], which use and modify information from many cortical systems and are needed to carry out activities of daily living. Functional changes such as declines in executive function domains and gait disturbances together with age related structural changes and neuropathology[172], cause increased recruitment and activation of frontal lobe resources[128, 173]. This increased recruitment manifests in an individual's gait [72], such as a decrease in walking speed, and at a certain point a transition from an automatic to a more self-aware gait starts to occur [23, 174]. These changes in gait are especially noticeable during more complex gait tasks and with cognitive impairment[175].

In this study we investigated the link between gait performance and executive function, as assessed by the Color Trails Test (CTT) in healthy older adults. In addition, we sought out the point on the executive function spectrum where executive function has an effect on

gait performance: the change point. This change point may indicate a threshold for transition from an automatic to a more self-aware gait and may highlight a target population for intervention. We examined two gait performance measures: gait speed and the relative decrease in gait speed (DTE, dual task effect) over three walking tasks (one single and two more complex dual gait tasks) and Color Trail Test – a clinical executive function test developed to reduce influence of language and culture. Poor gait speed and large Dual Task Effect was also assessed as a diagnostic test for poor executive function.

Previous studies have found executive function to be associated with: Dual Task Effect and gait speed during single [50] [207] (n=186 Einstein Aging Study, n=493) and dual gait tasks [128, 169](n=737, n=926 InChianti study) using the Trail Making Task (ΔTMT). The Trail Making Task assessed a specific element of executive function termed cognitive flexibility. Little research exists on the associations between gait task, gait speed and other such measures of executive function which do not have cultural or language influences such as the CTT used in this study. In addition, exploring this association during ecological gait tasks over the executive function spectrum of a large healthy nationally representative dataset, such as the Irish Longitudinal Study on Ageing (TILDA, n=4607), which holds a comprehensive overview of the population's health, is novel and builds on previous findings[127, 233]. Further investigation of this relationship is needed as it may pinpoint an executive function test score at which gait speed is significantly impaired, a possible automatic gait change point indicator.

Firstly, we hypothesised that poor executive function will be significantly correlated with slower gait speed and higher Dual Task Effect for all gait tasks. This would show that executive function is recruited during all gait conditions but to a greater extent during dual task conditions. Secondly, we hypothesised that the executive function/gait performance change point would indicate a transition from automatic to self-aware gait. This would show that there is a specific change point threshold for each gait task. Thirdly, we hypothesized that gait speed and Dual Task Effect will be more strongly linked to executive function during a cognitive compared with a motor dual task due to the increased task modality (motor and cognitive modes).

Further understanding and examination of the relationship between gait task, gait speed and executive function in a normative population with a large age range (50-91 years),

such as TILDA, would be particularly beneficial in order to validate gait tasks for clinically directed investigations, clinical diagnosis and intervention in older healthy adults.

5.2. Methods

5.2.1. Study Design

This study used baseline cross sectional data (n = 8504, 51% women, age = 63.14(10.21) yrs) from The Irish Longitudinal study on Ageing (TiLDA) after excluding incomplete Color Trails Test (CTT) and gait data gave complete covariate data from 4607 participants. Further detail of the study procedure can be found in Chapter 2: General Methods.

Data collection in the TILDA study comprised of three parts: a computer-assisted personal interview, a self-completion questionnaire and a health assessment. Participant characteristics detailed in this study were recorded during the computer-assisted personal interview. All neuropsychological and gait measure described in this study were assessed during the TILDA health centre assessment[232].

5.2.2. Gait and Cognitive Function Measures

This study examined performance on an executive function assessment test that was administered during the TILDA health assessment as per Chapter 2: General Methods. The Color Trails Test™ (CTT) [130, 131] was included in the neuropsychological assessment. In this study the difference measure (ΔCTT) [132] was employed to assess executive function, specifically cognitive flexibility.

This chapter also examined gait speed recorded with a GaitRite pressure sensing mat in the TILDA gait assessment as per Chapter 2: General Methods. Gait speed during the single and dual gait tasks were the measures of gait performance employed: gait speed for the single, dual motor and dual cognitive gait tasks. Dual Task Effect was also calculated for each individual for each dual task.

5.2.3. Analysis

Participants were classified according to their ΔCTT score to investigate the executive function spectrum within this population, to investigate how this related to gait speed and Dual Task Effect and to pinpoint where the effect of executive function on gait performance begins to occur.

Data was analysed using Stata version 10.1. (StataCorp, U.S.A). Paired t-tests were used ($p<0.05$) to investigate the effect of task on gait speed. To ensure the data was nationally representative, all analyses were weighted to age, sex and education of the Quarterly National Household Survey (2010) and by health status and socio-demographic factors to adjust for potential selection bias among those who attended the health assessment centre.

Three executive function classifications were investigated: Divisions, Tertiles and Deciles. Executive function divisions were examined as it was important to examine those with poor executive function in this population. However, comparison across the three executive function divisions may not be statistically robust due to the differences in participant numbers in each division: Good (n=2303), Intermediate (n=2074), Poor (n=226). For this reason executive function Tertiles were examined. Executive function Deciles were investigated in order to parse apart the exact point at which gait speed was significantly correlated with executive function. It was thought that examination of all three categories together would give a clearer picture of associations of executive function and gait performance in this population, in addition to those at possible risk of executive function impairment.

Executive function Divisions were subdivided into Good, Intermediate and Poor executive function divisions [128, 279, 280]. The Good executive function divisions included participants with a ΔCTT score below the median ΔCTT score of 50.2 seconds. This included 2303 participants, 50.2 percent of the population. The Intermediate executive function division included participants with a ΔCTT score between the median ΔCTT score of 50.2 seconds and the 95th percentile of 103.6 seconds. This included 2074 participants, 43.2 percent of the population. The Poor executive function division included participants with a ΔCTT score of over the 95th percentile of 103.6 seconds. This included 229 participants, 4.7 percent of the population.

Executive function Tertiles and Deciles of the population were also calculated. Executive function Tertile 1 (T1), Tertile 2 (T2) and Tertile 3 (T3) included particpants with a ΔCTT score under 40.3 seconds, between 40.3 and 59.3 seconds and over 59.3 seconds.

Executive function Deciles (D1-D10) included participants with the following ΔCTT scores: 0.3-25.4 (D1), 25.4-32.1 (D2), 32.1-38.2 (D3), 38.3-43.8 (D4), 43.8-49.0 (D5) ,49.0-54.4 (D6), 54.4-62.1 (D7), 62.1-71.8 (D8), 71.9-87.5 (D9) and 87.5-250.8 (D10) seconds.

Univariate and multiple linear regression analysis were employed to compare executive function categories across single and complex gait tasks for all three executive function categories. Differences in gait speed and Dual Task Effect were examined across the executive function spectrum of this population using a continuous executive function measure, and to explore any associations further three executive function classifications (Divisions, Tertiles and Declies) were then investigated with the highest level of executive performance as the reference group. Significance was set at $p<0.01$ to account for multiple comparisons (0.05 divided by five gait measures).

A separate model was explored for each outcome (gait speed in each gait condition; Dual Task Effect for cognitive and motor dual tasks), models unadjusting and adjusted for age, gender, height, level of education (primary, secondary, third level), and factors affecting gait: self-rated vision, number of chronic diseases and activities difficulties, presence of Parkinson's disease, arthritis, osteoporosis, hip or knee pain, or hip fracture and use of a walking aid as per Table 6 and Study Design were investigated. Marginal gait speed and Dual Task Effect scores were estimated across executive function classifications and adjusted gait speed and Dual Task Effect values were plotted to illustrate the possible change-points for each gait condition. In addition, sensitivity, specificity and predictive values for each gait speed and Dual Task Effect decile found to be statistically significantly correlated with executive function were calculated.

4.6. Results

A large diverse cohort was included in this analysis as can be seen in Table 6 (n=4607). Gait speed and percent decrements were significantly different for all gait task comparisons (two tailed paired t-test: $t < 0.05$). ΔCTT values were similar to previous population studies [131, 281] allowing for the difference in age and the healthy status of this cohort.

Unadjusted gait speed and Dual Task Effect values over executive function groups for each gait condition can be seen in Table 7. Gait Speed and Dual Task Effect were found to statistically significantly correlate with executive function (continuous ΔCTT) for all gait tasks. Thus, executive function groups were investigated. Gait Speed and Dual Task Effect of participants with 'poor' and 'intermediate' executive function, those in the lowest tertile (T3) and those in the lower deciles of executive function statistically significantly varied to those in the reference groups ($p<0.01$) for all gait tasks.

Adjusted gait speed and Dual Task Effect values across executive function groups for each gait condition can be seen in Table 8 and Figure 24. Gait speed for the single gait task did not vary by executive function (continuous ΔCTT) or level of executive function (division, tertile or decile). However, for both dual tasks, gait speed and Dual Task Effect were statistically significantly correlated with executive function (continuous ΔCTT). Participants with 'poor' and 'intermediate' executive function and those in the lowest tertile (T3) of executive function had significantly slower gait speed and greater Dual Task Effect than the reference groups ($p<0.01$) for both dual gait tasks, with the exception of gait speed for those in the 'intermediate" executive function group for the motor dual gait task ($p=0.028$). When executive function is considered in deciles, D10 had significantly greater Dual Task Effect for the motor dual task when compared to the reference group (D1); however an effect of executive function on gait speed and Dual Task Effect during the motor dual task can be seen to begin at decile D9. Under cognitive dual task conditions, the lowest two deciles (D9-10) had significantly slower gait speed and the lowest four deciles (D7-10) had significantly greater Dual Task Effect when compared to the reference group (D1). These points of transition and magnitude of executive function effects on gait speed under different gait conditions can be seen in Table 8 and Figure 24. Sensitivity, specificity, adjusted positive predictive values and adjusted negative predictive values at points where gait speed and DTE were statistically significant were found to be 58%, 81%,

17% and 79% respectively for a gait speed of under 1.07 m/s, 50%, 58%, 24% and 58% respectively for a Dual Task Effect of over 18.7% in the cognitive gait task and 56%, 92%, 10% and 89% respectively for a Dual Task Effect of over 3.6% in the motor gait task.

Table 6: Participant Characteristics, n=4607

Background Measures	Value
Age, years: mean±sd (range)	62.3±8.12 (50-91)
Gender, n female (%)	2515 (55)
Height: mean±sd (IQR) [cm]	166.2±9.08 (159.2-173)
Level of Education Achieved, %	
Primary	22%
Secondary	42%
Third Level	37%
Self-Rated Vision[a], % (n)	
Excellent	21% (979)
Very Good	38% (1759)
Good	33% (1515)
Fair	7% (309)
Poor	1% (43)
Chronic Disease, % (n)	
None	23% (1045)
One	29% (1330)
Two	23% (1079)
Three+	25% (1153)
Diagnosed Disease, % (n)	
Parkinson's Disease	0.3% (14)
Arthritis	27% (1255)
Osteoporosis	10% (474)
Chronic Pain, % (n)	
Hip	3% (134)
Knee	2% (75)
Activity Difficulties, % (n)	9% (395)

a Wearing corrective lenses if appropriate

Hip Fracture, % (n)	2% (114)
Used Walking Aid, % (n)	0.4% (17)
Cognitive Measures[a]	
MOCA, median (IQR)	26 (23-28)
MMSE, median (IQR)	29 (28-30)
CTT: mean±sd, median, IQR [s]	
CTT1	54.8±23.2, 49.75, 38.93-84.03
CTT2	109.5±39.2, 101.25, 82.19-158.78
ΔCTT	54.6±26.9, 50.2, 35.9-68.0
Gait Performance[b], mean±sd, Gait speed (GS): [m/s], Dual Task Effect (DTE): [%]	
Single Gait Task GS	1.36±0.2
Motor Dual Gait Task GS	1.33±0.2
Cognitive Dual Gait Task GS	1.11±0.3
Motor DTE	1.85±6.3
Cognitive DTE	18.18±13.8

a MOCA (Montreal Cognitive Assessment), MMSE (Mini Mental State Examination), CTT (Color Trail Test), CTT1 (Color Trail Test 1), CTT2 (Color Trail Test 2), ΔCTT (Difference in Time between CTT1 and CTT2).

b GS = Gait Speed, DTE = Dual Task Effect

Table 7. Unadjusted values of Gait Speed (GS [m/s]) and Dual Task Effect (DTE [%]) over Executive Function Divisions (Good, Intermediate and Poor), Tertiles (T1-T3) and Deciles (D1-10)

Executive Function		Single Task		Dual Motor Task				Dual Cognitive Task			
ΔCTT Level[a]	(ΔCTT [s], n)	GS [m/s]	P	GS m/s]	P	DTE [%]	P	GS [m/s]	P	DTE [%]	P
CONTINUOUS ΔCTT (IQR: 35.9-68.0 [s])		1.36±0.2	<0.001*	1.33±0.21	<0.001*	1.8±6.3	<0.001*	1.11±0.26	<0.001*	18.2±13.8	<0.001*
DIVISIONS											
Good	(<50.2, 2303)	1.38±0.00	-	1.36±0.00	-	1.4±0.1	-	1.15±0.01	-	16.7±0.3	-
Intermediate	(50.2-103.6, 2074)	1.34±0.01	<0.001*	1.31±0.00	<0.001*	2.1±0.1	<0.001*	1.09±0.01	<0.001*	19.2±0.3	<0.001*
Poor	(>103.6, 229)	1.28±0.02	<0.001*	1.23±0.02	<0.001*	4.1±0.6	<0.001*	1.01±0.02	<0.001*	21.8±1.0	<0.001*
TERTILES											
T1	(<40.3)	1.38±0.01	-	1.36±0.01	-	1.4±0.2	-	1.15±0.01	-	16.8±0.4	-
T2	(40.3-59.3)	1.36±0.01	0.002*	1.34±0.00	0.001*	1.5±0.2	0.708	1.13±0.01	0.006*	17.3±0.3	0.312
T3	(>59.3)	1.33±0.01	<0.001*	1.29±0.01	<0.001*	2.6±0.2	<0.001*	1.06±0.01	<0.001*	20.0±0.4	<0.001*
DECILES											
D1	(0.3-25.4)	1.38±0.01	-	1.35±0.01	-	1.4±0.3	-	1.15±0.01	-	16.2±0.7	-
D2	(25.4-32.1)	1.38±0.01	0.728	1.36±0.01	0.682	1.3±0.3	0.881	1.14±0.01	0.500	17.3±0.6	0.258
D3	(32.1-38.2)	1.40±0.01	0.117	1.38±0.01	0.132	1.4±0.3	0.938	1.17±0.01	0.446	16.6±0.7	0.648
D4	(38.3-43.8)	1.37±0.01	0.979	1.36±0.01	0.737	1.1±0.3	0.445	1.16±0.01	0.878	16.0±0.6	0.842
D5	(43.8-49.0)	1.36±0.01	0.159	1.33±0.01	0.099	1.7±0.3	0.511	1.13±0.01	0.121	17.0±0.6	0.368
D6	(49.0-54.4)	1.37±0.01	0.763	1.35±0.01	0.541	1.7±0.3	0.445	1.13±0.01	0.268	17.3±0.6	0.220
D7	(54.4-62.1)	1.36±0.01	0.262	1.33±0.01	0.107	2.0±0.3	0.121	1.11±0.01	0.008*	18.8±0.6	0.005*
D8	(62.1-71.8)	1.35±0.01	0.103	1.33±0.01	0.102	1.5±0.3	0.740	1.10±0.01	0.001*	19.1±0.6	0.003*
D9	(71.9-87.5)	1.32±0.01	<0.001*	1.29±0.01	<0.001*	2.2±0.3	0.056	1.06±0.11	<0.001*	19.7±0.7	<0.001*
D10	(87.5-250.8)	1.30±0.01	<0.001*	1.24±0.01	<0.001*	4.0±0.4	<0.001*	1.02±0.01	<0.001*	21.7±0.7	<0.001*

a Divisions, Tertiles and Deciles refer to classification according to ΔCTT values. All analyses were weighted to remove potential biases in data collected at health assessment in order to be nationally representative population sample.

Table 8: Adjusted values of Gait Speed (GS [m/s]) and Dual Task Effect (DTE [%]) over Executive Function Divisions (Good, Intermediate and Poor), Tertiles (T1-T3) and Deciles (D1-10)

Executive Function		Single Task		Dual Motor Task				Dual Cognitive Task			
ΔCTT Level[a]	(ΔCTT [s], n)	GS [m/s]	P	GS m/s]	P	DTE [%]	P	GS [m/s]	P	DTE [%]	P
CONTINUOUS ΔCTT (IQR: 35.9-68.0 [s])		1.36±0.00	0.184	1.33±0.00	<0.001*	1.87±0.1	<0.001*	1.11±0.00	<0.001*	18.1±0.2	<0.001*
DIVISIONS											
Good	(<50.2, 2303)	1.36±0.00	-	1.34±0.00	-	1.5±0.1	-	1.13±0.01	-	16.9±0.3	-
Intermediate	(50.2-103.6, 2074)	1.35±0.00	0.379	1.33±0.00	0.028	2.0±0.1	0.004*	1.10±0.01	<0.001*	19.0±0.3	<0.001*
Poor	(>103.6, 229)	1.35±0.01	0.390	1.30±0.01	0.008*	3.7±0.6	<0.001*	1.08±0.02	0.002*	20.8±1.0	<0.001*
TERTILES											
T1	(<40.3)	1.36±0.01	-	1.34±0.01	-	1.5±0.2	-	1.13±0.01	-	17.1±0.4	-
T2	(40.3-9.3)	1.35±0.00	0.265	1.33±0.00	0.239	1.5±0.2	0.967	1.12±0.01	0.200	17.4±0.3	0.520
T3	(>59.3)	1.35±0.00	0.169	1.32±0.01	0.002*	2.4±0.2	<0.001*	1.09±0.01	<0.001*	19.6±0.4	<0.001*
DECILES											
D1	(0.3-25.4)	1.35±0.01	-	1.33±0.01	-	1.5±0.3	-	1.13±0.01	-	16.5±0.7	-
D2	(25.4-32.1)	1.35±0.01	0.938	1.33±0.01	0.995	1.4±0.3	0.900	1.12±0.01	0.290	17.6±0.6	0.235
D3	(32.1-38.2)	1.37±0.01	0.143	1.35±0.01	0.162	1.5±0.3	0.960	1.15±0.01	0.489	16.9±0.7	0.661
D4	(38.3-43.8)	1.36±0.01	0.762	1.34±0.01	0.467	1.2±0.3	0.395	1.14±0.01	0.618	16.1±0.7	0.687
D5	(43.8-49.0)	1.35±0.01	0.522	1.32±0.01	0.327	1.7±0.3	0.542	1.12±0.01	0.339	17.1±0.6	0.497
D6	(49.0-54.4)	1.36±0.01	0.487	1.34±0.01	0.720	1.7±0.3	0.569	1.13±0.01	0.630	17.5±0.6	0.283
D7	(54.4-62.1)	1.36±0.01	0.418	1.34±0.01	0.797	2.0±0.3	0.208	1.11±0.01	0.142	18.8±0.6	0.010*
D8	(62.1-71.8)	1.36±0.01	0.819	1.34±0.01	0.869	1.5±0.3	0.903	1.10±0.01	0.041	19.0±0.6	0.008*
D9	(71.9-87.5)	1.34±0.01	0.284	1.31±0.01	0.076	2.1±0.3	0.123	1.08±0.11	0.003*	19.3±0.7	0.003*
D10	(87.5-250.8)	1.35±0.01	0.734	1.30±0.01	0.013	3.7±0.4	<0.001*	1.07±0.01	<0.001*	20.9±0.7	<0.001*

a Divisions, Tertiles and Deciles refer to classification according to ΔCTT values. All analyses were weighted to remove potential biases in data collected at health assessment in order to be nationally representative population sample. All analyses, except the values for GS and DTE for the continuous ΔCTT, were adjusted for age, height, gender, education, depression and factors affecting gait.

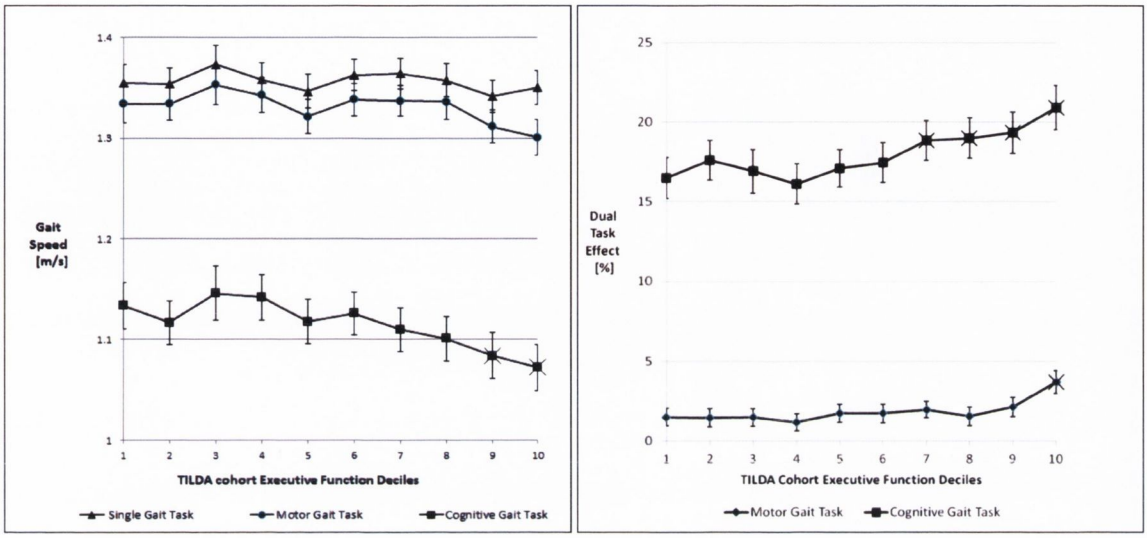


Figure 4:. ***Gait Speed (left) and Dual Task Effect (right) Predicted Values over Executive Function Deciles. Significant values denoted with an X.***

5.3. Discussion

This is the first study to investigate the relationship between executive function and Dual Task Effect in such a large cross-sectional nationally representative sample. In addition, the comprehensive overview of the population's health acquired as part of the TILDA dataset allows for relevant adjustments to be made thereby removing the effects of many possible confounding factors and increasing the clinical relevance of the results.

Our results confirm the first hypothesis of this study: that participants with higher executive function walked faster and had lower Dual Task Effect than participants with poorer executive function in both dual task conditions. This is in agreement with previous findings [23, 128, 169]. This indicates less executive recruitment and a greater ability to cope with these additional demands during walking. It also assumes a mutual cognitive/motor interference effect[174]. However, contrary to Hirota et al[208] and Holtzer et al[50], executive function was not associated with gait speed in the single task walk at normal pace. This indicates that a dual task walk requires greater executive recruitment compared to a single task walk. Overall however, regardless of executive function score, gait speed and Dual Task Effect were

significantly different across all gait conditions. This highlights a need for normative gait speed values over validated gait tasks.

As the TILDA study is longitudinal in nature, we have the opportunity to compare differences in this dataset over time to learn about incipient pathology and early age related locomotive and cognitive system changes. Thus, we have the opportunity to highlight and differentiate those with neurological pathology, those that are ageing benignly, or those experiencing accelerated cognitive or motor ageing. In addition, the efficacy of novel tools for clinical use, such as gait tasks, can be explored employing this longitudal dataset.

Our results also support our second hypothesis that the cognitive dual task would be more strongly linked with executive function than the motor dual task. Correlations between executive function test scores and gait speed differences were hypothesised to quantify a point of transition from automatic to a more consciously controlled gait and asssessing gait performance threshold levels for these points of transition during a complex gait task may highlight those with executive function impairments. Figure 24 indicates deciles at which the effect of executive function on gait speed and Dual Task Effect begin to occur. Those with the lowest 40% executive function scores (D7-D10: ΔCTT >54 seconds) had significantly greater Dual Task effect (>18.9%) in the dual cognitive gait task than the reference group, D1 (16.5%). This is despite the fact that a large proportion of these were not classed as having "poor" executive function (according to the 95th percentile of ΔCTT). In comparison, only the 10th decile (D10) had statistically significantly greater Dual Task Effect than the reference group in the motor dual task (3.7% compared with 1.5%), however, an effect can be seen in Figure 24 at D9 also (from 1.5% (D8) to 2.1%(D9), p=0.123).

Given that higher order cognitive processing needed to complete dual walking tasks dominate the pre-frontal cortex[198, 283], the results of this study suggest that those participants with lower executive function, reduced gait speed and higher Dual Task Effect have a greater reliance on the pre frontal cortex and thus a less automatic gait. Additionally, the fact that Dual Task Effect in the cognitive task increased with each decrease in executive function decile supports the theory that these change-points indicate a transition from an automatic gait to "self-aware" gait.

Overall, regardless of executive function score both gait speed and Dual Task Effect were significantly different across all three gait conditions from a simple walk (Gait speed: 1.4m/s) to carrying a glass of water while walking (Gait speed: 1.3m/s, Dual Task Effect: 2%) to reciting alternate letters of the alphabet while walking (Gait speed: 1.1m/s, Dual Task Effect: 18%). This highlights a shift in attentional resource allocation during different tasks, consequently changing the gait pace chosen by the participant. This supports previous findings [72, 128, 169], but is particularly pertinent and novel given the TILDA dataset represents a nationally representative population of relatively healthy older adults.

These results highlight the link between gait speed and executive function during complex gait tasks. However, this association was observed to exist even for those outside the "poor" executive function range. Therefore, the dual task walk is sensitive to executive function (as measured by ΔCTT) but has limited use as a biomarker for identifying only those with poor executive function. This can be seen in the poor sensitivity values that were found (50-58%: cognitive gait speed under 107 m/s, DTE over 3.6% (motor gait task) and over 18.7% (cognitive gait task)). Specificity was greatest for the motor gait task when employing the Dual Task Effect (92% for a DTE of over 3.6%) compared with the cognitive gait task (82%) when employing a gait speed measure (82%) or the Dual Task Effect measure (58%). Based on these results we would expect 50-58% of participants with abnormal executive function to have abnormal (positive) gait assessment tests, while 50-90% of those with normal executive function would have normal (negative) gait assessment tests. This can also be seen in the very low positive predictive values (10-24%) and high negative predictive values (58-89%) for all proposed gait assessment tests given these gait speed and DTE cutoffs. Other cognitive measures, such as sustained attention, or composite neuropsychological measures may highlight this association more than ΔCTT. Further research in this area should examine the influence of cognitive demands on gait performance and associations between other neuropsychological tests. This would ascertain if gait speed during specific gait tasks is a biomarker for a specific cognitive domain, clinically useful for a directed investigation or, as is thought presently, a broad marker of general health.

Investigating more complex dual task walks at a fast pace may probe automaticity and its link to cognitive function even further, when investigating healthy community dwelling older

adults, and probing realistic ecological environments. The sourcing and validation of an appropriate gait task for clinical use such as this would be highly beneficial. Future research could also utilise technology to measure the occurence of motor/cognitive events in relation to gait events to create true Dual Task effect performance measures and isolate any presence of strategies participants use and priorities they may have.

However, longitudinally the change-points seen in Figure 24 may be relevant for intervention where a high Dual Task effect may be the manifestation of poor executive function or as articulated by Holtzer et al[160]; having good executive function may protect against gait speed decline. These change-points were not found to predict those with poor executive function in the TILDA dataset in this study when employing a simple predictive test. Future analysis of new waves of data acquired longitudinally through TILDA will allow prospective investigation of those participants with significantly higher Dual Task Effect to assess presence of early cognitive impairment. This may manifest as increased dual task effect, slow dual task gait speed and poor Colour Trail Test scores. This is in agreement with Hausdorff et al (2013) that modelling both cognitive and motor function together is preferable to separate models, when investigating dementia development prediction models. This may be due to both motor and cognitive function being affected by a common underlying pathophysiology.

We hypothesise that participants with a negligible deficit in gait speed over all gait tasks had a largely automatic gait involving more efficient neural recruitment for the more complex tasks. Further understanding of the link between neurocognitive function and gait performance may lead to effective pre-emptive actions being taken such as cognitive and locomotive training. However, strategies, adaptations and neurocognitive processes at play for those with higher dual task effect are still unknown.

5.4. Conclusions

Overall, regardless of executive function score gait performance was significantly different across all gait tasks: 1.4m/s (single gait speed) vs. 1.3m/s (motor gait speed) vs. 1.1m/s (cognitive gait speed) and 2% (Motor Dual Task Effect) vs. 18% (Cognitive Dual Task Effect). For a community dwelling older population: Gait speed was found to be significantly associated

with executive function during dual task walking only which represent more realistic ecological environments. Therefore, a slow dual task gait speed may highlight difficulties with daily activities, and in particular those with a high Dual Task Effect in both dual tasks, may be a target population for intervention. Specific executive function/gait change-points were found. Further research may show that these change-points indicate a transition from automatic gait to self-aware gait.

5.5. Key Points

- Executive function contributes significantly to gait speed. The gait task that is performed has a large effect on this contribution.
- The results of this study suggest that there is a possibility to identify exact points of transition from automaticity of gait. This may be a useful possible biomarker for transition from normal functional decline during ageing to a point of reduced independence. This is clinically beneficial and may be employed in much the same way as the functional thresholds that have been specified in criteria for cognitive impairment diagnoses as per literature review in Chapter 1. These transition points were not found to be good predictors of poor executive function. However, this is a relatively young highly functioning population and longitudinal analysis or analysis in older or pathologic populations may reveal more accurate results.
- Future studies should focus on other elements of cognitive function and their relative contribution to gait performance.

CHAPTER 6: Study 4 - Independent Contribution of Specific Elements of Cognitive Function to Gait Speed during Dual Gait Tasks in a Population of Older Adults

The previous study, Study 3, explored the associations between executive function and gait performance. Findings show that there is a link between gait performance and executive function. However, investigating the relative contribution of several elements of cognitive function to gait performance would be beneifical in order to assess their independent contribution to gait performance in this cohort. The aim of the study described in this chapter, Study 4, was to isolate key elements of cognitive function that contribute most to gait performance in a nationally representative population of older adults. Study 4 examined the relative contributions of seven elements of cognitive function to gait performance (gait speed). In addition, effect of task and age interactions were also investigated. Knowledge gained about covariate adjustment from Study 1 and Study 3 were employed. I hypothesised that poorer short term memory, executive function and processing speed will be associated with slower gait speed in single and dual gait tasks.

A journal publication and a conference preceedings have been derived from research in this study.

Journal Paper

I.Killane, O. A. Donoghue' G. M. Savva, H. Cronin, R.A. Kenny, R.B. Reilly. Relative Association of Processing Speed, Short Term Memory and Sustained Attention with Task on Gait Speed: A Study of Community Dwelling People Fifty Years and Older *J Ger: Med Sci Fall 2014.*

Conference Proceedings

I. Killane, O. Donoghue, G. Savva, H. Cronin, R. A. Kenny, R. B. Reilly (3-7 July, 2013). Variance Between Walking Speed and Neuropsychological Test Scores During Three Gait

Tasks Across The Irish Longitudinal Study On Ageing (TILDA). Proceedings of the 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC'13), Osaka, Japan. Conf Proc IEEE Eng Med Biol Soc. 2013; 2013:6921-4. Doi: 10.1109/EMBC.2013.6611149.

6.1. Introduction

Gait speed may be a useful proxy for health and physical functioning. This is evidenced by the association between gait speed and mortality[2, 83, 87]. Gait control is a complex brain process and a recent review has confirmed the important contribution of the central nervous system to gait in non-demented older adults[107]. Global cognition has been shown to longitudinally predict gait speed decline[180, 189]. However, neuroimaging studies have shown links between slower gait and lower integrity of particular areas of the brain: the prefrontal cortex, the basal ganglia and medial temporal lobe[107]. Specifically, the prefrontal cortex plays a role in memory, executive function, sustained attention and information processing [89]. Sustained attention, the ability to maintain attention to a task over a period of time, is thought to have parietal and anterior cingulate cortices involvement also[134]. Together with processing speed, executive function, which is required for effective, goal orientated actions and attentional control, has been reported to be a fundamental mediator of cognitive ageing [23]. Sustained attention has been linked to higher risk of falls and frailty[134] in older adults but has not been examined in relation to gait. Poorer short term memory and executive function[189] has been associated with slow gait speed during simple single gait tasks, with some studies also including attention[190] and global cognition[191].

Multi-tasking plays an important role in our daily activities. Dual task paradigms, where two tasks are performed simultaneously, are often used to create more ecologically valid experimental environments. Slower dual task gait speed has been associated with greater variability in executive function[210] and poorer executive function, short term memory and composite speed/executive/attention scores[23, 50] in healthy older adults. These studies employed small number of older adults[50, 210] and did not report on measures of cognitive function such as visual reasoning, memory, processing speed or sustained attention. Neural

correlates of dual task processing remain unclear[164] but prefrontal cortex recruitment has been reported during dual gait tasks in older adults[41]. Dual task processing theories exist such as the bottleneck, central resource capacity, multiple resource and inhibitory system recalibration theories[165, 284], which suggest links exist between motor and cognitive processes.

Slower processing speed, has been linked to a build-up of white matter hyperintensities[9] in the brain. Declines in executive function are thought to be due to functional and structural declines in: the frontal cortex, the subcortex and the vascular system[126] and have been linked to slower performance in complex motor tasks[127, 128]. In addition, the effect of a dual task on gait speed increases progressively from health to cognitive impairment [71, 89, 129]. Therefore, a dual gait task may be more beneficial than a single gait task for assessing cognitive health in older adults and may aid in the assessment of any transitions to pre-pathology. Further understanding of the relationship between specific elements of cognitive function, the gait task employed and the gait measure recorded[285] needs to be evaluated over a wide age range in healthy older adults. The aim of this study was to explore the relative contribution of seven pertinent elements of cognitive function to gait speed, during dual gait tasks in a nationally representative population of community dwelling adults. We hypothesise that poorer short term memory, executive function and processing speed will be associated with slower gait speed in single and dual gait tasks.

6.2. Methods

6.2.1. Study Design

This study used baseline cross sectional data (n = 8504, 56% women, age = 63.14(10.21) yrs) from The Irish Longitudinal study on Ageing (TiLDA). Inclusions criteria for the study described in this chapter were valid gait and neuropsychological data, making 4431 participants eligible (55% women, 62.4(8.2) mean (SD) age). Further detail of the study procedure can be found in Chapter 2: General Methods. Participant characteristics are reported in Table 9.

Data collection in the TILDA study comprised of three parts: a computer-assisted personal interview, a self-completion questionnaire and a health assessment. Participant characteristics detailed in this study were recorded during the computer-assisted personal interview. All neuropsychological and gait measure described in this study were assessed during the TILDA health centre assessment[233].

6.2.2. Outcome Measures

This chapter examines performance on each element of cognitive function that were administered during the TILDA neuropsychological assessment as per Chapter 2: General Methods. This included short term memory, processing speed, executive function, sustained attention, visual reasoning and verbal fluency. The Montreal Cognitive Assessment (MOCA) assessed global cognition. Most neuropsychological tests measured more than one cognitive element, but for this study each task was classified according to it's main cognitive element. Short term memory was assessed by immediate recall and delayed recall measures. Processing speed was assessed by mean cognitive reaction time employing the Choice Reaction Time test (CRT)[138]. The delta Color Trail Test (ΔCTT) [130] measure assessed executive function. Visual reasoning was assessed by the Revised Cambridge Examination for Mental Disorders of the Elderly (CAMDEX-R) [133]. Verbal fluency was assessed by the MOCA Letter Fluency Task [108]. Sustained attention was measured using the Sustained Attention to Response Task (SART) coefficient of variation [238].

This study also examined average gait speed that was recorded during two passes over a GaitRite pressure sensing mat in the TILDA gait assessment as per Chapter 2: General Methods. The single and dual task gait speed was the measures of gait performance employed: gait speed for the single, dual motor and dual cognitive gait tasks. For each individual for each dual task, Dual Task Difference was also calculated.

6.2.3. Statistical Analyses

Descriptive statistics and linear regression models assessed the effect of neuropsychological test scores on gait speed. Three regression models were estimated for each of the three gait task. The first (Model1) examined the effect of each neuropsychological test on each gait task individually. The second (Model 2) examined each test individually controlling for age, gender, body mass index (BMI), educational attainment, depression, those taking more than five medications (polypharmacy) and comorbidity as per Table 9. Comorbidity included those with chronic conditions, memory impairment, poor vision, presence of fracture or pain as described in Chapter 2: General Methods and as per Table 9. Model 3, a single regression model, was estimated including all neuropsychological tests simultaneously as well as covariates as per Model 2 in order to estimate the independent effect of each neuropsychological test on gait speed for each gait task. In addition to investigating gait speed, Model 3 investigated DTD of each dual task in order to compare the effect of gait task on cognitive contribution. A p-value of 0.05 was used to indicate statistical significance for all tests, but Model 3 adjusted this to account for possible false positive results caused by multiple testing.

Multiple Testing Corrections methods are described in detail in Chapter 2: General Methods. Briefly a threshold p-value was set and applied to Model 3 only as the hypothesis of this study relates to the effect of elements of cognitive function on gait speed across three gait tasks after adjusting for other factors. The outcome of the STATA multproc program calculated a revised critical value of 0.011 for positive associations with seven cognitive tests at q=0.05 (using Stata multproc procedure[267]).

P-values are included in Table 10 for Model 3 in addition to the "*" symbol indicating statistical significance so the reader can make a judgement on the strength of the results.

Predicted changes in gait speed and DTD were calculated for each neuropsychological test utilising standardized beta coefficients. All analyses were weighted with respect to age, sex and education to the Quarterly National Household Survey (2010) to ensure data were nationally representative, in addition to health status and socio-demographic factors to account for those who did not attend a health assessment[233].

Interactions between seven age groups and each neuropsychological test score (e.g.: age group#MOCA teriles) were also investigated in Model 4. This included seven interaction variables in the same regression model, in place of the neuropsychological test scores used in Model 3, while also adjusting for gender, depressive symptoms, height and level of education. Adjusted gait speed values for each neuropsychological tertile (upper, lower and intermediate) at each age group for each walking task were created and can be seen in Figure 28 for Model 4.

6.3. Results

In Model 1, all elements of cognitive function contributed to and were highly statistically significantly correlated with gait speed for all gait tasks (Table 10). These associations were severely reduced after adjusting for covariates including age as can be seen in Figure 25 (Model 2). However, with the exception of delayed recall, executive function and visual reasoning for the single gait task all remained statistically significant.

In Model 3, 28%, 18% and 28% of the change in gait speed during the single, cognitive and motor gait tasks respectively (Table 10 and Figure 26), as well as 3% and 2% of the change in DTD during the cognitive and motor gait tasks respectively (Figure 27, Model 4), can be explained by covariate and cognitive function elements. Processing speed and short term memory (as measured by immediate recall) were statistically significantly associated with gait speed for all gait tasks (significant following adjustment for multiple comparisons except for the effect of recall on single task gait speed p=0.085). Sustained attention was also significantly independently associated with gait speed for the motor gait task. Delayed recall and visual reasoning were not independently associated with gait speed for any gait task. Figure 25 and Figure 26 detail the magnitude of gait speed changes for each element of cognitive function across gait task in Model 2 and Model 3. Figure 27 illustrates the effect of gait task (single task gait speed and motor and cognitive DTD) on cognitive contribution.

The affect of age group (years(n) 50-54 (873), 55-59 (1081), 60-64 (901), 65-69 (741), 70-74 (460), 75-79 (260), 80-91 (112)) on gait speed for all walking tasks over neuropsychological tertiles can be seen in Figure 28.

Table 9: Participant Characteristics, (N=4431)

Characteristics	***Values***
Female, n(%)	2405(55)
Age, mean(SD) [years]	62.0(8.0)
Body Mass Index, mean(SD) [Kg/m^2]	28.61(4.94)
Educational Attainment [n]	
Primary	919
Secondary	1827
Tertiary	1637
Depression	
Short Centre for Epidemiological Studies Depression Scale, Mean (SD), n≤ 16 (%)	4.34(4.0), 65(1.5%)
Polypharmacy, n(%)	773(17.5)
Comorbidity [n]	
Cardiovascular Disorders	1505
High Blood Pressure	1849
High Cholesterol	194
Angina	174
Heart Attack	36
Heart Failure	210
Heart Murmur	274
Diabetes	51
Stroke	77
Transient Ischemic Attack	152
Any Other Heart Condition	
Memory Impairment	
Alzheimer's Disease	1
Dementia	2
Serious Memory Impairment	10
Arthritis	1197
Osteoporosis	452
Parkinson's Disease	13
Cancer	257
Chronic Lung Disease	153
Asthma	423

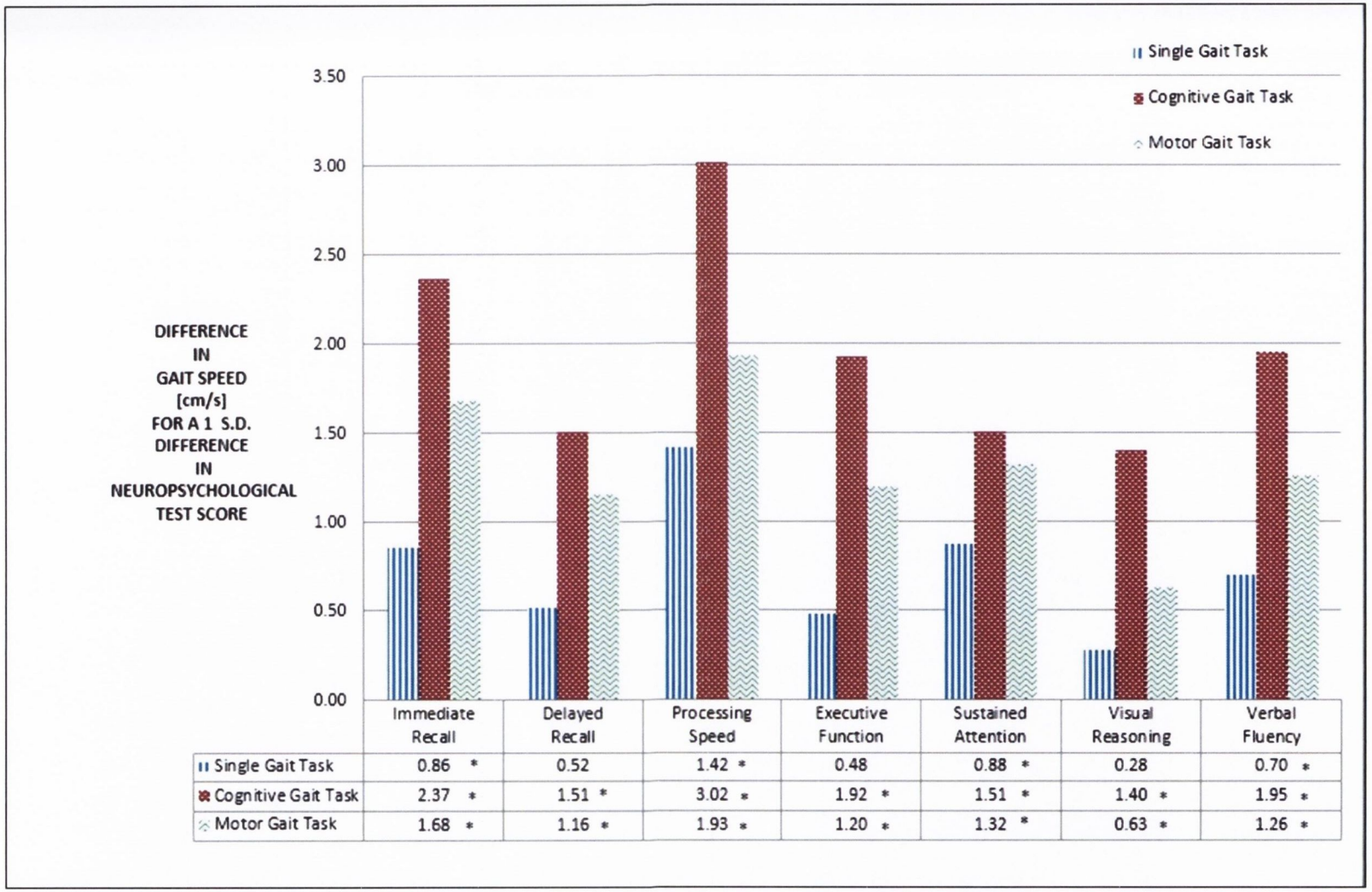
Self Reported	
Poor Vision	44
Hip or Wrist Fracture	510
Hip or Knee Pain	199
Walking Aid User	22
Number of Comorbidities	
0	903
1-2	2205
3+	1243
Gait Measures, mean(SD) [cm/s]	
Single Task Gait Speed	135.85(20.20)
n(%): <60cm/s,>100cm/s,>120cm/s	0.1,16.4,83.5
Cognitive Task Gait Speed	111.47(26.04)
Motor Task Gait Speed	133.49(20.64)
Cognitive DTD	24.34(18.72)
Motor DTD	2.48±8.2
Cognitive Gait Task, mean(SD) IQR [n]	
Letters Attempted	7.49(1.98), 6-9
Letters Correct	6.09(2.10),5-7
Cognitive Measures, mean(SD), IQR	
Global Cognition: MOCA	25.20(3.26), 24-28
Short Term Memory	
Immediate Recall [n]	6.00(1.58), 5-7
Delayed Recall [n]	6.30(2.21),5-8
Processing Speed: CRT [ms]	506.02(137.68), 550-434
Executive Function: ΔCTT [s]	53.6(26.1), 67-35
Sustained Attention: SART Coefficient of Variation [%]	30.44(15.8), 37-19
Visual Reasoning: Correct answers [n]	3.16(1.32), 2-4
Verbal Fluency [n]	12.31(5.0), 9-16

Table 10: Associations between Elements of Cognitive Function and Gait Speed For Each Gait Task: Model 1, Model 2 and Model 3

All participants (n=4344)												
	Single Gait Task				**Cognitive Gait Task**				**Motor Gait Task**			
Predictor	MODEL 1	MODEL 2	MODEL 3		MODEL 1	MODEL 2	MODEL 3		MODEL 1	MODEL 2	MODEL 3	
	Effect	**Effect**	**Effect**	**p**	**Effect**	**Effect**	**Effect**	**p**	**Effect**	**Effect**	**Effect**	**p**
Age			-6.68*	<0.0001			-7.02*	<0.0001			-6.70*	<0.0001
Gender			-2.16*	<0.0001			-2.86*	<0.0001			-2.38*	<0.0001
BMI			-3.54*	<0.0001			-2.47*	<0.0001			-3.38*	<0.0001
Education			1.00*	0.001			0.18	0.662			0.92*	0.003
Depression			-1.66*	<0.0001			-1.22*	0.003			-1.74*	<0.0001
Polypharmacy			-2.74*	<0.0001			-1.95*	<0.0001			-2.65*	<0.0001
Comorbidity			-0.84*	0.004			-0.08	0.877			-0.80*	0.010
Immediate Recall	3.36*	0.86*	0.58	0.085	4.60*	2.37*	1.53*	0.001	4.22*	1.68*	1.13*	0.001
Delayed Recall	3.04*	0.52	-0.04	0.929	3.87*	1.48*	-0.05	0.932	3.74*	1.16*	0.15	0.674
Processing Speed	3.42*	1.42*	1.18*	<0.0001	4.94*	3.07*	2.29*	<0.0001	4.01*	1.93*	1.49*	<0.0001
Executive Function	2.70*	0.48	0.02	0.945	4.24*	1.90*	0.94	0.040	3.51*	1.20*	0.48	0.160

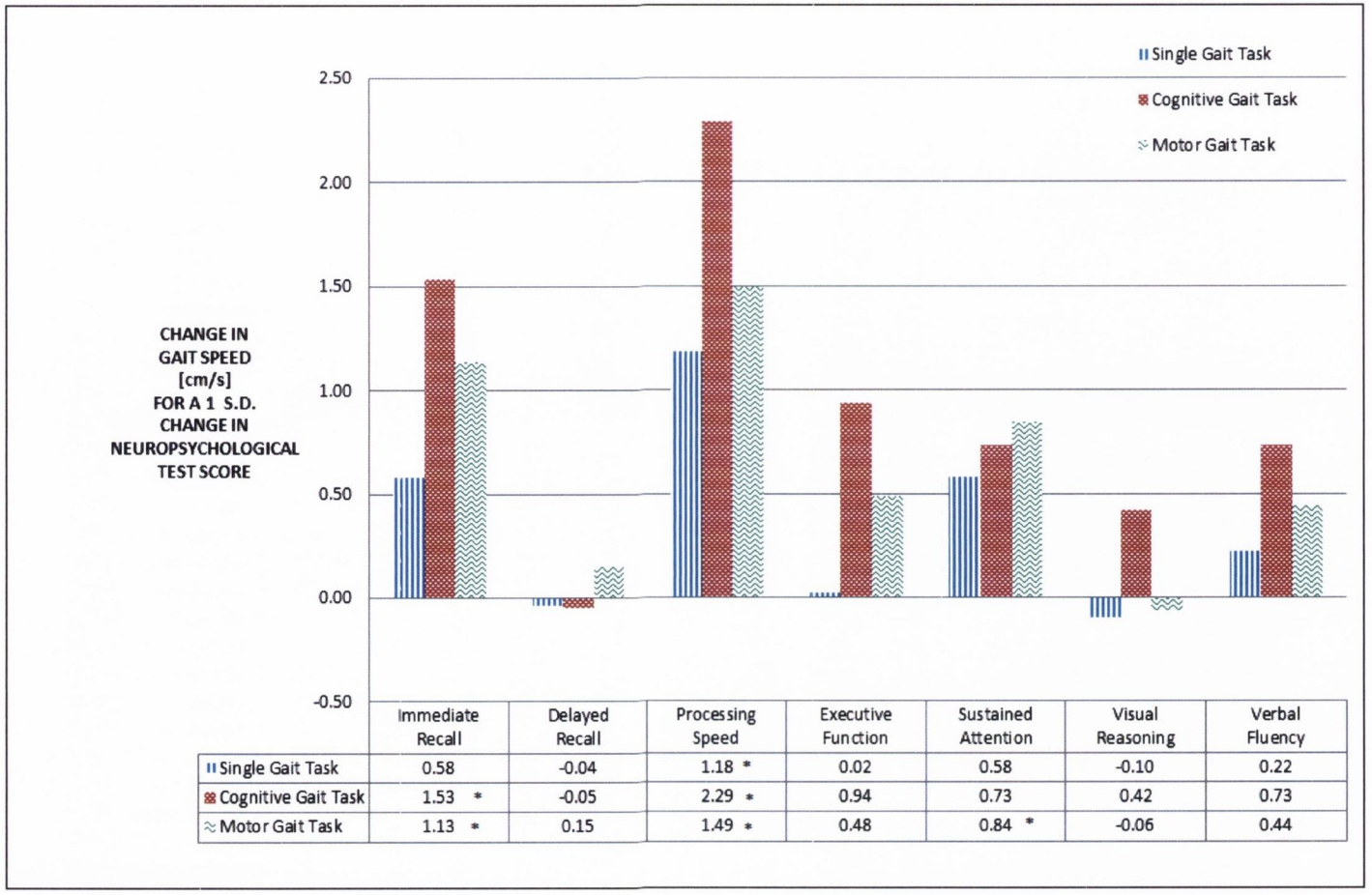
All participants (n=4344)												
	Single Gait Task				**Cognitive Gait Task**				**Motor Gait Task**			
Predictor	MODEL 1	MODEL 2	MODEL 3		MODEL 1	MODEL 2	MODEL 3		MODEL 1	MODEL 2	MODEL 3	
	Effect	**Effect**	**Effect**	**p**	**Effect**	**Effect**	**Effect**	**p**	**Effect**	**Effect**	**Effect**	**p**
Sustained Attention	3.60*	0.88*	0.58	0.064	4.24*	1.56*	0.73	0.089	4.18*	1.32*	0.84*	0.011
Visual Reasoning	2.62*	0.28	-0.1	0.750	3.56*	1.38*	0.42	0.321	3.07*	0.63*	-0.06	0.838
Verbal Fluency	2.18*	0.70*	0.22	0.453	3.17*	1.29*	0.73	0.089	2.81*	1.26*	0.44	0.176

Model 1and Model 2: *P<0.05, Model 3: *Adjusted P<0.011 Model 1: Univariate Analysis (R^2:1-7%), Model 2: Adjusted for covariates (R^2:17-28%), Model 3: Including all neuropsychological tests simultaneously adjusting as per Model 2. Effect represent predicted gait speed [cm/s] change for a 1 standard deviation change in the neuropsychological test



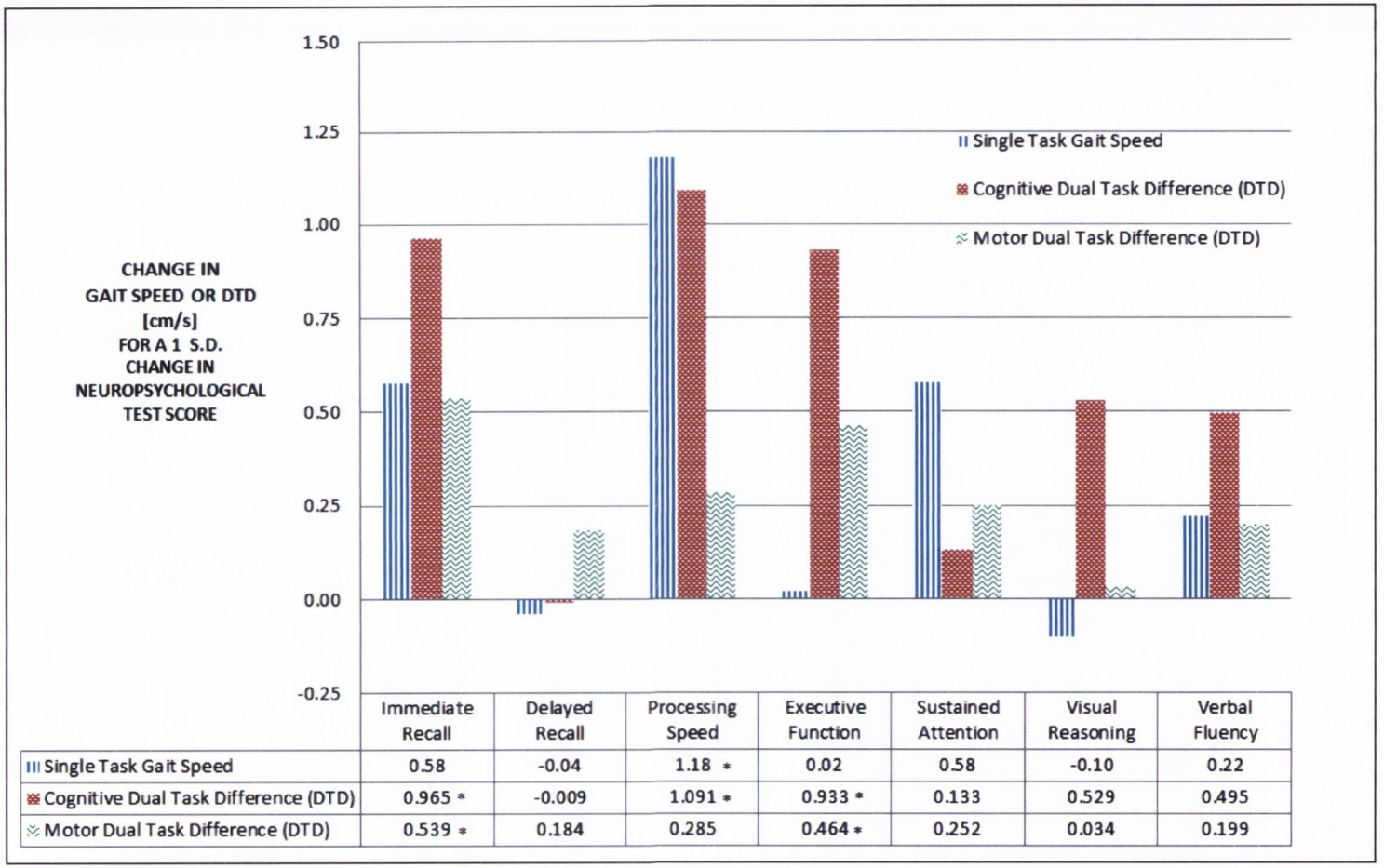
	Immediate Recall	Delayed Recall	Processing Speed	Executive Function	Sustained Attention	Visual Reasoning	Verbal Fluency
Single Gait Task	0.86 *	0.52	1.42 *	0.48	0.88 *	0.28	0.70 *
Cognitive Gait Task	2.37 *	1.51 *	3.02 *	1.92 *	1.51 *	1.40 *	1.95 *
Motor Gait Task	1.68 *	1.16 *	1.93 *	1.20 *	1.32 *	0.63 *	1.26 *

FIGURE **25**: Contributions of Elements of Cognitive Function to Gait Speed for All Gait Tasks: Model 2



	Immediate Recall	Delayed Recall	Processing Speed	Executive Function	Sustained Attention	Visual Reasoning	Verbal Fluency
Single Gait Task	0.58	-0.04	1.18 *	0.02	0.58	-0.10	0.22
Cognitive Gait Task	1.53 *	-0.05	2.29 *	0.94	0.73	0.42	0.73
Motor Gait Task	1.13 *	0.15	1.49 *	0.48	0.84 *	-0.06	0.44

Figure 26: Contribution of Elements of Cognitive Function to Gait Speed For All Gait Tasks: Model 3



	Immediate Recall	Delayed Recall	Processing Speed	Executive Function	Sustained Attention	Visual Reasoning	Verbal Fluency
Single Task Gait Speed	0.58	-0.04	1.18 *	0.02	0.58	-0.10	0.22
Cognitive Dual Task Difference (DTD)	0.965 *	-0.009	1.091 *	0.933 *	0.133	0.529	0.495
Motor Dual Task Difference (DTD)	0.539 *	0.184	0.285	0.464 *	0.252	0.034	0.199

Figure 27: Effect of Gait Task on Cogntiive Contribution: Model 4.

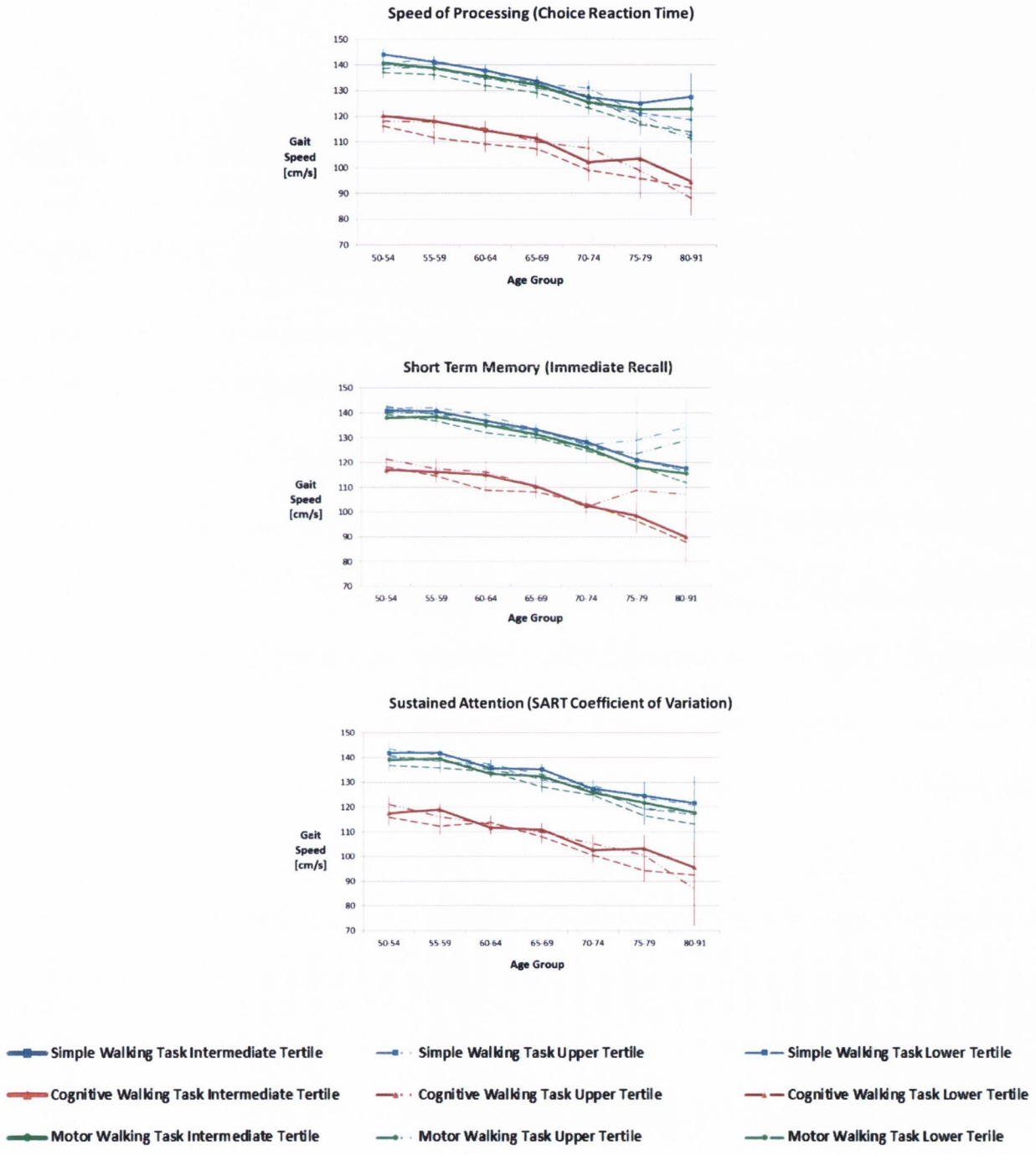


Figure 28 Cognitive, Gait Speed and Age Interaction across all Gait Tasks: Model 4

6.4. Discussion

This study explored the independent contributions of seven elements of cognitive function to single and dual task gait speed in a population representative of community dwelling older adults. Poorer processing speed, short term memory and sustained attention were the major cognitive contributors to slower gait speed for all gait tasks. Investigation of gait task effects showed the dual gait tasks to have a significant executive function element, not observed in the single gait task. These results form a baseline value for dual task gait speed in a population over fifty years of age, with sustained attention and the independent contribution of processing speed being highlighted.

Analysis of the data found slower processing speed and poorer short term memory to be the most statistically significant cognitive contributors to slower gait speed in all gait tasks. Sustained attention statistically significantly contributed to gait speed in the motor gait task and contributed, but not statistically significantly, to the single (0.58 cm/s, p=0.064) and cognitive (0.73 cm/s, p=0.089) gait tasks (Model 3). Executive function (0.94cm/s, p=0.040) and verbal fluency (0.73cm/s, p=0.089) also contributed to the cognitive gait task. These findings support similar studies by Mielke et al[191] and Watson et al[189] who also report memory and either, executive function or attention, to contribute to changes in gait speed during single gait tasks. Martin et al [190] found processing speed, but not short term memory, to significantly correlate with gait speed during single gait tasks. Research is lacking into the cognitive contributions to dual gait tasks which employ motor tasks while walking, such as carrying a glass of water. However, major contributors to dual gait tasks which employ a cognitive demand while walking have been reported to be composite speed/executive/attention scores [50] to gait speed (alternate letters), in addition to executive function and short term memory [165] to dual task changes (serial subtraction) [86] in healthy older adults. A comparison between similar studies is difficult due to the inclusion of different gait tasks, gait protocols, neuropsychological tests and outcome measures. Results may vary due to the multi-determinate nature of neuropsychological tests. In this study, sustained attention, visual reasoning and verbal fluency tests have an executive function component with verbal fluency requiring short term memory abilities also. Examining independent cognitive

contributions to gait speed has highlighted the large processing speed contribution. Holtzer et al[209] reported intraindividual variability (a measure similar to this study's sustained attention measure) and not processing speed, to be the only executive function component to predict changes in gait speed during single and cognitive gait tasks (serial subtraction) [209]. This study differentiates itself from previous literature, such as Holtzer et al, by investigating a more youthful population and a wider range of neuropsychological tests. However, both studies do highlight the role of a specific executive process in gait that monitors and optimizes responses.

Participants in this study walked faster than participants in previous studies[2] with over eighty percent walking over 120cm/s as per Table 9. Gait effects show the dual gait tasks to have a significant executive function contribution not shown in the single gait task as per Figure 27. This suggests that dual gait tasks may be more appropriate at assessing specific elements of cognitive function, such as executive function, but only when assessed using relative gait speed measures. However, when considering the gait speed measures alone in community dwelling older adults, as per Table 10 and Figure 25 and Figure 26, the dual gait task does not offer any greater insight into cognitive function over the single gait task. This is in agreement with literature which has utilised dual task differences in healthy older adults as a baseline value to differentiate those with cognitive impairment [71, 129].

The effects of confounding factors on neuropsychological test scores [30, 285] and gait speed [37] is well established in literature and can be seen in the increased variance explained from Model 1 (2% to 8%) to Model 2 (16 to 25%). In Model 3, younger age, greater height and less depressive symptoms for all walking tasks and having a higher level of education (simple and motor dual task only) statistically significantly contributed to faster gait speed. The large effect of greater age and cognitive walking task on reducing gait speed can be seen in Figure 28. This result indicates the importance of standardized validated walking tasks and gait speed outcomes for different age, height, depressive symptoms and educational groups.

Investigation of independent contributions to gait speed from a wider range of cognitive functions in a population representative of community dwelling older adults is a major strength of this study. In addition, cognitive contributions to dual gait tasks have been shown, with sustained attention and processing speed being specifically highlighted for the first time. These results build on novel research undertaken on the same cohort which have linked a mobility task, the Timed Up and Go task, with memory, processing speed and executive function[127].

This study investigated gait speed and dual task difference. Future studies should investigate other dual task measures.

Walking requires multiple cognitive processing such as multi-sensory integration, spatial awareness and proprioception[286]. Therefore, it follows that processing speed and sustained attention, an executive function requiring arousal and ability to focus attention, are important for gait speed especially during dual gait tasks. Memory, thought to be one of the first cognitive elements to be affected by ageing, is also highlighted here in the form of short term memory (immediate recall). The neural substrates linking these three cognitive processes to gait speed are not fully understood. However, functional imaging, non-human primate and behavioural studies have shown increased activation of the pre-frontal cortex during motor activity[287], shared neural mechanisms involved in attention and short term memory[288, 289], and mediating relationships between processing speed and pre-frontal cortex control[290] during ageing. We conclude that in community dwelling older adults both a slowing of processing speed and an increased dependence on prefrontal resources affects gait speed during all gait tasks, with many possible causes [291, 292]. Furthermore, this dependence on the pre-frontal cortex, a region involved in sustained attention, in conjunction with lower processing speed, mediates short term memory performance.

The results in this study furthers our understand of links between specific elements of cognitive function and gait performance during different tasks in community dwelling older populations. The wide age range and large size of the dataset: (50-91 years, n=4431) are unique and in agreement with the life-span perspective model of ageing recently recommended by Rosso et al[107].

6.5. Conclusion

Community dwelling participants that display poorer processing speed, short term memory and sustained attention walk more slowly during both single and dual gait tasks than those with higher levels of such resources. This result forms a baseline value for dual task gait speed in community dwelling adults over fifty years of age, but suggests that gait speed measured

during a dual task may not offer any greater insight than gait speed during a single task with respect to cognitive function in healthy older adults.

6.6. Key Points

- Sustained Attention, short term Memory and Speed of Processing are major contributors to gait speed during all gait tasks.
- Executive Function was found to have a significant effect on both dual gait tasks.
- These results give an insight into the differing cognitive requirements for different daily activities.
- Further research should investigate longitudinally if these findings are indicative of an age related change within the population.

CHAPTER 7: Study 5 - Gait Speed, Gait Task and Global Cognition in a community dwelling population over fifty years old.

It is important to explore specific elements of cognitive function in order to investigate specific elements of gait. However, investigations into global cognition may have more clinical benefit as global cognitive measures are more commonly employed clinically. The study described in this chapter explored the relative contributions of MOCA total score, MOCA domains and MOCA subscores to dual task gait performance in older adults. In addition, this study explored contributions from elements of cognitive function to association between global cognition and gait performance. This was achieved by investigating interaction between MOCA domains, MOCA Groups and gait performance. This study employed adjustments for covariates as per findings in the previous study, Study 4. In addition, this study was informed about associations about gait speed and MOCA from Study 1 and Study 2.

MOCA was chosen as the global cognitive measure to explore further for two reasons. Firstly, MOCA has been shown to have higher sensitivity to Mild Cognitive Impairment than MMSE [108, 110], but a similar sensitivity to more severe cognitive impairment. Exploratory analysis from Study 1 found global cognitive performance of the TILDA population, as measured with MOCA and MMSE, to be very high indicating a likelihood of milder forms of cognitive impairment, if any cognitive impairment, would exist in this population. Secondly, results from Study 1 show the MOCA scores to have larger variation than the MMSE scores. This possibly indicates that the MOCA scores better describe this population.

Gait speed was the parameter chosen to analyse MOCA contributions to dual gait tasks. In Study 4, the regression models with gait speed outcomes explained a higher percentage of variance based on the R-squared values (28-18%) than the regression models with dual task effect (2-3%) outcomes. This may indicate that our knowledge of gait speed variance is greater than our knowledge of dual task effect variance which allows the inclusion of more relevant covariates in the gait speed models. It also may indicate that the dual task effect is a more specific measure than the more general gait speed measure given that individual variances in baseline gait speed have been removed in the standardised Dual Task

Effect measure. However, gait speed has been used clinically as an outcome measure and this study was concerned with investigating more clinically relevant measures.

The aim of this study was to explore the variation in global cognition, as measured by the MOCA, within a nationally representative population. In addition, associations between subscores of the MOCA and gait during complex gait task were investigated. We hypothesised that specific MOCA domains and MOCA subscores would contribute to differences in gait speed during different gait tasks and that this association would differ across different global cognitive groups (as categorised by MOCA-Total Score).

Two conference presentations have been derived from resesearch in this chapter.

> I. Killane, O. Donoghue, G. Savva, H. Cronin, R.A. Kenny, R.B. Reilly (June 29-July 03 2014). Contributions of the Montreal Cognitive Assessment (MOCA) to Dual Task Gait Performance. Oral Presenation. The Joint World Congress of the International Society of Posture & Gait Research (ISPGR) and Gait and Mental Function (GMF), Vancouver, Canada.
>
> I. Killane, O. Donoghue, G. Savva, H. Cronin, R. A. Kenny, R. B. Reilly (28-30 Nov 2012). Exploring Correlations between Walking Speed and Cognitive Function using Montreal Cognitive Assessment (MOCA) subscores from The Irish Longitudinal Study on Ageing (TILDA). Poster Presentation. British Geriatrics Society (BGS) Autumn Scientific Meeting, Yorkshire, England.

7.1. Introduction

Global cognitive assessment tests (MOCA, MMSE) are employed in the diagnosis of cognitive impairment and so have strong associations with many neurological pathologies. In addition, poor performance on global cognitive assessment tests have been associated with increased risk of falls. Associations between slow gait speed and adverse effects such as multiple falls[293], reduced survival rate[2] and activities of daily living[3] has been discussed thoroughly in previous studies. However, poorer global cognition is also linked to reduced gait speed longitudinally. Some studies have found that poorer global cognition precedes slower gait [64]. Other studies have hypothesised that a slowing of gait speed precedes poorer global cogntion [192]. The association between poorer global cogntion scores and slower gait speed has also been found to be stronger when employing

higher attentional demanding gait task to measure gait speed such as the dual task paradigm. Gait Speed was the parameters chosen to analyse MOCA contributions to the dual gait tasks due to its potential clinical utility.

Recent literature by Julayanon et al (2014) [125] explored the utility of MOCA total score and MOCA domain scores at predicting conversion from Mild Cognitive Impairment to Alzheimer's Disease. Julayanon et al found participants with lower MOCA total scores and lower MOCA memory domain scores at greater risk of short term conversion from Mild Cognitive Impairment to Alzheimer's disease at 18 month follow up. Nearly seventy percent of participants converted to Alzheimer's disease, out of these over ninety percent had poor MOCA total score (< twenty out of thirty) and poor MOCA memory domain scores (< seven out of fifteen) at baseline. Julayanon et al also found that participants who had the highest conversion rate to Alzheimer's disease (73.9%) were those who scored poorly in multiple MOCA domains. The study described in this chapter also investigated interactions between MOCA domains and MOCA total score but investigates their interaction with gait speed also. In addition, this study explores the relationship between gait speed and MOCA subscores. Little research exists on the relationship between gait speed and MOCA subscores in ageing cohorts. However, a previous study has linked MOCA subscores with functional status post Stroke[116] finding specific Visuospatial/executive subscore contributions. Further understanding of the relationship between gait performance and cognitive domains, and their influence on global cognitive performance, might aid clinical assessment.

The study described in this chapter explored (i) the contributions of MOCA Total Score, (ii) the relative contributions of MOCA Domains and MOCA Subscores and (iii) the interactions between MOCA Total Score group (as categorised by MOCA Total score) and MOCA Domains, to dual task gait performance in older adults. Firstly, it was hypothesised that specific MOCA Domains and MOCA Subscores contribute to gait speed during different dual gait tasks. Secondly, it was hypothesised that the association between MOCA Domains and gait speed will differ for different MOCA groups.

7.2. Methods

7.2.1.Study Design

This study investigated baseline cross sectional data (n = 8504, 56% women, age = 63.14(10.21) yrs) from The Irish Longitudinal study on Ageing (TiLDA). Inclusions criteria for the study described in this chapter were valid gait and MOCA data, making 4855 participants eligible (54% women, mean (SD) age 61.84(8.4), MOCA 25.20(3.26)). Further detail of the study procedure can be found in Chapter 2: General Methods.

Data collection in the TILDA study comprised of three parts: a computer-assisted personal interview, a self-completion questionnaire and a health assessment. Participant characteristics detailed in this study were recorded during the computer-assisted personal interview. All neuropsychological and gait measure described in this study were assessed during the TILDA health centre assessment[232].

7.2.2.Outcome Measures

The Montreal Cognitive Assessment (MOCA) test was administered during the TILDA neuropsycholoigcal assessment as per Chapter 2: General Methods. The Montreal Cognitive Assessment (MOCA) assessed global cognition. MOCA total score, MOCA groups, eight MOCA Domains and twenty five MOCA Subscores were measured. Two MOCA Subscores were included that do not contribute points to MOCA total score: (i) second memory trial and (ii) number of words recited with the letter F (No. Of Words). In addition, three MOCA Groups, Poor, Intermediate and Good, were defined as those with MOCA total scores of (i) 0 to 23, (ii) 24 or 25 and (iii) 26 to 30, respectively.

Gait speed was recorded during the TILDA health assessment from a GAITRite™ pressure sensing mat during two complex walks: cognitive and motor dual gait tasks as per Chapter 2: General Methods. The motor dual gait task involved walking while carrying a glass of water. The cognitive dual gait task involved walking while reciting alternate letters.

7.2.3.Statistical Analyses

Data was analysed using STATA 12[263]. Descriptive statistics and linear regression models assessed the effect of global cognition test scores (MOCA) on gait speed for both dual tasks in order to parse apart contributions to gait speed from different MOCA Domains and Subscores. Specifically, MOCA total score, eight MOCA Domains and twenty five MOCA Subscores were investigated. Further detail on MOCA scores are described in Chapter 1: Literature review. Further detail on regression undertaken are described in Chapter 2: Methods of this thesis.

Four regression models were investgated: Model 1, Model 2, Model 3 and Model 4. All models employing multiple linear regression analyses constructed to predict the contribution of MOCA to gait speed for both dual gait tasks. Model 1 investigated MOCA Total Score contribution, Model 2 investigated the relative contribution of MOCA Domains, Model 3 investigated the relative contribution of MOCA Subscores and Model 4 explored the relative correlations between MOCA Group-MOCA Domains interactions.

The twenty five MOCA Subscores included in Model 3 have varying numbers of scoring systems. In order to reduce any effect the different scoring systems have on regression outcomes Model 3 investigated the relative contribution of MOCA Subscores to gait speed in two ways. Firstly, by investigating MOCA Subscores in their raw format and then by exploring MOCA Subscores using dichotomous categories. Dichotomous categories were generated for the five MOCA Subscores who had different scoring systems based on those participants below and above the tenth percentile for that MOCA Subscore.

The eight MOCA Domains included in Model 4 have varying numbers of scoring systems. Dichotomous categories were generated for the eight MOCA Domains by dividing participants into two groups partitioned at the fiftieth percentile for that MOCA Domain where allowable. Model 4 investigated the interactions between each MOCA Domain and MOCA Group to gait speed by exploring interactions between eight dichotomous MOCA Domains and three MOCA Groups.

All four Models adusted for age, gender, body mass index, educational attainment, depression and comorbidity. These factors were assessed as per analysis in Study 5 of this thesis.

7.3. Results

Table 11 shows results for MOCA Groups. Table 12 shows results for the dichotomous MOCA Domains. Table 13 shows results for the dichotomous MOCA Subscores. Table 14 and Table 15 show results of the multiple linear regressions Models. 17% and 27% of the variance in gait speed during the dual cognitive and dual motor gait tasks respectively were described by Model 1 (n = 4855), Model 2 (n=4528) and Model 3 (n=4528).

Table 14 displays results for Model 1 and Model 2. In summary, in Model 1 higher MOCA total scores were found to significantly contributed to faster walking speeds for both gait tasks ($p<0.001$). This corresponded to a 3.26 MOCA Total Score difference for a 1.79 cm/s (cognitive) and 1.66 cm/s (motor) gait speed difference. Model 2 describes the relative contribution of MOCA Domains to gait speed. The Visuospatial/Executive Domain was found to be the only MOCA Domain to independently statistically significantly contribute (highest significance and largest contribution) to differences in gait speed for both dual gait tasks (1.25 cm/s (cognitive) and 0.84 cm/s (motor) increase for a 0.95 point increase). The Attention Domain contributed to both dual gait tasks, however this was not a significant correlation for the motor gait task (0.59 cm/s increase in gait speed for a 0.88 point increase). In addition, the Language Domains statistically significantly contributed to gait speed for the dual cognitive gait task. Other MOCA Domains of note are the Delayed Recall ($p=0.09$) for the cognitive gait task and the Abstraction (0.068) and Orientation ($p=0.088$) Domains for the motor gait tasks.

Model 3 results, the relative contribution of MOCA Subscores to gait speed, are described in Table 15 and Figure 29. The Fluency Word Number subscore was found to independently contribute to gait speed for both gait tasks. The Trail and Cube subscores independently contributed to the cognitive gait task and the Attention Forward subscore independently contributed to the motor gait task. When investigating dichotomous MOCA Subscores all contributors remained the same with the exception of the Verbal Fluency Subscore independently contributing to gait speed in place of the Fluency Word Number Subscore for the cognitive gait task and Similarity 2 (watch-ruler) becoming significant for the motor gait task. This can be seen in Figure 29 also where for the dual cognitive gait task the Visuospatial/Executive, Attention and Language skills seem to be driving this contribution, specifically the Trail, Cube, Serial 7 and Letter Fluency (No. Of Words) subscores.

Figure 29 also shows the Attention, Language, Abstraction and Orientation skills driving the contribution for the motor dual gait task, specifically the Attention Forward, Letter Fluency (No. Of Words), Similarity 2 and Month subscores.

Figure 30 to Figure 32 show results for Model 4 which describes the interaction between MOCA Domains, MOCA Groups and gait speed for the motor and cognitive gait task. Figure 30 shows the observed unadjusted distribution of MOCA Domains over each MOCA Group. Figure 31 (cognitive) and Figure 32 (motor) show changes in gait speed for different MOCA Domain scores across MOCA Groups. For those with Poor MOCA scores, gait speed correlated with Visuospatial/Executive ($p<0.0001$), Memory ($p<0.05$) and Language ($p<0.01$) Domains for both gait tasks. The Orientation domain ($p=0.065$) and the Naming ($p<0.033$) domain also correlated with gait speed for the cognitive and motor gait task respectively. For those with Intermediate MOCA scores gait speed correlated with the Orientation ($p<0.01$) Domain. For those with Good MOCA scores gait speed correlated with the Visuospatial/Executive ($p<0.05$) domain for both gait tasks.

All covariates statistically significantly effect gait speed for both dual tasks for Model 1, Model 2 and Model 3 except for comorbidity for the dual cognitive gait task for all models ($p=0.439$ (Model 1), $p=0.282$ (Model 2), $p=0.277$ (Model 3)) and education for Model 2 ($p=0.197$) and Model 3 ($p=0.608$).

Table 11*: Summary of MOCA Groups*

MOCA Group	MOCA Total Score	N
Poor	< 24	1203
Intermediate	24/25	1031
Good	>25	2424

Table 12: *Summary of Dichotomous MOCA Domains*

MOCA DOMAIN	LOW CATEGORY		HIGH CATEGORY	
	SCORE [%]	N	SCORE [%]	N
VSEXEC [0-5]	0-80	2812	100	2062
NAMING [0-3]	0-67	1706	100	3168
MEMORY [0-5]	0-80	277	100	4267
ATTENTION [0-6]	0-83	1597	100	3277
LANGUAGE [0-3]	0-67	2651	100	2223
ABSTRACTION [0-2]	0-50	1514	100	3360
RECALL [0-5]	0-60	2894	80-100	1980
ORIENTATION [0-6]	0-83	286	100	4588

Table 13: Distribution of MOCA Subscores

n = 4560	MOCA SUBSCORE [Range]												
	VISUPSPATIAL/EXECUTIVE					NAMING			MEMORY	ATTENTION			
Percentile	**Trail [0-1]**	**Cube [0-1]**	**Contour [0-1]**	**Numbers [0-1]**	**Hands [0-1]**	**Lion [0-1]**	**Rhino [0-1]**	**Camel [1]**	**Memory Trial #2 [0-5]**	**Forward [0-1]**	**Backward [0-1]**	**Letters [0-1]**	**Serial Sevens [0-3]**
5th	0	0	1	0	0	0	0	1	4*	1	0	0	1
10th	0	0	1	1	0	1	0	1	5	1	0	1	2*
50th	1	0	1	1	1	1	0	1	5	1	1	1	3
75th	1	1	1	1	1	1	1	1	5	1	1	1	3
95th	1	1	1	1	1	1	1	1	5	1	1	1	3

n = 4560	MOCA SUBSCORE [Range]											
	LANGUAGE			ABSTRACTION		MEMORY	ORIENTATION					
Percentile	**Repeat [0-2]**	**Fluency [0-1]**	**Word # [0-31]**	**Sim1 [0-1]**	**Sim2 [0-1]**	**Recall [0-5]**	**Date [0-1]**	**Month [0-1]**	**Year [0-1]**	**Day [0-1]**	**Place [0-1]**	**City [0-1]**
5th	0	0	4	0	0	0	1	1	1	1	1	1
10th	1*	0	6*	0	0	1*	1	1	1	1	1	1
50th	1	0	9	1	1	2	1	1	1	1	1	1
75th	2	1	15	1	1	4	1	1	1	1	1	1
95th	2	1	21	1	1	5	1	1	1	1	1	1

*Indicates dichotomous category cut-off: Over 10th Percentile for Serial Sevens, Repitition, Word Number and Recall and over 5th percentile for Memory Trial 2. All other subscores are already in dichotomous categories.

Table 14: Model 1 and Model 2: Association between MOCA Total Score and Gait Speed (Model 1) and MOCA Domains and Gait Speed (Model 3) For Both Dual Tasks

MODEL 1: Predictor		**Cognitive Gait Task**	**Motor Gait Task**	**Model 2: Predictor**		**Cognitive Gait Task**	**Motor Gait Task**
Description	Std. Dev.	Beta (cm/s)	Beta (cm/s)	Description	Std. Dev.	Beta (cm/s)	Beta (cm/s)
Age	8.0 yrs	-0.339***	-0.395***	Age	8.0 yrs	-0.338***	-0.395***
Gender	-	-0.101***	-0.103***	Gender	-	-0.082***	-0.098***
BMI	4.94 Kg/m^2	-0.099***	-0.170***	BMI	4.94 Kg/m^2	-0.097***	-0.170***
Education	-	0.034*	0.058***	Education	-	0.020	0.048**
Depression	4.0 points	-0.061***	-0.098***	Depression	4.0 points	-0.063***	-0.096***
Comorbidity	-	-0.012	-0.053***	Comorbidity	-	-0.017	-0.056***
MOCA	3.26 points	0.069*** (1.79)	0.079*** (1.66)	VisuoExecutive	*0.95 points*	0.048** (1.25)	0.04* (0.84)
				Naming	*0.67 points*	0.022 (0.57)	0.014 (0.29)
				Memory Trial #2	*0.30 points*	-0.01 (-0.26)	-0.004 (-0.08)
				Attention	*0.88 points*	0.038* (0.99)	0.028 (0.59)
				Language	*0.85 points*	0.05** (1.30)	0.025 (0.53)
				Abstraction	*0.64 points*	0.004 (0.10)	0.028 (0.59)
				Recall	*1.53 points*	-0.026 (-0.68)	-0.011 (-0.23)
				Orientation	*0.31 points*	-0.017 (-0.44)	0.025 (0.53)

Std. Dev. = STANDARD DEVIATION of test or task

**Significance set to p<0.05 ** p<0.01 ***p<0.001*

All weighted in order to be nationally representative. All models adjusted for covariates : *age, gender, body mass index, education, depression and comorbidity.* R^2: Model 1 and Model 2: 17% (Cognitive), 27% (Motor).

TABLE 15: ASSOCIATION BETWEEN MOCA SUBSCORES AND GAIT SPEED FOR BOTH DUAL GAIT TASKS: EMPLOYING RAW MOCA SUBSCORES AND DICHOTOMOUS CATEGORIES OF MOCA SUBSCORES: MODEL 3

n = 4528	RAW SCORES			DICHOTOMOUS CATEGORIES		
Covariate		**Cognitive Gait Task**	**Motor Gait Task**		**Cognitive Gait Task**	**Motor Gait Task**
	Predictor	**[cm/s]**	**[cm/s]**	**Predictor**	**[cm/s]**	**[cm/s]**
VisuoExecutive	Trail [0-1]	0.884*	0.252	Trail [0, 1]	0.910*	0.252
	Cube [0-1]	0.858*	0.021	Cube [0, 1]	0.884*	0.042
	Contour [0-1]	0.234	0.231	Contour [0, 1]	0.208	0.231
	Numbers [0-1]	-0.078	0.483	Numbers [0, 1]	-0.052	0.483
	Hands [0-1]	0.104	0.378	Hands [0, 1]	0.104	0.378
Naming	Lion [0-1]	0.52	0.231	Lion [0, 1]	0.520	0.210
	Rhino [0-1]	0.286	0.252	Rhino [0, 1]	0.312	0.252
	Camel [1]	-	-	Camel [1]	-	-
Memory Trial #2	Memory Trial #2 [0-5 (No Pts)]	-0.312	-0.084	Memory Trial #2 [0-4 , 5] (No Pts)]	-0.026	0.042
Attention	Forward [0-1]	0.52	0.714*	Attn Forward [0, 1]	0.598	0.735*
	Backward [0-1]	-0.208	0.273	Backward [0, 1]	-0.156	0.273
	Letters [0-1]	0.546	0.378	Letters [0, 1]	0.546	0.336
	Serial Sevens [0-3]	0.754	0.000	Serial Sevens [0-2 , 3]	0.702	0.042
Language	Repeat [0-2]	0.39	-0.105	Repeat [0-1, 2]	-0.130	-0.336
	Fluency [0-1]	-0.026	-0.084	Fluency [0, 1]	1.014*	0.399
	Word # [0-31]	1.794**	1.155*	Word # [0-6, 7+]	0.494	0.735*
Abstraction	Sim1 [0-1]	-0.234	0.084	Sim1 [0, 1]	-0.182	0.105
	Sim2 [0-1]	0.286	0.609	Sim2 [0, 1]	0.338	0.630*
Recall	Recall [0-5]	-0.754	-0.273	Recall [0-1, 2+]	-0.234	0.021
Orientation	Date [0-1]	-0.078	-0.063	Date [0, 1]	-0.130	-0.084
	Month [0-1]	0.026	0.567	Month [0, 1]	0.026	0.567
	Year [0-1]	-0.026	0.525	Year [0, 1]	-0.026	0.525
	Day [0-1]	-0.182	0.294	Day [0, 1]	-0.208	0.273
	Place [0-1]	-0.52	0.021	Place [0, 1]	-0.52	0.000
	City [0-1]	-0.312	-0.273	City [0, 1]	-0.312	-0.315

*P<0.05, **P<0.01, ***P<0.001. All models adjusted for covariates: *age, gender, body mass index, education, depression and comorbidity*. R^2:Model 3, Raw Scores: 17.4% (Cognitive), 27.2% (Motor), Dichotomous Categorical Scores: 17.1% (Cognitive) and 26.9% (Motor)

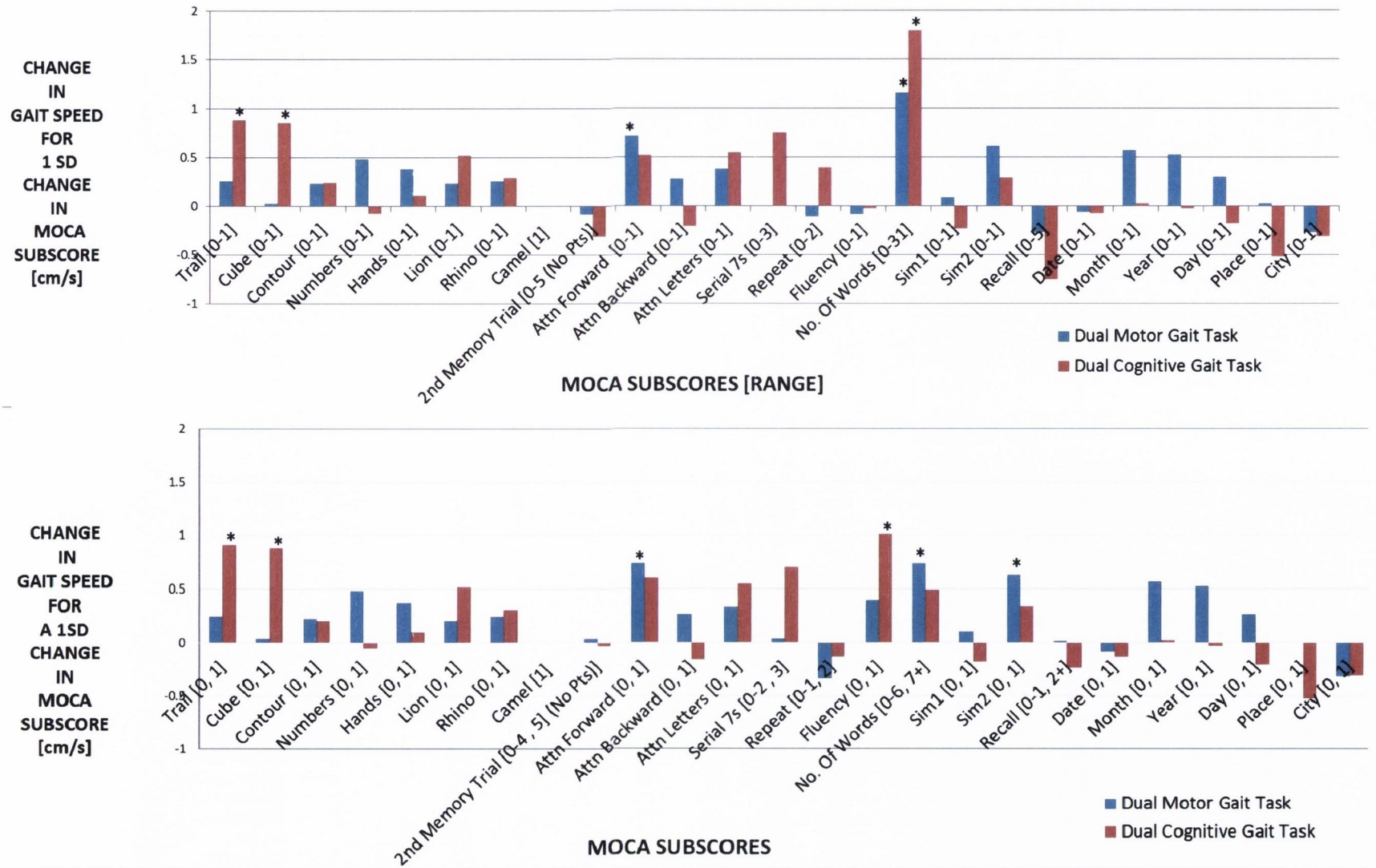
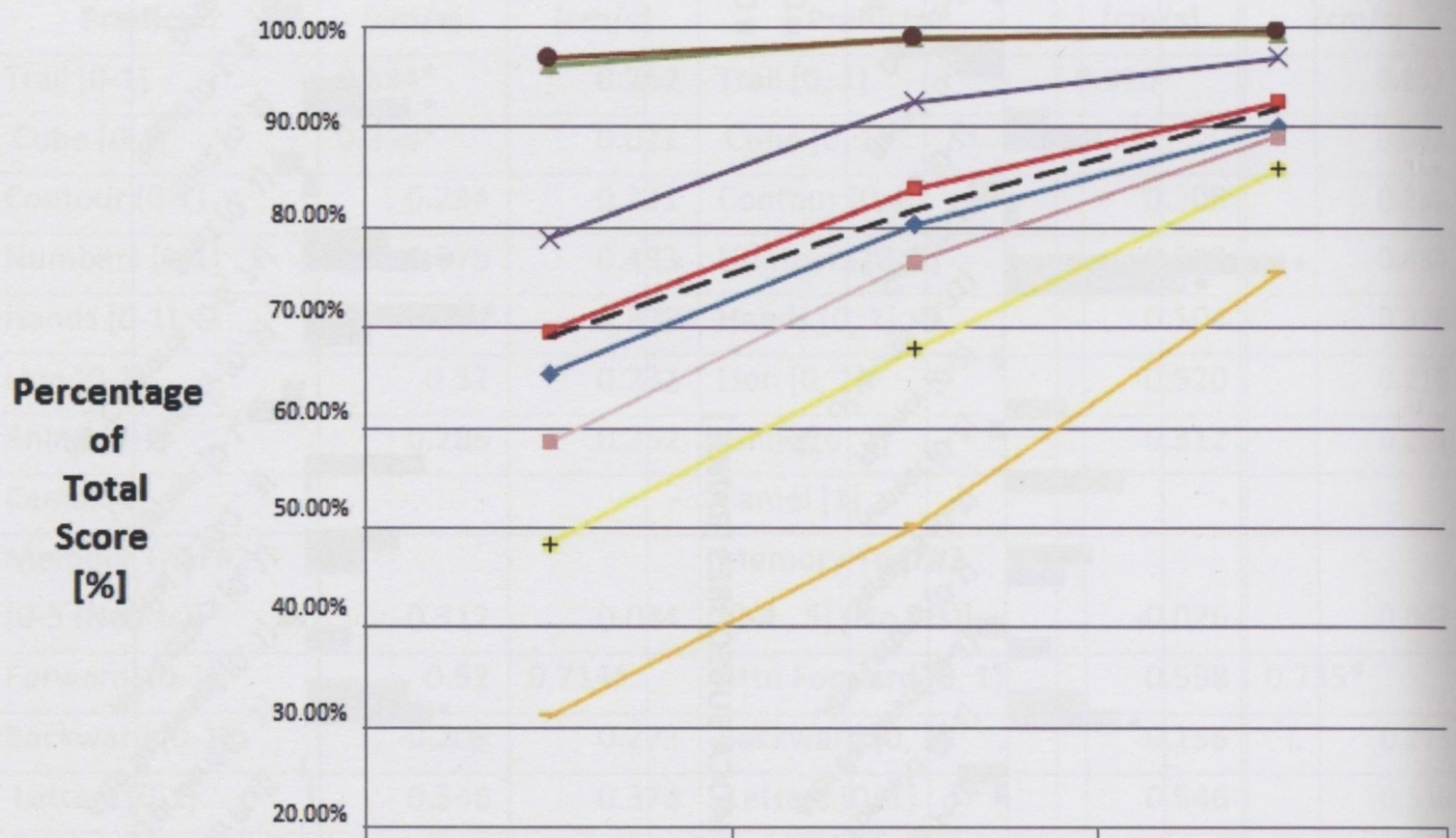


Figure 29: Model 3 - Contributions of MOCA Subscores TO Gait Speed employing raw MOCA Subscores (Top) and dichotomous MOCA Subscore categories (Bottom).



	Poor MOCA (<24) 104.6 [cm/s] (Cognitive Walk) 126.2 [cm/s] (Motor Walk)	Intermediate MOCA (24-25) 110.9 [cm/s] (Cognitive Walk) 133.2 [cm/s] (Motor Walk)	Good MOCA (>25) 113.7 [cm/s] (Cognitive Walk) 135.1 [cm/s] (Motor Walk)
Vsexec [% out of 5]	65.46%	80.26%	89.96%
Naming [% out of 3]	69.64%	83.91%	92.50%
Memory [% out of 5]	96.23%	98.88%	99.37%
Attention [% out of 6]	78.93%	92.52%	96.98%
Language [% out of 3]	48.38%	67.87%	85.74%
Abstraction [% out of 2]	58.56%	76.57%	89.03%
Recall [% out of 5]	31.25%	50.18%	75.43%
Orientation [% out of 6]	96.82%	98.85%	99.63%
MOCA Total Score [% out of 30]	69.06%	81.80%	91.88%

Figure 5: Observed values of MOCA Domain scores over each MOCA Group: MOCA Domain scores given as percentage of total score mean gait speed for each MOCA group listed (all adjusted for covariates: age, gender, body mass index, education, depression and comorbidity).

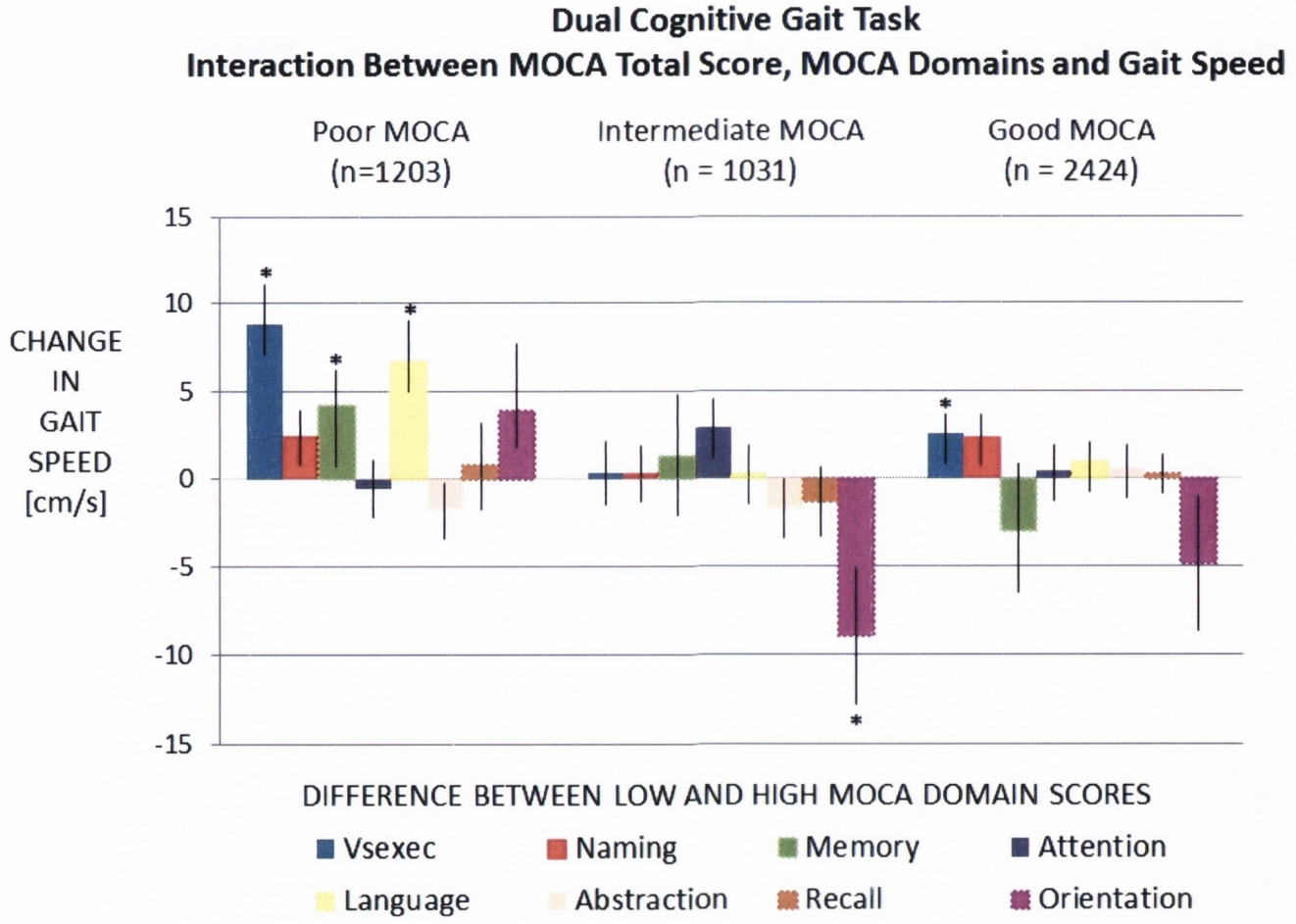


Figure 31: Model 4 - Contribution of each MOCA Domains to gait speed during the cognitive gait task across MOCA Group (all adjusted for confounding factors).

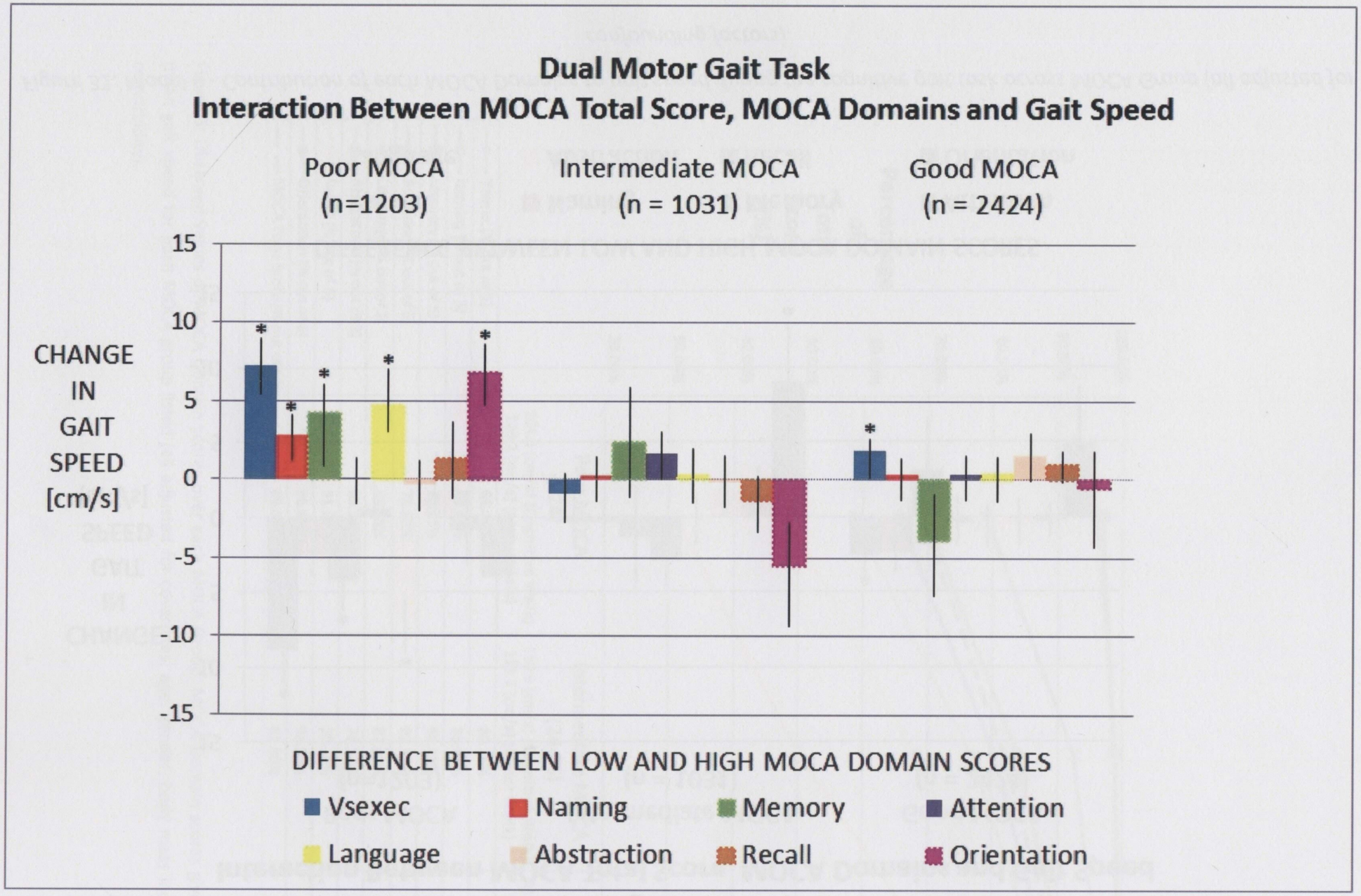


Figure 32: Model 4 - Contribution of each MOCA Domains to gait speed during the cognitive gait task across MOCA Group (all adjusted for confounding factors).

7.4. Discussion

Participants who walked more slowly performed worse on global cognition assessment tests. However, regardless of global cognition score higher verbal fluency (MOCA Subscore) is independently correlated with faster gait speed for both dual gait tasks in addition to cognitive elements specific to the dual gait task being performed. When MOCA total score is taken into account the relationship between gait speed and MOCA Domain is affected suggesting that the cognitive contribution to gait performance is dependent on global cogntion. Those with Poor MOCA scores (<24) possibly recruit more varied cognitive processes during complex gait tasks. Those with Intermediate MOCA scores (24/25) tend to have weaker MOCA Domain gait speed correlations which warrants further investigation. The results from this study suggest that compensatory strategies are different across MOCA Groups in a nationally representative population of adults fifty years and over. These results further highlight the need for further research into aspects of active cognitive reserve such as compensatory strategies at play during complex gait tasks. This may aid in the design of different interventions for different cognitive groups.

Global cognition affected the speed at which participants walked. Specifically, regardless of global cogntion executive processes were recruited for all gait tasks. Skills used in verbal fluency, attention and some visuoconstructive tasks are needed for all walking conditions, highlighting an executive and sensory requirement. More complex walking conditions may also recruit skills used in higher executive function and language tasks. These results are novel and show that specific motor activities are associated with different MOCA subscores: Visuospatial/Constructive skills (alternate letters task while walking), Attention Forward (carrying a glass of water while walking). Further research may allow clinical walking tests to become more ecologically sound, highlighting deterioration in specific activities of daily living.

These results indicate that there may be important information embedded within MOCA that is not included in the MOCA total score. Further research is needed to explore the effect of MOCA subscores, in particular those with an executive component, on MOCA total score during healthy ageing and pathology. Future research should focus on this

MOCA group-domain relationship and its association with performance in complex gait tasks longitudinally to aid in highlighting markers for early mild cognitive impairment.

7.5. Conclusion

- Regardless of global cognition, executive processes were recruited during all gait tasks.
- Specific motor activities are statistically significantly correlated with different MOCA subscores.
- Verbal fluency was highlighted for both dual gait tasks, in addition to cognitive elements specific to each dual gait task.
- Cognitive contribution to gait performance was found to be dependent on global cogntion.

CHAPTER 8: Study 6 - Measurement of Attention during Movement: Acquisition of Ambulatory EEG and Cognitive Performance from Healthy Young Adults

Simultaneous recording of cognitive processes during gait would be highly beneficial in order to probe deeper into the interactions between gait and cognitive function. In particular the recording of participants while they are performing normal daily activities would enhance our knowledge of cognitive processes at play during gait, for example during impaired gait or falls. Measuring neural responses through EEG during a motor-cognitive dual task was thought the best method to probe this interaction between gait and cognitive function in a quantitative manner. The hypothesis of this study was that measures of attention can be obtained through EEG during different exercise tasks but that the integrity of the attention measures recorded would be reduced in the exercise tasks which required vigorous movement. In addition, we hypothesised that cognitive load (as assessed by the measure of attention acquired) would increase for more intensive exercise tasks.

Initially we investigated which measures of cognitive function would be employed and could be measured during motion. Recording a measure of attention was chosen due to its strong links with gait. Several neuroimaging methods were explored and EEG was chosen to record attention during motion for its temporal accuracy and precision. Previous literature has found extensive contamination caused due to motion during EEG recordings and so this study investigated to what extent can these attentional processes be recorded during full ambulation.

The aim of this study was to obtain a direct objective measure of attention during motion and to investigate if the measure of attention was comparable across four different environmental conditions. Attention was assessed through reponses elicited by a standard, two-tone auditory discrimination task (the oddball task) recorded through EEG during different motor tasks. Specifically, the amplitude and latency of the P300 auditory evoked potential was the measure that assessed attention. The experimental design follows a progression into more valid

ecological environments by increasing motor tasks from control to sitting to cycling to treadmill walking experimental conditions.

A number of conference proceeding and conference presentations have been derived from resesearch in this chapter.

I. Killane, J. Gallego, G. Browett, R. B. Reilly (3-7 July, 2013). Measurement of Attention During Movement: Acquisition of Ambulatory EEG and Cognitive Performance from healthy Young Adults. Proceedings of the 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC'13), Osaka, Japan. Conf Proc IEEE Eng Med Biol Soc. 2013; 2013: 6397-400. doi: 10.1109/EMBC.2013.6611018

I. Killane, G.Browett, R.B.Reilly (2011), Measuring Neural Responses during Mild Exercise. International Conference on Ambulatory Monitoring of Physical Activity and Movement (iCAMPAM), Glasgow, Scotland.

I. Killane, G. Browett, R.B. Reilly (2011), Measuring Neural Responses during Sitting, Cycling and Walking. Seventeenth Annual Conference of the Section of Bioengineering of the Royal Academy of Medicine in Ireland (Bini17), Galway, Ireland.

8.1. Introduction

Recording human electro-cortical brain dynamics non-invasively during normal daily activities would have far-reaching clinical benefits. While this is not yet possible due to limitations in our understanding and measurement of neural processes involved in complex physical movement, the literature does suggest a strong link between locomotion and cognitive function[202, 294]. Attention is seen to play a central role in gait and locomotion[210], in particular as we age and with increased frailty. The study described in this chapter investigated if clinically useful electrophysiological measures of attention could be collected using an auditory task during sitting, walking and cycling. In addition, the differences in amplitude and latency between such signals was examined where a reduction in amplitude or increase in latency may indicate cognitive decline or cognitive load. P300 Event Related Potentials (ERPs) were recorded which reflect cortical activity and specifically P300 ERP have been shown to reflect attention and context updating[140].

Current practice of simultaneously measuring attention and locomotion is inadequate. Kinematic studies have mainly focused on using motion sensing systems, which are precise and quantitative, but do not allow simultaneous neural activity recording to measure attention[295]. In these studies indirect behavioral measures such as neuropsychological test scores are used to measure attention such as the subsequent studies described in this thesis. Current technology allows direct neurophysiological recordings to be taken in only extremely restrictive clinical environments due to susceptibility of signals to contamination[188]. However, some studies have recorded neural activity during controlled motion using exercise machines [184-186, 296, 297]. To allow insight into the extent by which attention varies during performance of specific motor activites developments in neural activity recording and processing are needed. The ability to measure changes in attention through recording neural activity during normal daily activities such as fully ambulatory walking would be highly clinically beneficial.

The aim of this study was to ascertain if a clinically useful attention measure could be collected in ecologically valid experimental environments. The attention measure was assessed as the magnitude of the amplitude and latency of the Auditory Event Related Potentials recorded through EEG. In addition, comparisons between the attentional measures across the sitting, cycling and walking test conditions were investigated.

This study examined participant responses elicited by a standard, two-tone auditory discrimination task (the oddball task[241]) in four different environmental conditions. The experimental design follows a progression into more valid ecological environments by increasing motor tasks from sitting to cycling to treadmill walking experimental conditions.

8.2. Methods

8.2.1.Study Design

Electrophysiological (EEG, EOG, EMG) recordings were taken for 7 healthy participants (aged 22 – 32 yrs, 4 female) while presented with an auditory oddball task as per Chapter 2: General Methods. Data was recorded in different experimental conditions: a control, a static (seated) and a dynamic (fixed cycling) experimental condition. Recordings were also taken for two participants during treadmill walking. Both cycling and walking occurred at a self-selected comfortable pace for the duration of the recording.

Experimentation restrictions occurred due to the ambulatory nature of the tasks that the participants were asked to perform so it was decided to use an auditory cognitive task (the Oddball Paradigm) played via wireless headphones instead of a visual "Oddball" displayed on a screen.

8.2.2.Data Analysis

P300 event related potentials (ERPs) were calculated as a measure of cognitive activity.

Data analysis included standard signal processing methods as per Chapter 2: General Methods. Peak P300 amplitudes and latencies were calculated and markers of muscle activity and inactivity were calculated from EMG data.

P300s were averaged for all target and non-target stimuli for all participants for each electrode position and peak amplitude and latency investigated as per Table 16 and Table 17.

8.3. Results

Auditory P300 data analysis showed that peak amplitude and component latency remained stable across all experimental conditions. This can be observed in Figure 34, Figure 35, Figure 36, Table 16 and Table 17 for the control, static and cycling conditions for seven participants. For the Cz electrode position, differences in P300 amplitude were 0.2-2% while P300 latency differences were 3-9%. There were no observed differences in P300 amplitude or latency between experimental conditions for all electrode locations.

A P300 signal was also recorded for the treadmill study which can be found in Table 17 for the control, static, cycling and treadmill experimental conditions for two participants. This shows that the P300 amplitude and latency also remained stable.

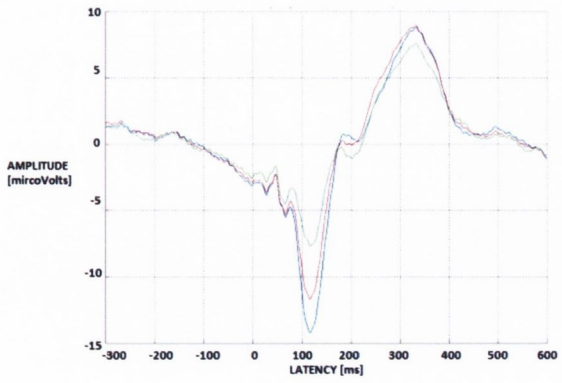


Figure 33: Participant grand averaged target stimulus response ERP data for control experiment at each electrode location (Cz (blue), CPz (red), Pz (green)): P300 occurring approximately 300 ms after onset of stimulus (based on 7 participants).

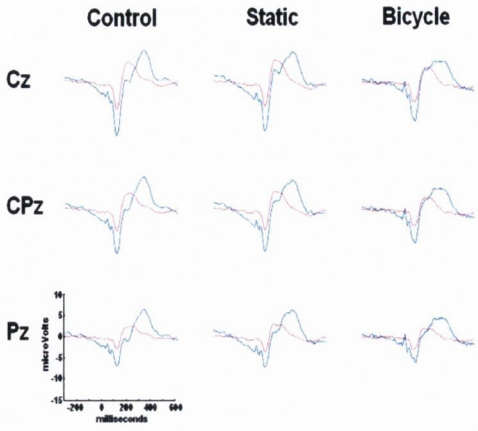


Figure 34: Participant grand averaged target and non target stimulus response ERP data (based on 7 participants) – typically target (blue) response peaks have higher amplitude and longer latencies, compared with non-target (red) response peaks.

Table 16: Participant grand averaged response for control, static and cycling conditions at each electrode location (Cz, CPz, Pz) (n= 7)

	Participant Grand Averaged P300 Amplitude and Latency		
	Electrode	**P300 Amplitude (μV)**	**P300 latency (ms)**
Control	Cz	8.85	330.86
	CPz	8.96	327.93
	Pz	7.62	327.93
Static	Cz	8.40	325.00
	CPz	8.00	318.16
	Pz	7.41	315.23
Bicycle	Cz	6.07	328.91
	CPz	5.98	325.98
	Pz	5.31	327.93

Table 17: Participant grand averaged response for control, static, cycling and Treadmill conditions at each electrode location (n=2)

	Participant Grand Averaged P300 Amplitude and Latency		
	Electrode	***P300 Amplitude (μV)***	***P300 latency (ms)***
Control	Cz	8.66	322.07
	CPz	9.37	322.07
	Pz	5.83	356.25
Static	Cz	9.32	320.12
	CPz	8.83	319.14
	Pz	7.86	322.07
Bicycle	Cz	9.76	325.00
	CPz	9.73	325.98
	Pz	8.79	333.79
Treadmill	Cz	9.57	282.52
	CPz	9.60	278.13
	Pz	8.00	291.80

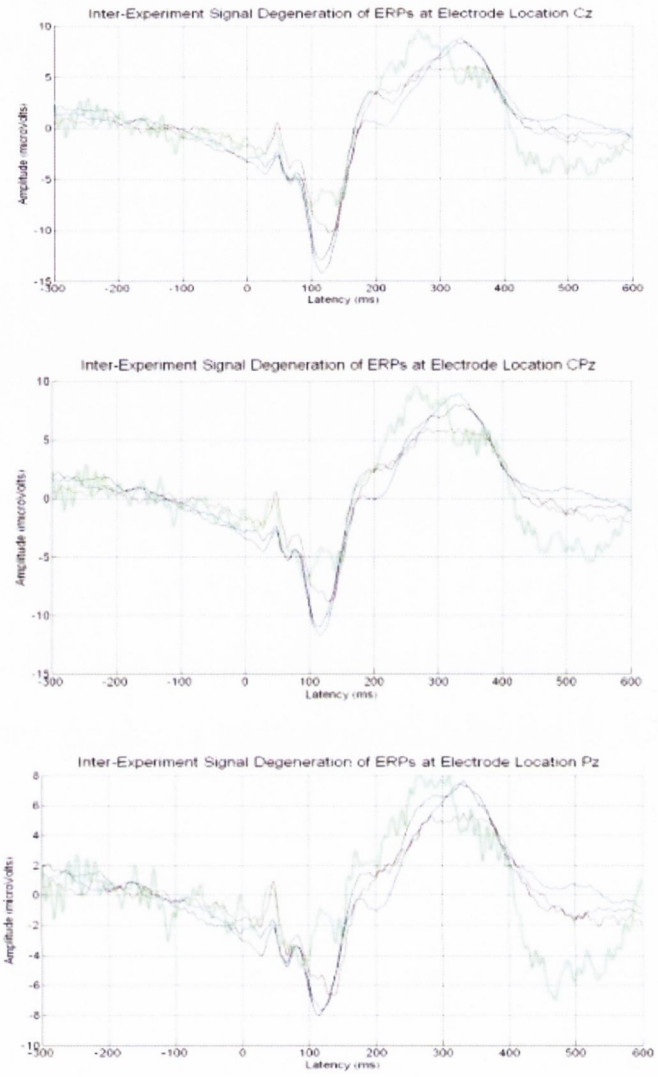


Figure 35: Inter condition signal variation; ERPs for all participants at electrode location Cz (left), CPz (centre) and Pz (right) for control (blue), static (black), cycling (red) and treadmill (green) experiments.

8.4. Discussion

Concurrent neuroimaging of locomotion and cognitive measures has traditionally been restricted by brain imaging constraints. The P300 is believed to underlie the neural mechanisms required to respond to changing cognitive demands, specifically attention and memory interaction. Reduction in amplitude or increase in latency can indicate cognitive decline or cognitive load. In addition, P300 amplitude and latency has been correlated with neuropsychological test scores during ageing [150]. Here recording of attentional resources in non-clinical environments (while sitting, cycling and walking) has

been shown to be possible for an auditory oddball task. It was found that P300 latency did not vary significantly across the four experimental conditions. This is consistent with findings that performance of a cognitive task during a relatively simple motor task did not present a significant Dual Task Effect (as assessed through EEG measures such as P300 latency) in healthy young adults [299]. This positive result opens up the possibility of recording electrophysical parameters during locomotion for patients with gait and cognitive disorders in more ecological environments, which would allow investigation of the effect of neurodegeneration on daily activities.

Future research should focus on increasing participant numbers, increasing experimental trials per participant to gain more accurate and statistically significant results and investigating different tasks to explore more cognitive sub-domains.

Most experimentation reported in the literature in the domain of gait and cognitive function has been carried out with non-human primates. However, there has been limited literature showing neuroimaging of human movement to be possible. A review of the literature found some studies involving motor tasks such as shooting, driving and golf-putting but the experimental protocol for these studies was generally very restrictive, with muscle activity extremely limited and movement kept to a minimum[184, 186, 188].

Therefore, it is encouraging to observe that the P300, a measure of cognitive function, can be recorded during cycling and on a treadmill. Full ambulatory monitoring that allowed investigation of gait and cognitive function quantitatively and precisely in more ecologically valid experimental environments would be highly beneficial. In this study we have shown that it is possible to quantitatively and precisely measure attention during controlled movements using EEG. This platform allows investigation of attentional cues in more ecological or real world environments thereby advancing neurological measurement systems. However, technology and analysis methods need to be improved to allow simultaneous recording of cognitive function and less restrictive movements. This would allow ambulatory EEG to be used to investigate changes in attention on performance of gait in studies on ageing and freezing of gait in Parkinson's disease [300].

8.5. Conclusion

The necessity for restrictions on movement during neurophysiological recordings means our understanding of the neural processes involved in complex physical movement and

measurement of such processes are limited. However, with recording of attentional resources in non-clinical environments shown to be possible here it opens up the possibility of investigating quantitatively the interaction between gait and attention by recording attentional resources through electrophysiological parameters such as the P300 component during the ageing process but also in movement disorders such as freezing of gait in Parkinson's disease.

8.6. Key Points

- Measures of attention can be acquired during gait.
- Results from this study found limitations to the technology available to analyse and interpret neural activity during movement in more complex tasks than were employed in this study.

The subsequent studies, Study 7 and Study 8, also shows the link between gait and attention, however Study 7 and Study 8 probe sustained attention contributions to gait performance through simultaneously measuring gait and cognitive function measures. In particular, Study 8 probes quantitative and precise continuous data. Continuing on from this study we can thus probe further (i) the link between gait and, global cognition and its sub-divisions such as attention, (ii) how locomotion affects performance in cognitive function and attentional tasks and how cognitive function affects movement. Furthermore, we can see if these effects occur for all participants equally and probe the effect of declining cognitive function on gait.

CHAPTER 9: Gait Variability and Sustained Attention in a Young Cohort and an Older Cohort

In Study 6 it was shown that a neurocognitive response during motion can be recorded with EEG during mild exercise. This cognitive response or measure changed somewhat in amplitude and latency during the movement task possibly showing a difference in the participant's focus of attention or a distraction to the task occurring during specific tasks. This follows the theory that there is a certain attentional capacity for each individual and this can be stressed during a complex dual task. Study 6 concluded that the stress of the cognitive task was minimal for this healthy cohort. However, it would be beneficial to examine changes in gait performance, such as an increase in stride time variability, in more detail during similar complex tasks. This chapter describes two studies, both investigated sustained attention and gait variability. Study 7 hypothesised that sustained attention will have an affect on gait performance in older adults such that those with high gait variability would have poorer sustained attention ability than those with lower gait variability. Study 8 hypothesised that gait measures acquired through novel analysis methods describe physiological function and are comparable to standard gait variability measures.

Stride time variability has been found to discriminate between performance differences in attention demanding gait tasks in young healthy adults [97, 301]. In addition, it has been reported in literature [247] that stride time variability, which represents stride-to-stride fluctuations, may descriminate important clinical features better than standard spatio-temporal gait measures such as gait speed. Stride time has been associated with ageing and neurological pathology[302]. This may also be the case for fluctuations in performance across a cognitive task. Gait and cognition expressed as means such as gait speed, dual task effects or point scores such as MOCA, MMSE and CTT are important to explore. However, other measures such as variability over a task can track performance changes over time. It is important to explore both mean and variability measures of gait and cognitive function in order to assess both mean population norms, in addition to specific performance levels of individuals across a task. However, variability measures are more difficult to

analyse especially for large datasets, given the large processing requirements, and there are conflicting opinions in literature [220, 247] on the accuracy of variability measures for instance when calculated with a small amount of sample points over short time series. Temporal aspects of both gait and cognitive function are described by variability measures and have been associated with many neurological functions and impairments [70, 98, 100]. It is therefore clinically relevant to further research variability measure of gait and cognitive function.

The aim of the studies in this chapter, Study 7 and Study 8, was to explore correlations between gait variability and sustained attention during dual gait tasks in a young healthy cohort (Study 8) and a community dwelling population over fifty years old (Study 7). In addition, standard linear and dynamic mathematical methods for calculating variability in gait and sustained attention were compared in Study 8. The studies described in this chapter build on findings from literature which found attention and gait variability to be key aspects in maintaining gait performance which need further investigation in order to increase understanding of the links between gait and cognitive function. Links between attention and gait were also highlighted in Study 6. Furthermore Study 5 specifically highlighted the contribution of sustained attention to gait performance. The studies described in this chapter explored variation in sustained attention and gait variability over time as this was highlighted in chapter 1 as a novel area of research.

Three conference presentations have been derived from research in this chapter as follows:

I. Killane N. Cosgrave, N. McDevitt , T. Foran , K.J. Sheehan , J. Gormley , R.A. Kenny, R.B. Reilly (June 29-July 03 2014). Comparison of Standard and Poincare Measures of Stride Time Variability. The Joint World Congress of the International Society of Posture & Gait Research (ISPGR) and Gait and Mental Function (GMF), Vancouver, Canada.

I. Killane, O. Donoghue, G. Savva, H. Cronin, R. A. Kenny, R. B. Reilly (22-26 June, 2013). Association between Gait Variability and Sustained Attention in a Community Dwelling Nationally Representative Population Sample. ID O.5.3. Second Joint World Congress of International Society for Posture & Gait Research (ISPGR) and Gait & Mental Function, Akita, Japan.

I. Killane, O. Donoghue, H. Cronin, R. A. Kenny, R. B. Reilly (18-19 Jan, 2013). Can meaning be found behind mean temporal gait parameters in an older Irish population sample?

Correlations between stride time variability and attention. Proceedings of the Nineteenth Annual Conference of the Section of Bioengineering of the Royal Academy of Medicine in Ireland (Bini19), Meath, Ireland.

9.1. Introduction

Gait variability is thought to reflect disruptions in intrinsic motor control. Increased variability in temporal gait parameters as we age have been associated with Alzheimer's disease and with increased risk of falling [303]. Links between gait variability and broad domains of cognitive function, such as executive functions, have been investigated previously; however, there has been less focus in the literature on the link with specific measures of executive function such as sustained attention. Sustained attention is the ability to maintain attention to task over a period of time and has been linked to frontal lobe damage [238] and higher risk of falling [216] in ageing.

Links between attentional domains and gait are not fully understood. Most studies to date have focused on the relationship between divided attention and gait. However, investigating gait and sustained attention is novel. The studies decribed in this chapter builds on work carried out in Study 4 exploring associations between gait speed and sustained attention. However, the studies described in this chapter have focused on the relationship between gait variability, gait tasks and variations in sustained attention.

Poincare analysis is employed in study 8 to analyse gait data. The Poincare method used which is employed in non-linear dynamics, has been reported on for some time in cardiovascular research to represents the nature of variations in intervals between heartbeats. Though not fully understood, variations in gait are also thought to reflect intrinsic disruptions, for example the higher temporal gait variability in patients with neurological disease.

Sustained attention is an important component of human executive control which allows purposeful function in accordance with our goals. Neuroimaging (EEG) studies have shown the sustained attention paradigm (SART) and sustained attention measures employed in Study 7

and Study 8 to be a sensitive metric in patient populations with deficits in their ability to sustain attention.

The sustained attention measures employed in Study 7 and Study 8 were variation in response times and errors of commission. Errors of commission are thought to measure a "drift" of controlled processing into an automatic response and have been linked to frontal lobe damage [238]. Greater variation in response time has been linked to higher risk of falling [216].

9.2. Study 7 - Sustained Attention and Gait Performance in a Nationally Representative Population of Older Adults (TILDA)

9.2.1.Methods

9.2.1.1. Study Design

This study used baseline cross sectional data data (n = 8504, 56% women, age = 63.14(10.21) yrs) from The Irish Longitudinal study on Ageing (TILDA) after excluding incomplete sustained attention response task (SART) and gait data gave complete covariate data from 4607 participants. Further detail of the study procedure can be found in Chapter 2: General Methods.

Data collection in the TILDA study comprised of three parts: a computer-assisted personal interview, a self-completion questionnaire and a health assessment. Participant characteristics detailed in this study were recorded during the computer-assisted personal interview. All neuropsychological and gait measure described in this study were assessed during the TILDA health centre assessment[233].

9.2.1.2. Gait and Cognitive Function Measures

Study 7 examined performance on gait and neuropsychological assessment tests that were administered during the TILDA health assessment as per Chapter 2: General Methods.

This study examined performance on sustained attention assessment tests that were administered during the TILDA neuropsychological assessment as per Chapter 2: General Methods. Sustained Attention to Response Task (SART)[238] was included in the neuropsychological assessment.

This study also examined gait variability recorded with a GaitRite pressure sensing mat in the TILDA gait assessment as per Chapter 2: General Methods. The single task stride time variability was the measures of gait performance employed.

9.2.1.3. Analysis

Participants with Parkinson's disease, Stroke and those with less than 8 steps of gait data were excluded. After these exclusions 3180 participants (56% women, mean±sd: age; 62.4±8.2 years) were eligible for inclusion in the analysis.

Multiple linear regression was employed to examine if gait variability differed across measures of sustained attention. Results were adjusted for age, height, gender, depression, education and factor affecting gait (as per Study 3 adjusted for self-rated vision, number of chronic diseases, arthritis, osteoporosis, disability, hip fracture, participants who used a walking aid and those who had hip or knee pain) and weighted to remove potential biases in data collected at health assessment in order to be nationally representative. Exclusion criteria include participants with Parkinson's disease, stroke and those with less than 8 steps of gait data. Post regression sustained attention measures (Coefficient of variation, errors of commission) were plotted against stride time variability adjusted for these covariates.

Sustained attention measures were categorized into poor and good sustained attention based on the median value. Multiple linear regression was employed to examine if gait variability differed for those with poor sustained attention compared to those with good sustained attention.

9.2.2. Results

Results show that an increase in stride time variability was independently associated with greater response time variation (β=0.0045, p=0.002) but not with greater errors of commission (β=0.024, p=0.171) after adjusting for stride time, age, height, gender, depression, education and factor affecting gait and, weighted in order to be nationally representative. Results can be seen in Table 18, Figure 36 and Figure 37. Gait variability was statistically significantly different for those with poor sustained attention compared to those with good sustained attention as per Table 19 and Figure 38.

Table 18 Correlations (p-value) between Sustained Attention Measures and Stride time variability and Effect (Beta) of differences in Gait Variability on Response Time Variation for all Regression Models.

Model (Adjusted for)	SART Response Time Variation		SART errors of commission	
	β	P	β	P
Model 1(Univariate)	0.0078	<0.001	0.0071	<0.001
Model 2 (Confounders[1])	0.053	<0.001	0.03	0.090
Model 3 *(Confounders, factors affecting gait[2])*	***0.052***	***0.001***	***0.03***	***0.074***
Model 4 (Confounders, factors affecting gait, stride time)	0.045	0.002	0.024	0.171

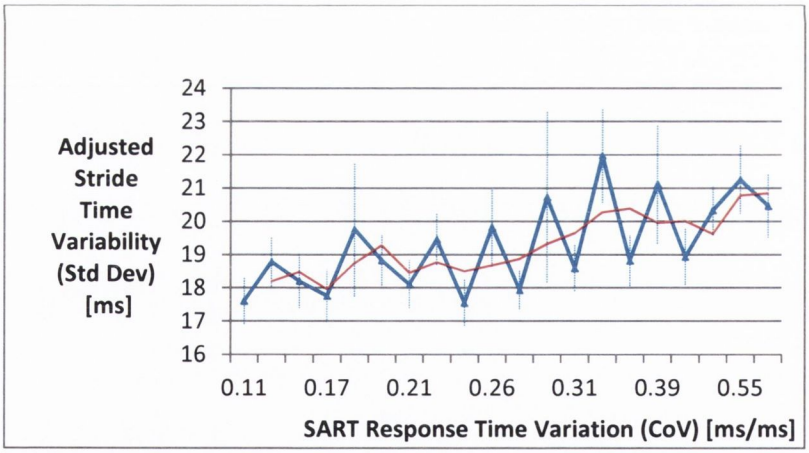


Figure 36: Adjusted Stride Time variability over SART response time variability (Model 3)

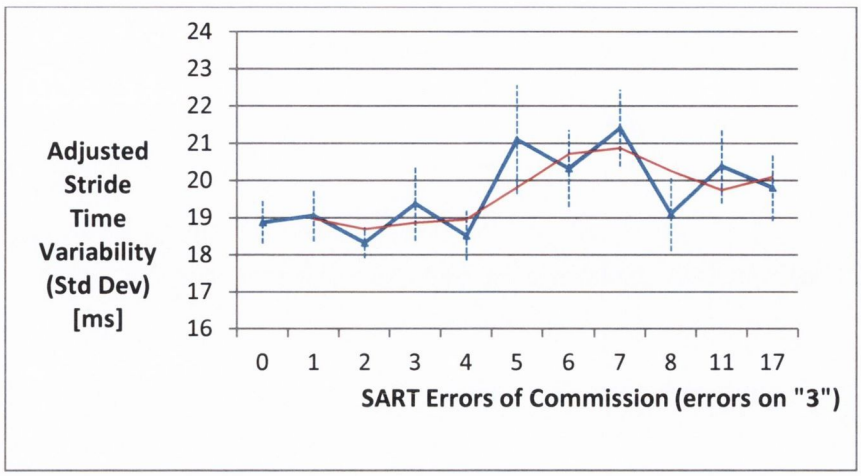


Figure 37: Adjusted Stride Time Variability over SART Errors of Commission (Model 3)

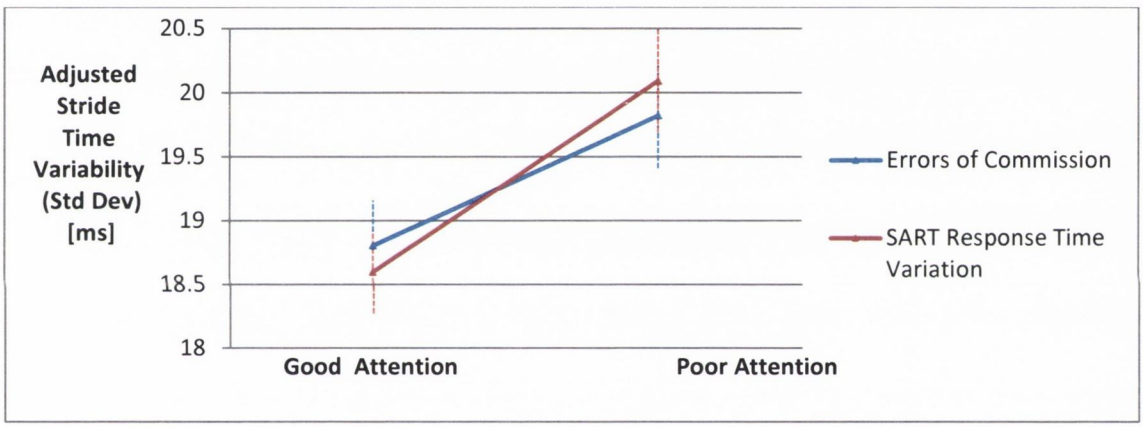


Figure 38: Correlations between sustained attention (Good and Poor) and SART error of commission (p=0.071) and SART response time variability (p=0.002).

Table 19: Association between Good and Poor Sustained Attention and Gait Variability

Task	Good Attention		Poor Attention		β	P
	SART Mean (S.E.)	Stride Time Mean (S.E.)	SART Mean (S.E.)	Stride Time Mean (S.E.)		
SART Errors on '3'	1.08 (0.8) [errors]	18.8 (0.36)[ms]	6.3 (3.9)[errors]	19.8 (0.41)[ms]	0.039	0.071
SART Response Time Variation	0.19(0.05)	18.6 (0.32) [ms]	0.42 (0.14)	20.1 (0.40) [ms]	**0.056**	**0.002**

9.2.3. Discussion

This study explored the relationship between sustained attention and variations in stride time during a simple gait tasks in a highly functioning older population after adjusting for covariates. Sustained attentional capacity was independently associated with stride time variability for Coefficient of Variation (p=0.002) but not for Errors of Commission (p=0.171)(errors on the number "3"). Stride time variability has been described in literature as a measure of gait rhythmicity. In this population individuals with poorer sustained attention walk with significantly more gait variability than those with better sustained attention abilities. The analysis in this study was exploratory in nature due to possible limitations in a short walk and the experimental set-up employed assessing gait variability. With this aim further analysis has continued with healthy young controls (Study 8). Further research is needed to explore how recruitment of endogenous attention, lapses in attention and gait variability change within individuals over the duration of a gait task using more ecological conditions such as more complex gait tasks, thus benefitting quality of life issues.

9.1. Study 8 - Sustained Attention and Gait Performance in Young Healthy Females

9.1.1.Methods

9.1.1.1. Study Design

Cross sectional data from 12 healthy female adults (age mean±sd: 26.0±4.0yrs) described the younger cohort.

9.1.1.2. Gait and Cognitive Function Measures

This study examined performance on gait and neuropsychological assessment as per Chapter 2: General Methods. Briefly, this study examined performance on sustained attention assessment tests and gait variability that was recorded with the CODAmotion system (Charnwood Dynamics, England) during one single gait tasks and two dual gait tasks: serial seven substraction task while walking, reaching while walking. Stride time standard deviation was the measure employed to assess gait variability. In addition, poincare analysis was undertaken.

9.1.1.3. Analysis

Four measures of gait variability were investigated: two standard measures and two poincare measures. The standard measures were coefficient of variation (CoV) and standard deviation (SD). The Poincare measures were SD1 and SD2. SD1, a measure of short term variability, and SD2, a measure of long term variability, were calculated from the width and the length of the Poincare plot respectively. CoV, SD, SD1 and SD2 were calculated using Matlab [MathWorks, Cambridge]. All gait variability measures were calculated for concatenated data of three ten metre walks.

A Poincare plot was generated which plotted each stride time interval against the subsequent interval, see Figure 39. Stride Time variability values were plotted over gait conditions employing groups means (Figure 40) and individual participant values (Figure 41 and Figure 42). One-way ANOVA tables were used to compare the ability of standard and Poincare measures to discriminate between STV in the three gait conditions using SPSS V21.0 [IBM, USA], see Figure 43.

9.1.2.Results

Battery failure resulted in complete data being acquired for a total of 8 participants. Results show that participants walked with statistically significantly ($p<0.05$) lower CoV, SD, SD1 and SD2 during the serial sevens gait condition compared to the reach gait condition (Tukey HSD, $p>0.05$), see Figure 39 to Figure 43. Both SD1 and SD2 were statistically significantly correlated with CoV and SD (Pearson's <0.94, $p<0.001$). All measures were able to detect differences in group means between gait conditions ($p<0.05$) with SD1 having the greatest significance (CoV: $p = 0.010$; SD: $p=0.018$, SD1: $p = 0.008$; SD2: $p = 0.029$).

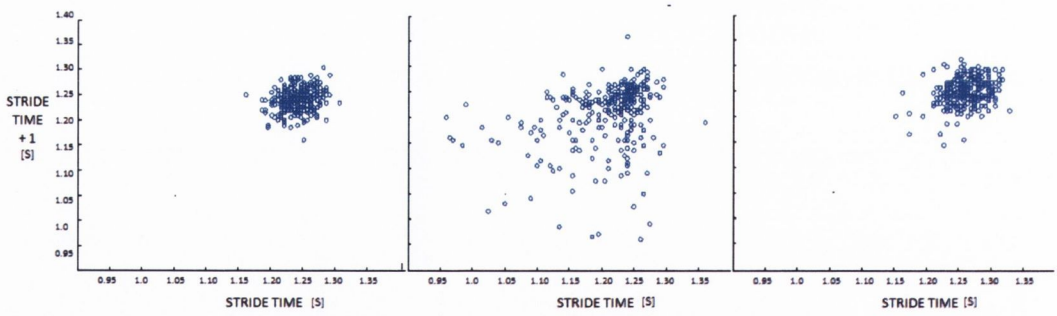


Figure 39: Poincaré plots representing STV over STV+1 for Participant 5 during the single (left), the reach gait tas (centre) and the serial-sevens (right) walking conditions.

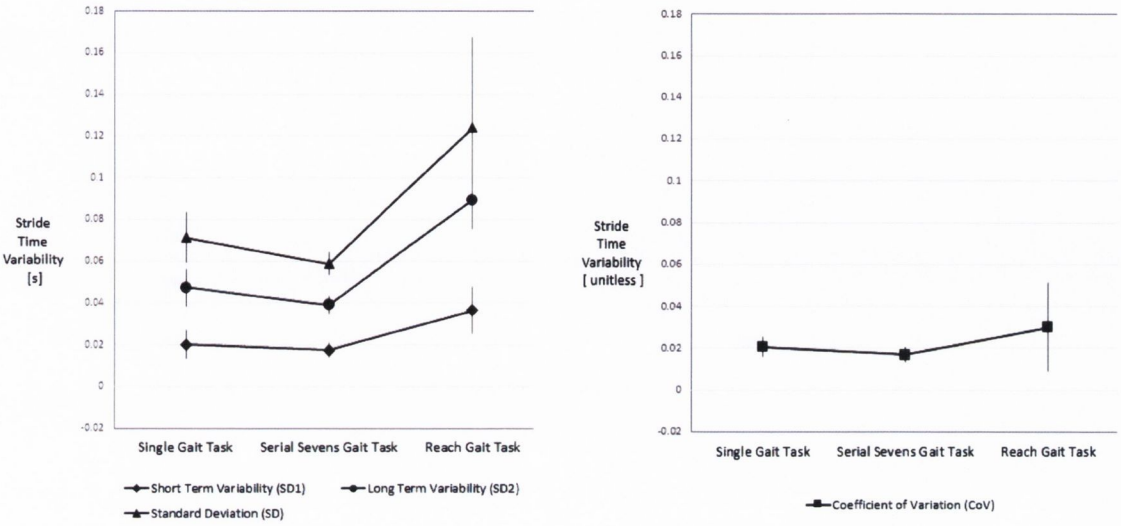


Figure 40: Mean Stride Time Variability during Each Gait Condition: SD1, SD2 and SD (left), SD (right)

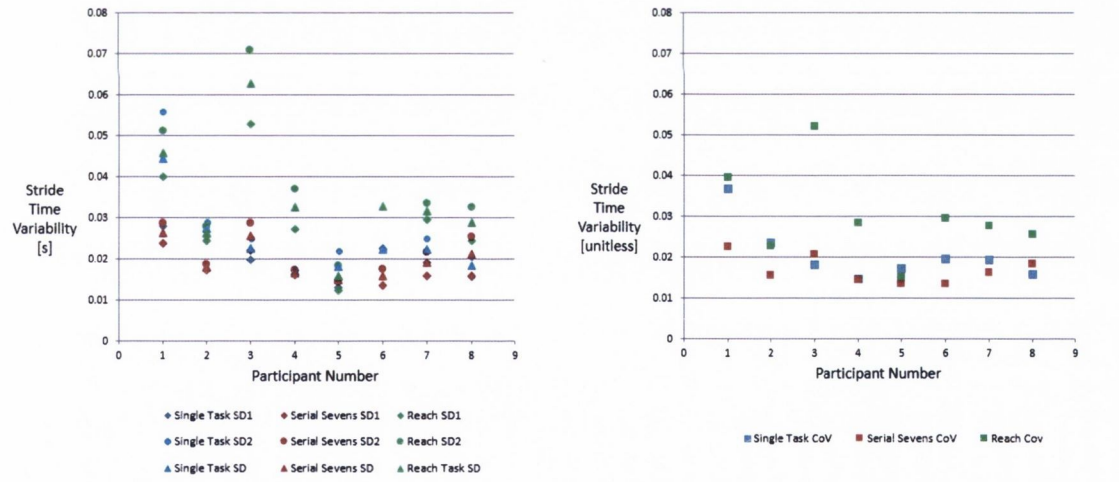


Figure 41: Poincare and Standard Stride Time Variability for Each Participant

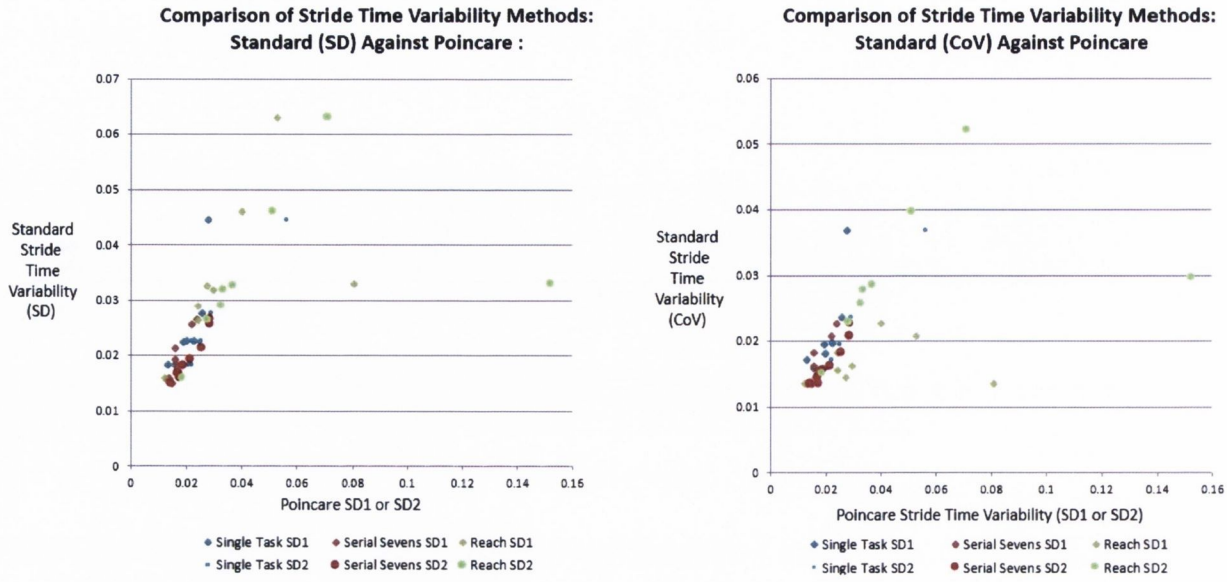


Figure 42: Comparison of Stride Time Variability Methods Standard against Poincare: Standard Deviation (SD) (left) and Coefficient of Variation (CoV) (Right)

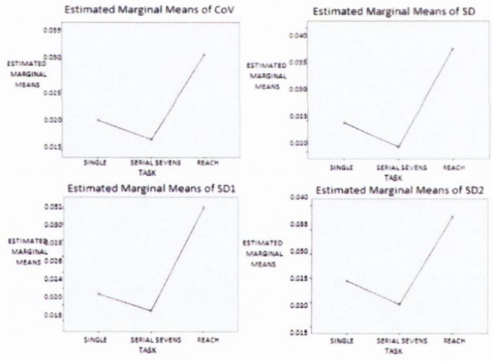


Figure 43: Post ANOVA Estimated Marginals Means for each gait condition for CoV (Top left), SD (Top Right SD1 (Bottom Left) and SD2 (Bottom Right).

9.1. Discusssion

The Poincare measures of gait variability, SD1 and SD2, are at least comparable with standard gait variability measures in younger individuals. They may represent a more descriptive measure in select populations or in other tasks. The Poincare method has been employed to describe heart rate dynamics with explicit physiological representation[261, 262] [260] [254,

255]. However, only a few studies have investigated the Poincare method in relation to gait [260] (minimum foot clearance) and so employing Poincare measures to describe temporal gait variability is novel. Using such analysis in future research may highlight intrinsic neurological disruption seen episodically or continuously through gait, thus enhancing our understanding of the higher neurological control of gait.

No significant relationship was found between sustained attention and gait variability assessed over a longer walk using linear and non-linear analysis methods (CODAmotion system in St James's Physiotherapy Dept.) in healthy young females. However, literature states that gait variability is low in healthy young adults during simple gait tasks and can reduce further with a slight increase in complexity of task such as in the reach or serial sevens dual gait task employed in this study. Future research should investigate a task with increased complexity which would allow a threshold or attentional capacity to be reached causing gait variability to increase.

This result indicates that it would be beneficial for future research to assess associations between gait variability and sustained attention over a longer walk in the TILDA population longitudinally. One particular novelty of the TILDA study is the collection of data from older adults from fifty years of age. Previous studies have assessed older adults a decade or greater older than the TILDA population. Assessing a small sample of the younger TILDA participants longitudinally over a longer walk would be novel and the smaller number of participants would allow for more complex mathematical analysis.

Results in this study open up the possibility of quantitatively investigating stride time variability using the Poincare method. The Poincare long term variability measure could be particularly beneficial to compare real life gait measures and their relationship with real life attentional measures (endogenous attention, lapses in attention) and their relationship to gait variability over time.

9.2. Key Points

a. Those in the TILDA dataset[26] with poorer sustained attention walk significantly more slowly in both simple and complex gait tasks.

The result employed two standard sustained attention measures assessed through the sustained attention to response task: Coefficient of Variation and Errors of Commission (errors on the number "3").

Sustained attention Coefficient of Variation is thought to be the most appropriate measure of sustained attention given it describes temporal variations and is standardised.

b. Exploratory analysis investigating association between temporal gait measures and sustained attention. Preliminary results show that those in the TILDA dataset with poorer sustained attention walk with significantly more gait variability than those with better sustained attention abilities[27].

c. No significant relationship was found between sustained attention and gait variability assessed over a longer walk using linear and non-linear analysis methods (CODAmotion system in St James's Physiotherapy Dept.).

d. These results open up the possibility of quantitatively investigating stride time variability using the Poincare method. This may open up the possibility of investigation of correlations between variability in performance during specific events of cognitive assessment tests such as SART and gait task across a task.

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[26] All results are representative of a community dwelling population of older adults over fifty years. Significant correlations between gait speed and sustained attention for both univariate linear regression and multiple linear regression which adjusted for covariates (Age, gender, body mass index, education, depression, polypharmacy, cardiovascular disorders, memory impairments, arthritis, osteoporosis, Parkinson's disease, cancer, chronic lung disease or asthma, self reported poor vision, hip or wrist fracture, hip or knee pain, or walking aid use).

[27] Adjusted for Age, Height, Gender, Depression, Level of Education and factors affecting gait (Self-rated Vision, Number of Chronic Diseases, Arthritis, Osteoporosis, disability, Hip Fracture, participants who Used a Walking Aid and those who had Hip or Knee Pain). Weighted to remove potential biases in data collected at health assessment in order to be nationally representative. Also excluding participants with Parkinson's disease, Stroke and those with less than 8 steps

9.3. Summary

The studies described in this chapter found no relationship between sustained attention and gait variability in healthy young females. In addition, gait variability was very low in this young cohort. This is in agreement with previous literature where gait variability is low in young adults during simple gait tasks. Gait variability was found to be very low in the TILDA population also. However, the gait mat employed in Study 7 was not found to have adequate sensitivity to record these low values. The kinematic system employed in Study 8 however, had the required sensitivity to record minor variations in gait and so results from this study are more trustworthy. In addition, the experimental set up used in Study 8 enhanced the accuracy of the result by recording gait for a longer amount of time (mean 295 strides in Study 8 and 8-x in Study 7).

There are fundamental research questions arising out of the studies described in this chapter. Firstly, is the relationship between gait and sustained attention due to common neural processes in both the gait task and the attention task separately. Furthermore, is it a specific recruitment of attentional resources for gait? Additionally, similar to Study 3, can this higher gait variability be seen as an automatic adaptation in those participants with lower attentional capacity. Longitudinal analysis may reveal if a larger gait variability is a biomarker for pathology. In particular, are changes in sustained attention, which may be displayed also during complex motor tasks, markers of incipient Mild Cognitive Impairment?

CHAPTER 10 Discussion

Summary

The studies described in this thesis aimed to investigate and quantify the relationship between gait and cognitive function with a view to employing gait as a window to cognitive function. The main findings from literature were outlined on the role that cognitive function has been found to play in gait performance in older adults and early stage cognitive impairment. In order to further explore and enhance our understanding of this relationship studies within this thesis carried out a number of experiments and employed various analysis methods. A number of studies described in this thesis examined this relationship in a nationally representative population (n=8504) while two other studies employed young healthy participants. The contribution of specific elements of cognitive function (executive function, attention) were examined in detail, in addition to a comprehensive exploration of the contribution of global cognition to gait. Gait speed and gait variability (stride time variability) were the gait measures investigated due to their respective associations with survival and incipient cognitive impairment. In addition, the many factors that affect both gait and cognitive function were examined, with age, the effect of task and global cognition being explored in detail. All thesis objectives and aims were examined by the studies within this thesis and are outlined within this discussion.

Research Question K was posed in Study 1 where distribution of within-participant and between-participant gait and cognitive function performance in a nationally representative populations was examined. Study 1 also tested the hypothesis that differences in performance in gait assessment tests and cognitive function tasks represent different physiological states. Study 1 hypothesised that those who perform poorly in gait or cognitive function tasks may be experiencing early age related changes or more sinister prodromal pathology such as mild cognitive impairment. Numerous gait and neuropsychological variables from the TILDA dataset were assessed and, where appropriate further variables were derived. The effect of task, age and gender on gait and cognitive function were also investigated. In addition, gait and cognitive variable characteristics

were examined to check if they met the assumptions of statistical methods. Conclusions from Study 1 along with the main findings from literature as per Chapter 1 found specific gait and cognitive function measures of interest when investigating gait and cogniton.

Study 3 examined higher control of gait (Research Question C) by examining automaticity of gait in simple and complex gait tasks in an older population employing the TILDA dataset also. Links between specific executive function test scores and gait performance (Research Question B) were also investigated by examining gait performance over the executive function spectrum in the TILDA dataset. Correlations between executive function test scores and gait speed differences were hypothesised to quantify a point of transition from automatic to a more consciously controlled gait. Assessing gait performance threshold levels for these points of transition during a complex gait task may highlight those with executive function impairments.

Study 2 investigated the clinical utility of gait performance by investigating the efficacy of gait speed as a biomarker for cognitive impairment (Research Question I). Standardised measures were employed in the form of gait and cognitive zscores. The effect of age was also investigated.

Study 5 investigated links between global cognition and gait performance (Research Question A) Interactions between gait speed, MOCA Domains and MOCA groups were also investigated. The association between gait speed during two complex gait tasks and (i) global cognition, (ii) eight MOCA domains and (iii) twenty fives MOCA subscores within the TiLDA dataset were assessed,thereby probing Research Question D also. Interactions between the contribution of specific elements of cognitive function to gait performance at different global cognitive categories (MOCA Test scores of: 0-24, 24 and 25, 26-30) were investigated. Results from this study may be clinically beneficial in particular in relation to design of interventions for healthy adults over fifty years of age and over a broad global cognition spectrum.

Study 4 explored Research Question A by examining the relative cognitive contributions to gait speed during simple and complex gait tasks. Similar analysis was employed as per Study 5. The association between five gait speed parameters (gait speed in single, cognitive and motor gait tasks and the dual task effects of both dual gait tasks) and seven neuropsychological test scores within the TiLDA dataset were assessed. In addition, the effect of gait task and age were also explored in this study (Research Question D). Extensive analysis of the affects of covariates and comorbidities on gait and cognition were explored in this study also, in particular the effect of age

as posed by Research Question G. Results from this study have been published in Journal of Gerontology: Medical Sciences: Special Edition on Physical Function and the Ageing Brain, Autumn 2014.

Study 6 explored if recording of attentional resources in non-clinical environments was possible (Research Question H). The P300 auditory evoked potential elicited using an auditory oddball task in young healthy adults during exercise assessed attention. Study 2 also investigated the effect of task by examining differences in attentional resources over three exercise tasks which were designed to increase in complexity of movement (Research question D).

In Study 7 and Study 8 temporal aspects of gait and cognitive function were investigated over continuous data. Correlations between sustained attention and stride time variability were investigated in older adults (Study 7) and in healthy young females (Study 8) posing Research Question E. Stride time variability was calculated by employing a gait cycle time measure as calculated by the electronic walkway software (GaitRite) and also by employing the Poincare method. The Poincare method has been employed in cardiovascular research but is novel in gait variability research. The Poincare method generates a long term gait variability measure. Little is known about the physiological meaning of this measure, however this measure may hold important information on the physiological basis of gait variability differences or changes over time and explore the higher control of gait (Research Question F).

10.3. Main Findings of the Thesis

The studies described within this thesis demonstrated that gait and cognitive function have a complex relationship. This was examined cross sectionally by investigating the first wave of the TILDA dataset, a nationally representative population of adults over fifty years employing a pressure sensing mat and neuropsychological test scores. Additionally, this was also examined cross-sectionally in young healthy participants in two other studies employing electromyography, a motion sensor system, neuropsychological test scores and an electrophysiological marker of attention.

A broad spectrum of gait and cognitive performance exists in a nationally representative sample of adults over fifty years of age (Research Question K)

Conclusions from Study 1 along with the main findings from literature as per Chapter 1 found specific gait and cognitive function measures of interest when investigating gait and cogniton. Cognitive domains such as global cognition, executive function and attention[50, 210], in addition to gait measures such as gait speed, dual task effects and temporal gait variability (e.g.: stride time variability) [70] were highlighted as measures of most interest when investigating the relationship between gait and cognitive function as detailed in Chapter 1. This was reiterated in results on gait and cognitive measures from the TILDA dataset in Study 1. The analysis in Study 1 also included additional measures such as sustained attention.

Gait and neuropsychological outcome measures in the TILDA dataset were observed to be as per those found in literature for relatively healthy cohorts taking account that this was a cohort with a younger mean age. In general, participants walked fast with low variation and had very good global cognition.

Study 1 observed global cognition to affect gait performance. This is in agreement with literature as summarized in Chapter 1. Study 1 also observed MOCA to be a particularly important factor when investigating gait and cognition in the TILDA cohort. Study 1 concluded that associations between cognitive function, employing both global cognition and specific elements of cognitive function, and gait require further in depth research.

Participant characteristics were observed to differ for the participants attending the TILDA health assessment compared with participants included in the entire TILDA dataset. This indicated that in order for the outcomes of the studies in this thesis to be representative of a population any analyses must be weighted to remove bias.

Many participant characteristics were found to affect gait or cognitive performance (Research Question K)

Age and gender were found to statistically significantly affect gait and global cognitive measures in Study 1. Education, depression, weight and height have also been reported in literature [30, 286] to affect measures of gait or cognition. Including these in regression

models allowed regression outcomes to indicate cognitive predictors of gait (or vice versa) independent of these particular characteristics.

Research Question K was also answered in Study 3 and Study 4. Study 3 examined factors affecting gait and included: self-rated vision, number of chronic diseases, activities difficulties, presence of Parkinson's disease, arthritis, osteoporosis, hip or knee pain, hip fracture and use of a walking aid. The regression models in Study 3 were adjusted for these factors affecting gait. Study 4 examined factors affecting gait, in addition to factors affecting cognitive performance and introduced a derived variable to incorporate all factors collectively termed "cormorbidity". These included (i) those taking more than five medications (ii) those diagnosed with cardiovascular disorders, memory impairments, arthritis, osteoporosis, parkinson's disease, cancer, chronic lung disease or asthma, (iii) those with self reported poor vision, hip or wrist fracture, hip or knee pain and (iv) those who use a walking aid. This variable was employed in regression models in Study 3, Study 4, Study 5 and Study 7 in order for outcomes of regression models to indicate cognitive predictors of gait independent of affects of these comorbidities.

Exploring cognitive predictors of gait in a regression model is an appropriate analysis method for the TILDA cohort(Research Question K)

Study 1 found a very high cognitive performance with a skewed distributions for this nationally representative population. This skewed distributions meant that the cognitive measures did not meet assumptions of linear regression analysis. This result, in addition to the affect of covariates, age and gender led to the conclusion that regression analysis exploring cognitive predictors of gait would be the most appropriate analysis method to employ in subsequent studies. Gait measures, such as the normally distributed gait speed, was employed as the dependent variable and cognitive parameters as the predictor variables in regression models in subsequent studies.

Gait speed changes with nature and difficulty of task (Research Question D)

Many studies described within this thesis found the nature and difficulty of the task to have an affect on gait performance. In particular, the gait task performed during the TILDA gait

assessment statistically significantly affected the self-selected gait speed at which the participants walked. Gait speed during the single gait task was found to statistically significantly differ from the motor gait task and the cognitive gait task ($p<0.05$). This indicates that outcome measures, such as gait speed, need to be validated during standardized gait task prior to the use of the gait task as a reliable clinical meaurement.

There may be specific executive function-gait speed change points which highlight transitions from automatic to more voluntary motor performance (Research Question C)

Little evidence exists about appropriate clinical gait tasks for neurocognitive assessment, given slow gait speed is associated with functional decline, poor survival and impaired executive function. Study 3 investigated automaticity of gait during three gait tasks across the executive function spectrum of a nationally representative older population: TILDA, n=4607, age (range): 50-91years. Associations between gait performance (gait speed and Dual Task Effect) and executive function (ΔCTT) were investigated. Differences in gait speed were compared across executive function groups, with a particular focus on those in the poor executive function group who are possibly at higher risk of transition to mild cognitive impairment. Significant change-points in gait across the executive function spectrum were explored using division (poor, intermediate, good based on $50^{th}/95^{th}$ percentiles), tertile and decile classification.

Regardless of executive function, gait speed and Dual Task effect were significantly different for all conditions. The cognitive dual gait task had the greatest effect on automaticity of gait, and, when employing diagnostic test efficacy[268, 279], was sensitive to but not predictive of executive function.

Slower gait speed was found to be correlated with lower scores on executive function tasks. Results show that those with poorer executive function had significantly ($p<0.01$) slower gait speed and greater Dual Task Effect when compared with the higher executive function division, tertile and decile for both dual tasks. However for the single gait task no statistically significant difference in gait speed were found for those in different executive function divisions, tertiles or deciles. Significant executive function-Dual Task Effect change-points were found for all gait tasks. For the motor gait task only those in the lowest decile of executive function had significantly slower gait speed when compared with higher deciles. For

the cognitive gait task change-points began to occur at decile seven (Dual Task Effect >18.9%), these included 1,700 participants (35% of the population), who were not classified with poor executive function.

These results bring into question using a single walking task at a self-selected pace when investigating community dwelling older populations and analysis of only CTT to assess executive function. These results suggest that gait speed (i) is associated with executive function and (ii) dependent on the nature and difficulty of the task. In agreement with the literature, gait speed for single and dual tasks differs by executive function divisions [128, 169]. This indicates that there is a relationship between pre-frontal areas pertaining to executive processes and the motor cortex performance. This may be either a general correlation between neural processing performance manifesting separately as poor ΔCTT scores and a slower gait speed, or the implication there is a common neural mechanism employed by both cognitive function and movement where slowing of gait is caused by an impaired pre-frontal cortex. The later theory seems more plausible given that the addition of a complex task affects the gait speed of even the participants who walked at a fast pace during the single task perhaps indicating a mutual cognitive/motor interference effect is manifested as a slowing of gait. Employing this theory, it was hypothesised that the finding from this study possibly highlight gait transitioning from an automatic to a more consciously controlled process. This suggest that those groups with poorer executive function have an increased reliance on the executive areas of the pre-frontal cortex when performing complex gait tasks which results in a slower gait speed. This may be relevant for preventative measures in the future where percent decline in a cognitive dual task, compared with the reference single task, may indicate a declining executive function as found here when taking ΔCTT as a measure of executive function.

In addition, as correlations between gait speed and executive function are dependent on gait task, this reliance on the pre-frontal cortex was hypothesised to increase with task complexity. Given the nature of the motor dual task (carrying a glass of water while walking) a large dual task effect (percent decline) for the motor dual task was hypothesised to indicate more likelihood of difficulties with normal activities of daily living. Assessing a gait performance threshold level during a complex gait task as a measure of healthy executive function could perhaps be a clinically beneficial to highlight those with executive function impairments.

Furthermore, executive function impairments have been linked to increased risk of falls so this type of gait performance threshold may be a useful marker for participants in need of falls interventions. However, under scrutiny gait speed at these points of transition during a complex gait task were found to be a poor diagnostic test for executive function. The results of this study highlight a strong relationship between executive function and gait speed. It would be beneficial to explore associations between executive function and gait relative to other elements of cognitive function.

Many elements of cognitive function contribute to simple and complex gait tasks. However, there is an additional executive function contribution during dual gait tasks (Research Question A and Research Question D)

For single gait tasks, associations have been reported between gait speed and cognitive domains. However, few studies have evaluated if this association is altered in dual gait tasks given gait speed changes with complexity and nature of task. Study 4 evaluated the relative contribution of specific elements of cognitive function (including sustained attention and processing speed) to dual task gait speed in a nationally representative population of community dwelling adults over fifty years. Linear regression models, adjusted for covariates, were constructed to predict the relative contributions of seven neuropsychological tests to gait speed changes and to investigate gait task effects. The mean age and gait speed of the population (n=4431, 55% women) was 62.4 years (SD = 8.2) and 135.85cm/s (SD = 20.20, single task) respectively.

Study 4 found that poorer processing speed, short term memory and sustained attention were major cognitive contributors to slower gait speed for all gait tasks (Research Question A). That is community dwelling participants that display poorer processing speed, short term memory and sustained attention walk more slowly during both single and dual gait tasks than those with higher levels of such resources. In addition, dual gait tasks require additional executive processes not found for the single gait task (Research Question D). These results give an insight into the cognitive requirements for daily activities. Several elements of cognitive function were independently associated with gait speed for all gait tasks. Processing speed

contributions were specifically highlighted. This result forms a baseline value for dual task gait speed.

Correlations between neuropsychological tests may account for the results from Study 4. However, speed of processing, short term memory and sustained attention were also the main contributors to gait speed in all gait tasks when regressing each neuropsychological test separately (univariate analysis) which does not have this limitations. Further research should investigate longitudinally if these findings are indicative of an age related change or cognitive function variations within the population. The contribution of executive function to gait speed was explored in Study 3, however insight may be gained from exploring the relationship between sustained attention and gait speed. This is explored in the next finding from Study 7 and Study 8.

Older adults with poorer sustained attention walk with significantly more gait variability; this association was not found for younger healthy females. In addition, divided attention had a similar relationship with gait variability in older adults (Research Question E)

Investigating associations between temporal gait measures and sustained attention was of interest and was examined in Study 7 and Study 8 in an older and a younger population respectively. Both studies employed two standard sustained attention measures assessed through the sustained attention to response task (SART): Coefficient of Variation and Errors of Commission (errors on the number "3"). Sustained attention coefficient of variation is thought to be the most appropriate measure of sustained attention given it describes temporal variations and is standardised. A pressure sensing mat (GaitRite) collected gait speed and stride time variability data in Study 7, which investigated the TILDA dataset, and a motion analysis system (CODAmotion) recorded stride time variability over a 3 minute long treadmill walk in Study 8, which investigated young healthy females. Results show that participants in the TILDA dataset with poorer sustained attention walk with significantly more gait variability than those with better sustained attention abilities. However, no significant relationship was found between sustained attention and gait variability assessed over a longer walk in young healthy females.

Study 8 (young cohort) had a different experimental set up to Study 7 with gait data being recorded for a longer amount of time (mean 295 strides) by a system with high accuracy. Gait variability was found to be very low in Study 7 (older cohort) and this may have affected results. The kinematic system employed in the young healthy female study had a higher sensitivity to recording minor variations in gait and so results from this study are more relevant.

Study 8 (young cohort) found no significant relationship between gait variability and sustained attention, when employing both Poincare and standard analysis methods. Gait variability was low in this young cohort. This is in agreement with previous literature where gait variability has been found to be low in healthy young adults during simple gait tasks [304-306]. Literature states that gait variability in healthy young adults can reduce further with a slight increase in task complexity. Similar to gait speed, gait variability has been found to increase when task complexity is at a sufficient enough a level to reach an individuals's attentional capacity threshold. . Future research is needed to explore this threshold in young and old cohorts. Furthering our knowledge of this relationship would allow further understanding of how recruitment of endogenous attention, lapses in attention and gait variability changes during gait. Further research employing analysis methods, such as the Poincare method, employed in this study would allow investigation of this relationship over the duration of a gait task using more ecologically valid experimental conditions such as more complex gait tasks. This would be clinically beneficial and may aid in the enhancement of quality of life.

Results from Study 7 (older cohort) suggest that it would be beneficial for future research to assess associations between gait variability and sustained attention over a longer walk in an older population longitudinally. One particular novelty of the TILDA dataset is the collection of data from adults from fifty years of age. Previous studies have assessed adults a decade or greater older than the TILDA population. Assessing a small sample of younger TILDA participants who are in mid-life longitudinally over a longer walk would be novel and the smaller number of participants would allow more complex mathematical analysis to be undertaken. Longitudinal analysis may reveal if changes in sustained attention, which are displayed also during complex motor tasks, are markers of incipient mild cognitive impairment.

Global cognition score affects the relationship between specific cognitive impairments and gait speed (Research Question A and Research Question G)

Investigations into global cognition may have more clinical benefit than exploring specific elements of cognitive function as global cognitive measures are more commonly employed clinically. The relative contributions of MOCA total score, MOCA domains and MOCA subscores to dual task gait performance in older adults was explored in Study 5. In addition, this study explored contributions of global cognition scores to gait performance-MOCA Domain associations, where MOCA Domains include: Visuo-spatial executive, Naming, Memory, Attention, Language, Abstraction, Delayed Recall and Orientation... MOCA was chosen as the global cognitive measure to explore as it was thought to better describe the population in question due to it having a higher sensitivity than MMSE to milder forms of cognitive impariment[108, 110].

Study 5 found that participants who walked more slowly performed worse on global cognition assessment tests (Research Question A). Parsing apart MOCA subscores and MOCA Domains scores found that regardless of global cognition those with higher executive function abilities (verbal fluency) walked faster for all gait tasks. In addition to this executive function contribution, cognitive elements specific to the dual gait task being performed were recruited. The statistical significant contributions to gait speed were the attention forward domain for the motor dual gait task and the trails for the dual cognitive gait task. This results hows the additional task performed during each dual gait task are explicitly related to the elements of cognitive function that they are proposed to probe: attentional abilities for carrying a glass of water when walking and cognitive flexibility abilities for reciting alternate letter of the alphabet when walking. This is a major conclusion of this study. These results highlight an executive and sensory requirement during complex gait tasks. This indicates that more complex walking conditions may recruit skills used in higher executive function and language tasks.

Furthermore, when MOCA total score is taken into account the relationship between gait speed and MOCA Domain is affected (Research Question G). Those with Poor MOCA scores (<24) possibly recruit more varied cognitive processes during complex gait tasks. Those with

Intermediate MOCA scores (24/25) tend to have weaker MOCA Domain gait speed correlations which warrants further investigation. This is an interesting result and indicates that global cognition needs to be taken into account when designing motor-cognitive interventions. Future research should assess if interactions between poor performance in specific MOCA domains and global cognition categories hold longitudinally for those participants who transition into different global cognitive categories.

These results are in agreement with Study 4 that found that many elements of cognitive function contributed to complex gait tasks. Study 4 also found that dual gait tasks also recruit additional executive processes (Research Question D and Research Question A). This study adds to these findings by showing that each dual gait task requires an additional executive contribution specific to the dual task being performed. Namely, additional attentional contributions for carrying a glass of water while walking (dual motor gait task) and additional cognitive flexibility for reciting alternate letters while walking (dual cognitive gait task). This result suggests that these dual gait tasks have a certain amount of validity and clinical efficacy as the findings from this study indicate that they assess the specific elements of cognitive function that they are purported to assess. This study also found that cognitive contributions to gait speed differ across global cognition category in clinically utilised assessment tests. This result may be beneficial for design of interventions as the result suggests that individuals with different level of cognitive function or impairment should be allocated to different interventions.

To the authors knowledge analysis of MOCA contribution to gait performance has not been investigated before. The results from this study show that specific motor activities are associated with different MOCA subscores. Further research may allow clinical walking tasks to become more ecologically sound, highlighting deterioration in specific activities of daily living. These results indicate that there may be important information embedded within MOCA in addition to that which is included in the MOCA total score. Further research is needed to explore the effect of MOCA subscores, in particular those with an executive component, on MOCA total score during healthy ageing and pathology. Future research should focus on this MOCA group-domain relationship and its association with performance in complex gait tasks longitudinally to aid in highlighting markers for early mild cognitive impairment.

Further information is needed prior to assessing slow gait speed as a possible biomarker for Mild Cognitive Impairment (Research Question I)

Gait speed during any gait task was not found to be a biomarker for cognitive impairment as measured by a MOCA score under 24 or a diagnosis of memory impairment in Study 2. However, when removing age effects from both gait and cognitive measures, by employing both gait and cognitive zscores, poor gait speed was found to have better sensitivity to cognitive impairment. This suggests that age in particular has a large effect on gait performance.

As per Altman (1994) the predictive values of any test, here a gait speed test, in clinical practice depend critically on the prevalence of the disorder (mild cognitive impairment) in the participants being tested. When compared to values found in literature both gait and cognitive performance in the TILDA dataset suggest the population can be described as highly functioning. Without further diagnosis from neuroimaging and blood tests it is unclear whether all participants with a MOCA of under 26 are mildly cognitively impaired. A Mild Cognitive Impairment diagnosis requires an abnormal result on a neuropsychological assessment test in addition to markers of cognitive impairment. It may be that if the Mild Cognitive Impairment diagnosis was further defined that the gait assessment task would have gained a higher predictive value. Literature does state that gait speed may be a more general marker of health and gait parameters that have been associated with more specific elements of cognitive impairment such as gait variability may gain higher predictive values. Furthermore, correlations were only found between gait and cognitive function in this researchwhen covariates were adjusted for. Future studies should adjust for this along with other covariates. Age in particular has a large effect on gait performance.

In conclusion, gait speed during was not found to be a biomarker for mild cognitive impairment as measured by a MOCA score under 26 during any gait task in Study 2. Further research should include adjustment for covariates.

A measure of attention can be acquired during mild exercise (Research Question H)

Study 6 investigated if clinically useful electrophysiological measures of attention can be collected during ecologically valid experimental environments. Literature has reported that attention (as assessed with dual gait tasks or neuropsychological assessment test) plays a central role in the relationship between gait and cognitive function. Acquiring such neural activity non-invasively during normal daily activities would have far-reaching clinical benefits. However, neuroimaging restraints require neurophysiological recording to be taken only in extremely restrictive experimental environments. This requires participants to restrict movement which has meant that our understanding of the neural processes involved in complex physical movement and measurement of such processes are limited. Most studies employing direct neurophysiological recording have investigated non-human primates. However, some studies have shown neuroimaging of human movement to be possible with EEG signal acquisition during performance of very restrictive motor tasks in extremely controlled clinical environments.

Study 6 investigated if a measure of attention could be collected through EEG during simple and complex tasks. Partipants performed an auditory task while seated and during mild exercise performed on an exercise bicycle and a treadmill. Electrophysiological (EEG, EOG, EMG) recordings were taken for healthy young participants (n=7: seated task, cycling tasks, n=2: treadmill task) while presented with the auditory task, an auditory oddball task, which elicited a P300 event related potential. The amplitude and latency of the auditory P300 event related potential assessed attention where the reduction in amplitude or increase in latency has been shown to indicate cognitive decline or cognitive load.

Study 6 found that peak amplitude and component latency remained stable across all experimental conditions. P300 amplitude and latency also remained stable between experimental conditions for all electrode locations. For the Cz electrode position there were 0.2-2% P300 amplitude and 3-9% P300 latency differences. Study 6 also found that P300 latency did not vary significantly across the four experimental conditions. This is an encouraging result and shows the P300, a measure of attentional resources, can be recorded in non-clinical environments (while sitting, cycling and walking).

This is consistent with findings that performance of a cognitive task during a relatively simple motor task does not present a significant change in P300 latency in healthy young adults. This is also in agreement with Study 8 which found the relationship between gait and attention

remained unchanged across tasks in heathy young adults. This positive result opens up the possibility to quantitatively investigate the interaction between gait and attention during the ageing process but also in movement, gait and cognitive disorders in more ecological valid experimental environments, which would allow investigation of the effect of neurodegeneration on daily activities.

In this study we have shown that it is possible to quantitatively and precisely measure attention during controlled movements using EEG. This platform allows investigation of attentional cues in more ecologically valid environments thereby advancing neurological measurement systems. This may allow ambulatory EEG to be used to investigate the effect of changes in attention on performance of gait in studies on ageing and in neurological diseases [300].

Currently, EEG is being employed in other studies to investigate participants with Parkinson's disease who have gait disorders such as freezing of gait. Differences in the involvement of specific elements of cognitive function, attention in particular, during ecologically valid experimental environments is of interest in those with Parkinson's disease who experience freezing of gait and those who do not freeze. Further research in this area could highlight that training employing complex motor-cognitive tasks may increase executive function abilities. This may allow interventions to be designed to target key elements of cognitive function which affect gait and may reduce the occurrence of gait disorder episodes such as freezing of gait.

Future research should focus on improving technology and analysis methods to allow recording of accurate quantitative neural measures or processes during substantial movement. Full ambulatory monitoring that would allow simultaneous recording of gait and cognitive function quantitatively and precisely in more ecological environments, such as in participant's homes, would be highly beneficial. Investigation of the P300 ERP, using new active EEG technology, show that new opportunities to probe cognitive function during real life tasks are being created. Future research should focus on increasing participant numbers, increasing experimental trials per participant to gain more accurate and statistically significant results and investigating different tasks to explore more cognitive sub-domains.

Recording of attentional resources in non-clinical environments has been shown to be possible in Study 6. This opens up the possibility of investigating the link between gait and

attention and changes in attention by recording attentional resources through electrophysiological parameters such as the P300 component during motion for patients with gait and movement disorders.

There is a clinical advantage to investigating independent result outcomes to account for cognitive contributions to gait performance (Research Question J)

There is a clinical advantage to the methods employed in the study 4 and Study 5 which show relative cognitive contributions to gait performance. This method is not always employed in literature possibly due to the constraint of the complex regression analysis needed which requires large participant numbers. However, it has allowed the examination of the relative contribution of cognitive function to gait performance within the studies described in this thesis. Furthermore, employing this type of method may have stronger clinical relevance as it allows for an independent comparison of the neuropsychological assessment test employed to assess cognitive function. Results of this nature give a broad understanding of the major contributions to gait performance and what affect this has in relation to covariates also. The ability to compare both (i) the tasks to be included in cognitive-motor interventions, and (ii) the utility of different neuropsychological assessment tests to assess different cognitive groups, are two clinically relevant outcomes.

When examining cohorts of older adults it is wise to adjust for covariates instead of excluding those with pathology or impairment (Research Question K)

Study 2 investigated the utility of gait speed as a biomarker for cognitive impairment by employing zscore measures with an age adjustment. Throughout the studies undertaken in this thesis age was found to be the largest significant contribution to the relationship between gait and cognitive function. However, age, motor performance and cognitive performance have complex interactions and results from Study 2 highlights the difficulty of removing age effects in analysis and not excluding all other effects.

In order to calculate an appropriate zscore a healthy cohort had to be generated. This process was not as fruitful as anticipated due to a "healthy" cohort being exceptionally difficult to define and categorise in a population of older adults. Study 2 found that any gait-cognitive

effects were removed after adjusting for age using age adjusted zscores and so Study 2 concluded that age is too strong a covariate to adjust out of in this population. Therefore it is more appropriate to adjust within a regression model where all participants are included and their specific characteristics are adjusted for. The analysis undertaken in Study 4 has also highlighted the main characteristics and comorbidities that affect gait and cognitive function. This finding was of particular benefit to other regression models included in other studies within this thesis and elsewhere.

The utility of Poincare method for analysis in gait research (Research Question F).

Gait variability was examined with a view to gaining an insight into the timing aspects of motor control where we hypothesised that control of central temporal gait-cognitive behaviour may be localised to the basal ganglia. Poincare measures were employed to describe gait variability as it is thought that they have a physiological basis. Study 8 found the novel measures of gait variability, SD1 and SD2, to be at least comparable with standard gait variability measures in young healthy females. It was suggested that the Poincare measures may represent a more descriptive measure in select populations or in other tasks. Using such analysis in future research may highlight intrinsic neurological disruption seen episodically or continuously through gait, thus enhancing our understanding of the higher neurological control of gait, in addition to any higher control at play during compensatory strategies or adaptations in gait.

The results from Study 8 open up the possibility of quantitatively investigating stride time variability using the Poincare method. Fundamental research questions have arisen out of the studies described in this thesis.Firstly, is the relationship between gait and sustained attention due to common neural processes in both the gait task and the attention task separately or a specific recruitment of attentional resources for gait? Secondly, and similarly posed by other studies, can differences found in gait such as higher gait variability be seen as an automatic adaptation in those participants with lower attentional capacity? The cumulative results from Study 6, Study 7 and Study 8 are encouraging but highlight the need for further discussion on these research questions. However, results from Study 8 do suggest that there is a benefit to examining correlations between gait and attention measures in young healthy adults.

Specifically, correlations between direct and quantitative gait and attention measures, such as those extracted from continuous gait data and continuous cognitive data, have been found to hold promise. We hypothesise that stride time variability has exact physiological, and more specifically neurological, correlates steming indirectly from higher basal ganglia timing control. We also hypothesise that the Poincare long term variability measure is best placed to describe this physiological correlation. In particular, the Poincare method has historical validity in cardiology research and includes variations both short and long term variability over a complete trial. Future studies should investigate the correlation between variations in performance in gait variability recorded over a long walk and sustained attention recorded over a similarly long Sustained Attention to Response Task. In addition, employing the same measure (such as the Poincare long term variability measure) calculated in the same manner, to describe variations in stride time and sustained attention would eliminate any data interpretation problems as found in Study 5 (difficulties when employing many different measures, recorded over very diverse tasks and differing protocols). This would allow further exploration of any relationship between real life attentional measures (endogenous attention, lapses in attention) and temporal gait parameters variations over time. We hypothesise that the temporal gait variability measures will correlate with the sustained attention measures (response time variation: a temporal measure also). We further hypothesise that this would indicate that variations in times of events in the motor cortices and cortices involved in sustained attention are correlated. This would be in agreement with results from Study 5 which found processing speed a major contributor to gait performance. However, it would indicate a central control of timing in both motor and cognitive processes. This leads to final hypothesis that the correlation of these timing of events within this broad cortical network suggests a sub-cortical control. In addition, exploring these hypothesises would highlight which dual task theory is at play during simple and complex tasks: multiple resource, bottle-neck or central resource.

10.3. Limitations of this Research

Multiple linear regression is thought to be a powerful tool for statistically modeling a response, however previous literature has detailed the limitations of the linear regression method employed in this research [307-310]. Similarly to alternative statistical methods, in

order to have confidence in statistical outcomes from linear regression experiments are required to be designed in a planned controlled manner, distribution of resultant data is required to be checked for errors and assumptions of specific methods need to be verified. Neglecting to probe the data for potential errors could result in statistical outcomes being misleading or incorrect inferences being drawn These general limitations of statistical methods were minimised in the studies described in this thesis due to the extensive planning of the TILDA study design [233-235, 311, 312]. Thisallowed for a controlled assessment environment in as much as is possible in an observational study Each assessment was designed by a cross-disciplinary team of experts including statisticians, gerontologists, psychiatrists, nurses, economists, bioengineers, neuroscientists, kinematic experts among others which, in addition to the representative nature of the large dataset, allowed for the experimental protocol to probe relevant clinical questions and instilled confidence in resultant data. In addition, considerable data-mining was undertaken to check for errors (experimental, calculation, typographical etc.) in the data collected.

One of the main limitations of the regression approach when employing data from an observational study, such as the TILDA study, is that a statistical significant relationship between a response and a predictor variable does not imply a cause-and-effect relationship[309], but means that the predictor contributes information for the prediction of the response. Regression diagnostics are also required to verify that the data meet the normality, homoscedasticity, linearity and independence assumptions[313]. Furthermore, it is imperative to correctly specify the statistical model (variables of most interest included/redundant variables excluded) for resultant outcomes to be meaningful and expert knowledge of the research area is required for correct interpretation of results[307]. Care is also needed in order to rule out other possible reasons for significant gait-cognitive function correlations, such as education or cardiovascular effects. When employing a regression approach the statistical significance of any variable is greatly affected by its range[307] so examination of the influence of outliers and variable distributions to find any errors in variables is required. Multicolinearity, correlation of predictor variables, is also an issue in regression as it increases the likelihood of rounding errors in calculation of result and can cause misleading significance values.

In the research described in this thesis any limitations of the linear regression approach was minimised by a thorough examination of the dataset prior to analysis with particular emphasis on meeting regression assumptions. A journal paper was published [314], see appendix 5 and study 4, which details the methods employed including: a formal method of detecting multicolinearity, variance inflation factor and a step-wise regression approach which exposed redundant variables and variables of most interest. Gait and cognitive function covariates, highlighted in literature and through analysis of the TILDA dataset, were included in this step-wise regression. Difference measures were examined, such as dual task effect, which standardised results and allowed for any significant difference to be likely due to real effects, the effect of the addition of a task while walking for example.

Taking into account these limitations a multiple variate regression approach was chosen to be employed in this research for its flexibility when examining effect of covariates and its superior post analysis functionality. In the author's opinion this functionality and flexibility allowed for a greater exploration of the gait-cognitive function relationship than other statistical methods would have allowed. Future research could explore other methods, such as poisson regression and mixed effect[160], on this dataset longitudinally to explore the validity of the hypotheses and predictions outlined in this thesis. However, in order to definitively prove any cause-and-effect a randomised controlled trial designed experiment would need to be undertaken..

Another statistical approach, such as a repeated measures method[309], could have been chosen to examine this gait-cognitive function relationship. This type of analysis would have allowed differences in gait performance in the population (dependent variable) to be assessed cumulatively during the three gait tasks (three related groups). Methods such as analysis of variance (ANOVA), analysis of covariance (ANCOVA) or mixed regression with repeated measures are alternative approaches that could have been employed on the dataset cross-sectionally. In repeated measures methods all sources of variance between participants are excluded from the experimental error and the only variance that exists is the within participant variance[308]. However, many of the assumptions that apply to linear regression also apply to these repeated measures methods: normality, homoscedasticity, independence[315] and interference such as order effect also affects results. Future studies

should validate the result of this research and further explore the research questions outlined in this thesis employing these methods.

Interactions between age and specific elements of cognitive function were examined in Study 4 employing a bilinear interaction term (cross-product term) within the regression analysis. However, future studies should explore gait-cognitive function interactions, in addition to interactions between gait measure and between cognitive function measures employing alternative interaction methods such as analysis of variance interaction models.

Certain experimental limitations may also exist in this research. Counterbalancing was employed in Study 7 and Study 8, however counterbalancing was not employed during the gait or cognitive assessments in TILDA (Study 1 to Study 5) where all gait tasks were performed in the same order: single gait task, dual motor gait task, dual cognitive gait task Counterbalancing has been shown to reduce order effects[316], such as boredom, fatigue and practice effects[317]. It was thought that a counterbalancing approach would not be appropriate in the gait assessment in the TILDA study as the single gait task would need to be explained and performed before the more complex dual gait tasks were performed. It was also decided that there would not be counterbalancing between the two dual gait tasks and this may be a limitation of the TILDA protocol. Results from Study 1 to Study 5 which employed the TILDA dataset show a large difference in gait speed between the dual gait tasks. Participants walked statistically significantly faster ($p<0.05$) during the dual motor task (performed second) when compared with the dual cognitive task (performed last). We can assume that any practice effect that may have existed would have increased performance in the dual cognitive gait task (faster gait speed) and if counterbalancing had been employed this gait speed difference between dual tasks would have been even greater. We can also assume that there would not have been a boredom effect given that the dual tasks were designed to be complex and participants were allowed to adjust their pace to their capacity ("self-selected pace"). Any fatigue effects were minimised with regular breaks for participants as per literature[318].A further experimental limitationsthat exists in this research is that study 1 to study 5 which employed the TILDA dataset did not include a single cognitive task such as reciting alternate letters of the alphabet task while seated. Measures acquired during the single cognitive task such as number of letters recited and letter errors would give a measure of baseline cognitive performance. Inclusion of such a measure would allow for a more

comprehensive interpretation of dual task effect and would allow for the exploration of priority of task. A possible measure that could be derived employing this single cognitive measure is a composite cognitive dual task performance score (cognitive task errors plus gait performance). Future studies should include a measure to assess baseline performance in both single cognitive and single gait tasks, in addition to dual gait task measures. This may isolate the presence or absence of strategies participants use and priorities they may have.

10.3. Future Application and Directions

Study 7 described results gained from gait variability analysis as measured using a pressure sensing mat. Future studies would gain from acquisition of continuous gait data over a longer time such as in Study 8. This could be achieved by employing different equipment or an alternative experimental set-up. A longer pressure sensing mat, accelerometry or gyroscopes could measure gait data over a longer period of time. In addition, changing the experimental set up to adjust the gait protocol to a continuous walk for instance around the perimeter of a room which could including several passes of a pressure sensing mat positioned at one or two points along the walk. The continuous walk would allow gait variability values to be obtained over the entire trial. This would allow more complex mathematical analysis to be undertaken such as in Study 8 which employed the CODAmotion system to record healthy young females during a treadmill walk but without the limitations of constant speed. Measuring continuous gait data does have substantial benefits in particular in home monitoring to assess performance in everyday activities and any changes during advsere events.

Furthermore, this thesis suggests that correlations between continuous gait data and continuous cognitive function data would be an interesting area to focus on in future research. Cognitive function may be recorded directly through acquisition of neural signals employing electroencephalography, magnetic resonance imaging and near infrared spectroscopy among others. Further research is needed to assess the benefit and limitations of each system to acquiring specific elements of cognitive function that pertain to gait. Furthermore, there are still limitations to recording gait and cognitive function simultaneously due to movement artefact and environmental contamination. However, recording of long streams of continuous gait and cognitive function data separately may aid in finding

correlations between any arrthymias in the gait or cognitive function data. This may inform neurological disease in addition to increasing our understanding of links between motor and cognitive processes. Increased knowledge of the links between motor and cognitive processes may highlight our understanding of which dual tasking theories (multiple resources, bottleneck etc) are at play, in addition to increase our understanding of transitions from automaticity.

Study 2 through Study 8 of this thesis explored correlations between gait and neuropsychological assessment tests. Some neuroimaging studies have investigated and hypothesized on the neural correlates of some of the neuropsychological assessment tests employed in the studies described in this thesis. Many of the neuropsychological assessment tests employed in this thesis are gold standard clinical assessment tests employed in disease diagnoses. However, it would be beneficial if there were further neuroimaging evidence of the specific neural correlates of each neuropsychological assessment tests. This would allow more accurate understanding of the anatomical and functional processes involved in each element of cognitive function which are assessed in each neuropsychological assessment test. This would allow further understanding of the explicit function of specific brain regions and behavioural manifestations. In addition, our understanding of the interactions between brain region, function and behaviour may be heightened. This initially could be explored during health and then with impairments. In particular, this would add to the many highly informative studies employing neuropsychological assessment tests already carried out and allow a definitive conclusions be drawn on the executive pre-frontal lobe involvement in gait.

Study 1 through to Study 5 and Study 7 investigated the TILDA dataset. Inclusion of an intervention within this longitudinal study with pre and post assessments would be highly beneficial. In particular, exploring the effect of cognitive and motor training on the TILDA participants may expose evidence of a possible bi-directional link between gait and cognitive function during health. The intervention could be in the form of a single motor or cognitive task or a dual task. In particular, employing simple dual motor cognitive tasks utilizing extremely controlled experimental conditions to probe exacting research questions based on changes to specific elements of cognitive function (sustained attention, divided attention, cognitive flexibility) would be very informative. In addition an altered version of the TILDA motor and cognitive dual gait task paradigms could be performed using treadmill and a virtual

reality system to allow acquisition of electrophysiological signals through a high density electroencephalography system as per Gwin et al[185]. To increase the ecological validity of the experiment and to meet requirement of the original TILDA protocol the treadmill could be multi-directional and have feedback from body worn sensors to allow the participant's gait speed be self selected. In addition, the virtual reality screen could span to the participants peripheral visual field and objects on the screen could adjust to the dynamics of the participant to allow for null optical expansion. This would be particularly important as Brown et al [319-321] have found that the multi-sensory information that a participant collects, such as visual cues, informs and adapts dynamics such as reducing gait speed. In addition, literature has shown the type of stimuli employed during virtual reality to have differing effects on motor planning. Stimuli within virtual reality can be employed to act as targets to participants during motor planning in the stride leading up to the object. Participants can perceive these stimuli as repellents or attractors further adapting gait from its ecological or usual state. Visual cues such as these can also be adjusted themselves or in relation to other objects. This may be an interesting way to create more ecologically valid experimental environments such as are experienced at home with stationary or moving obstacles and with tasks that are pre-planned or those requiring immediate action. This may increase our knowledge of reasons for adverse events such as falls in addition to the changes that occur in performance leading up to events.

In addition to the above, certain direct research questions arise from this thesis and warrant exploration in future studies. In particular, the relationship between executive function and gait performance is possibly the most studied relationship in the gait and cognitive function research area. It is my opinion that a critical point has been reached and a further collective effort may aid in unravelling this relationship. One study that could be undertaken arising out of the findings of the studies described in this thesis could probe the longitudinal relationship between those with poor executive function, slow gait speed and high gait variability to assess whether this may be a target group for intervention. All elements of executive function could be examined utilizing many measures such as a broad spectrum of neuropsychological assessment tests (such as color trails test, verbal fluency) and computerized assessment tests (such as SART, finger tapping). Gait measures could be assessed with a broad array of equipment. Results gained from investigating the relationship between poor executive

function, slow gait speed and high gait variability in a large cohort of older adults would draw a line under this area of research.

Other possible more general studies or research areas which would be of benefit to undertake are the investigation of (i) direct and indirect links between gait and cognitive function, (ii) characterisitcs of gait variations during stressful situations (iii) links between behavioural and neuroimaging studies. Literature has found that varying task focus seems to elicit more significant changes in dual task intervention[203]. This result highlights again the possible direct link between motor and cognitive function processes during movement. Future research may gain from the mapping of direct and indirect linkages between gait and cognitive function. This would allow a comparison of data already generated. In addition, a review of anatomical areas of interest in neuroimaging studies or found to be of interest for a particular pathology (Mild Cognitive Impairment, Alzheimer's Disease or Parkinson's Disease) would be of benefit. This may allow dual task paradigms to be designed to explicitly focus on these specific neurological region.

Recent studies have started to probe the influence of cognition on movement disorders. Current research is investigating participants with Parkinson's Disease who have freezing of gait employing EEG and virtual reality environments. Gait and cognitive differences such as processing of information, performance on specific elements of cognitive function and multi-sensory integration are all emerging areas of interest in those who freeze. In addition, intervention efficiacy is also being examined. Current research is questioning whether interventions which employ complex tasks have greater improvements in cognitive flexibility and reduce freezing episodes. Alternatively, is another specific element of cognitive function being trained which may be improving performance? Findings from this research could highlight complex motor-cognitive tasks which increase cognitive and gait performance that may reduce the occurrence of gait disorder episodes such as freezing of gait. Findings from this research have been accepted for the Irish Institute of Clinical Neuroscience Registrar's prize in Cinical Neuroscience.

10.3. Conclusions

In conclusion, cognitive function and gait have been shown to be measures of interest when examining healthy older adults, however their relationship and the neural mechanisms at play are not clear and much research is needed to gain definitive knowledge. Findings from the body of described this thesis reveal a complex relationship between gait and cognitive function with many cognitive contributions required during complex gait tasks. However, this relationship is dependent on the gait task performed, global cognitive ability and the age of the participant. In addition, results are affected by the measures employed and included in analysis. One particular important finding is that participants recruit additional executive function processes during more complex gait tasks. Future research in this area should probe the possible neural processes involved in gait, through novel experimental procedures such as ambulatory EEG. Further knowledge of gait and cognitive performance in younger and older healthy populations are needed prior to gaining accurate results on any transitions to impairment. Various measures need to be investigated in order to understand the relationship between gait and cognitive function as poorer performance can be manifested in many ways: gait speed reduction, dual task effect increases, difference in temporal measures of gait, cognitive or neurological function.

Appendices

Appendix 1: Diagnostic Criteria for Mild Cognitive Impairment and Dementia

Table 20: Diagnostic Criteria, The Diagnostic and Statistical Manual for Mental Disorders – DSM5 [63]

I.	**Mild and Major Neurocognitive Disorders**
	Major Neurocognitive Disorder
	A. Evidence of <u>significant</u> cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor or social cognition) based on: 1. Concern of the individual, a knowledgable informant, or the clinican that there has been a significant decline in cognitive function; and 2. A <u>substantial</u> impairment in cognitive performance, preferably <u>in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).</u> B. The cognitive deficits <u>interfere</u> with <u>independence in everyday activities</u> (ie., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications). C. The cognitive deficits do not occur exclusively in the context of delirium. D. The cognitive deficits are not better explained by another mental disorders (e.g., major depressive disorder, schizophrenia).
	Mild Neurocognitive Disorder
	A. Evidence of <u>modest</u> cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor or social cognition) based on: 1. Concern of the individual, a knowledgable informant, or the clinican that there has been a significant decline in cognitive function; and 2. A <u>modest</u> impairment in cognitive performance, preferably

	documented by standardised neuropsychological testing or, in its ansense, another qualified clinical assessment. B. The cognitive deficits do not interfere with capacity for independence in everyday activities (ie., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required). C. The cognitive deficits do not occur exclusively in the context of delirium. D. The cognitive deficits are not better explained by another mental disorders (e.g., major depressive disorder, schizophrenia).
	Note: For Both Major and Mild Neurocognitive Disorder specify whether due to: **Alzheimer's disease, Frontotemporal lobar degeneration, Lewy body disease, Vascular disease, Traumatic brain injury, Substance/medication use, HIV Infection, Prion disease, Parkinson's disease, Another medical condition, multiple etiologies, Unspecifies** and specify: Either **Without behavioural disturbance** (If the cognitive disturbance is not accompanied by any clinically significant behavioural disturbance) or **With behavioural disturbance (specify disturbance) (**If the cognitive disturbance is accompanied by a clinically significant behavioural distrubance (e.g., psychotic symptoms, mood disturbance, agitation, apathy, or other behavioural symptoms)). For Major Neurocognitive Disorder Only specify current severity: **Mild** (Difficulties with instrumental activities of daily living (e.g., housework, managing money)), **Moderate** (Difficulties with basic activities of faily living (e.g., feeding, dressing), **Severe** (Fully dependent).
II.	**Mild and Major Neurocognitive Disorders Due to Alzheimer's Disease**
	A. The criteria are met for major or mild neurocognitive disorder B. There is insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired). C. Criteria are met for either probable or possible Alzheimer's Disease as follows: **For major neurocognitive disorder:** **Probable Alzheimer's disease** is diagnosed if either of the following is present; otherwise, **possible Alzheimer's disease** should be diagnosed.

	1. Evidence of a causative Alzheimer's disease genetic mutation from family history or genetic testing. 2. All three of the following are present: a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing). b. Steadily progressive, gradual decline in cognitive function, without extended plateaus. c. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline). **For mild neurocognitive disorder:** **Probable Alzheimer's disease** is diagnosed if there is evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history. **Possible Alzheimer's disease** is diagnosed if there is no evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history, and all three of the following are present: 1. Clear evidence of decline in memory and learning. 2. Steadily progressive, gradual decline in cognitive function, without extended plateaus. 3. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline). D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.
VII.	**Mild and Major Neurocognitive Disorder due to Parkinson's Disease**
	A. The criteria are met for major or mild neurocognitive disorder B. The disturbance occurs in the setting of established Parkinson's disease. C. There is insidious onset and gradual progression of impairment.

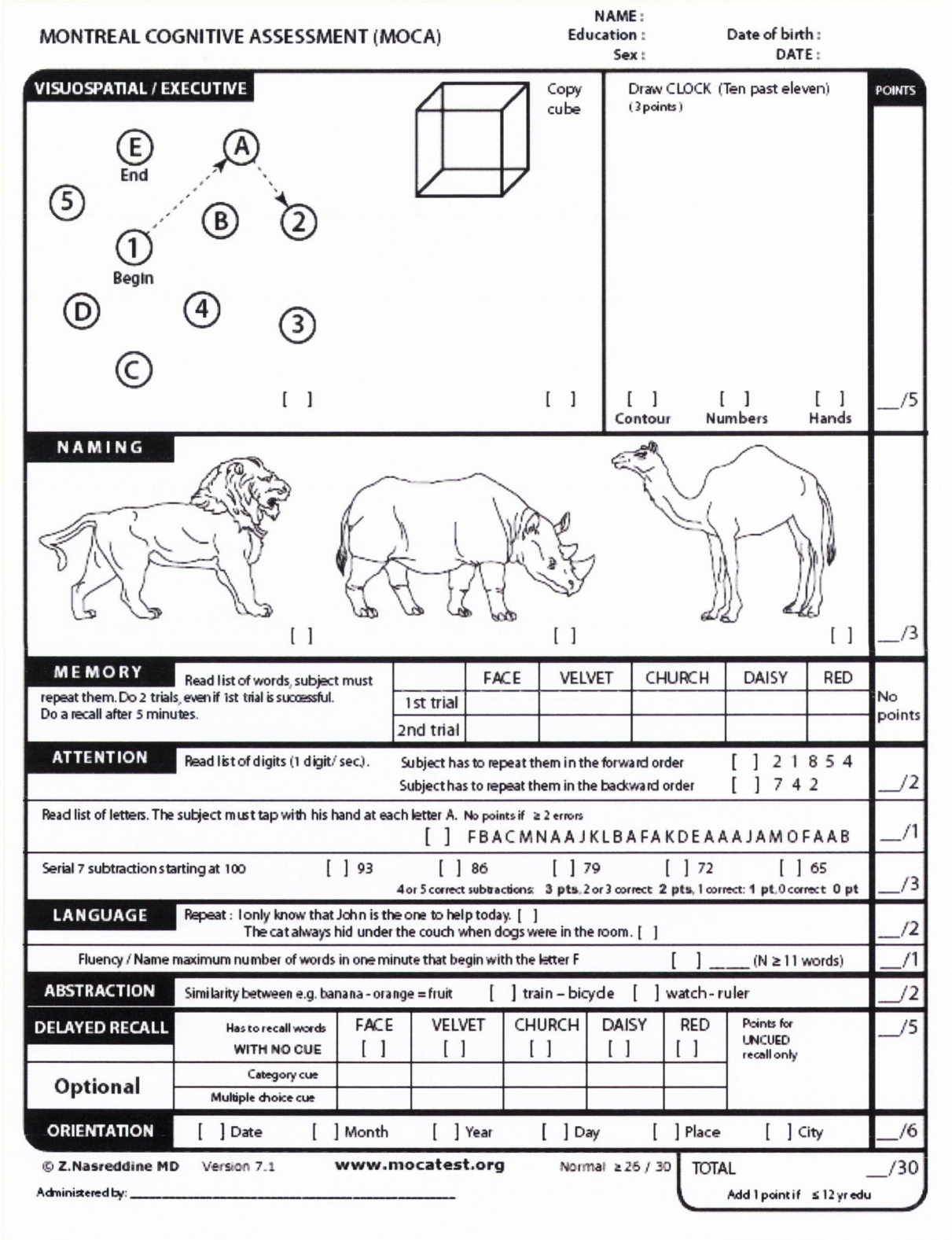
	D. The neurocognitive disorder is not attributed to another medical condition and i snot better explained by another mental disorder. **Major or mild neurocognitive disorder probably due to Parkinson's disease** should be diagnosed if 1 and 2 are both met. **Major or mild neurocognitive disorder possibly due to Parkinson's disease** should be diagnosed if 1 or 2 is met: 1. There is no evidenece of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline). 2. The Parkinson's disease clearly precedes the onset of the neurocognitive disorder.
V.	**Mild and Major Vascular Neurocognitive Disorder**
	A. The criteria are met for major or mild neurocognitive disorder B. The clinical features are consistent with a vascular etiology, as suggested by either of the following: 1. Onset of the cognitive deficits is temporally related to one or more cerebrovascular events. 2. Evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function. C. There is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for th eneurocognitive deficits. D. The symptoms are not better explained by another brain disease or systemic disorder. **Probable vascular neurocognitive disorder** is diagnosed if one of the following is present; otherwise **possible vascular neurocognitive disorder should be diagnosed.** 1. Clinical criteria are supported by neuroimaging evidence of significaqnt parenchymal injury attributed to cerebrovascular disease (neuroimaging-supported). 2. The neurocognitive syndrome is temporally related to one or more

	documented cerebrovascular events. 3. Both clinical and genetic (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) evidence of cerebrovascular disease is present. P**ossible vascular neurocognitive disorder** is diagnosed if the clinical criteria are met but neuroimaging is not available and the temporal relationship of the neurocognitive syndrome with one or more cerebrovascular events is not established.
IV.	**Mild and Major Neurocognitive Disorder with Lewy Bodies**
	A. The criteria are met for major or mild neurocognitive disorder B. The disorder has insidious onset and gradual progression. C. The disorder meets a combination of core diagnostic features and suggestive diagnostic features for either probable or possible neurocognitive disorder with Lewy bodies. **For probable major or mild neurocognitive disorder with lewy bodies**, the individual has two core features, or one suggestive feature with one or more core features. **For possible major or mild neurocognitive disorder with lewy bodies,** the individual has only one core feature, or one or more suggestive features. 1. Core diagnostic features: a. Fluctuating cognitive function with pronounced variations in attention and alertness. b. Recurrent visual halucinations that are well formed and detailed. c. Spontaneous features of parkinsonism, with onset subsequent to the development of cognitive decline. 2. Suggestive diagnostic features: a. Meets criteria for rapid eye movement sleep behaviour disorder. b. Severe neuroleptic sensitivity. **D.** The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental,

	neurological, or systemic disorder.
III.	**Mild and Major Frontotemporal Neurocognitive Disorder**
	A. The criteria are met for major or mild neurocognitive disorder B. The disturbance has insidious onset and gradual progression. C. Either (1) or (2): 1. Behavioural variant: a. Three or more of the following behavioural symptoms: i. Behavioural disinhibition ii. Apathy or inertia iii. Loss of sympathy or empathy iv. Perserverative, stereotyped or compulsice/ritualistic behaviour. v. Hyperorality and dietary changes. b. Prominent decline in social cognitive function and/or executive abilities. 2. Language variant: a. Prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension. D. Relative sparing of learning and memory and perceptual-motor function. E. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological or systemic disorder. **Probable frontotemporal neurocognitive disorder** is diagnosed if either of the following is present; otherwise **possible frontotemporal neurocognitive disorder** should be diagnosed. B. Evidence of a causative frontotemporal neurocognitive disorder genetic mutation, from either genetic testing or family history. C. Evidence of disproportionate frontal and/or temporal lobe involvement from neuroimaging. **Possible frontotemporal neurocognitive disorder** is diagnosed if there is no

	evidence of a genetic mutation, and neuroimaging has not been performed.
VII.	**Mild and Major Neurocognitive Disorder due to Another Medical Condition**
	A. The criteria are met for major or mild neurocognitive disorder. B. There is evidence from the history, physical examination, or laboratory findings that the neurocognitive disorder is the pathophysiological consequence of another medical condition. C. The cognitive deficits are not better explained by another mental disorder or another specific nerocognitive disorder (e.g., Alzheimer's disease, HIV infection).
IX.	**Mild and Major Neurocognitive Disorder due to Multiple Etiologies**
	A. The criteria are met for major or mild neurocognitive disorder. B. There is evidence from the history, physical examination, or laboratory findings that the neurocognitive disorder is the pathophysiological consequence ofmore than one etiological process, excluding substances (e.g., neurocognitive disorder due to Alzheimer's disease with subsequent development of vascular neurocognitive disorder). C. The cognitive deficits are not better explained by another mental disorder and do not occur exclusively during the course of a delirium.
X	**Unspecified Neurocognitive Disorder**
	This category applies to presentations in which symptoms characteristic of a neurocognitive disorder tht cause clinically significant distress or impairment in social, occupational, or other important areas of fucntionaing predominate but do not meet the full criteria for any of the disorders in the neurocognitive disorder diagnostic class. The unspecified neurocognitive disorder category is ued in situations in which th eprecise etiology cannot be determined with sufficient certainty to make an etiological attribution.
	Note this table excludes the following Mild and Major Neurocognitive Disorders: Mild and Major Neurocognitive Disorder due to Traumatic Brain Injury, Prion Disease, Huntington's Disease, HIV Infection and Substance/Medication-Induced Mild and Major Neurocognitive Disorder.

Appendix2: The Montreal Cognitive Assessment (MOCA)



MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube

[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: 3 pts, 2 or 3 correct 2 pts, 1 correct: 1 pt, 0 correct 0 pt

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

© Z.Nasreddine MD Version 7.1 www.mocatest.org Normal ≥ 26 / 30

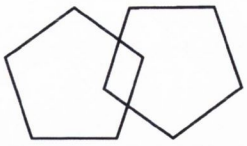
TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Screening Tool: The Mini-Mental State Examination (MMSE)

Patient _____ Examiner _____ Date _____

Maximum	*Score*	
		Orientation
5		• What is the (year) (season) (date) (day) (month)?
5		• Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3		• Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat until he/she learns all 3. Count trials and record. Trials _____
		Attention and Calculation
5		• Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
		Recall
3		• Ask for the 3 objects repeated above. Give 1 point for each correct answer.
		Language
2		• Name a pencil and watch.
1		• Repeat the following "No ifs, ands or buts."
3		• Follow a 3-stage command: "Take a paper in your hand, fold it in half and put it on the floor."
1		• Read and obey the following CLOSE YOUR EYES.
1		• Write a sentence.
1		• Copy the design shown. 

_____ **Total Score**

ASSESS level of consciousness along a continuum _____

Alert Drowsy Stupor Coma

"Mini-Mental State." A Practical Method for Grading the Cognitive State of Patients for the Clinician. *Journal of Psychiatric Research*, 12(3): 189-198, 1975. Used with permission.

more information on reverse

Appendix 4: Generation of a Healthy Cohort in the TILDA dataset

Introduction

This study aimed to generate a healthy cohort within the TILDA population. This healthy cohort was defined as those participants not affected by previously diagnosed disease, disorders or impairments which have been found to affect gait and cognitive function. We hypothesised that executive function would be greater in those within this healthy cohort when compared with the TILDA population.

Methods

Particiant characteristics in the TILDA dataset were examined and categorised into those arising from General, Central or Peripheral processes. These participant characteristics were collected during the computer aided personal interview (CAPI) by participants responding to the question "Has a doctor ever told you that you have?" when asked about: chronic diseases, parkinson's disease, arthritis, osteoporosis, as well as those who self reported their health, activities difficulties, number of falls in the past year, poor vision, chronic pain, walking aid use, hip or wrist fracture and hip or knee pain. Frailty was was defined by having three or more of low gait speed, low grip strength, unintentional weight loss, self-reported exhaustion, and low physical activity. Disturbed walking was assessed by a trained nurse during the TILDA gait assessment for both dual gait tasks (motor and cognitive). In order to generate a healthy cohort univariate linear regression was employed to investigate assocations between participant characteristics and gait speed during the single gait task as per Table 16.

A variable was derived called Healthy Participants. Healthy Participants was generated by excluding those participants who had characteristics that were found to be statistically significantly associated with gait speed during the single gait task.

Results

Table 16 shows that many participant characteristics were found to be statisticaly significantly associated to gait speed during the single gait task. This resulted in only 147 participants being classified as healthy and included in the Healthy Participants cohort as per Table 17.

The age range of the Healthy Participants cohort was observed to be younger than the age range for the total population (51-79 years (age range), 69 years (90^{th} percentile)). However, executive function was not observed to be greater in this cohort based on the number of participants in each executive function (ΔCTT) tertiles and percentiles (n = 58 (Tertile 1), 44 (Tertile 2), 45 (Tertile 3), ΔCTT[s] (percentile): 24.38 (10%), 30.62(25%), 47.38 (50%), 62.47(75%), 79.28 (90%)).

Table 21: Associations between Participant Characteristics and Gait Speed during the Single Gait Task (n=4661[28], significance level set to p=0.05)

Characteristic			**Significant P value**
General	**Self Rated Health**	Excellent/Very Good (2757)	-
		Good (1372),	Yes
		Fair/Poor (526)	Yes
	IADL[29]	0 (4474)	-
		1 (133)	Yes
		2 (34)	Yes
		3 (11)	Yes
		4 (4)	Yes
		5 (1)	omitted
		6 (4)	Yes
	Chronic Disease	0 (1057)	-
		1(1343)	Yes
		2(1087)	Yes
		3+ (1174)	Yes
	Number of Falls[30]	0 (3734)	-

[28] Those with no missing gait or executive function data
[29] IADL = Independent Activities of Daily Living

		1 (608)	No
		2+ (317)	Yes
Central	**Parkinson's Disease (PD)**	No PD	-
		PD	Yes
	Self Rated Vision	Excellent (985)	-
		Very Good (1781)	Yes
		Good (1533)	Yes
		Fair (317)	Yes
		Poor or less (45)	Yes
Peripheral	**Arthritis (AR)**	No AR (3384)	-
		AR (1277)	Yes
	Osteoporosis (OS)	No OS (4184)	-
		OS (477)	No
	Chronic Pain	No pain (2985)	-
		Mild (505)	Yes
		Moderate (815)	Yes
		Severe (352)	Yes
	Disability	No activity difficulties (4255)	_
		IADL only (100)	Yes
		ADL only (219)	Yes
		IADL + ADL (87)	Yes
	Frailty	Not Frail (3272)	-
		Prefrail (1227)	Yes
		Frail (64)	Yes
	Walking Aid Use	Yes (24)	-
		No (4637)	Yes
	Disturbed Walk Motor[31]	Yes (1)	-
		No (5648)	No
	Disturbed Walk Cognitive[32]	Yes (68)	-
		No (4593)	Yes
	Hip Fracture	Yes (118)	-
		No (4542)	No
	Knee Pain	Yes (77)	-
		No (4584)	Yes
	Hip Pain	Yes (138)	-
		No (4523)	Yes

[30] Number of falls in the past year
[31] Disturbed Walk in the Motor Gait Task
[32] Disturbed walk in the cognitive gait task

Table 22: Generation of the Healthy Participants cohort. Participant Characteristic found to be statistically significantly associated with gait speed as per Table 16 and number of participants left in the population after excluding for this characteristic.

Characteristic to Exclude		**After Exclusion (n)**
Total Before Exclusion		**4661**
General	Self rated health less than excellent	2757
	Any IADL impairments	2715
	Any Chronic Diseases	805
	More than 2 falls in the past year	676
Central	Parkinson's Disease	676
	Self Rated Vision less than excellent	201
	Arthritis	201
Peripheral	Chronic Pain	169
	Any Disability	169
	Frail	148
	Use Walking Aid	148
	Disturbed Gait[33] (Motor)	148
	Disturbed [3] (Cognitive)	148
	Hip Fracture	148
	Knee Pain	148
	Hip Pain	147
Healthy Participants (Total After Exclusion)		**147**

[33] Disturbed Gait: Gait during any gait task which included distrubances such as pauses, short steps and stepping backwards.

Discussion

Executive function, as measured by ΔCTT, was not observed to differ for those with healthy gait and cognitive function compared with the general population. Literature suggests that the methods employed in this study have skewed results and removed the likelihood of a cognitive and a gait impairment occurring simultaneously.

Table 23: Possible Events: Participants with no impairments (gait or cognitive), both impairments, a cognitive impairment only and a gait impairment only.

No Gait Impairment **No Cognitive Impairment**	**Cognitive Impairment Only**
Gait Impairment Only	**Cognitive AND Gait Impairment**

As per the Berkson Paradox [322] the methods employed in this study have inflated the conditional probability of cognitive impairment occurring, given that it or gait impairment occurs. The methods employed in this study have excluded cases where neither cognitive impairment or gait impairment occur which has allowed the conditional probability to be higher than the unconditional probability. That is by selectively excluding those with gait impairments, the subset of interest (those with cognitive and gait impairments) have also been excluded.

This leads to the conclusion that many factors affect gait speed during the single gait task and that these should be adjusted for in order to gain a true indication of the affect of cognition on gait. However, future studies should adjust for these covariates instead of excluding partipants who experience them. Adjusting for these covariates, such as through regression analysis, will allow a greater number of participants to be included in analysis as only those with missing values will be excluded. It may be

beneficial also for any future studies to examine the relationship between cognitive function, gait and other participant characteristics, such as disease, through an interaction analysis which may expose any biases that exist.

Appendix 5: Support for section 10.3: “Limitations of this Reseach”.

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Variance Between Walking Speed and Neuropsychological Test Scores During Three Gait Tasks Across The Irish Longitudinal Study on Aging (TILDA) Dataset

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Abstract— This study investigated the relationship between neuropsychological test scores and gait speed in three gait tasks using baseline cross-sectional data from 4694 healthy adults (54% women, age (mean±sd) 62.4±8.2) from The Irish Longitudinal study on Aging (TILDA). Global cognition, short term memory, speed of processing, executive function and sustained attention were measured by a detailed battery of neuropsychological tests. Gait speed was recorded from a GaitRite™ pressure sensing mat during a single walk and two dual walking tasks; dual cognitive walk (alternate letters) and dual motor walk (carrying a glass of water). Correlations between neuropsychological test scores and the three gait speed outcomes were investigated using univariate and multiple linear regressions models; firstly adjusting for age, gender, height, education and depression only and then including all neuropsychological test scores in the same regression model and adjusting as previously. It was found that short term memory, speed of processing and attention were significantly correlated with gait speed in all three gait conditions, with global cognition and executive function also significantly correlated with gait speed in the dual cognitive walk. The nature and complexity of the task performed affected gait speed with the addition of the cognitive task while walking causing a larger reduction in gait speed than the addition of the motor task. This indicates that for this healthy nationally representative population sample there is a link between neural processes involved in movement and cognition and this association differs depending on the gait task performed.

I. Introduction

The link between gait and cognitive function is being increasingly recognized. Global cognition has been shown to predict longitudinal gait speed decline[1]. In turn, slow gait speed has been shown to predict survival rate [2]and those at risk of falling[3]. However, there is limited knowledge on the specific contributions of each cognitive subdomain to gait speed. Some studies have found global cognition, short term memory and executive function to play the biggest part [1, 4], others also including attention[5], however not all studies probe speed of processing or attention domains. Further understanding of the relationship between gait and cognitive sub-domains might inform clinical assessments and rehabilitation strategies, in addition to contributing to the understanding of underlying pathology.

Locomotion is a complex task engaging the motor cortex, cerebellum, basal ganglia, and involving feedback to the proprioceptive, visual, and vestibular sensors producing precise motor commands and resultant coordinated muscle firing and limb movements in a healthy person. However, aging and pathology change higher neurological areas of movement control.

Mild cognitive impairment (MCI) refers to slight cognitive disturbances that do not meet the criteria for dementia and can be measured using global cognitive scales. Patients with MCI have cognitive impairments beyond that expected for their age and education[6] but without interfering severely with their activities of daily living. People with MCI have a significant rate of conversion to Alzheimer's disease, but also a slower walking speed and a higher risk of falling than healthy controls.

More specifically speed of processing and executive function have been thought of as the main mediators of age related cognitive decline[7]. Slowing of processing speed as we age is thought to be due to global deterioration in white matter integrity, whereas declines in executive function are thought to be due to functional and structural declines in the frontal cortex. Executive function is required for effective, goal orientated actions and for control of attentional resources needed for activities of daily living[8]. Executive function measures have been linked to slower walking speed, disruptions of gait and balance and to higher risk of falls [9]. Attention is a subcategory of executive function and it is seen to play a central role in gait[10]. Sustained attention refers to the ability to maintain attention to a task over a period of time and has been linked to higher risk of falls[11] but has not been examined in relation to gait speed. Memory is also an important factor as it is one of the first cognitive domain to be affected by aging, however good memory has been shown to have an influence on recording of falls[12].

Research is needed to determine the relationship between attention, task complexity, task prioritization, awareness of limitation and gait speed in an older cohort to investigate pre-pathological signs within gait. Studies to date have focused on a small set of neuropsychological batteries or based findings on small subject numbers. The aim of this study was to probe the relationship between six pertinent neuropsychological test scores and gait speed in three gait

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conditions in a large nationally representative community dwelling older population sample.

II. Procedure

This study used baseline cross sectional data from 4694 healthy adults (54% women, age (mean±sd) 62.4±8.2) who participated in The Irish Longitudinal study on Aging (TiLDA), a nationally representative study.

A. Methods

Gait and neuropsychological data were investigated from the TILDA health assessment. A 4.88m GAITRite™[CIR Systems Inc., NJ, USA] pressure sensing mat recorded gait speed during two walks at normal pace for a single walk and two dual walking tasks: motor and cognitive. The dual motor walk involved walking while carrying a glass filled one inch from the top with water. The dual cognitive walk involved walking while reciting alternate letters of the alphabet. The walking tasks began 2.5 meters before the start of the mat and continued for 2 meters at the end of the mat to facilitate acceleration, deceleration and turning.

The Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MOCA) are two types of 0 to 30-point global cognitive screening scales with memory, visuoconstructional, attention, concentration, memory, language and orientation components. MOCA, in addition, includes a larger executive function component and has been shown to have greater sensitivity at detecting MCI than MMSE[13]. A cut-off test score in MMSE of 26 is commonly used as healthy cognition, under 24 as severe cognitive impairment and in MOCA under 26 for MCI.

Sustained attention was measured using the Sustained Attention to Response Task (SART) coefficient of variation[14]. Repeated digits were presented sequentially from '1' to '9' on a screen in front of participants (300 ms inter-stimulus interval, 207 numbers) while participants pressed a button for every digit except for the digit '3'.

Short term Memory was assessed using a ten word recall which tested immediate and delay recall.

The Color Trail Test (CTT)[15] consists of two parts. Part 1 involves connecting numbers in ascending order with a pencil as quickly as possible, and part 2 additionally requires alternating between pink and yellow numbers. Both parts were timed and the difference in time between part 1 and part2 (ΔCTT) was the executive function measure used.

Speed of Processing was measured using the Choice Reaction Time test (CRT) mean reaction time. A yes/no stimulus appeared on the screen and participants responded by pressing a corresponding yes/no button (100 repetitions).

Data was analyzed using Stata 12 [StataCorp LP, Texas, USA]. Paired t-tests were used ($p<0.05$) to investigate the effect of task on gait speed. Correlations between neuropsychological test scores and gait speed for each gait condition were investigated using univariate and multiple linear regressions models. Statistical Model 1 investigated correlations between gait speed and each neuropsychological test scores using univariate regression, Statistical Model 2 also adjusted for age, gender, depression, height and level of education. Statistical Model 3, included all neuropsychological test scores in the same regression model, while adjusting as previously. In order to compare the relative contributions of the most statistically pertinent neuropsychological test scores Statistical Model 4 only included the most statistically significant ($p<0.3$) neuropsychological test scores from Statistical Model 3 and adjusted as previously. Significance values can be seen in Table II (Statistical Model 1, 2 and 3) and beta coefficients and standard errors in Table III (Statistical Model 4) to indicate their relative contribution. No variables were omitted due to collinearity (variance inflation factor >10).

TABLE I. Summary of Participant Characteristics, (N=4694)

Characteristics	*Description*	*Value*
Gender	Female [n,%]	2557 54%
Age	Mean±sd [years]	62.4±8.2
Height	Mean±sd [m]	1.66±0.09
Education	Participants achieving Primary, Secondary, Tertiary Education [n]	1045,1940, 1707
Depression	Short Centre for Epidemiological Studies Depression Scale, CES-D: Mean±sd, n ≤ 16 (%)	4.39±4.02 113 (3%)
Falls	Self-reported falls in the last year: None, One, Two or more [n,%]	3759, 616, 317 80%, 13%, 7%
Walking Speed	Single Walk [m/s]	1.35±0.20
	Dual Walk (Cognitive) [m/s]	1.11±0.26
	Dual Walk (Motor) [m/s]	1.33±0.21
Global Cognition	MMSE: Mean±sd, n < 26, 24 (%)	28.60±1.85 (6, 2)
	MOCA: Mean±sd, n < 26 (%)	25.30±3.26 (48)
Short Term Visual Memory	Ten Word Recall Test: Immediate Recall (Range, IQR Median)	1-10, 4-8, 5
	Ten Word Recall Test: Delayed Recall (Range, IQR Median)	1-10, 3-9, 5
Speed of Processing	CRT Mean Reaction Time [s]	0.815 ±0.27
Executive Function	ΔCTT [s]	54.4±27.2
Sustained Attention	SART Coefficient of Variation [%]	0.31±0.16

III. Results

Characteristics from 4694 participants included in the analysis can be seen in Table I. Gait speed was found to be significantly different for all gait conditions (two tailed paired t-test: $t<0.05$). All neuropsychological test scores were highly statistically significant correlated with gait speed for all gait conditions in Statistical Model 1 and 2 (Table II), with the exception of ΔCTT for the single walk (Statistical Model 2).

In Statistical Model 3, 23%, 17% and 24% of the variance associated with gait speed for the single walk, dual cognitive and dual motor walks respectively can be explained by personal (age, gender, height, depression and education) and neuropsychological factors (global cognition, short term memory, speed of processing, executive function and attention) with MOCA, immediate recall, ΔCRT and SART coefficient of variation statistically significantly correlated

TABLE II. CORRELATIONS OF NEUROPSYCHOLOGICAL TEST SCORES WITH GAIT SPEED DURING THREE WALKING TASKS

Predictor	Single Walk			Dual Cognitive Walk			Dual Motor Walk		
	p value			p value			p value		
	Statistical Model 1	Statistical Model 2	Statistical Model 3	Statistical Model 1	Statistical Model 2	Statistical Model 3	Statistical Model 1	Statistical Model 2	Statistical Model 3
	p	p	p	p	p	p	p	p	p
Global Cognition: MOCA	<0.005	0.021	0.046	<0.005	<0.005	0.055	<0.005	<0.005	0.258
Global Cognition: MMSE	<0.005	0.013	0.766	<0.005	0.011	0.593	<0.005	<0.005	0.799
Short Term Memory: Immediate recall	<0.005	<0.005	0.006	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005
Short Term Memory: Delayed recall	<0.005	0.008	0.722	<0.005	<0.005	0.601	<0.005	<0.005	0.518
Speed of Processing: ΔCRT	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005
Executive Function: ΔCTT	<0.005	0.217	0.466	<0.005	<0.005	0.046	<0.005	<0.005	0.673
Sustained Attention: SART Coefficient	<0.005	<0.005	0.005	<0.005	<0.005	0.046	<0.005	<0.005	0.002

Statistical Model 1 used univariate linear regression. Statistical Model 2 also adjusted for age, height, gender, education and depression n. Statistical Model 3 used a multiple linear regression including all neuropsychological test scores and adjusting as per Statistical Model 2: n= 4451, 4405 and 4402 and R2 = 0.25, 0.17 and 0.23 for single, dual cognitive and dual motor gait speed.

(<0.3) with gait speed in all gait conditions, but MMSE and delayed recall were not. ΔCTT was significantly correlated with gait speed in the cognitive gait task only. In Statistical Model 4 (Table III) 23%, 17% and 23% of the variance associated with gait speed for the single, dual cognitive and dual motor walks were explained by personal and neuropsychological factors with immediate recall, ΔCRT SART coefficient of variation statistically significantly correlated with gait speed in all gait conditions. MOCA and ΔCTT were significantly correlated with gait speed in the dual cognitive walk also.

IV. DISCUSSION

This study examined the relationship between measures of cognitive function and gait speed. Short term memory, speed of processing and sustained attention were found to be the most significant cognitive factors affecting gait speed for all gait conditions, with global cognition and executive function significantly correlated with gait speed for the dual cognitive walk also. The nature and difficulty of the task performed affected gait speed with the addition of the cognitive task while walking causing a larger reduction in gait speed than the addition of the motor task. These results indicate that for this healthy nationally representative older population sample, even a simple gait task may involve many cognitive processes with different processes recruited depending on that nature and difficulty of the task.

All cognitive domains were statistically significantly correlated to gait speed for all gait conditions in Statistical Model 1 and in Model 2 after adjusting for confounding factors (age, height, gender, education and depression). The effect of confounding factors can be seen in the reduced statistical significance of most cognitive domains from Statistical Model 1 to 2. However, immediate recall, speed of processing and SART coefficient remain highly statistically significant throughout all regression models. This shows the importance of adjusting for confounding factors to aid in highlighting variables of most interest.

When comparing the relative statistical significance of all cognitive domains in the same regression model (Statistical Model 3), MMSE and delayed recall are no longer statistically significantly correlated with gait speed for any gait condition. This indicates that any statistical significant variance in gait speed can be explained by the other cognitive test scores included in Statistical Model 3 such as MOCA and immediate recall. In addition, MMSE scores (28.60±1.85) were very high with reduced variance compared with MOCA scores (25.20±3.26). These findings support literature which shows MMSE to be a less appropriate scale than MOCA to assess a healthy cohort due to its lower sensitivity to MCI.

Percentage variance (R-squared) associated with gait speed for all gait conditions from Statistical Model 3 to Statistical Model 4 are very similar, indicating that the neuropsychological test scores included in Statistical

TABLE III. CORRELATIONS OF NEUROPSYCHOLOGICAL TEST SCORES WITH GAIT SPEED DURING THREE WALKING TASKS: STATISTICAL MODEL 4

Predictor	Single Walk			Dual Cognitive Walk			Dual Motor Walk		
	β	S.E.	p	β	S.E.	p	β	S.E.	p
Global Cognition: MOCA	-0.203	0.110	0.065	-0.303	0.142	0.033*	-0.06	0.110	0.581
Short Term Memory: Immediate recall	0.598	0.195	0.002*	1.145	0.262	<0.005*	0.9	0.195	<0.005*
Speed of Processing: ΔCRT	-0.008	0.001	<0.005*	-0.015	0.002	<0.005*	-0.01	0.001	<0.005*
Executive Function: ΔCTT				-0.034	0.016	0.040*			
Sustained Attention: SART Coefficient	-5.259	1.968	0.008*	-5.41	2.703	0.046*	-6.43	2.03	0.002*

Statistical Model 4 shows results for a multiple linear regression including neuropsychological variables that had a p value of <0.03 in Statistical Model 3 and adjusting as per Statistical Model 2. n=4451, 4405 and 4402 and R2=0.24, 0.17 and 0.23 for single, dual cognitive and dual motor gait speed.

Model 4 explain almost all of the variance in gait speed for each gait condition.

Statistical Model 4 found short term memory, speed of processing and sustained attention to be the most statistically significant cognitive contributors to gait speed variance for all gait conditions. Walking requires multiple cognitive processing tasks such as multi-sensory integration, spatial awareness and proprioception. Therefore, it follows that speed of processing and attention, an executive function, are therefore important for gait speed. Memory, the first cognitive domain to be affected by aging, is also highlighted here as an important factor in the walking speed of this healthy older adult sample.

In addition, in Statistical Model 3 and 4 executive function was found to be statistically significantly correlated to the dual cognitive walk only. This was reflected in reports from participants who found this dual walk more difficult than the single walk or dual motor walk. This result indicates that participants recruited executive function resources when performing the dual cognitive walk. Global cognition (MOCA) also affected gait speed when performing the dual cognitive walk and this may also be due to the large executive function component within MOCA.

This study found short term memory, speed of processing and sustained attention to be the most statistically significant cognitive contributors to gait speed for all gait conditions. These findings support similar studies by Mielke et al[4] and Watson et al[1] who found memory and executive function or attention to contribute to gait speed variance, however these studies did not probe speed of processing or sustained attention contributions. Future research should be undertaken to calculate percentage of variance that each cognitive subdomain contributes to gait speed using standardized beta coefficients. This increased understanding of the links between neurocognitive function and gait activity may aid in the diagnosis of motor cognitive dysfunctions and allow effective pre-emptive actions to be taken.

In addition, we hypothesize that for this healthy nationally representative population sample there is a link between neural processes involved in movement and cognition and this association differs depending on the gait task performed.

V. Conclusion

In this study it has been shown that memory, attentional and speed of processing capacity are statistically significantly correlated to the gait speed at which a person walks during simple and more complex gait tasks. Global cognition and executive function also play a role when simultaneously performing a motor and cognitive task. The nature and difficulty of the gait task affects the speed at which a person walks: the addition of a cognitive task causing a much larger reduction in gait speed than the addition of a motor task. This indicates that for this healthy nationally representative population sample there is a link between neural processes involved in movement and specific cognition sub-domains and this association and the neural resources involved differ depending on the gait task performed.

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