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## Gait characteristics as indicators of cognitive impairment in geriatric patients

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
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# 1

## GENERAL INTRODUCTION



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## **The aging society**

As wisdom and experience come with age, old adults are of significant value to their families, local communities, and to society in general. Today, populations in most countries show a substantial increase in longevity, resulting in an increased proportion of old adults aged over 65 worldwide [1]. The personal and societal value of extending life, however, seems to heavily depend on whether those added years are spent in good health or are compromised by disease and disability. Unfortunately, the number and severity of clinical conditions steadily increases with age [2]. According to the World Health Organisation, it therefore remains a sustained challenge to 'not only add years to life, but to also add health to years'.

## **'Healthy aging' vs. 'geriatric aging'**

Even 'healthy aging' results in the accumulation of physiological, psychological, and social changes over time. For example, the loss of muscle fibres leads to an annual reduction in leg strength of 1-2% after age 50 [3]. Brain volume shrinks by 5% per decade after age 40, resulting in a brain tissue loss of up to 20% by age 80 [4]. When the degree of decline in physical and/or psychological functioning exceeds the degree of decline expected based on the aging process alone, old adults are usually referred to geriatricians or other specialists with expertise in the treatment of geriatric conditions and diseases [2]. Typical geriatric conditions include sarcopenia, delirium, weight loss, cognitive impairment, osteoporosis, and recurrent falls. Such conditions are often characterized by multiple aetiological factors and interacting pathogenetic pathways [5]. Geriatric patients can thus be defined as a vulnerable segment of old adults, in whom the presence of a minor condition may eventually result in a catastrophe. For example, a mild infection in geriatric patients may cause confusion, which could lead to a fall, and result in a hip fracture. 'Geriatric aging' can therefore be conceptualized as the natural aging process accompanied by multiple comorbidities that require specialized geriatric care to slow functional decline.

## ***Study population of the present thesis***

The experimental studies (Chapters 3-5) examine geriatric patients recruited from the MC Slotervaart hospital in Amsterdam between 2014 and 2017. They visited the geriatric diagnostic dayclinic for a comprehensive evaluation of physical, cognitive, and psychological function. Geriatric patients visiting the geriatric department present with a mean age of approximately 80 years and an average life expectancy of about 4 years. This characterization is based on many years of descriptive data collected at the MC Slotervaart hospital.

## **Cognitive impairment in the geriatric population**

A major cause of disability in geriatric patients results from the presence of cognitive impairment, as it affects memory, thinking, behaviour, emotions, and/or perceptions [6]. Population studies report prevalence rates of cognitive impairment ranging between 5% and 29% in community-dwelling old adults aged over 65 [7], and the presence of cognitive impairment is often considered as a precursor to the development of dementia. In fact, approximately 10-15% of old adults with diagnosed cognitive impairment yearly develop dementia [7]. Because geriatric patients are usually considerably older than 65, prevalence and conversion rates are certainly higher in this population. Over the years, several terms have been introduced to define the transitional state between normal aging and the development of dementia. 'Benign senescence forgetfulness' was one of the first

descriptors of this transition state, and was considered as a manifestation of the normal aging process [8]. Later, the Canadian Study of Health and Aging introduced the term 'cognitive impairment no dementia', which refers to cognitive impairment of insufficient severity to constitute dementia [9]. Since 1997, this concept has been refined and is nowadays recognized as a pathological condition, i.e., not a manifestation of normal aging, and is widely known as 'Mild Cognitive Impairment' (MCI) [10]. MCI involves the evolution of cognitive impairment in one or more cognitive domains (e.g., memory, executive and visuo-spatial function) beyond the expected decline based on an individual's age and education. In MCI, the impairment is not severe enough to compromise daily life or to meet the criteria for dementia [10]. Nevertheless, clinicians and researchers still use various terms and criteria to define cognitive impairment. In this thesis, the umbrella term 'cognitive impairment' is used to refer to those definitions, unless studies specified the disease (e.g., MCI).


### ***Gait characteristics as indicators of cognitive impairment***

Even though there is no cure yet to reverse cognitive neurodegeneration, tailored interventions (e.g., medication, psychotherapy, psychoeducation, environmental modifications, physical activity) can slow disease progression and reduce symptoms [6]. The effectiveness of disease-modifying interventions is greatest in early phases of cognitive impairment and decreases with disease progression [11]. The identification of cognitive impairment in early stages is therefore crucial. Current models use demographic, genomic, vascular, behavioural, neurological and neuropsychological variables to predict dementia-related pathology [12]. Because those models insufficiently discriminate patients at-risk from patients not at-risk (Area Under the Curve ranging from AUC=0.50 to AUC=0.87) [13], there is a need for extra markers. In addition to usual predictors, the present thesis studied gait characteristics as potential non-invasive indicators of cognitive impairment in geriatric patients.

### **Experimental, neuroscientific, and behavioural evidence for the relationship between gait and cognitive impairment**

Motor and cognitive functions were initially considered two distinct entities. This view originated from the 'mind-body' dualism: a philosophical view that advocates that mental phenomena are not physical and that the body and mind are two distinct features [14]. Nowadays, studies from multiple scientific fields emphasize the inter-relatedness between motor and cognitive functions. For example, the brain works better and the risk to develop neurodegenerative disorders decreases with an increase in physical fitness [15, 16]. Similarly, neurodegenerative disorders such as dementia and Parkinson's disease often cause severe weight loss [17].

The inter-relatedness between motor and cognitive functions is also reflected in human walking. Walking involves the execution of goal-directed actions, and is thus a process which heavily relies on memory and on executive function to anticipate and interpret the environment and behaviour of others. In this process, gait and cognition show distinct patterns of associations [18, 19]. For example, recent studies showed that information processing was associated with gait rhythm, fine motor speed with tandem walking, and executive function with gait speed [19]. Neuro-imaging studies confirmed the link between gait and cognition by showing that walking utilizes brain areas that are responsible for executive, memory, and visuo-spatial functions, as well as motor areas such as the motor



cortex, the cerebellum, and the basal ganglia [20]. Brain areas involved in gait and cognitive function thus partly overlap and changes in gait can therefore be expected with the onset of cognitive impairment. White matter damage may be the underlying common cause of the concurrent changes in gait and cognition, as white matter tracts connect all those cortical and sub-cortical inputs. Indeed, smaller brain volumes and white matter lesions have been associated with MCI and dementia [21], but also with decline in global cognition in cognitively healthy old adults [22]. This white matter damage in turn has been associated with gait dysfunction (gait speed of  $<0.5$  m/s), even in old adults free from dementia [23].

Perhaps the most explicit observation illustrating the connection between gait and cognition comes from motor-cognitive dual-task studies. During a dual-task, individuals perform a cognitive and a motor task simultaneously. Two decades ago, Lundin-Olssen and colleagues reported that 80% of frail old adults who stopped walking while talking experienced at least one fall in the next six months, in contrast to only 24% of old adults who were able to concurrently walk and talk without stopping [24]. The results showed that the motor and cognitive tasks (partly) rely on the same cognitive resources, and that attention should be allocated to both tasks. The change in performance from single- to dual-task walking reflects the degree of motor-cognitive interference and is referred to as 'dual-task cost' (DTC). Because patients with a cognitive impairment have limited cognitive capacities, DTC in patients with cognitive impairment or dementia is usually higher than in age-matched controls [25-29], depending on the nature and difficulty of the cognitive task [30]. Because a cognitively demanding task while walking places an additional stressor to the brain, dual-task walking has the potential to reveal subtle cognitive impairment in the brain that remains invisible with single-task walking. Methods incorporating dual-task paradigms therefore have become the reference method for assessing interactions between motor and cognitive functions.

### **The gait-cognition link in light of the 'loss of complexity' theory**

Because geriatric patients show degradation in multiple interacting systems, the gait-cognition link could be placed in a theoretical framework to better understand the coupling and coordination between elements of the aging neuro-musculo-skeletal system (NMSS) (i.e., gait and cognition). To this idea, a key-phenomenon of the aging NMSS was considered, namely the 'loss of complexity' (LOC). The LOC theory is derived from the field of non-linear dynamics and suggests that even healthy aging is associated with a (neuro)physiological breakdown of system elements that causes a loss of overall complexity [31]. Physiologic systems exist at molecular, subcellular, cellular, organ, and systemic levels, in which a healthy physiological system is characterized by complex networks of control mechanisms that allow individuals to flexibly adapt to unpredictable situations in daily life [31]. The original studies that recognized and quantified the complexity of physiological systems (instead of focussing on mean values of discrete physiological variables) were in the field of cardiology. The results underscored that a normal sinus rhythm in heartbeats in healthy young adults were not strictly regular but instead revealed with a complex type of variability [32, 33]. With natural aging, a degeneration in tissues and organs leads to a progressive loss of complexity in physiological systems, resulting in a decreased ability to adapt to physiological stress. This loss of complexity is unavoidable and even present in healthy aging [31]. Additional physiological deterioration is marked by an even greater


loss of complexity. For example, declines due to sensory impairment [34] and frailty [35] resulted in a reduced complexity of postural fluctuations. Similarly, fallers (who generally present with physiological declines in sensory and neuromuscular functions [36]) were characterized by a loss of gait complexity [37, 38]. In the present thesis, it was postulated that physiological decline caused by cognitive impairment was also reflected in gait function. A loss of gait complexity would be characterized by an increase in gait regularity and predictability [39], outcomes that will be clarified in the paragraphs below.

### **The dynamic nature of walking: what's in someone's gait?**

Researchers have been using gait speed extensively as a comprehensive index of old adults' locomotor performance [40]. A ubiquitous observation from previous studies is an age-related slowing of gait speed. Even 'healthy aging' is associated with a slowing of habitual gait speed of as much as 16% per decade after the age of 60 [41-43]. A gait speed below 1.0 m/s signifies potential clinical conditions such as mobility impairment, recurrent falling, a loss of independence, and possibly poor cognitive function. In addition, gait slowing has been associated with hospitalization and even mortality [44]. The value of measuring gait speed in old adults is therefore increasingly endorsed and gait speed has even been proposed as the 'sixth vital sign' [45] and a test used in geriatric clinics [40, 46].

The original observation of the relationship between gait slowing and cognitive impairment was reported nearly two decades ago. The data showed that a slow gait speed in the oldest-old preceded cognitive impairment 3 years later, with old adults who developed cognitive impairment vs. those who remained cognitively stable walking 0.69 m/s and 0.95 m/s at baseline, respectively [47]. Similarly, Buracchio and colleagues reported an acceleration in gait slowing up to 12.1 years before cognitive impairment became clinically manifested [48]. More recently, multiple studies confirmed those initial findings, and highlighted the potential of a slow gait speed as a precursor of MCI and dementia in initially healthy old adults who were recruited from the community [49-51]. Gait speed expressed in one of its elements, such as stride time and stride time variability (assessed with the Coefficient of Variation), have also been linked to cognitive impairment, in which a higher stride time variability was associated with future decline in memory and executive functioning [52], and with the development of MCI [53, 54]. A meta-analysis underscored that higher stride time variability represented a motor phenotype of MCI, with patients with vs. without MCI presenting with a stride time variability of  $3.8\pm 6.7\%$  and  $2.0\pm 1.8\%$ , respectively [55]. Most of the above studies were performed in relatively young old adults (age ranging from 65-75) recruited from the community. Less is known, however, about geriatric populations who are older and present with many co-morbidities.

In addition to gait speed as a summary index of mobility, fine-grained, dynamic gait outcomes describe features of gait not apparent in gait speed. The quantification of such gait dynamics can be achieved when walking is viewed as a dynamic task. Indeed, walking requires continuous interactions between body segments, the body and the environment, and necessitates both, anticipatory and reactive responses. For example, when one walks from point A to point B, we are able to adapt our gait to a variety of unexpected circumstances. We can easily manage to walk on different surfaces, anticipate to upcoming traffic, and avoid obstacles that block the road, while controlling and coordinating our



moving body parts such as our legs, arms, trunk, and the head [56]. Old adults are even more challenged to control and coordinate moving body parts [57], as they experience a loss of muscle strength, and a reduction in the ability to detect and process sensory as well as proprioceptive information [58]. Apart from individuals with severe cognitive and/or physical dysfunction, even old adults are able to flexibly adapt to all kind of circumstances. Yet, our steps are not independent of each other but instead depend on previous as well as on steps we anticipate to make. For example, when we stumble, the length of our next step will be larger in order to compensate for this 'miss-step'. Previous steps may unravel why this compensation was successful or unsuccessful. Similarly, patients can walk very slowly but highly stable or very fast but highly unstable, and everything in between. Analysing time-dependent fluctuations, i.e., how gait evolves over time, may unravel the cause of slow gait in terms of gait coordination and reactions to perturbations [38, 39, 56, 59-61]. The time-series correlation between the constituent events of gait can reveal underlying gait disorders or pathologies. Using traditional gait measures such as gait speed and (coefficient of variation of) stride time may mask the temporal interdependence between successive steps, as those measures simply average step-related information over time. In summary, the quantification of time-dependent fluctuations during walking potentially increases our understanding of the relationship between gait and cognitive impairment, and may help to underpin the neural control of gait.

### ***Tools and concepts to quantify gait dynamics***

Dynamical systems theory provides tools and concepts to quantify time-dependent fluctuations during walking [38, 39, 59, 60, 62, 63]. A continuous monitoring of a patients' gait pattern is required to capture those time-dependent fluctuations. There are a variety of ways to continuously monitor gait (e.g., optoelectric systems), but the advantage of accelerometry is that walking remains relatively unconstrained and can be measured outside laboratory settings over long walking distances and durations [64]. Because the regulation of balance during walking is known to be reflected in acceleration signals of the lower trunk (because of its proximity to the body's center of mass) [65], trunk accelerations can accurately reflect center of mass behaviour during gait [64]. From trunk acceleration signals, dynamic gait outcomes can be computed that quantify time-dependent fluctuations and patterns throughout the gait cycle [38, 39, 59, 60, 62, 63]. For example, the Index of Harmonicity reflects gait smoothness [62], autocorrelation procedures are used to examine gait regularity and symmetry [59], and the maximal Lyapunov exponent can be computed as an indicator of gait stability [66]. In this thesis, the term 'gait dynamics' is used to refer to such dynamic aspects of walking. In general, gait dynamics are indicative of overall gait coordination, adaptability, and the ability to respond to perturbations.

There is a limited number of studies that examined gait dynamics in patients with cognitive impairment. Patients with dementia compared with age-matched controls present with high gait variability and low gait stability [67]. Another study reported low gait variability and irregular trunk acceleration patterns in dementia patients [68]. With respect to other conditions, gait dynamics discriminated young and old adults [69], individuals with and without a clinical condition [70, 71], and fallers and non-fallers [37, 38, 72-74]. Healthy old adults (aged 46-75) had a less variable, more predictable, and less symmetrical gait as compared to healthy young adults (aged 18-45). Patients with a flexed posture presented

with a more variable, and less regular trunk accelerations as compared to patients with a normal posture [70]. Studies concerned with gait dynamics in relation to fall-status showed that a high fall risk was associated with a less smooth and less stable gait [73], with a more variable and less stable gait [74], and with less gait complexity [37, 38]. Gait dynamics thus showed potential to identify clinical as well as non-clinical conditions.

### **A multivariate approach**

Because of the high number of comorbidities, a multivariate approach is necessary to examine the link between gait and cognition in geriatric patients. As mentioned before, geriatric conditions are often characterized by multiple aetiological factors and interacting pathogenetic pathways [5]. Those geriatric conditions are likely to be inter-related. For example, conditions that are typically present in geriatric patients are known to interact with gait performance, such as a flexed posture [70], muscle weakness [75], and polypharmacy [76]. Also, gait characteristics tend to correlate with one another. For instance, gait speed highly correlates with stride time. While gait speed and stride time individually may have limited power in the identification of cognitive impairment, the combination of these two measures can be substantially higher. In addition to the fact that statistical assumptions are not met, performing univariate analyses for each individual outcome could mask clusters / dependencies in the data. Therefore, multivariate analyses were performed using Partial Squares Discriminant Analyses (PLS-DA) [77] in chapter 3 and 4. PLS-DA combines features from Principal Component Analysis and usual regression analysis. Covariance structures are modelled, and underlying latent clusters are extracted.

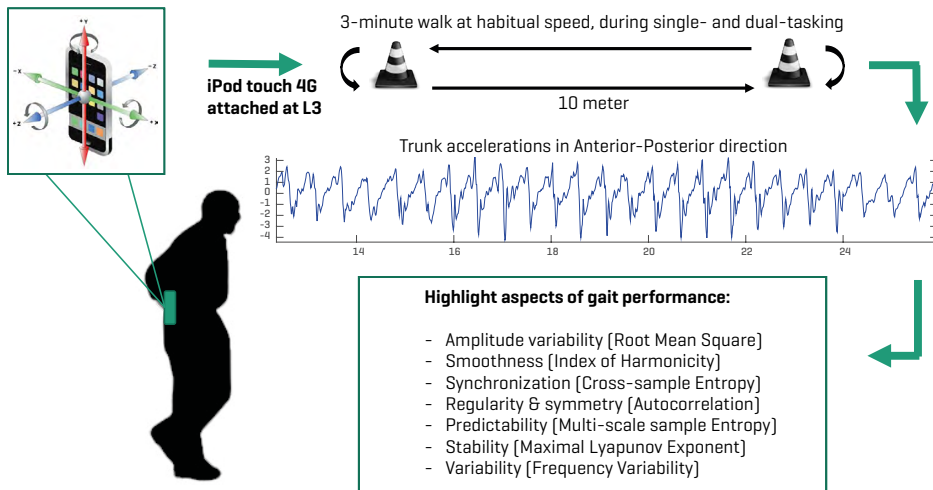
### **Objectives of the thesis**

Most of the existing literature on the relationship between gait and cognitive impairment is concerned with relatively young and healthy old adults, while our sample of geriatric patients is older and presents a high number of co-morbidities known to interact with gait function. In addition, previous studies predominantly focussed on gait speed as indicator of cognitive impairment, while fine-grained, dynamic gait outcomes potentially increase the specificity of the gait-cognition link, and may help to underpin the neural control of walking. Therefore, the main objective of this thesis was to increase our understanding of the relationship between gait and cognition in geriatric patients. To this aim, multivariate analyses were used to study multiple gait outcomes in relation to cognitive status. Ultimately, gait characteristics could serve as non-invasive indicators of cognitive impairment in this vulnerable population. To achieve this main goal, sub-objectives were twofold: (1) to characterize the gait pattern of geriatric patients with and without cognitive impairment, as compared to younger and healthier old adults, and (2) to examine whether and how gait characteristics can contribute to the identification and/or prediction of cognitive impairment and falls. It was hypothesized that geriatric patients with cognitive impairment presented with a slower, more regular and less complex gait pattern as compared to cognitive intact geriatric patients. In addition, it was expected that gait outcomes derived from an extensive gait analysis could add to usual diagnostics to identify and/or predict cognitive impairment and falls.

Figure 1 illustrates the gait protocol and measures that were used in Chapters 3-5. In addition to usual screening procedures at the MC Slotervaart hospital, patients walked for 3-minutes, during single- and dual-tasking. Trunk accelerations in Anterior-Posterior (AP),



Medio-Lateral (ML), and Vertical (V) signals were derived from an iPod touch 4G. The figure shows an example of a raw acceleration signal in AP direction, from which trunk outcomes, i.e., gait dynamics, were calculated in 3D. Considering the explorative nature of the studies, multiple gait outcomes were quantified. While all outcomes reflect the dynamic nature of walking, they quantify different aspects of the gait pattern, using different properties of the acceleration signal (e.g., amplitude, frequency, time-scales, phase-space).



**Figure 1.** The gait protocol and measures that were used in Chapters 3-5. In addition to usual screening procedures at the MC Slotervaart hospital, patients walked for 3-minutes, during single- and dual-tasking. Trunk accelerations in Anterior-Posterior (AP), Medio-Lateral (ML), and Vertical (V) signals were derived from an iPod touch 4G. The figure shows an example of a raw acceleration signal in AP direction, from which trunk outcomes, i.e., gait dynamics, were calculated in 3D.

## Outline of the thesis

To obtain an overview of the existing literature concerned with the relationship between gait characteristics and cognitive impairment in old adults, chapter 2 systematically reviewed evidence from longitudinal studies that revealed associations between baseline gait function and future cognitive decline. Chapter 3 studied the contribution of an extensive cognitive- and gait evaluation in the classification accuracy of fallers and non-fallers. Chapter 4 examined gait characteristics and their discriminative power in healthy old controls, and in geriatric patients with- and without cognitive impairment. The gait outcomes that revealed with the highest discriminative power were studied in a prospective design in chapter 5. This pilot study investigated how baseline gait outcomes correlated with future cognitive decline.

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