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Gait characteristics as indicators of cognitive impairment in geriatric patients

Lisette Kikkert

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GAIT CHARACTERISTICS AS INDICATORS OF
COGNITIVE IMPAIRMENT IN GERIATRIC PATIENTS

Lisette
Kikkert

Gait characteristics
as indicators of cognitive impairment
in geriatric patients

LISETTE KIKKERT

Colophon

This PhD-thesis was an international cooperation, 'a co-tutelle', between the Rijksuniversiteit Groningen [the Netherlands] and the Université Grenoble Alpes [France].

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Gait characteristics as indicators of cognitive impairment in geriatric patients

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Gait characteristics as indicators of cognitive impairment in geriatric patients

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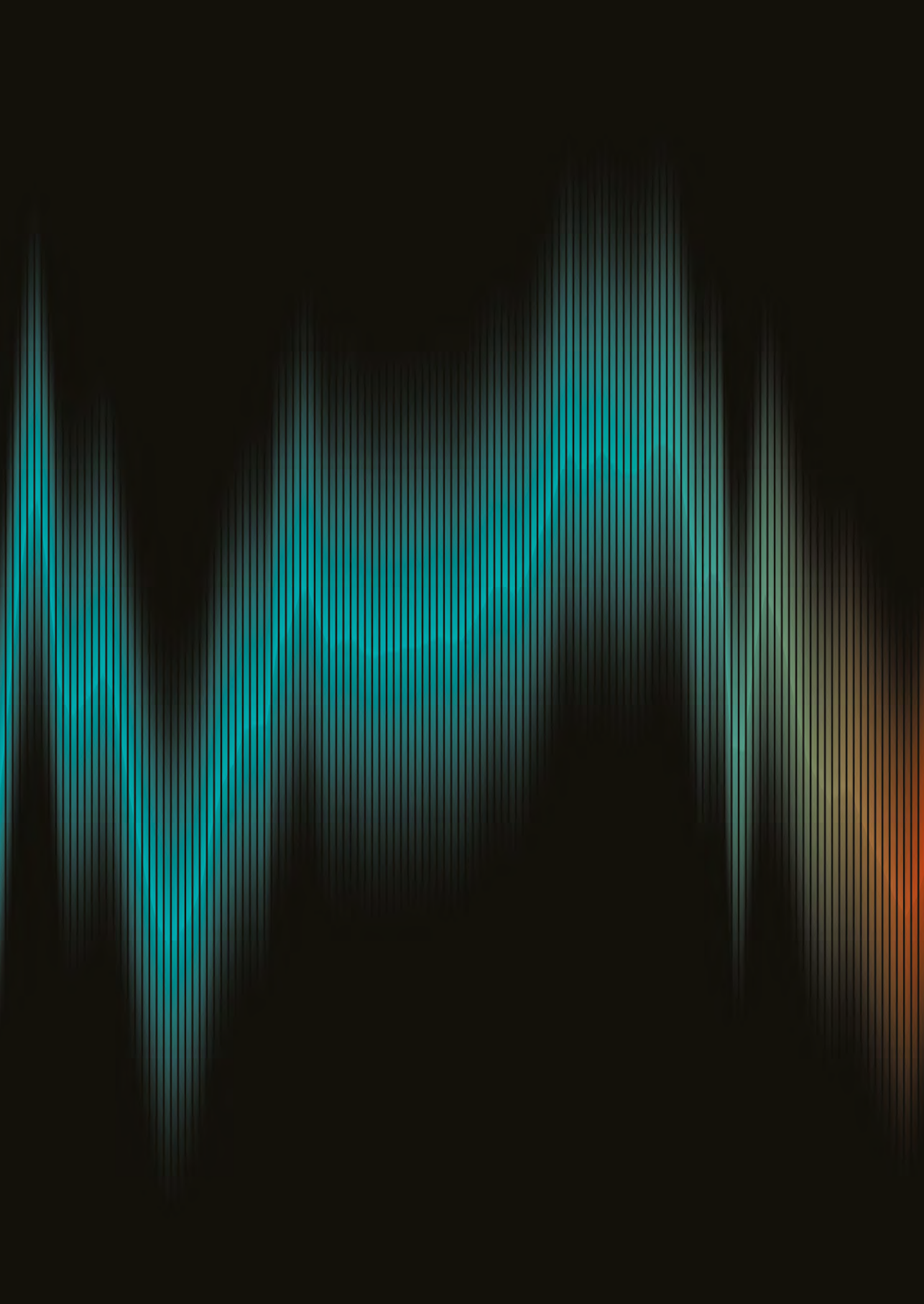


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
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1

GENERAL INTRODUCTION



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).

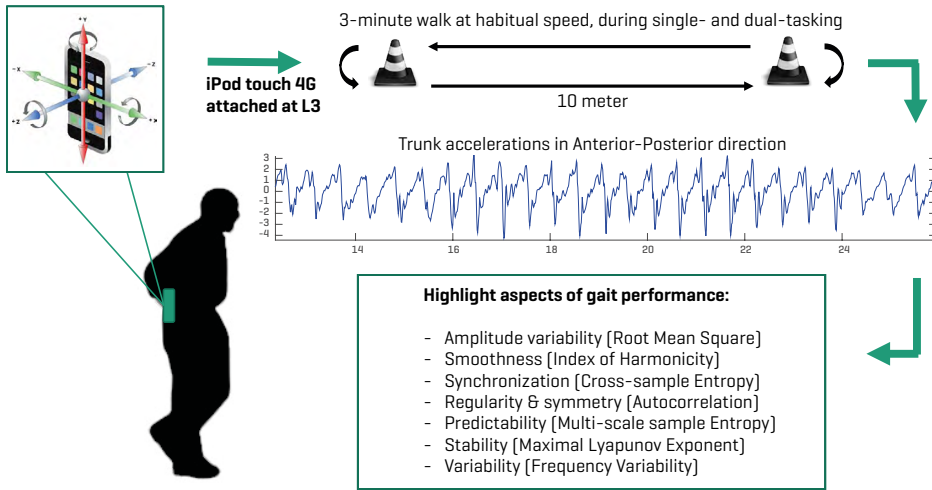


Figure 1. The gait protocol and measures that were used in Chapters 3-5. In addition to usual screening procedures at the MC Slotervaart hospital, patients walked for 3-minutes, during single- and dual-tasking. Trunk accelerations in Anterior-Posterior (AP), Medio-Lateral (ML), and Vertical (V) signals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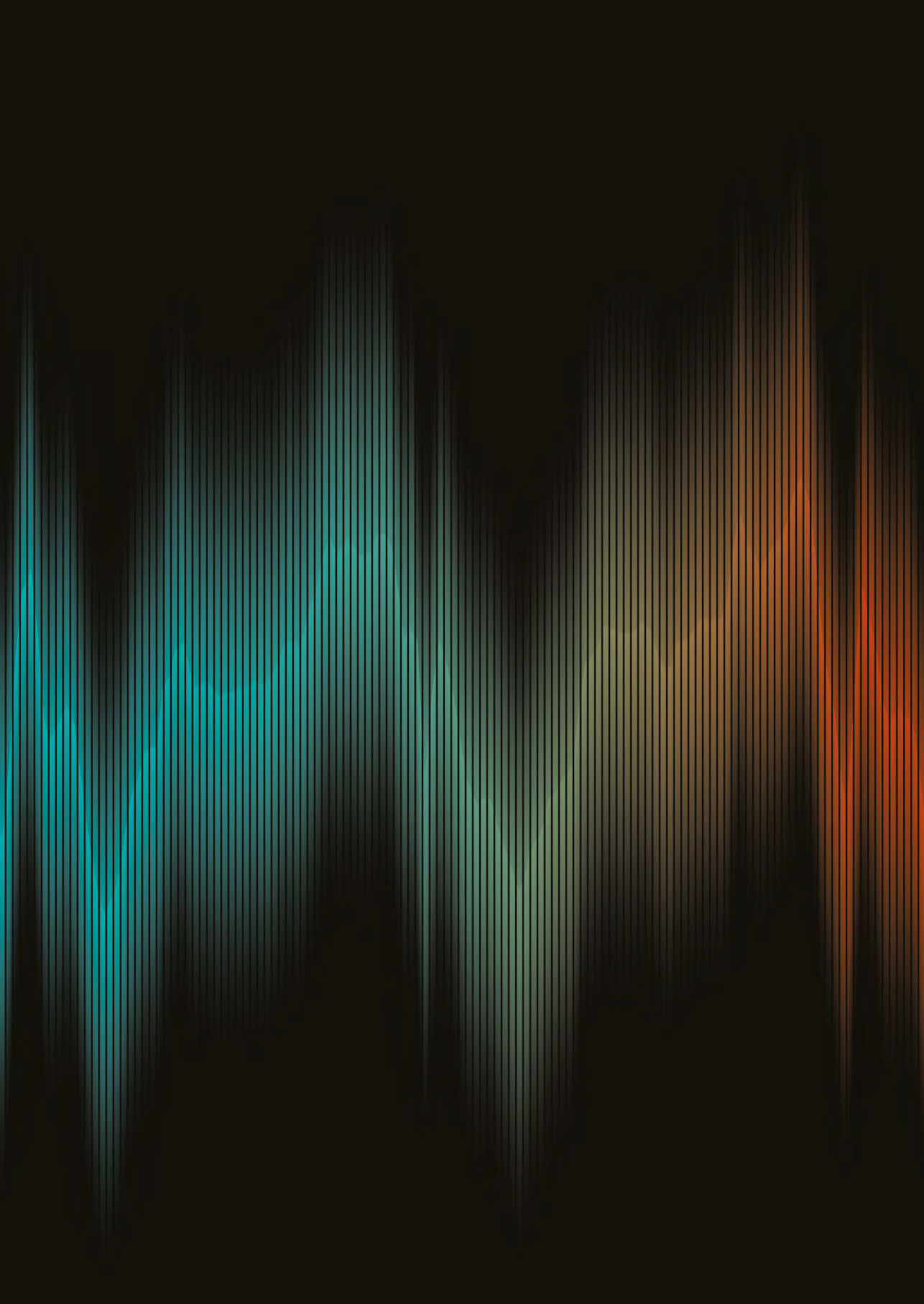


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2

WALKING ABILITY TO PREDICT FUTURE COGNITIVE DECLINE IN OLD ADULTS: A SCOPING REVIEW

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ABSTRACT

Early identification of individuals at risk for cognitive decline may facilitate the selection of those who benefit most from interventions. Current models predicting cognitive decline include neuropsychological and/or biological markers. Additional markers based on walking ability might improve accuracy and specificity of these models because motor and cognitive functions share neuroanatomical structures and psychological processes. We reviewed the relationship between walking ability at one point of (mid)life and cognitive changes at follow-up. A systematic literature search identified 20 longitudinal studies. The average follow-up time was 4.5 years. Gait speed quantified walking ability in most studies (n=18). Additional gait measures (n=4) were step frequency, variability and step-length. Despite methodological weaknesses, results revealed that gait slowing (0.68-1.1 m/sec) preceded cognitive decline and the presence of dementia syndromes (maximal odds and hazard ratios of 10.4 and 11.1, respectively). The results indicate that measures of walking ability could serve as additional markers to predict cognitive decline. However, gait speed alone might lack specificity. We recommend gait analysis, including dynamic gait parameters, in clinical evaluations of patients with suspected cognitive decline. Future studies should focus on examining the specificity and accuracy of various gait characteristics to predict future cognitive decline.

Keywords: Dementia, cognitive impairment, biomarker, gait, MCI, prediction models



INTRODUCTION

Rationale

The increase in the number of old adults nearly parallels the incidence of age-associated dementia worldwide [1, 2]. Data suggest that the pathophysiological processes of dementia may start several years or even decades before the eventual diagnosis [3, 4]. Patients progress from a preclinical phase during which the disease might have already started in the brain without overt clinical symptoms, followed by a period characterized by the presence of Mild Cognitive Impairments (MCI), culminating in a diagnosis of dementia [5]. In the absence of a cure, key strategies of disease management include early diagnosis, delaying disease onset, and a slowing of disease progression [6, 7]. Therefore, identifying markers that predict dementia is a major subject of current interest [8, 9].

Prediction of dementia is often studied in the context of MCI [10], which is a transitional state between a cognitively intact condition and dementia [11]. Patients with MCI have cognitive dysfunctions beyond those expected as a result of normal aging, yet the level of impairment is not severe enough to compromise the ability to perform activities of daily living [12]. Even though the published values vary, a recent review analysing population data (> 300 participants) estimated the prevalence of MCI to range from 16 to 20% in patients over age 60. Approximately 10 to 15% of these patients develop dementia annually [13]. This conversion rate is high, making it important to differentiate between patients who will develop dementia and those who will remain cognitively fit. Early identification of patients at risk for dementia might help to select those individuals who would benefit most from future interventions to delay disease onset and slow the progression of neurodegeneration [14].

Biomarkers in prediction models for dementia

Biomarkers are used to identify pre-dementia symptoms and can be broadly classified as (1) cognitive markers (test scores measuring cognitive functioning such as memory and executive function) and (2) biological markers (such as measures derived from cerebrospinal fluid and brain imaging). The most accurate predictors are memory tasks measuring long-delay free recall [15-19], the cerebrospinal fluid (CSF) markers A β 1-42/t-tau ratio [15, 20-22], and volumes of the hippocampal and entorhinal cortices [15, 20, 23-25]. However, single predictors seem to be insufficiently sensitive to predict conversion from MCI to dementia. Therefore, prediction models ultimately employ a combination of markers [26]. Nevertheless, such predictions are far from perfect, as age, duration of follow-up, subtype of MCI diagnosis, degree of cognitive decline (early versus late stage of MCI), and outcome (e.g., AD, mixed dementia) all seem to affect conversion rates [16]; [27]; [28]. For example, a recent study showed that both neuropsychological assessment and MRI variables can predict conversion to AD with 63% to 67% classification accuracy in patients with MCI both younger and older than 75, while CSF biomarkers reached this rate only in patients younger than 75 years old [16]. A systematic review about risk prediction models for dementia concluded that sensitivity and specificity values vary broadly between studies, (Area Under the Curve ranging from AUC = 50 to AUC = 87). In particular, specificity is low in numerous prediction models [29], complicating the clinical use of such models.

Taken together, these observations show that it remains a persistent challenge and should be a research priority to develop dementia prediction models that ultimately employ a combination of markers to differentiate between old adults who will and who will not develop dementia. Current prediction models show low to moderate predictive ability with large variability, making it necessary to explore new markers. A possible candidate is motor function, in which walking ability may serve as a potential marker in the prediction of cognitive decline [30-32].

Walking ability as a predictor of cognitive decline

The original observation of a correlation between motor and cognitive impairments was reported nearly two decades ago. The data suggested that motor slowing (e.g., low walking speed) precedes cognitive decline in healthy older adults [33], a finding substantiated by the relationship between reductions in gait function and the development of dementia [34]. Numerous cross-sectional and longitudinal studies have recently confirmed these initial findings [35-38].

Viewing walking as a complex task could increase its validity to serve as a marker for early cognitive decline. Indeed, imaging and brain stimulation studies suggest that higher brain centres are involved in the planning and execution of normal human locomotion [39] and balance [40, 41]. The widespread network of brain areas that control walking involves regions responsible for attentional, executive and visuospatial functions as well as areas needed to perform and control motor tasks, such as the cerebellum, basal ganglia and motor cortex [42]. Thus, there is an overlap between areas that control walking and areas that control cognitive functioning, explaining the relationship between dementia-related pathology and gait dysfunction. The co-occurrence of decline in both cognitive and gait function favours a 'common-cause' mechanism [43]. There is considerable evidence for the role of white matter damage in age-related cognitive decline and dementia [44, 45]. In addition, reduced grey and white matter volumes in multiple brain regions and white matter hyperintensities are associated with gait dysfunction (gait speed of <0.5 m/s) in old adults free from dementia [46].

Perhaps the simplest demonstration of the interrelationship between gait and cognition comes from dual task studies in which subjects perform a walking and cognitively demanding task concurrently [47]. 'Dual task cost', i.e., the magnitude of deterioration in gait performance measured during single vs. dual tasking, arises from the two interfering tasks competing for the same cortical resources [48]. It is noteworthy that dual task costs are often higher in cognitively impaired compared to cognitively intact elderly [48-51].

The effects of decline in cognition on walking are especially expressed in the slowing of gait. A ubiquitous observation from cross-sectional studies is the reduction of gait speed in patients with MCI [52-54] and dementia [37, 38, 51, 55]. In addition to gait speed, spatial variability and stride time variability (STV) tend to increase in patients with MCI [56, 57]. However, for the time being, most studies have cross-sectional designs and are restricted to gait speed as a measure of walking ability.



Aims

The co-occurrence of gait dysfunction and decline in cognitive function as derived from cross-sectional studies suggests that measures of walking ability could serve as a marker in the identification of individuals at risk to develop dementia. To verify the possibility that gait dysfunction precedes cognitive decline, we set the aim of the present review to scope evidence from longitudinal studies that assessed whether or not there is a relationship between walking ability at one point of (mid)life and cognitive decline years later. In addition, we critically evaluate and discuss methodologies used to determine this relationship and to formulate recommendations for future studies to expand the preclinical phase of dementia.

METHODS

Scoping review

A scoping review method was adopted to explore the depth of evidence for the putative role of walking ability in the prediction of cognitive decline. A scoping review provides an appropriate method to systematically scan and evaluate evidence within a specific area of research and to identify gaps in the existing literature, allowing variation in methods between studies selected for inclusion [58, 59].

Literature search

A systematic literature search was performed for studies published from 1980 till May 2015 in PubMed and Embase using keywords specific to Embase thesaurus (EMtree) and to PubMed in the form of Medical Subject Headings (Mesh), combined with non-specific terms. We used a cognitive term (cognitive decline, MCI, cognitive impairment, dementia), combined it with a walking term (gait, walking, locomotion, motor performance, motor slowing), and terms representing a longitudinal study design (follow-up, longitudinal, long-term, prospective, cohort, predict). Filters further focused the search by removing various clinical conditions. Figure 1 presents the syntax.

Inclusion, exclusion criteria

The inclusion criteria were specified as followed: (1) Quantitative gait analysis measurements at baseline, (2) Study populations consisting of older adults with a mean age of 65 or older with significant cognitive decline or cognitive decline clinically diagnosed (e.g., MCI, dementia, Alzheimer's disease) at follow-up, (3) a longitudinal study design, and (4) English as publication language. The exclusion criteria were specified as followed: 1) Cognitive impairment with clinical diagnosis other than related to dementia (e.g., Multiple Sclerosis, Huntington's disease, and Parkinson's disease), 2) animal research, and 3) case studies. Duplicates and reviews were removed. Two reviewers were involved in the literature search and independently selected studies for in- and exclusion. Disagreement between the researchers was discussed until they reached consensus.

Data analysis

The literature revealed two types of studies investigating the relationship between walking ability and future cognitive decline, which are presented separately in the review: 1) longitudinal studies that examined associations between baseline walking ability and

within-person change in cognition at follow-up (with most results presented as beta-values) and 2) longitudinal studies that established risk estimates for cognitive decline at follow-up, with measures of walking ability as predictors (with most results presented as hazard ratios or odds ratios).

RESULTS

Literature search

The literature search revealed 431 studies of which after screening for title and abstract, 50 were assessed for eligibility by full-text analysis. Finally, 20 articles met the criteria for inclusion. A flowchart of the literature search and selection process is presented in figure 1.

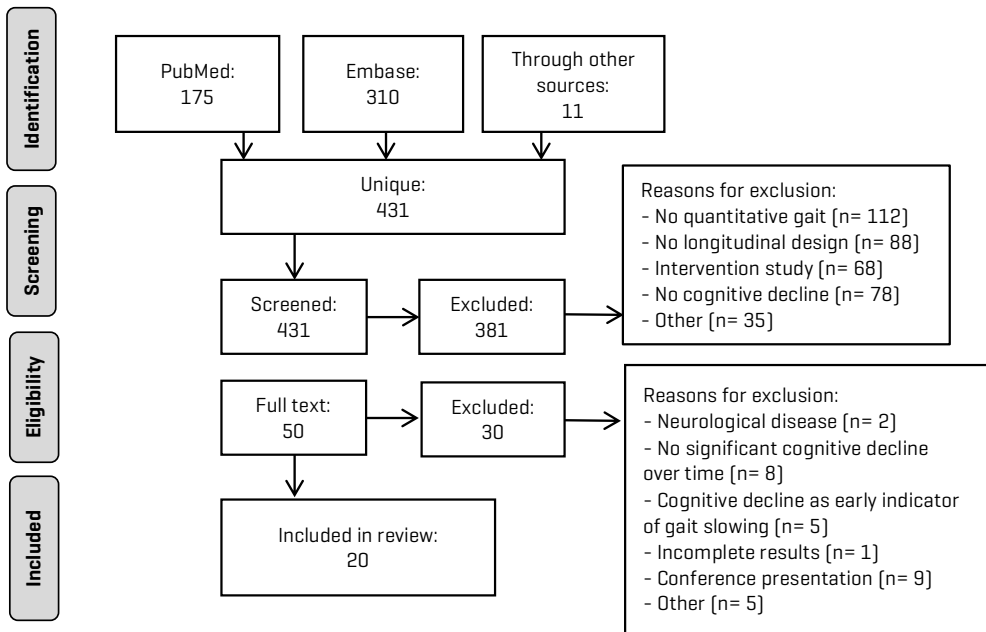



Figure 1. Syntax of literature search and selection process.

Study characteristics

Studies included in the current review were heterogeneous in terms of number of participants (ranging from 52 to 2776), age (> 60 to > 80) and length of follow-up (ranging from 2 to 9 years) and are based on data from 24,368 participants. Retention rate was 71% between baseline and follow-up measurement (n = 19 studies), with mortality accounting for most of the attrition. Two studies (10%) were sex-homogeneous (Table 2; Ref. 2 & 14) and sixteen studies (80%) showed large age ranges (> 10 years) or high standard deviations from the mean age (> 3 years). Patients were cognitively healthy at baseline in most studies (n = 17). Three studies included patients with pre-dementia syndromes at baseline [60-62]. Statistical models were adjusted for cofounding variables grossly representing the



following domains: sociodemographic (age, sex, education, gender), behavioural (physical activity, smoking), clinical conditions (heart disease, stroke, diabetes mellitus, hypertension, osteoporosis, arthritis, depression and pain), visual functioning (visual acuity), health-related (BMI, blood pressure) and genetic factors (APOE ε4 allele).

Measures of walking ability and cognitive function

Walking ability was mainly quantified using gait speed (n = 18 studies; 90%), either measured over a certain distance or by the completion of a bidirectional walk. Only a few studies (n = 3, Table 1; Ref 2 & 8 and Table 2; Ref 9) quantified walking by other gait characteristics such as step frequency, stride length, cadence, stance time, swing time and double support time. One study assessed multiple aspects of walking as revealed by factor analysis, namely pacing (loading on gait speed and step length), rhythm (loading on cadence and timing measures) and variability (loading on stride length variability and swing time variability) [63]. For the assessment of cognition as main outcome at follow-up, four studies (20%) used measures of global mental state (assessed by mini mental state examination (MMSE) or modified versions) (Table 1; Ref 1, 2, 4 & 5), four studies (20%) used measures of specific cognitive functions (e.g., memory, executive functioning and processing speed) (Table 1; Ref 3, 6, 7 & 8), and twelve studies (60%) used diagnoses of dementia syndromes (e.g., dementia, AD, MCI, vascular dementia) (Table 2; Ref 1, 2, 3, 4, 6, 8, 9, 10, 11, 12, 13 & 14). Cognitive state at baseline was assessed using various measurement instruments to indicate global mental state, such as the MMSE, and guidelines to indicate dementia syndromes, such as DSMM IV and clinical dementia rating (CDR) scale.

The relationship between walking ability and future cognitive decline

Longitudinal studies that examined associations between baseline walking ability and within-person change in cognition at follow-up

Table 1 presents the eight studies that determined the relative association between baseline walking ability and within-subject change in cognition at follow-up (n = 9,984). Baseline walking ability was quantified with gait speed in five studies (62.5%) with a mean habitual gait speed of 1.00 m/s (n = 7,532) measured on a straight course with distances ranging from 2.5 meters to 7 meters. The other three studies could not serve as a reference because the authors reported gait speed as ranges instead of a mean value (Ojagbemi et al., 2015) or used walking tasks involving a turn that slows gait and would bias the data in the present patient description (Alfaro-Acha et al., 2007; Katsumata et al., 2011).

Standardized beta-coefficients were reported as outcome measure with positive values indicating a yearly increase or preservation of cognition in relation to a unit higher gait performance at baseline, and negative values indicating a yearly decline in cognition in relation to a unit lower gait performance at baseline. For example, a unit increase in time to walk 8-feet predicts 0.21 points decline in MMSE score per year ($\beta = -0.21$, [64]). One study reported estimated test scores on mental state to indicate cognitive decline in relation to baseline walking ability and found an increase of 2.00 and 2.31 in square root of number of errors in the Japanese version of the MMSE, for slow and fast TUG time respectively [65]. All associations were relative to baseline walking ability of the reference group.

With respect to studies using measures of mental state as main outcome, slow gait speed at baseline was associated with decline in MMSE score at follow-up ($\beta = -0.21, p < 0.01$) (Table 1; Ref 1). In addition, longer step length in men at baseline was associated with preserved MMSE score at follow-up ($\beta = 0.162, p < 0.05$) (Table 2; Ref 2). Furthermore, faster gait speed at baseline correlated with preserved MMSE score at follow-up, but only under fast speed instructions ($\beta = 0.038, p < 0.05$) (Table 1; Ref 4). Finally, longer time to complete the TUG test was associated with decline in the Japanese version of the MMSE ($p = 0.03$) (Table 1; Ref 5). With respect to studies using measures of specific cognitive functions as main outcomes ($n=4$), faster gait speed at baseline was associated with preservation of executive functioning ($\beta = 0.036, p < 0.01$; $\beta = 0.060, p < 0.01$) (Table 1; Ref 3 & 6), memory ($\beta = 0.031, p < 0.05$; $\beta = 1.24, p < 0.01$) (Table 1; Ref 3 & 7), processing speed ($\beta = 0.025, p < 0.05$) [36] and visuospatial functioning ($\beta = 0.042, p < 0.05$) (Table 1; Ref 6) at follow-up. In addition to gait speed, impaired pacing at baseline was associated with a decline in the digit symbol test and letter fluency task (both relying on executive functioning) at follow up ($\beta = -0.73, p < 0.001$ and $\beta = -0.46, p < 0.001$, respectively) (Table 1; Ref 8). Impaired rhythm at baseline was associated with decline in memory at follow-up ($\beta = -0.15, p < 0.05$) (Table 1; Ref 8).

In summary, slow gait speed (under habitual and fast speed instructions) at baseline was related to decline in global mental state, executive function, memory performance, processing speed and visuospatial function, after a mean follow-up period of 4.3 years. Shorter step length in men and longer time to complete the TUG test at baseline were associated with decline in measures of global mental state at follow-up. Impaired rhythm at baseline was associated with decline in memory functioning and impaired pacing with decline in executive functioning at follow-up. The results indicate that slow gait speed precedes decline in mental state as well as in specific cognitive functions. Although there is limited evidence for gait characteristics other than gait speed, the results signify that dysfunctions in those characteristics also precede cognitive decline.

Longitudinal studies that established risk estimates for cognitive decline, with measures of walking ability as predictors

Table 2 summarizes 14 studies that examined the relative risk for cognitive decline, predicted by walking ability at baseline ($n = 14,384$). Participants developed dementia (43%), Alzheimer's disease (29%), vascular dementia (14%), MCI (7%) or other diagnosed cognitive impairment (50%), in which some studies examined multiple syndromes. Mean baseline gait speed of participants who remained free from significant cognitive decline at follow-up was 1.11 m/s, based on four studies providing this information ($n = 2,921$). In contrast, mean baseline gait speed of participants who developed dementia, MCI and cognitive impairment was respectively 0.8 m/s ($n = 2631$), 0.91 m/s ($n = 204$) and 0.68 m/s ($n = 85$). The other seven studies either used gait speed ranges, gait variability, pace or rhythm measures, or did not distinct between cognitive subgroups. Gait speed was measured over walking distances ranging from 2.5 meters to 9 meters.

Outcomes are presented as risk ratios (hazard ratio, odds ratio or relative hazard). Odds ratios (OR) were reported most often, with values above one signifying a higher relative risk compared to the reference group. For example, patients with slow versus fast gait speed at baseline were 2.28 times more likely to be diagnosed with dementia at follow-up



[66]. Second, hazard ratios (HR) were reported with values < 1.0 indicating a risk reduction in cognitive decline with better gait performance at baseline and values > 1.0 indicating increased risk at cognitive decline predicted from gait performance at baseline, both proportionally to a comparison group. For example, patients with motoric cognitive risk (MCR) syndrome had an 11-fold risk (HR = 11.1) to develop dementia at any given point in time [60]. One study reported a relative hazard of 1.57 [67], meaning that patients with slower gait speed at baseline were 1.57 times more likely to have developed dementia after 7 years compared to the reference group. Another study reported a transition point in the acceleration of gait speed decline 12.1 years prior to cognitive decline [68], indicating that changes in gait were already visible 12.1 years prior to significant cognitive decline.

With respect to studies using dementia as main outcome, slow gait speed at baseline was related to an increased risk for dementia at follow-up (OR = 2.28, $p < 0.05$; RH = 1.57, $p < 0.05$; HR = 2.72, $p < 0.05$; OR = 5.6; OR = 10.4; HR = 0.79, $p < 0.001$; HR = 0.78, $p < 0.01$; OR = 1.61, $p < 0.05$) (Table 2; Ref 1, 2, 11-14, respectively). Also, impaired rhythm and high variability at baseline were related to increased risks for dementia at follow-up (HR = 1.48, $p < 0.05$ and HR = 1.37, $p < 0.05$, respectively) (Table 2; Ref 10). In addition to studies examining the risk for dementia, several studies revealed that slow gait speed at baseline was also related to increased risk for Alzheimer's disease (OR = 3.38, $p < 0.05$; HR = 0.81, $p < 0.01$) (Table 2; Ref 1 & 13) as well as vascular dementia (HR = 11.10, $p < 0.001$) (Table 2; Ref 11) at follow-up. Note that in some studies patients were diagnosed with MCI at baseline (Table 2), explaining the large risk ratios [38, 61, 62]. Impaired pacing was also related to increased risk for vascular dementia (HR = 1.61, $p < 0.05$) (Table 1; Ref 10). The risk for significant cognitive impairments other than dementia syndromes at follow-up was determined using various definitions, for example > 3 points decline in MMSE score, > 0.5 points at the CDR scale, and more than 9 points decline in digit symbol substitution test (DSST) score. All studies concluded that slow gait speed at baseline predicted a significant increase in risk for cognitive impairment at follow-up. One study found shorter step length to be related to increased risk for cognitive decline and found higher risks for step length compared to gait speed and for gait under fast speed instructions compared to habitual gait speed [69].

In summary, slow gait speed at baseline was related to an increased risk for dementia, Alzheimer's disease, and significant cognitive decline as defined in specific studies, after a mean follow-up period of nearly 5 years. In addition, poor gait rhythm and high gait variability were related to increased risk for dementia, and worse performance on the pace factor was related to increased risks for vascular dementia. Altogether, the longitudinal data shows that slowed gait speed appears before cognitive decline is detected. Despite the limited number of studies reporting on other gait characteristics, the results of these studies point in the same direction.

DISCUSSION

The present scoping review aimed to examine the relationship between walking ability and future cognitive decline. The main finding supported the hypothesis that walking ability at baseline, independent of gait characteristic, has the potential to predict future cognitive decline through (1) an association between poor walking ability at baseline and within-person decline in cognition at follow-up and (2) a higher risk for cognitive impairment/dementia with poor walking ability at baseline as predictor variable. We provide an in-depth analysis of methodological inequalities between studies and synthesize the information into one key recommendation, i.e., clinicians should add walking ability as a quantitative and simple preclinical measurement to the array of tests used to predict cognitive decline in old adults.

The analyses of the longitudinal studies, with a mean follow-up period of 4.3 years, that examined associations between baseline walking ability and within-person change in cognition at follow-up (Table 1) revealed that slow gait speed (1.00 m/s) at baseline preceded decline in global mental state as well as in specific cognitive functions. A role for walking ability in the prediction of cognitive decline is supported by the finding that slower gait speed at baseline predicted increased risks for diagnostic outcomes related to dementia, after a mean follow-up period of nearly 5 years (Table 2). Mean baseline gait speed of old adults who developed dementia, MCI and cognitive impairment was respectively 0.8 m/s ($n = 2631$), 0.91 m/s ($n = 204$) and 0.68 m/s ($n = 85$), in contrast to mean baseline gait speed of participants who remained free from significant cognitive decline (1.11 m/s). Mean gait speed values are far beneath standard values of 1.15 [70], 1.22 (Hortobágyi et al., 2015), and 1.30 m/s [71] reported previously. In contrast, a mean gait speed of 1.00 m/s or lower is often used as a cut-off point for high risks for negative health outcomes such as hospitalization and death [72]. To rule out frailty, a reference of > 0.90 m/s is used [73]. Together, subject and gait characteristics suggest that the results are relevant to older adults who are cognitively healthy at baseline, mostly not frail, but less fit than healthy older adults. (Table 2).

Walking ability in the prediction of cognitive decline

Gait speed is most often used to evaluate the relationship between walking ability and future cognitive decline. This finding is not unexpected because gait speed is associated with many adverse health and clinical outcomes in healthy and mobility-impaired old adults [72, 74]. Slowing of habitual gait speed represents an important characteristic of reduced physical capacity as a result of the aging process, with slowing of gait speed up to 16% per decade in individuals over 60 [66, 71, 75]. A possible explanation for slow gait speed preceding the development of cognitive decline is that it may represent a marker of lesions in the brain resulting from pathophysiological changes related to cognitive decline. Age-related cognitive decline and dementia have been associated with white matter damage [44, 45]. This damage in white matter volumes in turn has been found to affect gait speed (gait speed of < 0.5 m/s), even in older adults free from dementia [46]. Thus, slowing of gait speed might be an early indicator of the presence of brain lesions. An additional explanation for the association between slow gait speed and cognitive decline may be found in the relationship between muscle strength and slow gait speed. Loss of muscle strength has been associated with high levels of inflammatory markers, low levels of corticosteroids and high oxidative

Table 1. Walking ability in the prediction of cognitive decline: longitudinal studies that examined associations between baseline walking ability and within-person change in cognition at follow-up.

Author, Year	Study	No. of participants	Follow-up (years)	Base-line age	Baseline gait (mean \pm SD)	Baseline cognition
Alfaro-Acha et al., 2007 [64]	Hispanic Established Population for the Epidemiological Study of the Elderly	1218	7	>65	Timed 8-foot walk (s): 7.7 \pm 6.4	MMSE: 26.5 \pm 2.9
Auyeung et al., 2011 [79]	General Population of Older Chinese	1514 men	4	>65	Gait speed (m/s): 1.04 \pm 0.21 Step length (m): 0.58 \pm 0.07	MMSE: 27.4 \pm 2.25
		1223 women	4		Gait speed: 0.94 \pm 0.19 Step length: 0.51 \pm 0.07	25.8 \pm 2.80
Gale et al., 2014 [36]	The English Longitudinal Study of Ageing	2654	6	60-90	Gait speed (m/s): 0.92 \pm 0.27	EF ^a : 19.57(5.85) Verbal memory ^b : 9.53(3.13) Proc speed ^c : 18.8(5.50)
Deshpande et al., 2009 [84]	The InCHIANTI study	584	3	>65	Gait speed (m/s): Usual: 1.23 \pm 0.26 Fast: 1.49 \pm 0.33 Dual-task: 0.98 \pm 0.28	MMSE: N.A.
Katsumata et al., 2011 [65]	Keys To Optimal Cognitive Aging (KOCO) Project	192	3	>80	- Fast or normal TUG time (<14s) - Slow TUG time (>14s)	JMMSE: N.A EF: N.A Memory: N.A
Mielke et al., 2013 [96]	Mayo Clinic Study of Aging	1158	4	70-89	Gait speed: 1.09 (95% CI 0.95,1.27)	Memory ^d : 0.21(-0.39,0.86) Language ^e : 0.26(-0.30,0.82) EF ^f : 0.34(-0.26,0.83) Visuospatial ^g : 0.26(-0.38,0.80) Global cognition ^h : 0.30(-0.25,0.90)

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Follow-up cognition	Main results	Change in cognition (in relation to baseline gait)
N.A.	Subjects in the lowest 8-foot walk time quartile (≥ 9 s) had greater cognitive decline over 7 years than those in the highest quartile (< 4 s) ($p < 0.001$). A unit increase in walk time predicts 0.21 points decline in MMSE score per year.	<u>Timed 8-foot walk:</u> β (SE) MMSE: -0.21 (0.06)**
N.A.	Shorter step length in men was associated with a lower MMSE score after 4 years ($p < 0.05$). A unit increase in step length predicts 0.162 points increase in MMSE score per year.	<u>Step length men:</u> β (95% CI) MMSE: 0.162 (0.013, 0.309)*
EF ^a : 19.03(6.28) Verbal memory ^b : 9.21(3.34) Proc speed ^c : 17.57(5.45)	Slower gait speed at baseline was associated with cognitive decline at follow-up in all domains ($p < 0.01$; $p = 0.015$; $p = 0.038$ respectively). A unit increase in gait speed is associated with 0.036, 0.031 and 0.025 less decline in cognitive functioning per year, respectively.	<u>Gait speed:</u> β (SE) EF: 0.036(0.013)** β (SE) verbal memory: 0.031(0.013)* β (SE) proc speed: 0.025(0.012)*
> 3 points decline in MMSE score	Slow gait at fast speed was a predictor of cognitive decline over 3 years ($p < 0.021$). A unit increase in gait speed was associated with 0.038 less decline in MMSE score per year.	<u>Gait speed:</u> β (SE) MMSE: 0.038(0.016)*
JMMSE: N.A EF: N.A Memory: N.A	Slow TUG time was associated with decline in JMMSE functioning after 3 years ($p = 0.03$) but was only cross-sectional associated with EF and memory. An increase of 2.00 and 2.31 in square root of number of errors in the JMMSE, for slow and fast TUG time respectively.	<u>Estimated test score global cognitive functioning:</u> Slow TUG (95% CI): 2.00(1.85,2.15) Normal TUG (95% CI): 2.31(2.08,2.55)
Memory ^d : N.A. Language ^e : N.A. EF ^f : N.A. Visuospatial ^g : N.A. Global cognition ^h : N.A.	A faster gait speed at baseline was associated with less cognitive decline in the following domains (EF $p = 0.001$, visuospatial $p = 0.013$, global cognition $p = 0.001$). A 1 m/s increase in gait speed was associated with a 0.060, 0.042 and 0.049 higher z-score in cognitive domains per year, respectively.	<u>Gait speed:</u> β (SE) EF: 0.060 (0.016)** β (SE) visuospatial: 0.042 (0.017)* β (SE) global: 0.049 (0.013)**



Table 1. Continued

Author, Year	Study	No. of participants	Follow-up (years)	Base-line age	Baseline gait (mean ± SD)	Baseline cognition
Ojagbemi et al., 2015 [97]	Ibadan study of aging (ISA)	1042	2	>65	Gait speed N.A. Gait quartiles	10-word delayed recall test: N.A.
Vergheze et al., 2007 [63]	Einstein Ageing Study	399	5	>70	Gait factors: Pace Rhythm Variability	Memory ⁱ : N.A. Digit symbol: N.A. Letter fluency: N.A. Digit Span: N.A.

NOTE. ***p < 0.001, **p < 0.01, *p < 0.05.

a. EF measured with animal naming b. Measured with intermediate and delayed recall c. Measured with the letter cancelation task d. Wechsler Memory Scale-Revised Logical Memory and Visual Reproduction tasks and the Auditory Verbal Learning task e. Boston naming test and category fluency f. Free and Cued Selective Reminding Test g. Picture completion and block design h. Global cognitive test scores i. Trial making test B and Digit Symbol Substitution subtest. SD= standard deviation, SE= standard error, CI= confidence interval, SD= standard deviation, EF= executive functioning, (J)MMSE= (Japanese version of) the Mini Mental State Examination, proc. Speed= processing speed, TUG= Timed Up and Go, N.A.= not available.

Follow-up cognition	Main results	Change in cognition (in relation to baseline gait)
10-word delayed recall test: 11.49±0.32	A slower baseline gait speed was independently associated with poorer follow-up cognition ($p=0.001$). The slowest gait category (>6.52s 3m) had 1.24 less words recalled at follow-up, compared to the fastest gait category (<4.82s 4m).	<u>Gait speed:</u> β (95% CI) recall test: 1.24 (0.48,2.00)**
Memory [†] : N.A. Digit symbol: N.A. Letter fluency: N.A. Digit Span: N.A.	Impaired pace and rhythm scores predicted cognitive decline in memory ($p=0.02$), digit symbol ($p<0.001$) and letter fluency ($p<0.001$). A 1 point increase in rhythm was associated with 0.15 points decrease in memory per year. A 1 point increase in pace score was associated with 0.73 and 0.46 decrease in digit symbol and letter fluency per year, respectively.	<u>Rhythm factor:</u> β (95% CI) memory: -0.15(-0.28,-0.02)* <u>Pace factor:</u> β (95% CI) digit symbol: -0.73(-1.15,-0.31)*** β (95% CI) letter fluency: -0.46(-0.82,-0.11)***

Table 2. Walking ability in the prediction of cognitive decline: longitudinal studies that established risk estimates for cognitive decline, with measures of walking ability as predictors.

Author, Year	Study	No. of participants	Follow-up (years)	Age	Baseline gait (by final diagnosis)	Baseline cognition
Abellan van Kan et al., 2012 [66]	The EPIDOS-Toulouse Cohort	647	7	>75	Gait speed (m/s): CH: 0.9±0.2 Dementia: 0.8±0.2	CH: SPMSQ >8
Abbott et al., 2004 [67]	The Honolulu-Asia Aging Study	2257	7	71-93	Timed 10 feet walk: N.A.	CH: CASI >74
Buracchio et al., 2010 [98]	Oregon Brain Aging Study (OBAS)	204	9	>65	Gait speed (m/s): CH: 0.96±0.23 MCI: 0.91±0.24	CH: MMSE ≥24, CDR=0, no depression (GDS)
Camicioli et al., 1998 [33]	Oregon Brain Aging Study	85	3	>65	Timed 30-foot walk (s): CH: 9.6±2.3 IC: 13.2±4.5	CH: CDR=0
Deshpande et al., 2009 [84]	The InCHIANTI study	584	3	>65	Gait speed (m/s): Usual: 1.23±0.26 Fast: 1.49±0.33 Dual-task: 0.98±0.28	CH: MMSE: N.A.

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Clinical decline or diagnosis at follow-up (cognitive measure)	Main results	Change in cognition (in relation to baseline gait)
<u>AD:</u> National Institute of Neurological Disorders/Alzheimer's Disease and Related Disorders Association <u>Dementia:</u> DSMM IV	Gait speed decline was an independently associated factor for subsequent dementia and AD as a continuous (m/s) and as a categorical variable ($p < 0.05$).	<u>Continuous gait speed:</u> OR (95% CI) dementia: 2.28(1.32,3.94)* OR (95% CI) AD: 3.38(1.80,6.33)* <u>Categorical gait speed:</u> OR (95% CI) dementia: 2.38(1.28,4.43)*
<u>Dementia:</u> DSMM III	Men who walked 10 feet in > 6 seconds, incidence was 20.2/1000 person-years compared with 13.1 per 1000 person years for those with gait times of 3 seconds or less.	<u>Timed 10 feet walk:</u> RH (95% CI) dementia: 1.57(0.77,3.21)*
<u>MCI:</u> CDR ≥ 0.5	The decrease in gait speed accelerated by 0.02 m/s/year ($p < 0.001$) occurring 12.1 years prior to the onset of MCI. Approximately 14 years prior to diagnosis in men, and 6 years in women.	<u>Change point</u> Years (95% CI): Men: 14.2(8.7, UNK) Women: 6.0(4.6, 9.5) Combined: 12.1(8.1, UNK)
<u>Impaired cognition:</u> CDR: >0.5	Patients who developed cognitive impairments had longer time to walk 30 feet at baseline compared to patients who remained cognitively intact ($p < 0.001$). Every 1-second increase was associated with an increased odds of cognitive impairment of 1.26 ($p = 0.05$).	<u>Timed 30-foot walk:</u> OR (95% CI) IC: 1.26(1.01, 1.6)*
<u>Significant cognitive decline:</u> > 3 points decline in MMSE score	Participants in the slowest quartile of usual (<1.08m/s) and 'dual task' speed (<0.81) were more likely to develop SCD ($p = 0.019$ and $p = 0.024$). Participants in the third (1.49-1.30m/s) as well as fourth (<1.30m/s) quartile of fast speed were more likely to develop SCD ($p = 0.005$ and $p = 0.002$). All compared to the fastest gait quartile.	<u>Usual gait speed:</u> OR (95%CI) (<1.08) SDC: 2.32(1.15–4.90)* <u>Fast gait speed:</u> OR (95% CI) (third) SCD: 2.71(1.35–5.46)** OR (95% CI) (fourth) SGD: 3.17(1.50–6.68)** <u>Dual-task gait speed:</u> OR (95% CI) (<0.81) SCD: 2.08(1.10–3.93)*



Table 2. Continued

Ho et al., 2001 [99]	General Population of Older Chinese	988	3	>70	Timed 16-foot walk (s): 11.2±5.76	<u>CH:</u> CAPE [®] : Score >8
Inzitari et al., 2007 [100]	Health Aging and Body Composition Study	2776	5	70-79	Gait speed: N.A. Gait quartiles	<u>CH:</u> DSST: 37±0.29
Marquis et al., 2002 [101]	The Oregon Brain Aging Study	108	6	>65	Time 30 feet walk (steps/s): CH: 1.73±0.31 PCI: 1.66±0.42	<u>CH:</u> MMSE ≥24
Taniguchi et al., 2012 [69]	General Population of Older Japanese	266 men 400 women	2.7	>70	Gait speed, step length, step frequency: N.A. Gait tertiles	<u>CH:</u> MMSE ≥24
Verghese et al., 2007 [63]	Einstein Ageing Study	399	5	>70	Gait factors: Pace Rhythm Variability	<u>CH:</u> N.A.
Verghese et al., 2013 [38]	Einstein Aging Study	767	3	>70	Gait speed (m/s): N.A.	<u>MCR:</u> IC, slow gait, intact IADL and no dementia (DSMM, IV) <u>Not-MCR</u>

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<u>Impaired cognition:</u> CAPE [®] : Score ≤7	Slow 16-foot gait time, was a predictor of cognitive impairment in men and women (p<0.05). Every 1-second increase was associated with an increased odds of cognitive impairment of 1.03 in women and 1.06 in men (p = 0.05).	<u>Timed 16-foot walk:</u> OR (95% CI) IC: women: 1.03(1.0,1.07)* men: 1.06(0.98,1.15)*
<u>Impaired cognition:</u> DSST <31.2±0.5	Participants with a relatively slow gait speed (<1.05m/s) were more likely to decline in DSST (>9 points) compared to participants with a high gait speed (≥1.35m/s) (p=0.01).	<u>Gait speed:</u> OR (95% CI) IC: 1.74(1.21,2.51)**
<u>PCI:</u> CDR ≥0.5	Time to walk 30 feet contributed independently to the time of onset PCI. A 1-second increase in time to walk 30 feet increased risk of 1.14 times of developing PCI (p=0.09).	<u>Timed 30-foot walk:</u> HR PCI: 1.14*
<u>Impaired cognition:</u> > 3 points in MMSE	Men in the slowest gait tertile of fast speed were 4.42 times as likely to develop cognitive decline compared to men in the fastest gait tertile (p<0.01) for step length. Women in the slowest gait tertile at usual gait speed were 2.43 (p<0.05) times for gait speed and 5.76 (p<0.01) times for step length as likely to develop cognitive impairment compared to women from the fastest gait tertile. At fast gait speed, these risks are 2.45 (p<0.05) and 3.18 (p<0.01) for respectively gait speed and step length.	<u>Fast gait speed:</u> <u>Step length:</u> OR (95% CI) IC: 4.42(1.65,11.84)**
<u>Dementia:</u> DSMM, IV <u>AD:</u> DSMM, IV + neuroimaging <u>Vascular dementia:</u> DSMM, IV + neuroimaging	A 1 point increase on baseline rhythm and variability factor scores was associated with increased risk of dementia with 1.48 (p=0.03) and 1.37 (p=0.02) respectively and a 1 point increase on baseline pace was associated with an increased risk of vascular dementia with 1.60 (p=0.02).	<u>Usual gait speed:</u> OR (95% CI) IC: <u>Gait speed:</u> 2.43(1.03,5.72)* <u>Step length:</u> 5.76(2.15,15.44)** <u>Fast gait speed:</u> OR (95% CI) IC: <u>Step length:</u> 3.18(1.35,7.49)** <u>Gait speed:</u> 2.45(1.02,5.89)* <u>Rhythm:</u> HR (95% CI) dementia: 1.48(1.03,2.14)* <u>Variability:</u> HR (95% CI) dementia: 1.37(1.05,1.78)* <u>Pace:</u> HR (95% CI) vascular: 1.60(1.06,2.41)*
<u>AD:</u> DSMM, IV <u>Vascular dementia:</u> DSMM IV + neuroimaging	Participants with MCR were at higher risk of developing dementia (p=0.013) and vascular dementia (p<0.001).	<u>Gait speed:</u> HR (95% CI) dementia: 2.72 (1.24,5.97)* HR (95% CI) vascular: 11.10(4.00,30.82)***



Table 2. Continued

Waite et al., 2005 [62]	The Sydney Older Persons Study	630	3 and 6	>75	5 meter- returned walk time: N.A. gait quartiles	<u>CH Dementia</u> <u>Preclinical</u> <u>phase</u>
Wang et al., 2006 [61]	Adult Changes in Thought (ACT) study	2288	6	>65	Timed to walk 10 feet: N.A. gait quartiles	<u>CH:</u> CASI >86 <u>MCI:</u> CASI ≤90
Welmer et al., 2014 [102]	Swedish National study on Aging and Care in Kungsholmen	1985	6	>60	Gait speed: 1.1±0.4 CH: 1.2±0.3 Dementia: 0.8±0.3	<u>CH:</u> MMSE >24

NOTE. ***p<0.001, ** p<0.01, *p<0.05.

SE= standard error , SD= standard deviation, CI= confidence interval , RH = relative hazard, OR= odds ratio, HR= hazard ratio, AD= Alzheimer's disease, IC= impaired cognition, MCI= mild cognitive impairment, PCI= persistent cognitive impairment, SPMSQ= short portable mental status questionnaire, CASI= cognitive abilities screening instrument, DSM-IV= diagnostic and statistical manual of mental disorders, CH= cognitively healthy, CDR= clinical dementia rating scale, GDS= geriatric depression scale, MCR= motoric cognitive risk syndrome, preEP= pre-extrapyramidal features, MMSE= Mini Mental State Examination, CAPE= clifton assessment procedure for the elderly, DSST= digit symbol substitution test, IADL= instrumental activities of daily living, SCD= significant cognitive decline, UNK= unknown, N.A.= not available.

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<p><u>Dementia:</u> DSMM IV + CDR <u>Impaired cognition:</u> mild or moderate dysfunction in cognition, insufficient for dementia <u>PreEP:</u> Slowed 5 meter-returned walk + (bradykinesia, tremor and/or rigidity). <u>Dementia and AD:</u> DSMM IV + National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer’s Disease and Related Disorders Association</p>	<p>Those with cognitive impairment in combination with gait and motor slowing (preEP) were the most likely to dement over the 3- and 6-year period compared to CH elderly. Sensitivity levels are high (80.4%) but specificity levels low (36.9%)</p> <p>Better performance of 10-foot timed walk at baseline was associated with less risk of dementia ($p<0.001$) and AD ($p<0.01$), per 1 point increase in test score. In MCI patients, better gait performance was associated with lower risk of dementia ($p<0.01$).</p>	<p><u>5-meter returned walk:</u> OR (95% CI) dementia: over 6 years 5.6(2.5,12.6) over 3 years 10.4(3.6,30).</p> <p><u>Timed 10-foot walk:</u> HR (95% CI) dementia: 0.79(0.70,0.81)(0.71,0.81) HR (95% CI) with MCI at 0.78(0.66,0.91)</p>
<p><u>Dementia:</u> DSMM IV</p>	<p>Each SD slower baseline gait speed increased the likelihood of incident dementia. Slowing of gait speed appears to occur secondary to slowing of processing speed in the path leading to dementia.</p>	<p><u>Gait speed:</u> OR (95% CI) dementia: 1.61(1.31,1.98)</p>



stress [76, 77], which in turn are strongly related to cognitive decline [78]. Slow gait speed might thus represent a hallmark for a loss of muscle strength, resulting from the early pathophysiological changes in the process of cognitive decline. Taken these observations together, a plausible assumption is that physical impairment is one of the core features in the development of cognitive decline. Therefore, gait speed may be a useful proxy in the prediction of cognitive decline in old adults.

While gait speed is an important marker of mobility and cognitive function, focusing on gait speed alone might be overly simplistic. Explaining, when gait was expressed in one of its elements (step length), the relation with cognitive decline in women was stronger than with gait speed [69]. Furthermore, step length in men correlated with future cognitive decline, while the association between gait speed and cognitive decline remained non-significant [79]. Thus, the relationship between gait slowing and future cognitive decline is presumably strengthened when gait speed is expressed in its more specific elements.

A more comprehensive gait analysis that moves beyond gait speed, including dynamic metrics of gait (e.g., gait smoothness, regularity, stability; [37, 51]0)), could increase the specificity of the relationship with future cognitive decline. For example, studies included in the present review showed that pace, rhythm and variability of gait were uniquely related to decline in specific cognitive functions and types of dementia [80]. Because comorbidities and other conditions (e.g., low back pain, osteoarthritis, medication) and their detrimental effects on gait speed are common in older adults, dynamic metrics of gait compared with gait velocity might be more sensitive to predict cognitive decline. For example, cross-sectional studies showed that indices of gait variability have the potential to distinguish between fallers and non-fallers [81, 82], age-groups [83], and patients with different conditions [37, 50, 51]. Therefore, measures of gait variability and stability could possibly strengthen the gait cognition link.

The type of gait test in terms of speed instructions or dual tasking can also affect the sensitivity of the prediction of cognitive decline. Compared with habitual gait speed and gait speed during 'walking-while-talking' in 660 old adults aged over 65, only fast gait speed (1.49 m/s) was associated with cognitive decline at 3-year follow-up [84]. However, the speed of the gait test may interact with gender because step length at maximum walking speed predicted cognitive decline in men but not in women during a median follow-up of 2.7 years in the 16.5% of the originally cognitively intact 853 old adults age over 70 [69]. While intuitively it seems attractive to propose that fast vs. habitual gait speed is more effective in predicting cognitive decline, additional longitudinal studies are needed that assess variants of gait tests along the continuum of gait challenges. One way to improve the interpretation of dual-task performance is to measure performance in each single task and also in the dual task condition and determine whether or not the decline in gait speed during dual tasking is caused by insufficient cognitive recourses or rather by an over-allocation of resources to the cognitive task [85]. In addition, gait might be differentially affected by the complexity and type of the dual task [50]. Considering these observations, the relationship between walking ability and future cognitive decline is likely to be influenced by speed instructions as well as by the type of cognitive task.

Methodological considerations

Studies included in the present scoping review were heterogeneous in terms of number of participants, age, duration of follow-up, and measures used to indicate walking ability and cognitive state. In some cases, assessable information was inconsistent and/or incomplete. For example, it appeared difficult to interpret the exact size of the effect on cognitive function because absolute or 'net' change in cognitive decline when measured at follow-up was rarely reported. Predictions reached significant values whereas effects sizes appeared to be small, which might be the result of a large number of participants included.


In addition to methodological considerations regarding interpretation of clinical relevance, critical notes with respect to measures indicating walking ability and cognitive function needs to be addressed. For example, some studies used a very short distance, such as 8 feet, to indicate gait speed. Considering acceleration and deceleration phases, this distance might be too short to measure gait speed [86]. In addition, measures of global mental state were often used to indicate baseline cognitive state as well as to determine cognitive decline at follow-up. However, the MMSE has been proposed solely suitable as a screening tool to indicate whether patients need further cognitive testing [87]. Thus, measures of MMSE optimally should be expanded with more specific neuropsychological testing. Despite such methodological limitations, the results converge towards a consensus that measures of walking ability could serve as a marker in the prediction of cognitive decline.

Public health priority

The composition of accurate markers in the prediction of cognitive decline/dementia is crucial to select those individuals who might benefit most from intervention strategies. Evidence from longitudinal studies show that the presence of vascular risk factors, including for example diabetes, high blood pressure, smoking, high cholesterol and being overweight increases the risk for developing dementia later in life [88, 89]. Additionally, physical activity and individualized diet reduce the risk for dementia [90-93]. Modifying vascular risk factors by adopting a healthy lifestyle might thus preserve cognitive functions and/or postpone dementia. As a result, several large-scale prevention studies target vascular and lifestyle related risk factors, aiming to develop multi-domain interventions to prevent cognitive decline among older adults: the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), the Prevention of Dementia by Intensive Vascular Care (PreDIVA), the Multi-domain Alzheimer Preventive Trial (MAPT) and the European Dementia Prevention Initiative (EDPI) project. In summary, the effectiveness of interventions to slow the process of neurodegenerations starts with the selection of individuals at risk for cognitive decline, emphasizing the need to improve current dementia prediction models.

Limitations and recommendations

A possible limitation of our review is that we excluded studies that used observational gait analysis, which reduced the number of studies included in the review. However, sub-clinical gait abnormalities might be underestimated by observational gait analysis in the absence of quantitative methods [94]. Furthermore, the included studies may have suffered from the 'survival effect', meaning people who reached vs. those who dropped out were healthier at baseline. Such a bias tends to underestimate how accurately walking ability



can predict cognitive decline in the future. We also note the limitation that only 4 studies reported results separately for men and women. Therefore, we cannot be totally sure that the conclusions are not biased by combined analysis for men and women, supporting future studies to take into account sex-differences. Moreover, it is worth mentioning that the present study exclusively examined the relationship between walking ability and future cognitive decline, while the literature has shown more variables that predict cognitive decline, and that are also correlates of walking ability (such as medication use, diabetes and obesity). Therefore, prediction models should employ a combination of variables. Finally, the large heterogeneity between studies made it impossible to make a direct comparison between studies by means of a quantitative meta-analysis. Although we did not perform a meta-analysis but rather qualitatively discussed the results, the literature was searched systematically.

The results imply that there is an urgent need to examine the relationship between various gait characteristics on the one hand, and specific cognitive functions and dementia syndromes on the other hand. While there is a clear conceptual basis for the sensitivity of for example measures of gait variability in the prediction of cognitive decline, as derived from cross-sectional studies, longitudinal evidence is currently lacking. In addition, there is a need to develop guidelines that standardize administration, instructions, and distances for tests assessing walking ability [95]. Considering measures of cognitive state, consistent and specific measures could increase clinical interpretation, as for now the MMSE is mostly used to indicate and to rule out cognitive decline, while the MMSE has found to be unsuitable for such purposes. Finally, the types of task in terms of speed or dual task seem to influence the relationship between walking ability and future cognitive decline. It remains to be seen whether more vs. less challenging gait tests actually predict cognitive decline more accurately, as for now the longitudinal data are inconclusive.

Conclusions

It is a health priority to improve dementia prediction models. The present scoping review aimed to determine the relationship between walking ability at baseline and future cognitive state. The results emerging from 20 studies demonstrated that gait slowing preceded cognitive decline in mental state, specific cognitive functions and syndromes related to dementia, and support the hypothesis that measures of walking ability could serve as a marker in the prediction of cognitive decline. Therefore, we recommend to include quantitative gait analysis in the clinical routine evaluation of individuals with suspected cognitive decline. Future research should reduce methodological inequalities and specify the relationship between various gait characteristics and specific cognitive functions and dementia syndromes. The next step would be to examine whether the incorporation of walking ability in dementia prediction models actually increases disease prediction and classification accuracy.

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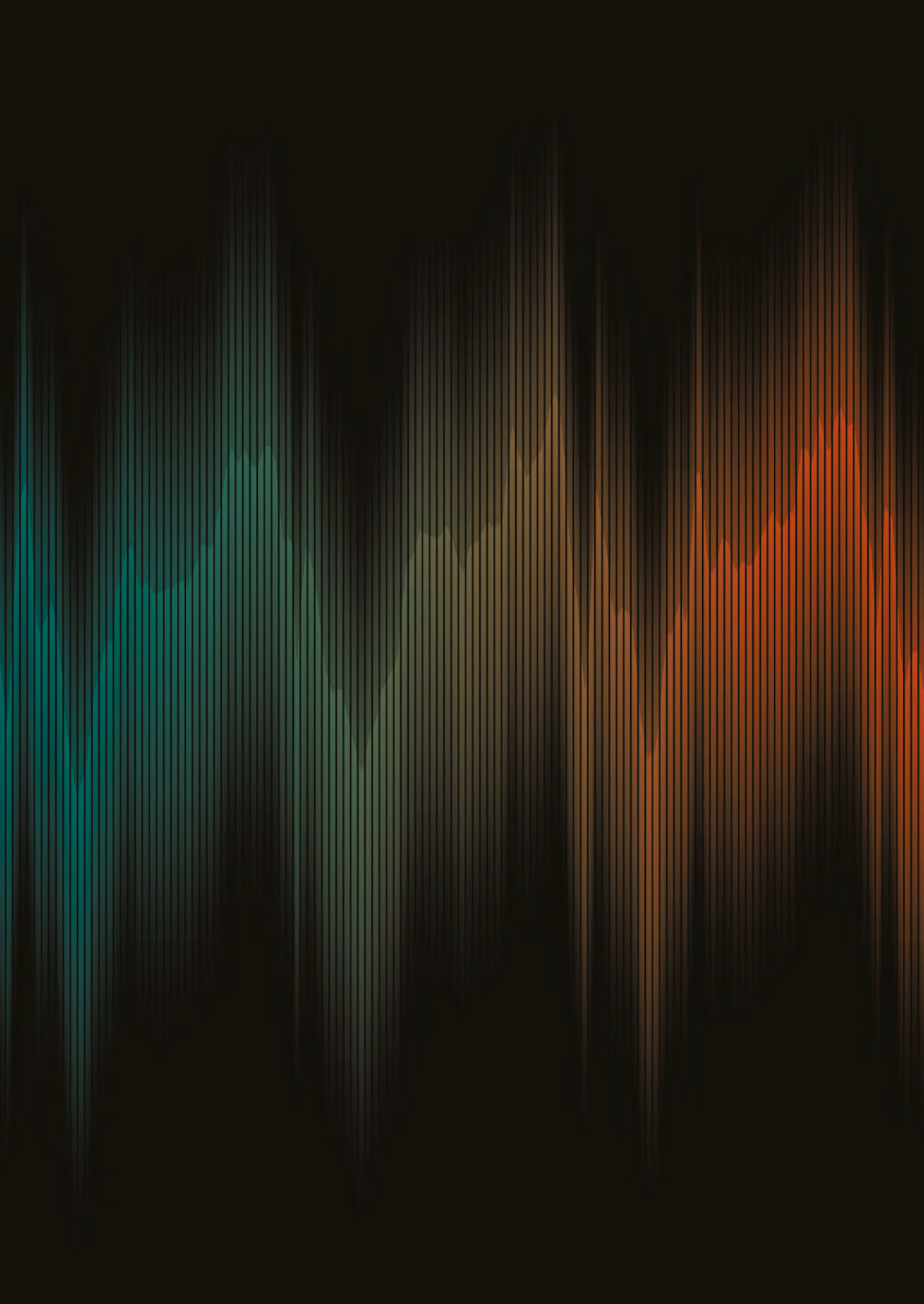


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3

GAIT DYNAMICS TO OPTIMIZE FALL RISK ASSESSMENT IN GERIATRIC PATIENTS ADMITTED TO AN OUTPATIENT DIAGNOSTIC CLINIC

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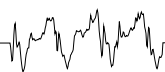
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ABSTRACT

Fall prediction in geriatric patients remains challenging because the increased fall risk involves multiple, interrelated factors caused by natural aging and/or pathology. Therefore, we used a multi-factorial statistical approach to model categories of modifiable fall risk factors among geriatric patients to identify fallers with highest sensitivity and specificity with a focus on gait performance. Patients ($n = 61$, age = 79; 41% fallers) underwent extensive screening in three categories: (1) patient characteristics (e.g., handgrip strength, medication use, osteoporosis-related factors) (2) cognitive function (global cognition, memory, executive function), and (3) gait performance (speed-related and dynamic outcomes assessed by tri-axial trunk accelerometry). Falls were registered prospectively (mean follow-up 8.6 months) and one year retrospectively. Principal Component Analysis (PCA) on 11 gait variables was performed to determine underlying gait properties. Three fall-classification models were then built using Partial Least Squares–Discriminant Analysis (PLS-DA), with separate and combined analyses of the fall risk factors. PCA identified 'pace', 'variability', and 'coordination' as key properties of gait. The best PLS-DA model produced a fall classification accuracy of $AUC=0.93$. The specificity of the model using patient characteristics was 60% but reached 80% when cognitive and gait outcomes were added. The inclusion of cognition and gait dynamics in fall classification models reduced misclassification. We therefore recommend assessing geriatric patients' fall risk using a multi-factorial approach that incorporates patient characteristics, cognition, and gait dynamics.



INTRODUCTION

Approximately 30% of all old adults aged 65 or older experience a fall at least once a year. Falls are associated with pain, functional impairments, morbidity, psychological side effects, and even mortality [1]. Preventing falls therefore remains a health care priority and early identification of individuals at risk is the first step in fall prevention. Older compared with younger adults are more likely to fall due to age-related declines in sensory, cognitive, and neuromuscular function, leading to an impaired gait [2]. Consequently, impaired gait and balance, in addition to demographic characteristics (e.g., gender, age, anthropometry, polypharmacy), are related to falls in community dwelling adults [3].

Age-related slowing of gait is the most documented gait outcome, with habitual gait speed slowing by 16% per decade after age 60 [4-6]. A gait speed below 1.0 m/s signifies potential clinical or sub-clinical impairment, such as mobility impairments, recurrent falling, loss of independence and institutionalization [4]. While most studies are concerned with gait speed as main mobility outcome, gait speed alone may lack sufficient specificity because multiple age- and clinical conditions also induce gait slowing (e.g., low back pain, osteoarthritis, and Parkinson's disease). In addition to gait speed, a variety of measures can quantify the dynamic nature and time-dependent variations of gait, such as detrended fluctuation analysis [7], sample entropy [8], harmonic ratio [9] and index of Harmonicity [10], reflecting the presence of long range correlations, gait predictability, gait symmetry, and gait smoothness, respectively. Each of these gait dynamics reflect a unique characteristic of gait and can be considered as complementary to each other. However, some gait measures are inter-related [11]. For instance, the coefficient of variation of stride time increases as gait speed decreases [12]. Factor analysis takes these inter-relations into account and reduces the dimensionality of the gait data by identifying underlying clusters of gait characteristics. Previous studies identified such gait clusters, reflecting different aspects of gait performance related to speed, variability, rhythm, coordination [13-16]. Hence, extracting properties of gait can provide fundamental insights into the meaning of gait function.

With respect to falling, accuracy of fall prediction models increases when characteristics of gait are included [17, 18]. For example, gait smoothness prospectively discriminated fallers from non-fallers in community dwelling old adults with a sensitivity of 68.8 % and a specificity of 84.2% [18]. In addition, the accuracy of fall prediction models based on clinical tests commonly used in fall risk assessments such as questionnaires, handgrip strength, and neuropsychological tests, increased by 0.14 when comprehensive gait analysis was added (AUC from 0.68 to 0.82, sensitivity: 70%; specificity: 81% [17]).

The accuracy of fall prediction models may be population-dependent and may not be generalizable to patients admitted to geriatric outpatient clinics. Geriatric patients are referred based on general or specific decline by a general practitioner, and are typically characterized by a combination of physical, psychological, and social problems. Hence, these patients can be considered vulnerable and present with an increased risk for adverse events such as falling, hospitalization, and ultimately death [19]. Geriatric outpatients thus differ from age-matched controls recruited from the community, and multiple comorbidities profoundly affect gait. Geriatric patients do not only walk slower than the clinical threshold

of 1.0 m/s [4, 20], but chronic conditions also modify gait dynamics. For example, 50% of geriatric patients use polypharmacy, which increases the risk for falls [21, 22]. Also, nearly 50% of geriatric patients suffer from osteoporotic vertebral fractures, a condition associated with an increase in thoracic kyphosis, decrease in gait stability, and increased fall risk [23, 24] which may be caused by osteoporotic vertebral fractures (VFs). Moreover, up to 30% of geriatric patients above age 60 present with sarcopenia, which is also associated with gait slowing and an increased fall risk [25]. Finally, the prevalence of cognitive impairment ranges from 22-71% in old adults above age 65 [26] and contributes to slow gait, increased gait variability, decreased gait stability, and increased fall risk [27].

Geriatric patients can thus be characterized by a unique set of variables that increases their risk for a fall. Hence, one approach to identify fallers is by grouping fall risk factors into categories, e.g., demographic characteristics typically assessed in clinical practice, cognitive function, as well as detailed gait performance, and use a multi-factorial data analysis method. Such an approach would allow us to examine the role of each factor in fall risk. Subsequently, it facilitates the development of personalized interventions strategies to modify medication [22], cognition [28], and physical activity levels [6]. The latter interventions can be considered crucial to fall-prone, geriatric patients. The present study therefore aims to statistically model categories of fall risk factors that identify geriatric fallers with the highest sensitivity and specificity, with a focus on gait. To this aim, we pursued two complementary objectives: (1) to identify unique gait properties by extracting underlying clusters from 11 gait measures and remove redundancies in these measures using factor analysis and (2) to examine if the sensitivity and specificity of a fall risk model improves when adding first cognitive measures to demographics, and adding then gait factors identified by the factors analysis. We hypothesized that different gait measures sum into the key features of gait, related to speed and dynamics. Because comorbidities are known to significantly affect geriatric patients' gait performance, we expect that sensitivity, specificity or both will increase fall classification when gait properties are added to the statistical model.

METHODS

Study Population

The present study included 61 patients (41 women and 20 men) of a database of patients that visited the geriatric dayclinic of the MC Slotervaart Hospital, Amsterdam between 2011 and 2013 [23, 29, 30]. Patients were admitted to the dayclinic based on a medical referral by a general practitioner and underwent extensive screening for physical, psychological, and cognitive functions. All outcome measures except for gait function, hand grip strength, and fall status were part of standard procedures at the diagnostic geriatric dayclinic of the MC Slotervaart hospital. Inclusion criteria were: age 70 or older. Exclusion criteria were: (1) Inability to walk for at least three minutes without a walking aid, (2) inability to speak and understand the Dutch language, and (3) having mobility disability caused by neurological or orthopaedic conditions, limiting function in one or both legs. The Medical Ethical Committee of the MC Slotervaart Hospital approved the study protocol. Written informed consent was obtained from all participants or their legal representatives.



Outcome Measures

Determination of Fall Status

A fall was defined as unintentionally coming to rest on the ground, floor, or other lower level [31]. Patients were interviewed retrospectively about the number of falls over the past year. Also, falls were prospectively registered with a 'fall calendar', for which patients were contacted monthly up to 12 monthly by telephone follow-up, with a minimum of 6 months. For patients with an MMSE-score below 24, fall history was obtained from a caregiver. A patient was classified as 'faller' when one or more falls occurred retrospectively or prospectively. Because the purpose of the present study was to examine (modifiable) factors involved in fall risk, we aimed to include the whole spectrum of fallers, including retro- and prospective fallers. Therefore, the study design was essentially cross-sectional.

Patient Characteristics

Demographic information including age, gender, and body mass index (BMI) were recorded. Maximal grip strength of the dominant hand [32], was quantified with a Jamar hand-held dynamometer (average of 3 trials). The number of comorbidities was categorized with the Charlson Comorbidity Index (CCI) [33]. Medications were classified according to the Anatomical Therapeutic Chemical (ACT) codes (WHO, 2013) and quantified as the total number of 'Fall Risk Increasing Drugs' (FRIDs), including psychotropic and diuretic drugs [22]. Lateral X-rays of the thoracic spine were analyzed to determine the degree of thoracic kyphosis, indicated by the Cobb angle between the superior endplate of the second thoracic vertebra and the inferior endplate of the twelfth thoracic vertebra [23]. Finally, fall risk was assessed according to the Longitudinal Aging Study Amsterdam (LASA) fall risk profile [34].

Cognitive Function

Global cognition was assessed with the Mini Mental State Examination (MMSE) with scores below 24 denoting cognitive impairment [35]. The 7-minute screen [36] was administered to assess memory and executive function using the Benton's Temporal Orientation (BTO), the Enhanced Cued Recall (ECR), the animal verbal fluency and the clock drawing test.

Gait Performance

All patients walked 160 meters at habitual speed on an 80-meter long hallway. A tri-axial accelerometer (87x45x14 mm; sample frequency 100 Hz; Dynaport® MiniMod, McRoberts BV, The Hague, the Netherlands) was attached to the lower back at the level of the third lumbar spine segment to measure medio-lateral (ML) and anterior-posterior (AP) trunk accelerations. Vertical (V) acceleration signals were not analysed because peaks in these signals sometimes showed clipping and were therefore unreliable. Acceleration signals were analysed with custom-made software in MATLAB (version 2014b; The MathWorks, Inc). Except for the calculation of the Sample Entropy, the signals were corrected for horizontal tilt and low-pass filtered with a 2nd order Butterworth filter with a cut-off frequency of 15 Hz. Outliers due to turns were removed from the data using a median filter. We determined 11 gait outcomes, reflecting different and complementary gait properties.

Walking speed was calculated by dividing distance walked by the time. Peak accelerations from AP signals were used to detect time indices of left and right foot contacts. Mean and coefficient of variation (CV) of stride times were computed from the time interval between

two consecutive ipsilateral foot contacts. Step consistency was quantified by the standard deviation (SD) of the relative phase between sequential ipsilateral indices of foot contact [37]. Higher SD of the relative phase implies a more inconsistent gait pattern. Long-range correlations between strides were quantified by the scaling exponent α using detrended fluctuation analysis [7]. A value of $0.5 \geq \alpha \geq 1$ suggests the presence of long-range correlations and signifies that future fluctuations in strides are more accurately predicted by previous fluctuations.

The Root Mean Square (RMS) of the AP and ML acceleration quantified the variability in the magnitude of the trunk accelerations. The Index of Harmonicity (IH) was computed to examine the smoothness (frequency content) of the signal, using spectral analysis. Perfect smooth trunk accelerations would reveal an IH of 1 [10]. To quantify the degree of predictability of trunk acceleration time series, the Sample Entropy (SEn) was calculated [38]. A complete predictable (periodic) signal will adopt a SEn of 0, with a larger SEn representing a less predictable gait.

Statistical Analysis

Principal Component Analysis (PCA) with a Varimax rotation and Kaiser normalization was performed on the 11 gait variables to determine underlying gait properties, and to reduce the dimensionality of the data to unique factors. The number of extracted principal components (PC's) was determined by analysing the scree plot which reveals the percentage explained variance by each component (usually referred as 'factor scores'). PC's with eigenvalues larger than 1 were considered eligible for inclusion in the final model. The regression coefficients of the extracted PC's were then used for further analyses [14].

To examine the contribution of different fall risk factors, three Partial Least Squares Discriminant Analyses (PLS-DA) were performed using the PLS_toolbox for MatLab (version 3.7.1; Eigenvector Research Inc.). PLS-DA combines PCA and regression analysis and can handle data consisting of a large number of independent, highly collinear, inter-related variables with relatively few observations (subjects) [39]. Note that such a handling of multicollinearity is important, in particular with respect to gait outcomes (e.g., gait speed and stride time are highly correlated [40]). In the PLS-DA analyses, patient characteristics, cognitive and gait measures represented the independent variables (X), and fall-status the categorical, dependent variable (Y). The analysis seeks to find underlying latent variables (LV's) to investigate fundamental relations between the matrices X and Y by modelling the covariance structures in these two spaces, and removing common variance. All variables were normalized to unit variance. The optimal number of LV's was determined using the scree plot and defined at the level where a plateau phase in the goodness of prediction (Q2) was reached [39]. Cross-validation was performed using venetian-blind (number of data-splits: 7).

Three models were developed based on: (1) only patient characteristics, (2) patient characteristics and cognitive function, and (3) patient characteristics, cognitive function, and the regression coefficients derived from the factor analysis; the gait factors. Outcome measures of the PLS-DA included scores (individual patient's observations) and weights (contribution of fall risk factors to the model), quantifying the relationship between fall risk factors and fall status. The variance explained reflected how variables are clustered within

each LV. Classification accuracy of the models was quantified as sensitivity, specificity, and area under the curve (AUC) based on Youden's criterion, and visualized with receiving operating characteristic (ROC) curves, with an AUC of 1 representing a perfect fit.

RESULTS

Patient characteristics

Table 1 shows characteristics for fallers (mean age 80.2±4.7) and non-fallers (78.8±5.1).

Falls

Retrospective fall data was registered from all 61 patients during the interview. From six patients, follow-up fall calendar data was obtained for less than 6 months, because patients changed address, or withdrawn from participation and did not want to be contacted any longer. The mean follow-up duration was 8.6 months. Twenty-five patients were classified as fallers (41%); 18 retrospective fallers, 19 prospective fallers, and 12 patients fell during the last year as well as during follow-up.

Table 1. Patient characteristics for fallers and non-fallers (mean ± SD).

Variable	Fallers (n = 25)	Non-fallers (n = 36)	
<i>Patient characteristics</i>			
Body Mass Index (kg/m ²)	27.7 ± 4.2	26.0 ± 3.5	
Handgrip ^a (Newton)	23.7 ± 8.0	27.2 ± 8.8*	
Charlson Comorbidity Index ^b	1.6 ± 1.4	1.3 ± 1.2	
Longitudinal Aging Study Amsterdam fall risk profile ^d	8.0 ± 1.2	2.4 ± 0.4*	
Cobb Angle ^c (degrees)	52.0 ± 14.5	50.0 ± 12.7	
Fall Risk Increasing Drugs ^b (number)	1.3 ± 1.2	1.3 ± 1.4	
<i>Cognition</i>		<i>Scale</i>	
Mini Mental State Examination ^a	23.1 ± 4.8	23.8 ± 3.7	0 - 30
Benton's Temporal Orientation test ^b	19.2 ± 6.4	10.0 ± 3.3	0 - 113
Enhanced Cued Recall test ^a	11.7 ± 4.1	10.4 ± 5.0	0 - 16
Clock Drawing test ^a	10.1 ± 2.5	10.6 ± 2.5	0 - 14
Verbal Fluency test ^a	13.3 ± 1.5	14.1 ± 0.9	0 - 40

* p < 0.05.

^a. A higher score indicates better performance. ^b. A higher score indicates worse performance.

^c. Values above >50 affect postural control. ^d. A score of ≥ 8 points indicates an increased risk for recurrent falling.

Gait Analysis

Three PC's with eigenvalues > 1 and absolute factor loadings > 0.4 explained 67.50% of the total variance of the 11 gait measures. PC1 reflected measures related to gait speed, stride times, and the amplitude of trunk accelerations and was labelled 'pace'. PC2 and PC3 represented measures related to gait variability and coordination respectively, and were labelled 'variability' and 'coordination' (Table 2). These three identified gait components were then used for the PLS-DA analyses below.

The PLS-DA Models

Table 3 and Figure 1 show the results of the three PLS-DA models. Model 1 included 3 LV's, model 2 also included 3 LV's, and 5 LV's were extracted for model 3. Note that in all models, LV1 explains most of the variance in the independent variables (X) and falls (Y), followed by LV2 and by LV3, but based on the Q2 criteria, five LV's were included. Classification accuracy of the first model with patient characteristics increased from 0.86 to 0.90 (AUC) when cognitive measures were added. Model accuracy further increased from 0.90 to 0.93 (AUC) when the principal gait components derived were subsequently added. In particular specificity increased in the second model from 60% to 72% and reached 80% when gait measures were included.

Table 2. Loadings of the gait variables (eigenvalue >1 and absolute loadings > 0.4) as revealed by PCA with Varimax Rotation.

Gait measures	Pace	Variability	Coordination
Walking Speed	-.848		
Root Mean Square AP	-.844		
Root Mean Square ML	-.820		
Index of Harmonicity ML	.791		
Stride Time	.748		
CV Stride Time	.583	.435	
Step Consistency		.781	
Long range correlations		-.774	
Sample Entropy AP		.677	
Sample Entropy ML			.850
Index of Harmonicity AP			.512

CV = Coefficient of Variation; AP = Anterior-Posterior; ML = Medio-Lateral.

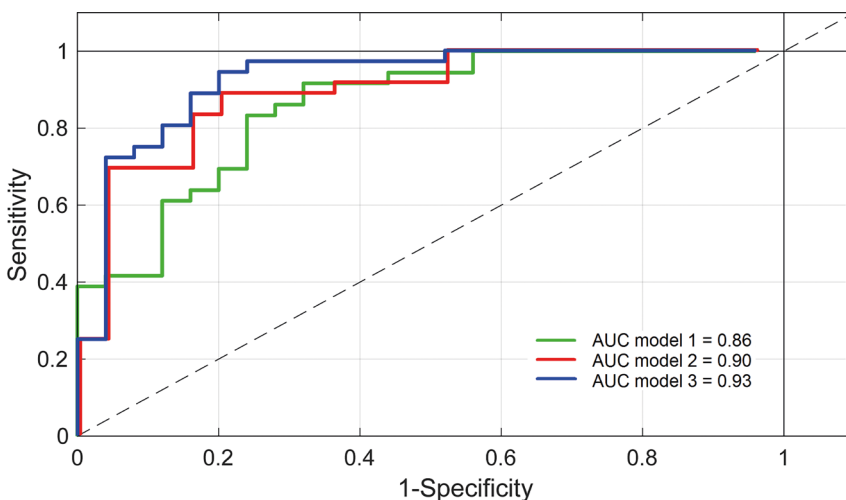


Figure 1. Receiving Operating Characteristic - curves for the three fall classification models. Model 1 = Patient characteristics; Model 2 = Patient characteristics + cognitive outcomes; Model 3 = Patient characteristics + cognitive outcomes + gait outcomes. AUC = Area Under the Curve.



Table 3. Characteristics of the three PLS-DA models: Number of latent variables, variance explained in X (fall risk factors) and Y (fall-status), and classification accuracy of fallers and non-fallers.

Model	Factors included	Number of LV's	X-block (%)	Y-block (%)	Sens. (%)	Spec. (%)	AUC	
1	Patient characteristics	3	LV1	23.7	32.5	92	60	0.86
			LV2	15.0	6.5			
			LV3	15.9	0.7			
			Sum	54.5	39.7			
2	Patient characteristics + cognition	3	LV1	15.1	34.5	89	72	0.90
			LV2	13.1	9.5			
			LV3	20.5	2.1			
			Sum	48.7	46.1			
3	Patient characteristics + cognition + gait	5	LV1	31.8	33.6	92	80	0.93
			LV2	7.8	13.5			
			LV3	18.4	1.3			
			LV4	7.5	1.4			
			LV5	5.3	0.8			
			Sum	52.4	50.7			

LV = Latent Variable; AUC = Area Under the Curve; Sens = sensitivity; Spec = specificity

Table 4 presents the amount of explained variance per independent variable of each included LV of the final model (model 3). The results signify that X-variables are clustered within the LV's. Motor performance (gait components and handgrip strength) and the LASA were mainly presented in LV1, cognitive function in LV2 and LV3, and patient characteristics in LV4 and LV5.

Biplots of the final model provide a graphical representation of the Y-variable (falls) and weights of the X-variables (patient characteristics, cognitive outcomes, and gait outcomes) with respect to the LV's (Fig 2). Fallers and non-fallers present in sharply separated clusters. The coordinates (size) of the weight vectors reflect the importance of the X-variable to the LV's. In this figure, the direction of the vectors reflects how these X-variables relate to fallers or non-fallers. The weights show that LASA, BTO, BMI and gait pace are particularly relevant in the identification of fallers, whereas handgrip, clock drawing, verbal fluency, gait variability, and gait coordination are relevant in the identification of non-fallers.

Table 4. Explained variance (%) per independent variable of the 5 extracted Latent Variables in model 3.

Independent variable	LV1	LV2	LV3	LV4	LV5	Sum
<i>Gait</i>						
Gait Pace	12.2	0.0	6.0	2.2	1.0	22.2
Gait Variability	0.3	5.9	5.5	7.2	2.1	21.0
Gait Coordination	20.4	13.3	1.3	0.4	3.6	39.0
<i>Cognition</i>						
Mini Mental State Examination	7.7	0.5	58.7	7.5	4.6	86.6
Benton's Temporal Orientation test	1.7	0.5	58.7	0.5	1.3	62.7
Enhanced Cued Recall test	6.3	5.5	53.4	0.1	4.8	70.0
Clock Drawing test	9.1	12.9	21.7	0.7	8.5	52.0
Verbal Fluency test ^a	10.4	15.5	28.1	16.1	0.1	70.3
<i>Patient characteristics</i>						
Fall Risk Increasing Drugs	2.8	8.2	2.3	18.4	4.5	36.2
Charlson Comorbidity Index	0.2	6.0	9.0	21.1	0.0	36.4
Body Mass Index	3.8	8.3	4.1	28.9	26.4	71.5
LASA	74.4	2.4	0.7	1.4	5.6	84.5
Handgrip	40.9	15.6	8.9	0.2	0.6	66.2
Cobb Angle	2.5	0.8	0.0	0.0	10.6	13.9

LV = Latent Variable; LASA = Longitudinal Aging Study Amsterdam

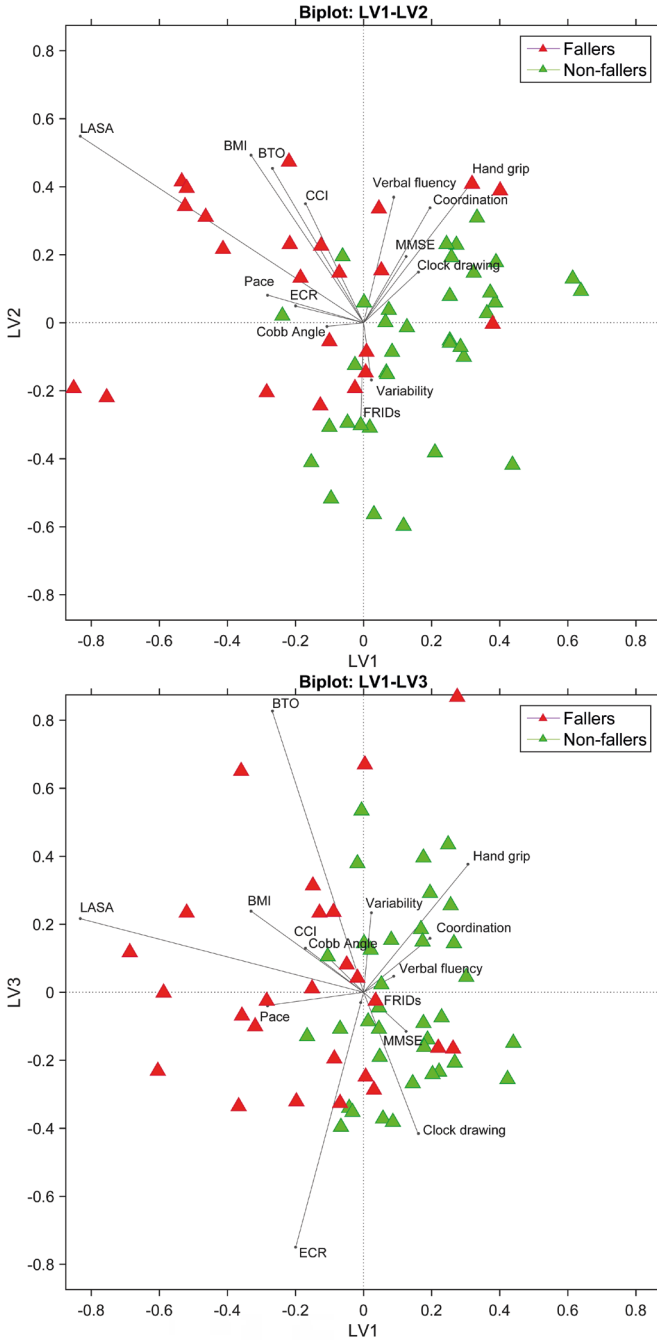
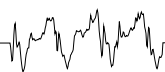


Figure 2. Biplots of Latent Variables (LV's 1 vs. 2 (left trace) and LV's 1 vs. 3 (right trace) provide a graphical representation of the response variable (fall-status) and weights of the independent variables (patient characteristics, cognitive, and gait factors) with respect to the included LV's. As clearly shown, fallers and non-fallers (green and red respectively) are clustered. Weight vector size reflects the importance of the variable to the model. The direction of the vector refers to whether variables mainly relate to classification of fallers (sensitivity) or non-fallers (specificity). BMI = Body Mass Index; CCI = Charlson Comorbidity Index; LASA = Longitudinal Aging Study Amsterdam; FRIDs = Fall Risk Increasing Drugs; MMSE = Mini Mental State Examination; BTO = Benton Temporal Orientation; ECR = Enhanced Cued Recall.



DISCUSSION

We applied a factor analysis to speed- and dynamic-related measures of gait and we then statistically modelled combinations of factors that classified geriatric fallers with the highest sensitivity and specificity. The factor analysis identified pace, variability, and coordination as key properties of gait. A model that included patient characteristics, cognitive function, as well as gait performance produced high classification accuracy (AUC=0.93) and showed an increase in specificity from 60% to 80% compared to a model that only included patient characteristics. We discuss how a successful fall risk assessment in the future will most likely include a large array of variables to optimize the identification of fallers among geriatric outpatients.

First, PCA applied to 11 gait variables revealed three unique gait properties: pace, variability, and coordination. 'Pace' comprised speed-related measures, namely gait speed, stride time, and the amplitude of AP and ML accelerations (RMS). 'Variability' and 'coordination' are considered as gait properties that reflect the dynamics of gait and were mainly derived from trunk accelerations. The loading structure was consistent, except for the IH in ML direction, which loaded on the pace component (absolute loading: 0.791) while it was expected to load on the coordination component. This might imply that IH ML is related to gait speed. In general, the extracted components were comparable with components identified by previous studies [13-16].

Second, three PLS-DA models were generated and compared (Table 2 and Fig 1). The first model based on patient characteristics already produced high classification accuracy (AUC=0.86). LASA clearly outperformed the other variables, as indicated by the size of the weight vectors. LASA provides an extensive screening tool consisting of nine fall-related factors such as dizziness, fear of falling, alcohol intake, fall history, and education level [34]. Although sensitivity of this first model was quite high (80%), specificity remained relatively low (60%). A low specificity (i.e., true negative rate) hampers clinical application because non-fallers will be erroneously identified as fallers and such misclassifications may induce fear of falling and unnecessary interventions.

Adding cognitive measures to the model increased specificity by 12%, to 72% (Table 3). Age-related decline in gait and cognition co-occurs because brain areas that control gait partly overlap with brain areas that control cognitive function [2]. Gait dysfunction can thus be expected in the presence of cognitive impairment [27, 41] and an impaired gait control in turn increases fall risk. On the other hand, old adults rely on executive functions in daily activities that require divided attention (e.g., in traffic and walking while talking). Impairment in executive functions may thus cause dangerous situations and increase fall risk.

Adding gait outcomes to the model further increased the models' specificity by 8%, to 80% (Table 3). Progressive age-related deterioration in neuromuscular and neurophysiological function engenders decline in sensory systems, sarcopenia, slower movement time and central processing, all linked to deficits in gait and balance [42]. In particular gait components 'variability' and 'coordination' accounted for the increase in specificity, as indicated by the size and direction of the corresponding vectors towards non-fallers (high

specificity). These results support the idea that speed-related measures such as gait speed and (CoV) stride time (captured by the pace domain) may be sufficient for classifying fallers only. They do, however, lack specificity that could result in misclassification of non-fallers. Gait speed is widely recognized as an important variable associated with many clinical conditions later in life [4]. The results of the present study show that combining gait speed and speed-related measures with dynamic gait measures will increase specificity and thus classification accuracy. Hence, gait dynamics could be added to measures usually addressed in clinical practice. Nowadays, extensive gait analysis is more easily accessible for clinical practice due to the rapid development of off-the-shelf smartphones, iPods and similar smart devices. Equipped with built-in accelerometers and gyroscopes, the devices are light, inexpensive, easy to handle, and thus suitable to analyse gait in a clinic [43]. However, despite technological advances, we note that future studies should examine the clinical applicability of such smart devices.

While one could question whether the 8% gain in specificity is it worth to add gait performance to the screening assessments, we signify the importance of a correct fall prediction on a clinical level. Misclassification (non-fallers that are classified as fallers) may induce fear of falling and unnecessary interventions and therefore hampers clinical application. Future studies could compare the sensitivity of gait dynamics with existing fall risk tools that examine physical function in the identification of fallers and non-fallers, such as the Physiological Profile Assessment (PPA) test [44]. Such tests may complement each other and reduce the need for excessive testing. In addition, the integration of test results could help to unravel underlying mechanisms of gait dysfunction and neurophysiological changes.

Because of typical challenges associated with clinical research (e.g., recruitment, retention) in this patient group, the sample size of the present study was relatively small ($n=61$). As a consequence, because standardization of the follow-up period would induce an in-balance of fallers and non-fallers groups, we choose not to exclude the patients who did not complete the fall calendar for all 12 months. Although exclusion of those patients did not significantly change the results, we recognize this as a potential limitation. Finally, the generalizability of the present study can be considered challenging. However, an increasing number of hospitals is nowadays equipped with a specialized geriatric outpatient clinic. Therefore, assessments used in the present study are often part of regular screening methods, which facilitates applicability and generalizability.

In conclusion, geriatric patients represent a vulnerable population with an increased risk for falling. Fall risk assessment including modifiable fall risk factors revealed high classification accuracy (AUC = 0.93). Although patient characteristics can accurately identify fallers, the evaluation of executive function and gait dynamics reduced misclassification with an increase in specificity from 60% to 80%. Therefore, we underscore the need for a multifactorial approach in fall risk assessment in geriatric patients, including a comprehensive evaluation of patient characteristics, cognitive function, and gait performance. These fall risk factors should ultimately be targeted by individualized interventions to reduce fall risk.



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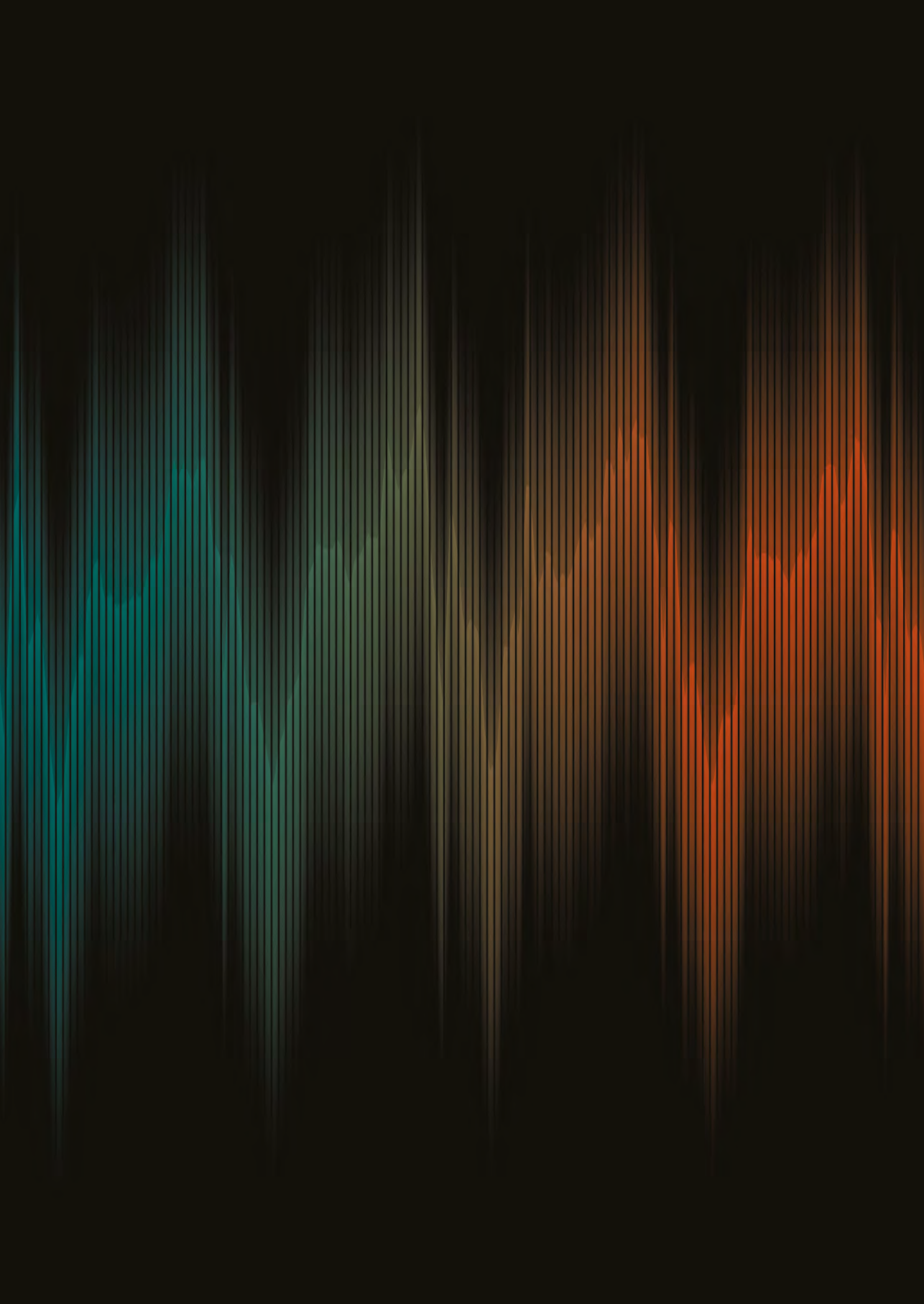
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4

GAIT CHARACTERISTICS AND THEIR DISCRIMINATIVE POWER IN GERIATRIC PATIENTS WITH AND WITHOUT COGNITIVE IMPAIRMENT

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ABSTRACT

Background: A detailed gait analysis (e.g., measures related to speed, self-affinity, stability, and variability) can help to unravel the underlying causes of gait dysfunction, and identify cognitive impairment. However, because geriatric patients present with multiple conditions that also affect gait, results from healthy old adults cannot easily be extrapolated to geriatric patients. Hence, we (1) quantified gait outcomes based on dynamical systems theory, and (2) determined their discriminative power in three groups: healthy old adults, geriatric patients with- and geriatric patients without cognitive impairment. *Methods:* For the present cross-sectional study, 25 healthy old adults recruited from community (65 ± 5.5 years), and 70 geriatric patients with ($n=39$) and without ($n=31$) cognitive impairment from the geriatric dayclinic of the MC Slotervaart hospital in Amsterdam (80 ± 6.6 years) were included. Participants walked for 3 minutes during single- and dual-tasking at self-selected speed while 3D trunk accelerations were registered with an iPod touch G4. We quantified 23 gait outcomes that reflect multiple gait aspects. A multivariate model was built using Partial Least Square- Discriminant Analysis (PLS-DA) that best modelled participant group from gait outcomes. *Results:* For single-task walking, the PLS-DA model consisted of 4 Latent Variables that explained 63% and 41% of the variance in gait outcomes and group, respectively. Outcomes related to speed, regularity, predictability, and stability of trunk accelerations revealed with the highest discriminative power ($VIP>1$). A high proportion of healthy old adults (96% and 93% for single- and dual-task, respectively) was correctly classified based on the gait outcomes. The discrimination of geriatric patients with and without cognitive impairment was

poor, with 57% (single-task) and 64% (dual-task) of the patients misclassified. *Conclusions:* While geriatric patients vs. healthy old adults walked slower, and less regular, predictable, and stable, we found no differences in gait between geriatric patients with and without cognitive impairment. The effects of multiple comorbidities on geriatric patients' gait possibly causes a 'floor-effect', with no room for further deterioration when patients develop cognitive impairment. An accurate identification of cognitive status thus necessitates a multifactorial approach.

Keywords: Gait dynamics, Cognitive impairment, Multivariate analysis, iPod touch, Trunk accelerations, Discriminant analysis, Geriatric patients.

INTRODUCTION

Even healthy aging modifies gait. Declines in muscle mass and quality, decreased sensory functions, reductions in muscle activation, and a reorganization of the cortical and spinal circuits controlling posture and gait underlie the age-related evolution of gait slowing and abnormalities [1, 2]. Indeed, habitual gait speed decreases as much as 16% per decade, starting at age 60 [3]. Because a slow gait speed predicts numerous clinical conditions later in life [4], gait speed is perhaps the most studied feature of physical performance affected by age.

Notwithstanding the attractiveness of gait speed as a simple summary index of mobility, numerous other characteristics of gait have been established to quantify and diagnose age- and pathology-related gait abnormalities. For example, stride-to-stride variability quantified by the Coefficient of Variation (CoV) is 5.3% in elderly fallers compared to 1.1% in age-matched non-fallers [5]. Measures derived from trunk acceleration signals can be used to characterize postural control during walking and standing by means of quantifying the frequency content, amplitude, self-affinity, variability, synchronization, regularity, and local stability of the lower trunk [6-9]. In the present study, we use the term 'gait dynamics', and refer to outcomes that are indicative of the dynamic nature of the gait pattern and reflect its stable and adaptive features. Gait dynamics can discriminate young and old adults [10], individuals with and without a clinical condition [11, 12], fallers and non-fallers [9, 13-16], and older adults with and without cognitive disorders [17, 18].

However, the results of the latter studies cannot easily be extrapolated to geriatric patients who typically suffer from many clinical conditions that also interact with gait performance. Among many, sarcopenia [19], thoracic kyphosis [11], polypharmacy [20], and cognitive impairment [21] can individually and in combination negatively affect gait. We therefore suspect that different combinations of gait measures are distinctive for geriatric patients vs. healthy old adults. Considering the abundant evidence supporting the effects of cognitive impairment on gait and its potential validity to serve as an early marker of cognitive impairment [21], we also expect that geriatric patients with additional cognitive impairment present with distinct gait characteristics. However, due to a lack of brain and neurophysiological correlates of specific gait outcomes, it is not yet possible to specify exactly which gait outcome corresponds to a clinical condition. A detailed gait analysis, including dynamic gait measures, can therefore help to unravel the underlying causes of gait dysfunction, and identify and predict clinical conditions. The identification of cognitive impairment could be even more accurate during walking while performing a cognitive dual-task [17, 22]. Because gait and cognitive function partly rely on the same cortical resources [23], performing a cognitive demanding task while walking stresses the system and potentially enlarge the effects of cognitive impairment on gait [17, 22].

Hence, the purpose of the study was to determine gait characteristics in three groups: healthy old adults and geriatric patients with and without cognitive impairment. Our hypothesis is that a detailed gait analysis (e.g., measures related to speed, self-affinity, stability, and variability) will (1) quantify unique gait characteristics of the three groups, and (2) accurately discriminate geriatric patients vs. healthy old adults, and geriatric patients with and without cognitive impairment. We derived gait outcomes from trunk acceleration



signals in 3D during single- and dual-task walking. Because certain gait outcomes are inter-related while others are complementary to each other, we performed a Partial Least Square – Discriminant Analysis (PLS-DA). PLS combines principal component and regression analyses and extracts gait features by modelling the covariance structures [24]. By delineating and quantifying the information contained in the dynamics of gait, we can identify gait features that are unique to healthy old adults, and geriatric patients with and without cognitive impairment.

METHODS

Participants

Seventy patients were recruited from the geriatric outpatient dayclinic of the MC Slotervaart hospital in Amsterdam between January 2015 and July 2016 (mean age 80 ± 6.6 ; 53% women). Inclusion criteria were: age 65 or older. Exclusion criteria were: (1) inability to walk for at least three minutes without a walking aid, (2) having neurodegenerative disorders other than related to dementia (e.g., Parkinson's), (3) inability to speak fluently Dutch, and (4) having mobility disability caused by pain or by neurological or orthopaedic conditions, limiting function in one or both legs. The Medical Ethical Committee of the MC Slotervaart Hospital approved the study protocol. Data of an additional group of 25 independently living healthy old adults (mean age 65 ± 5.5), recruited from the community, were also included [10]. The latter group of old adults were carefully questioned about their health, and were excluded if they had a history of orthopaedic, cognitive, or neurological problems, or if they used medication that would affect gait or postural control. Hence, this group can be considered a cognitive and physical healthy control group consisting of relatively young older adults.

Age, height, weight, BMI, The Charlson Comorbidity Index (CCI) [25] and the number of medications used (> 4 denoting polypharmacy), were extracted from medical records. Grip strength of the dominant hand was quantified with a Jamar hand-held dynamometer. Patients were diagnosed for cognitive impairment by a geriatrician and a neuropsychologist based on (1) medical records and (2) cognitive performance on the Mini Mental State Examination (MMSE) (range 0-30) [26] and the 7-minute screen (7MS) test. The 7MS assessed memory and executive function using the Benton's Temporal Orientation (range 0-113), the Enhanced Cued Recall (range 0-16), the animal verbal fluency (range 0-45) and clock-drawing test (range 0-14) [27]. Based on the evaluation of the two clinical experts, patients were categorized as either cognitive impaired or cognitive intact, with the cognitive impaired group including patients with a diagnosis for Mild Cognitive Impairment (MCI) or dementia.

Procedures and data analysis

Participants walked for three minutes at a self-selected speed on a 10-m long course that was marked with cones, under single- and dual-task conditions. In order to capture time dependent (over multiple stride cycles) patterns in the entire accelerations signals, participants were instructed to keep walking, and make comfortable turns around the cones. Because we were interested in the entire gait pattern over the 3 minutes and steps are considered dependent, turns were included in the analysis. When patients did not succeed to walk for 3 minutes, the longest continuous part of the signal was used for

the analysis. A phonetic fluency task was introduced in the dual-task condition, in which participants were asked to name as many words starting with the letters 'g', 'p', or 'r' (one minute per letter) while walking. A cognitive single-task with letters 'd', 'a', and 't' was used as control condition [28].

Trunk accelerations were registered with an iPod touch G4 (iOS 6, Apple Inc.; sample frequency $\pm 100\text{Hz}$) that was fixed with a belt near the level of lumbar segment L3. The validity and reliability of gait and standing posture parameters derived from trunk accelerations have been reported previously [29]. A custom-made application 'iMoveDetection' was used to collect and store acceleration data from the built-in tri-axial accelerometer of the iPod [29]. Anterior-posterior (AP), medio-lateral (ML), and vertical (V) acceleration signals were analysed with custom-made software in MATLAB (version 2014b, The MathWorks Inc.). The signals were detrended, corrected for horizontal tilt, and low-pass filtered (Butterworth filter, 4th order; cut-off frequency 10 Hz).

Gait outcomes

We computed 23 gait outcomes. Gait speed was calculated by dividing distance walked (m) by time (s). The variability of the amplitude of accelerations was indexed by the Root Mean Square (RMS). The Index of Harmonicity (IH) was calculated as an indicator of smoothness, using the power spectrum of accelerations. The IH was estimated as the cumulative sum of the power spectral density of the fundamental frequency (step frequency), divided by that of the subsequent 9 harmonics. An IH of 1 represents a perfect smooth gait [8].

The Cross-sample Entropy (Cross-SampEn) quantified the degree of synchronization between AP and ML, AP and V, and ML and V accelerations. Cross-SampEn is the negative natural logarithm of the conditional probability that epochs with length m that match point-wise in the two related signals, repeat itself for $m+1$ points, within a tolerance of r (in the present study $m = 2$ and $r = 0.2$). A Cross-SampEn of 0 reflects perfect synchronization between the signals [30].

Gait regularity and symmetry was calculated for AP and V accelerations using the unbiased auto-correlation function of the acceleration signal. The signal was phase shifted with a window approximating average step and stride time. The first peak in the autocorrelation coefficient function relates to step- and the second to stride regularity. A value of 1 reflects perfect regular steps or strides [31]. The difference between step and stride regularity revealed gait symmetry, with 0 representing a perfect symmetric gait [7].

Multi-scale sample Entropy (Mscale-En) is an indicator of gait predictability. Multi-scale entropy takes the complexity of a system into account by calculating the predictability of a signal over time scales with increasing length. A 'coarse-graining' process is applied to the acceleration signals; non-overlapping windows of data points with an increasing length τ are constructed, with τ representing the time scale with a tolerance of r (in the present study $\tau = 7$ and $r = 0.2$). A complete predictable signal will adopt a Mscale-En value of 0 [32].

Local stability of trunk acceleration patterns was expressed as the λ_{\max} , i.e., maximal Lyapunov exponent, calculated with the Wolf algorithm as this algorithm is most appropriate



to evaluate local dynamic stability from relatively small data sets [33]. For the present study, we used an embedding of $n = 5$ dimensions, with a time delay τ of 10 samples (0.1s). Larger λ_{\max} indicate greater sensitivity to local perturbations.

Finally, stride frequency variability (FreqVar) was computed from AP accelerations. FreqVar was estimated as the relative fluctuations in phase progression [6].

Statistical analysis

Differences in participant characteristics were examined with a one-way ANOVA with Bonferroni post-hoc test using SPSS version 24. Significance level was set at $p < 0.05$.

A Partial Least Squares Discriminant Analysis (PLS-DA), using the PLS_toolbox for MatLab (version 3.7.1; Eigenvector Research Inc.) was applied. PLS is a combination of principal component and regression analysis, and can handle data with a large number of highly collinear, inter-related variables (gait outcomes) with relatively few observations (participants) [24]. In contrast to usual regression analysis, PLS allows to study interrelations among multiple, interacting gait outcomes. Such a multivariate analysis thus controls for dependencies among gait outcomes and enables to consider the data in an overarching way. Note that this dealing with multicollinearity is crucial, in particular with respect to gait outcomes (e.g., gait speed and stride time are highly correlated). The PLS-DA model identified the internal covariance structure among gait outcomes (X-matrix) that best modelled group (Y-matrix) by removing common variance and by finding underlying latent variables (LV's). The optimal number of LV's was determined with the scree plot [24]. All variables were normalized to unit variance. For a more detailed mathematical explanation we refer to the study of Wold and colleagues [24]. The amount of variance explained of each gait outcome by the LV's indicated the modelling power of those outcomes in predicting the group. Note that a gait outcome without variation may be completely explained by the model, while this outcome may be unimportant to predict group. The Variable Importance in Projection (VIP) value reflects the importance of each individual gait outcome to the particular group. Gait outcomes with a VIP-score > 1.0 are considered important to the model and have a high discriminative power [24].

Violin plots based on the Kernel density distribution showed the distribution of gait outcomes for the three groups, and revealed peaks, bumps, and valleys in the shape of distributions [34]. The size of the kernels demonstrates the density between individual scores, with a large size reflecting heterogeneity among patients.

RESULTS

Thirty-nine of 70 geriatric patients were diagnosed with cognitive impairment (56%; 10 patients with dementia and 29 with MCI). Geriatric patients were significantly older (80 ± 6.6 years) than healthy old adults (65 ± 5.5 years). Geriatric patients with and without cognitive impairment presented with 1.8 serious comorbidities on average and met the criterion for polypharmacy (> 4). Both geriatric patient groups were comparable for all outcomes (age, BMI, handgrip strength, medication use, number of comorbidities), except for cognitive

function. Cognitive impaired geriatric patients performed significantly worse on the MMSE and on all sub-scales of the 7MS (Table 1). In addition, all groups performed significantly different on the cognitive single-task ($p < 0.00$), with a score of 14.2 words/minute for healthy old adults, and 10.3 and 7.4 words/minute for cognitive intact and cognitive impaired geriatric patients, respectively.

Gait outcomes were computed from 298 ± 50 strides on average (mean walking time 177 s, mean stride frequency 1.76 Hz) for single-task walking. For dual-task walking, outcomes were derived from 297 ± 45 strides on average (mean walking time 185 s, mean stride frequency 1.61 Hz).

Table 1. Characteristics of the 95 participants (mean \pm SD)^a

	Healthy old adults (n=25)	Cognitive intact geriatric patients (n=31)	Cognitive impaired geriatric patients (n=39)
<i>Demographics</i>			
Age (years)	65 \pm 5.5	79 \pm 5.3	82.0 \pm 7.2 ^{A, B}
Height (cm)	168 \pm 8.6	167 \pm 9.4	166 \pm 8.2
Weight (kg)	71.3 \pm 12.2	73.3 \pm 14.6	68.0 \pm 12.5
Body Mass Index	25.0 \pm 3.6	26.3 \pm 5.3	23.5 \pm 6.2
Gait speed ST (m/s)	1.20 \pm 0.10	0.88 \pm 0.22	0.81 \pm 0.22 ^{A, B}
Gait speed DT (m/s)	1.01 \pm 0.12	0.69 \pm 0.19	0.68 \pm 0.22 ^{A, B}
<i>Cognitive function</i>			
MMSE	N.A.	27.4 \pm 2.3	23.9 \pm 3.8 ^C
BTO	N.A.	4.2 \pm 13.8	17.1 \pm 29.9 ^C
Enhanced Cued Recall	N.A.	14.9 \pm 1.7	10.5 \pm 4.4 ^C
Clock drawing	N.A.	11.8 \pm 1.8	9.8 \pm 2.6 ^C
Verbal fluency	N.A.	18.2 \pm 6.6	12.3 \pm 4.1 ^C
<i>Geriatric syndromes</i>			
CCI	N.A.	1.9 \pm 1.8	1.7 \pm 1.3
Handgrip strength (kg)	N.A.	26.3 \pm 6.4	26.0 \pm 7.2
Medications (number)	N.A.	6.4 \pm 4.1	5.5 \pm 3.4

Significance set at 5%. ^A = significant difference between healthy old adults and geriatric patients; ^B = significant difference between healthy old adults and cognitive impaired geriatric patients; ^C = significant difference between geriatric and cognitive impaired geriatric patients. N.A. = Not applicable; MMSE = Mini Mental State Examination; BTO = Benton's Temporal Orientation; CCI = Charlson Comorbidity Index; ST = single task; DT = dual task.

Gait characteristics for the 3 groups

For single-task walking, the PLS-DA model contained 4 LV's that explained 63% and 41% of the variance in gait outcomes (X) and group (Y), respectively. Gait outcomes are logically grouped and divided over the 4 LV's, with the first LV explaining most of the variance in X and Y. Similarly, the PLS-DA model for dual-task walking consisted of 4 LV's, explaining 67% and 38% of the variance in respectively gait outcomes (X) and group (Y). VIP-values per group indicated the importance of the gait outcomes to the particular group. Gait outcomes related to speed, regularity, predictability and stability of trunk accelerations revealed with the highest discriminative power (VIP>1) for both single- and dual-task walking (Table 2).



The interpretation of the above results necessitates the direction of the relationship between gait outcomes and participant group. Violin plots show the distribution of the 23 normalized gait outcomes for the three groups during single-task walking (Figure 1). Both geriatric patient groups walked slower than healthy old adults. In addition, geriatric patients presented with smaller amplitude magnitude (RMS), more synchronization of trunk accelerations (Cross-Sample Entropy), less regularity and symmetry (step and stride regularity and symmetry), less stability (λ_{\max}), and more stride variability (Frequency variability). Gait smoothness (Index of Harmonicity) and gait predictability (Multiscale Entropy) were comparable for geriatric patients and healthy old adults, and showed large kernel sizes. As visible from the violin plots, differences between cognitive intact and cognitive impaired geriatric patients were small for individual gait outcomes.

Table 2. PLSDA model details during single- and dual-task walking for the three groups^a

Gait outcome	Variance captured per LV (%)					VIP-values					
	LV1	LV2	LV3	LV4	Total	Single-task			Dual-task		
						HO	CI	CIM	HO	CI	CIM
Gait speed	78	5	1	3	86	1.4	0.5	1.3	1.7	1.2	1.5
RMS AP	58	4	0	0	62	1.0	0.7	0.8	1.1	1.2	0.9
RMS ML	47	1	12	3	62	1.3	0.5	1.2	1.3	0.9	1.1
RMS V	76	0	3	2	81	2.0	1.2	1.9	2.2	1.6	1.8
IH AP	53	1	3	1	58	1.3	0.9	1.5	1.1	0.8	0.9
IH ML	0	0	24	8	33	0.2	0.4	0.5	0.1	0.0	0.2
IH V	3	11	11	13	37	0.3	1.7	0.2	0.2	0.1	0.1
Cross-SEn AP-ML	42	19	0	6	68	0.8	1.2	0.7	1.0	1.4	0.8
Cross-SEn AP-V	34	3	15	20	72	0.8	0.3	0.7	1.1	0.7	1.0
Cross-SEn ML-V	30	4	8	19	61	0.7	0.9	0.9	1.2	0.8	1.1
Step Reg AP	57	2	8	5	72	1.0	0.5	0.9	1.1	0.7	0.9
Step Reg V	77	0	4	0	82	1.4	0.3	1.3	1.3	1.0	1.0
Stride Reg AP	73	0	9	3	85	1.4	0.5	1.3	1.3	0.9	1.0
Stride Reg V	82	0	10	1	93	1.5	0.3	1.3	1.5	1.1	1.1
Symmetry AP	30	2	11	4	47	0.5	0.8	0.7	0.5	0.3	0.6
Symmetry V	44	3	24	0	71	0.9	0.9	1.4	0.9	0.6	0.8
Mscale-En AP	19	1	26	5	51	0.3	0.2	0.7	1.8	0.6	3.6
Mscale-En ML	0	47	0	5	51	0.7	3.2	0.3	0.4	0.6	0.5
Mscale-En V	18	20	16	0	53	1.2	3.5	1.0	1.0	2.4	1.4
max-Lyap AP	23	0	8	14	45	0.7	0.4	0.8	1.4	1.0	1.1
max-Lyap ML	20	20	24	2	66	1.5	2.3	1.4	0.5	0.3	0.6
max-Lyap V	53	4	5	2	64	1.3	1.1	1.4	0.3	3.5	0.8
FreqVar AP	35	3	0	3	41	1.0	0.7	0.8	0.3	1.2	0.4

^aExplained variance (%) per LV for the single-task model, and VIP-values for healthy old (HO) adults, Cognitive Intact (CI) geriatric and Cognitive Impaired (CIM) geriatric patients during single- and dual task walking. A VIP > 1.0 denotes considerable importance of the gait outcome to the particular group (bold). LV = latent variable; VIP = Variable Importance in Projection; RMS = Root Mean Square; IH = Index of Harmonicity; Cross-SEn = Cross Sample Entropy; Mscale-En = Multi-scale Entropy; max-Lyap = maximal Lyapunov Exponent; FreqVar = Frequency Variability; AP = Anterior-Posterior; ML = Medio-Lateral; V = Vertical.

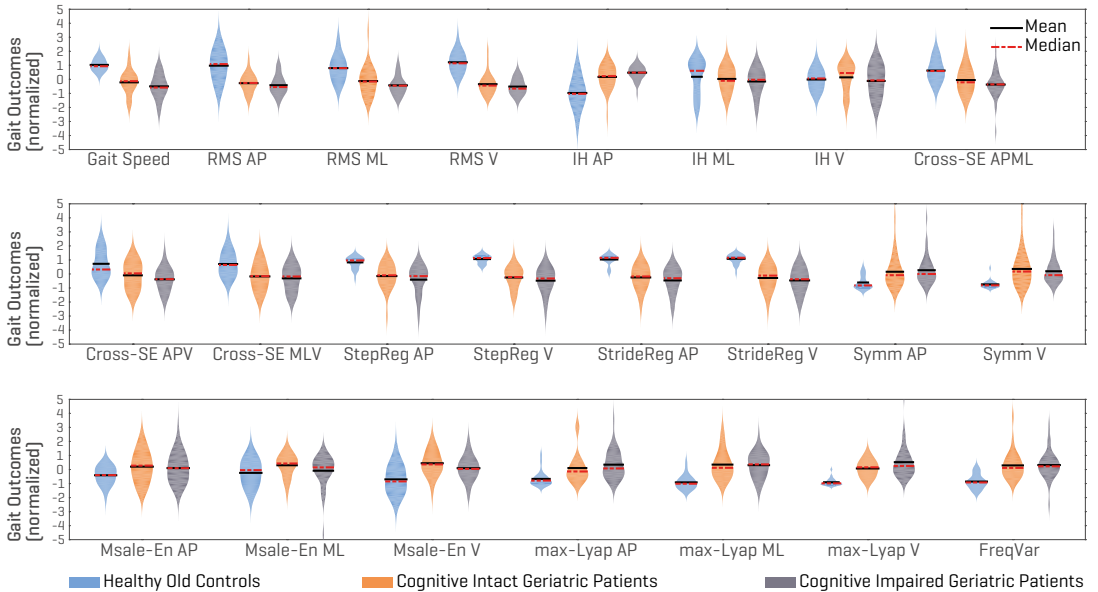


Figure 1. Violin plots based on the kernel density distribution show the distribution of gait outcomes. The violins show gait outcomes for healthy old adults ($n=25$), cognitive intact ($n=31$), and cognitive impaired geriatric patients ($n=36$) during single-task walking. A more compact and less elongated kernel denotes greater density and homogeneity across gait outcomes. Black and dashed red lines indicate mean and median values, respectively. Outcomes are standardized to unit variance for plotting purposes only. RMS = Root Mean Square; IH = Index of Harmonicity; Cross-SampEn = Cross Sample Entropy; Mscale-En = Multiscale Entropy; max-Lyap = maximal Lyapunov Exponent; FreqVar = Frequency Variability; AP = Anterior-Posterior; ML = Medio-Lateral; V = Vertical.

Discrimination of groups

For single- and dual-task walking, 24 (96%) and 23 (92%) of the 25 healthy old controls were correctly classified based on the gait outcomes, respectively. Fifteen (48%) and 11 (35%) of 31 cognitive intact geriatric patients were correctly classified during single- and dual-task walking. Fifteen (38%) and 14 (36%) of 39 cognitive impaired geriatric patients were correctly classified based on respectively single- and dual-task walking (Figure 2). The multivariate models for single- and dual-task conditions were comparable in terms of discriminative ability (VIP-scores), and classification accuracy.

DISCUSSION

We examined gait characteristics and their discriminative power in healthy old adults and geriatric patients with- and without cognitive impairment. Twenty-three accelerometry-based gait outcomes were calculated while subjects walked for 3 minutes at habitual speed with and without a cognitive dual-task. Gait outcomes related to speed, regularity, predictability, and stability of trunk accelerations revealed with the highest discriminative power ($VIP > 1$), and were thus most important in the identification of the three groups of old adults in terms of their gait. Despite the correct classification of a high proportion of

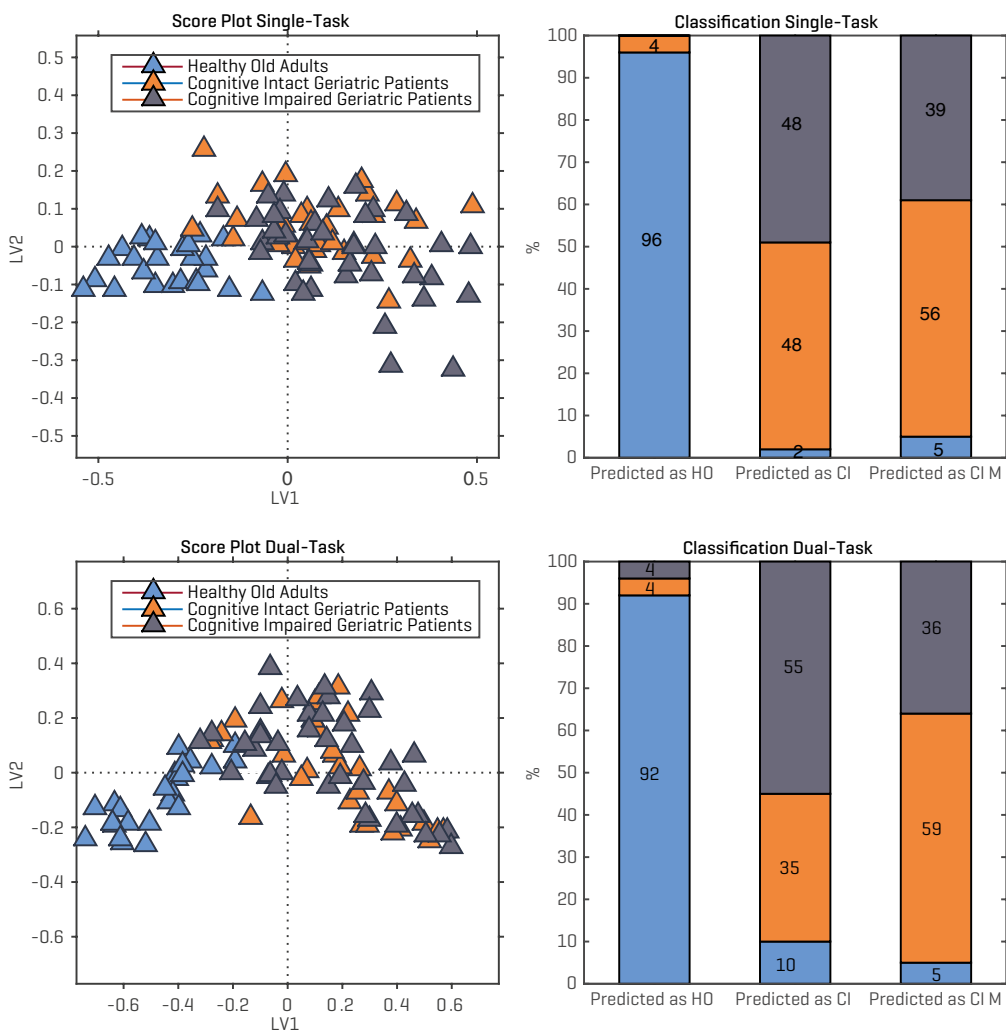


Figure 2. Score plots and classification accuracy. Score plots (left panel) visualize the individual participant scores and shows the relationship between gait outcomes and participants of each group with respect to the first two Latent Variables for single-task (upper panel) and dual-task walking (lower panel). Healthy old adults present in a sharply separated cluster, while 57% and 64% of geriatric patients with cognitive intact (CI) and cognitive impaired (CIM) geriatric patients are misclassified for single- and dual-task, respectively (right panel).

healthy old adults (96% and 93% for single- and dual-task, respectively), the classification of geriatric patients with and without cognitive impairments was poor: 57% (single-task) and 64% (dual-task) of the patients were misclassified. We discuss gait characteristics for the three groups, and the lack of discrimination between geriatric patients with and without cognitive impairments.

Gait speed and speed-related outcomes (e.g., RMS, AP Index of Harmonicity) were important in the characterization of groups. Geriatric patients walked substantially slower (0.81 m/s) than healthy old adults (1.20 m/s) but gait speed was similar in patients with (0.88 m/s) and without (0.81 m/s) cognitive impairment. These values compare well with normative gait speed data for healthy old adults [35] and patients with cognitive impairment [21]. In general, age-related gait slowing results from a decline in neuromuscular and neurophysiological functioning that for example engenders sarcopenia and a slower reaction time [1]. Considering geriatric patients' higher age compared with healthy old adults, the slower gait speed was expected. Because cross-sectional and longitudinal studies reported that cognitive impairments are strongly associated with gait slowing [21], we also expected but found only 0.07 m/s additional gait slowing in our patients. This result is in agreement with a recent population study that concluded that a slow baseline gait speed was only modestly related to future cognitive decline, and provided no early marker of clinical progression from MCI to dementia [36].

With regards to gait regularity, predictability, and stability, gait outcomes in ML and V direction were particularly important, as indicated by the large VIP-scores. Geriatric patients vs. healthy old controls walked less regular, less predictable, and less stable. Especially, gait control in ML direction is crucial in maintaining balance and gait alterations in this direction have been associated with dynamic instability, numerous pathologies, as well as with adverse life-events such as falling [9]. The decline in gait regularity and stability in geriatric patients may be related to a decline in executive functioning. Because imaging studies reported associations between the activation of wide brain networks and gait speed, especially in cognitively impaired old adults, gait is far from and automatically controlled motor task and involves cognitive functioning [37]. In particular, reductions in executive function may result in inaccurate control of limb movements and diminished feed-back that caused gait irregularity and instability [38]. For instance, differences in step and stride regularity have been suggested to reflect differences in the motor control of propulsion and braking phases of gait [7], a process highly depending on lower limb control and accurate feedback mechanisms. In support of this explanation, structural and functional neuroimaging data suggest that prefrontal brain areas (the areas executive functions are predominantly located) are most susceptible to age-related decline [39]. Even though geriatric patients with vs. without cognitive impairments did score worse on the executive function tests, there was no corresponding decline in gait regularity and stability. Those results compare to a recent study [40], but are in contrast to studies that reported a lower gait regularity in patients with MCI or dementia during single- tasking [41] and dual-tasking [42]. Subject characteristics may account for these discrepancies between studies, as our patient group was relatively old and presented with multiple geriatric conditions that are known to affect gait.

With respect to the classification accuracy, the gait outcomes revealed close to perfect classification of the healthy old group (96% and 92% for single- and dual-task, respectively). However, the discrimination between geriatric patients with and without cognitive impairments was poor, with 57% (single-task) and 64% (dual-task) of the patients misclassified. This finding was unexpected, as the cognitively impaired vs. cognitive intact geriatric patients scored significantly lower on global cognition (3.5 points lower MMSE



score), and on executive and memory functioning. Furthermore, an additional cognitive stressor in the dual-task condition did not improve the discrimination between the geriatric patient groups. The number of clinical conditions per se can substantially affect geriatric patients' gait [20]. The effects of comorbidities in our patients presumably sum to a level that causes a floor-effect so that when cognitive impairment adds to the symptoms, gait does not deteriorate any further, even if tested under dual-task walking.

Our data are in line with a lack of gait differences between frail and cognitively impaired old adults during single- or dual-task walking [40]. The latter study quantified gait kinematics derived from lower trunk accelerations in old adults aged >75 who meet Fried's criteria for frailty. Despite the relatively short walking distance (5m), they found that the gait kinematics were highly sensitive to distinguish frail groups and healthy old controls, but not between frail patients with and without cognitive impairment during either single- or dual-task walking. Our and previous data [40] thus raise the possibility of a clinical threshold beyond which the use of only gait outcomes to identify cognitive impairment is insufficient. We interpret these findings to mean that: (1) the prediction of cognitive impairment from gait abnormalities may be most effective in early phases of cognitive decline, where the influences of comorbidities on gait are limited. Hence, in frail geriatric patients, (2) the identification of cognitive decline requires a multi-variate approach, including physical, cognitive, pharmacological, and behavioural measures.

Although most aspects of gait performance (e.g., related to speed, regularity, predictability, and stability) appeared important in the characterization of the groups, some outcomes produced low discriminative power. A possible explanation could be that our geriatric patients were very heterogeneous, as indicated by the large kernel sizes of for example gait synchronization (Cross-sample Entropy), and gait smoothness (Index of Harmonicity) (Figure 1). Given this variety in gait patterns, and because geriatric patients often present with a shuffling gait, we calculated gait outcomes that are independent of step detection and recommend the use of such an approach in geriatric patients. An accurate, automatic, detection of foot-contact indices from acceleration signals is difficult, and already achieves an error rate of 7.4% in healthy old adults [43]. This error rate is expected to increase with gait slowing and/or shuffling; conditions very common among geriatric patients.

Despite the relatively low sample size, which can be considered a potential limitation of the study, we speculate that the outcomes can be generalized to similar population groups (i.e., age-matched healthy old adults and geriatric patients admitted to outpatient clinics). Although both geriatric patient groups were comparable in terms of age, sex, weight, height, BMI, number of comorbidities, gript strength, and medication use (Table 1), we cannot exclude the effects of potential other factors on gait function (e., thoracic kyphosis). Finally, the present analysis only focused on gait aspects derived from 3D-trunk accelerations. Future studies are encouraged to study the discriminative ability of for example gait kinetics to identify cognitive impairment.

Conclusions

In conclusion, gait outcomes related to speed, regularity, predictability, and stability of trunk accelerations were most important in the characterization of patient groups and revealed with a large discriminative power. Such measures were highly sensitive to discriminate healthy old adults from geriatric patients but could not discriminate geriatric patients with and without cognitive impairment during single- or dual-task walking. Thus, our data suggest that caution is needed to predict geriatric patients' cognitive status from gait performance alone. We propose that an accurate identification of cognitive impairment requires a multivariate approach that comprises not only a comprehensive gait analysis, but also other physical, cognitive, and behavioural measures.

LIST OF ABBREVIATIONS

3D = three dimensional; PLS-DA= Partial Least Squares - Discriminant Analysis; VIP = Variable Importance in Projection; BMI = Body Mass Index; CCI = Charlson Comorbidity Index; MMSE = Mini Mental State Examination; 7MS = 7-Minute Screen; BTO = Benton's Temporal Orientation; ECR = Enhanced Cued Recall; AP = Anterior-Posterior; ML = Medio-Lateral; V = vertical; RMS = Root Mean Square; IH = Index of Harmonicity; Cross-SampEn = Cross-sample Entropy; Mscale-En = Multi-scale sample Entropy; λ_{\max} = maximal Lyapunov exponent; FreqVar = stride frequency variability; LV = Latent Variable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Medical Ethical Committee of the MC Slotervaart Hospital approved the study protocol.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIAL

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. PLS_toolbox for MatLab (version 3.7.1; Eigenvector Research Inc.) was used to analyse the data. This software requires a license for non-academics.



COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS’ CONTRIBUTIONS

CL, TH, and JvC designed the study protocol. LK collected and analyzed the data, with close supervision of CL. Results were interpreted by CL, TH, NV, JvC, and LK. LK wrote the first draft, and NV, BA, JvC, TH, and CL contributed significantly in revising the manuscript. All authors read and approved the final manuscript.

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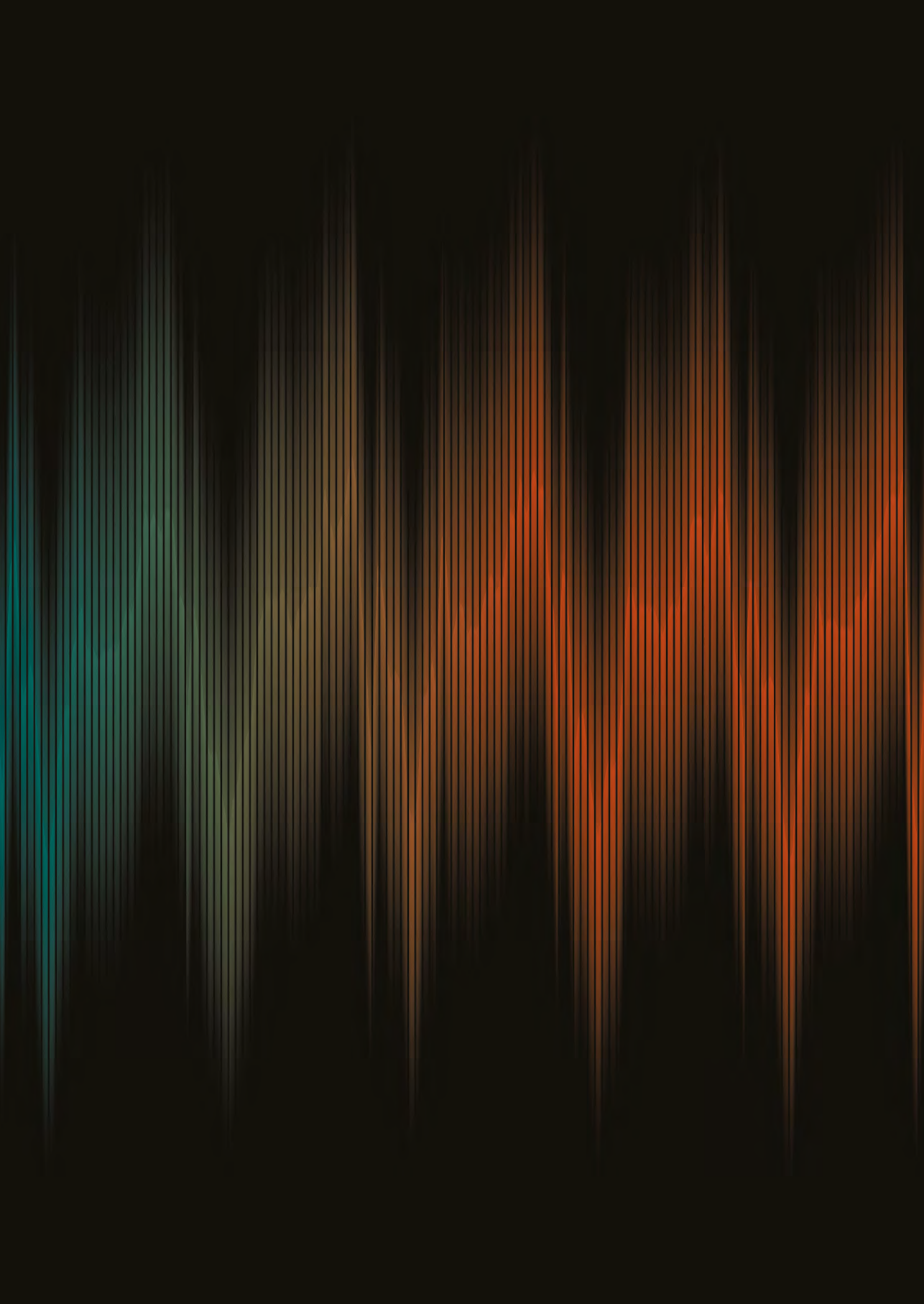
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5

THE RELATIONSHIP BETWEEN GAIT DYNAMICS AND FUTURE COGNITIVE DECLINE: A PROSPECTIVE PILOT STUDY IN GERIATRIC PATIENTS

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ABSTRACT

Background: Walking ability recently emerged as a sub-clinical marker of cognitive decline. Hence, the relationship between baseline gait and future cognitive decline was examined in geriatric patients. Because a 'loss of complexity' (LOC) is a key-phenomenon of the aging process that exhibits in multiple systems, we propose the idea that age- and cognition-related LOC may also become manifested in gait function. We hypothesized that a LOC is reflected in dynamic gait outcomes and that such outcomes could increase the specificity of the gait-cognition link. *Methods:* 19 geriatric patients (age 80.0±5.8) were followed for 14.4±6.6 months. An iPod collected 3D-trunk accelerations for 3 minutes. Cognition was evaluated with the Mini Mental State Examination (MMSE) and the Seven-Minute screen (7MS) test. The Reliable Change Index (RCI) quantified the magnitude of cognitive change. Spearman's Rho coefficients (ρ) indexed correlations between baseline gait and future cognitive change. *Results:* Seven patients showed reliable cognitive decline ('Cognitive Decline' group), and 12 patients remained cognitively stable ('Cognitive Stable' group) over time. Future cognitive decline was correlated with a more regular ($\rho=0.579^*$) and predictable ($\rho=0.486^*$) gait pattern, but not with gait speed. *Conclusions:* The increase in gait regularity and predictability possibly reflects a LOC due to age- and cognition-related (neuro)physiological decline. Because dynamic vs. traditional gait outcomes were more strongly correlated with future cognitive decline, the use of wearable sensors in predicting and monitoring cognitive and physical health in vulnerable geriatric patients can be considered promising. However, our results are preliminary and do require replication in larger cohorts.

Key words: Geriatric patients, Frailty, Cognitive impairment, Gait analysis, Non-linear dynamics, Prediction, Loss of complexity.



INTRODUCTION

Medical developments have substantially extended human lifespan. An increase in age, however, comes hand in hand with co-morbidities such as cognitive decline, muscle weakness, frailty, polypharmacy, and falling [1]. Hence, we can anticipate an increase in the number of 'older old adults' who will need specialised geriatric care (i.e., geriatric patients) to slow functional decline. Cognitive impairment is a frequent geriatric condition substantially affecting independence, mobility, and quality of life (WHO, 2017). If applied in time, tailored interventions could delay disease onset and perhaps extend the asymptomatic phase. Predicting future cognitive loss is therefore important in this vulnerable population, in which walking ability has recently emerged as a non-invasive sub-clinical marker that predicts cognitive decline [2].

The view that walking is no longer considered an automatic task supports its potential to serve as an early marker of cognitive decline. Because brain areas affected by cognitive impairment partly overlap with brain areas activated during walking [3], subtle, pre-clinical changes in gait could be precursors of evolving cognitive impairment. Such an overlap gave rise to the concepts of the 'Motoric Cognitive Risk' syndrome [4], a 'Gait Phenotype' of cognitive decline [5], and the 'Motor Signature' of cognitive decline [6]. Longitudinal studies confirmed the close relation between gait and cognition [2, 7], with the majority of prediction studies focussing on gait speed as main predictor of cognitive decline [2]. Individuals who developed Mild Cognitive Impairment (MCI) or dementia presented with a slower baseline gait speed (0.91 and 0.80 m/s, respectively) as compared to individuals who remained cognitively intact (1.11 m/s) [2]. While a slow walking speed provides an important marker of multiple adverse outcomes (e.g., falling, hospitalization, and even survival) [8], more delicate gait measures could unravel why geriatric patients walk slow, with final gait speed being the cumulative result of interactions between multiple, subtle gait functions. Hence, we hypothesize that those gait details could increase the specificity of the gait-cognition link. Key-principles of the aging neuro-musculo-skeletal system (NMSS) provide a theoretical framework for the latter hypothesis.

Although age- and pathology related declines in neural, sensory-motor, cognitive, and muscular function, i.e., declines in NMSS, are generally examined separately, such a view limits our understanding of the aging NMSS as a whole [9]. Because vulnerable geriatric patients show degradation in multiple interacting systems, we propose the idea to place the gait-cognition link into a more encompassing perspective to better understand the coupling and coordination between elements of the NMSS (i.e., gait and cognition). To this idea, we consider a key-phenomenon of the aging NMSS, 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 [10]. This loss of complexity in turn leads to a reduced adaptive capacity and most likely to poor functional outcomes such as frailty and an increased fall risk [11]. Indeed, frail vs. healthy old adults and fallers vs. non-fallers are characterized by a global loss of complexity [11], and a loss of complexity indicates transitions from healthy to frail aging [12]. (Neuro)physiological decline and cognitive impairment may add to this loss of complexity, and possibly becomes manifested in gait function. A loss of gait complexity

is characterized by an increased gait regularity/predictability, in which perfect regular signals would resemble a sine function. Coordination dynamics constitutes a conceptual framework to quantify complexity caused by physiological breakdown because it can capture changes of functional status over time by means of for example indexing coupling and self-organisation properties [9].

Trunk accelerations have demonstrated their ability to quantify non-linear coordination dynamics of gait function including self-affinity, regularity, complexity, variability, and stability [13-16]. Such gait dynamics describe overall gait coordination and the ability to overcome or adequately respond to perturbations. Cross-sectionally, gait dynamics distinguished old adults with- and without cognitive impairment, with cognitively impaired old adults presenting with a less variable and less stable gait pattern [17]. Longitudinally, adding gait dynamics to clinical tests increased the accuracy of a fall prediction model by 14% [18], and the specificity of a fall classification model from 60% to 80% [19]. However, less is known about the longitudinal link between gait dynamics and cognitive decline. In addition to more traditional outcomes such as gait speed, it is quite possible that an age- and pathology-related loss of complexity is expressed in detailed dynamic gait outcomes derived from non-linear analyses. Gait dynamics could therefore assist to index and predict long-term cognitive change and provide insights into (unconscious) strategies old adults use to compensate for this anticipated cognitive loss. Hence, the aim of the present prospective pilot study was to examine the relationship between baseline gait function and future cognitive decline, and to identify indicators of future cognitive decline in terms of a geriatric patient's gait. We hypothesize that a loss of complexity of the aging NMSS translates to gait function, and is reflected in measures that quantify dynamic aspects of gait.

METHODS

Patients

Seventy geriatric patients were recruited from the geriatric diagnostic day clinic of the MC Slotervaart hospital in Amsterdam between January 2015 and July 2016 (mean age 80 \pm 6.6; 53% women). Patients were referred by a general practitioner based on general or specific decline, and underwent extensive screening for physical and cognitive functioning during their seven-hour visit. Inclusion criteria were: age 65 or older. Exclusion criteria were: (1) Inability to walk for three minutes without a walking aid, (2) the presence of neurological disorders other than dementia-related (e.g., Parkinson's disease), (3) having neurological or orthopaedic disabilities that limit mobility function (e.g., recent surgery), and (4) inability to speak and understand Dutch. Only patients at risk for (further) cognitive deterioration were invited for a re-evaluation in approximately one year. However, this referral depended on subjective and objective evaluations of the clinical geriatrician who treated the patient. Hence, 19 patients were included in the present pilot study. While all patients were at risk for cognitive impairment, 10 out of 19 patients actually had a diagnosis of MCI at baseline. The protocol was approved by the Medical Ethical Committee of the MC Slotervaart hospital. Because some of the test results could directly be used by the involved clinical geriatrician (e.g., gait speed, hand grip strength, and frailty), the tests were part of a standard clinical evaluation when a researcher was present who could administer the measurements. It was therefore not necessary to obtain informed consent from patients.



Demographic information including age, height, weight, and Body Mass Index (BMI) were extracted from medical records. The Charlson Comorbidity Index (CCI) quantified the number and severity of comorbidities, and polypharmacy was denoted when patients used >4 medications. Cognitive performance was evaluated with the Mini Mental State Examination (MMSE) and with the 7-minute screen (7MS) test. The 7MS assessed memory function using the Benton's Temporal Orientation (BTO) (range 0-113) and the Enhanced Cued Recall (ECR) test (range 0-16), and executive and visuospatial function using the animal verbal fluency (range 0-45) and clock-drawing test (range 0-14). A logistic regression formula based on the four sub-tests resulted in a total 7MS-score, with a score of 0 corresponding to a 50% chance that a patient has dementia, and negative and positive scores corresponding to a lower and higher than 50% chance to have dementia, respectively. We refer to our previous study for references of the cognitive screening batteries [19]. The Reliable Change Index (RCI) quantified the magnitude of cognitive change and to determine whether the changes in cognition were clinically meaningful and statistically reliable, with a RCI of >1.96 indicating a significant change between baseline and follow-up outcomes ($p < 0.05$) [20]. Patients who showed a reliable decline in both, MMSE and 7MS-score (average RCI-score >1.96) were coded as the 'Cognitive Decline' group. Patients who remained cognitively stable or showed non-significant changes in cognition formed the 'Cognitive Stable' group. Figure 1 illustrates the study protocol.

Procedures and pre-processing

At baseline, patients walked for three minutes at habitual gait speed on a 10-m long course marked with cones. Accelerations of the lower trunk (near the level of the 3rd lumbar vertebra) were registered using a built-in accelerometer of an iPod touch G4 (iOS 6, Apple Inc.; sample frequency ± 100 Hz). The validity of gait and standing posture parameters from trunk accelerations as indicated by intra- class correlation (ICC) was high (ICC = 0.85–0.99), and test–retest reliability was good (ICC = 0.81–0.97) in old adults, under varying conditions [21]. A custom-made application 'iMoveDetection' stored the acceleration signals in anterior-posterior (AP), medio-lateral (ML), and vertical (V) directions [21]. The signals were then transferred via blue tooth to an online platform and analysed with custom MATLAB software (version 2014b, The MathWorks Inc.). All time series were de-trended, corrected for horizontal tilt, and low-pass filtered using a 4th order Butterworth filter (cut-off frequency 10 Hz).

Gait outcomes

We previously identified gait outcomes that characterized the same population of geriatric patients with and without cognitive impairment in a cross-sectional study (submitted), and therefore included those outcomes in the present longitudinal analysis. In addition, average stride time and the Coefficient of Variation (CoV) of stride time were computed. Time indices of foot contacts were manually identified from peaks in the AP acceleration signals to calculate stride-related gait outcomes. The magnitude of the resultant vector of the AP, ML, and V signals was calculated according to the following equation: $R = \sqrt{AP^2 + ML^2 + V^2}$. The dynamic gait outcomes were quantified over this 'summary' signal. Table 1 describes stride-related (outcomes 1-3) and dynamic (outcomes 4-7) gait outcomes.

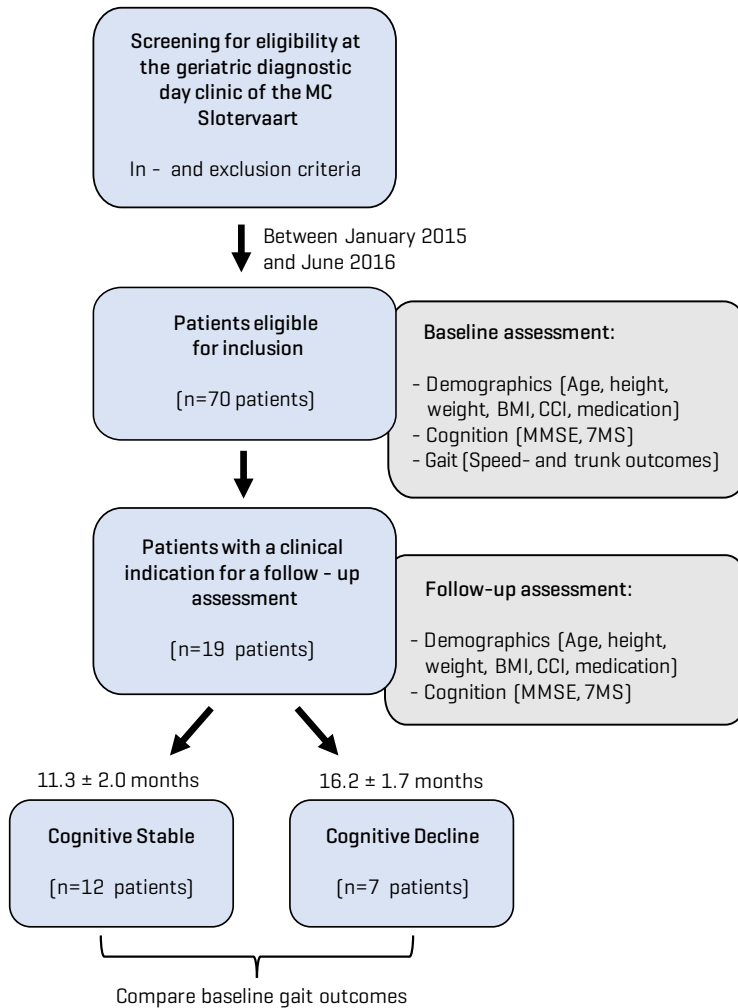


Figure 1. Syntax of the study protocol.

Abbreviations used in Figure 1: BMI= Body Mass Index; CCI= Charlson Comorbidity Index; MMSE= Mini Mental State Examination; 7MS= Seven Minute Screen.



Statistical analysis

Statistical analyses were performed using SPSS version 24. Group differences ('Cognitive Decline' vs. 'Cognitive Stable') were examined with the Mann-Whitney's U test, and within-group differences (baseline vs. follow-up) with a repeated measure analysis of variance (ANOVA). Correlations between baseline gait and longitudinal cognitive change in MMSE and 7MS scores were computed using Spearman's Rho correlation coefficients (ρ) for non-linear data. Perfect monotonic relations would reveal a ρ of 1 or -1. Significance was set at 0.05.

Table 1. Descriptions and formula of the quantified gait outcomes.

<i>Gait outcome</i>	<i>Formula</i>	<i>Description</i>
(1) Gait speed (m/s)	$\text{Speed} = \frac{\text{Distance (m)}}{\text{Time walked (s)}}$	Average walking speed.
(2) Stride time (s)	$\text{Stride time} = \frac{\text{Time walked (s)}}{\text{Number of strides}}$	Stride time reflects the average time from heelstrike-to-heelstrike of the ipsilateral foot.
(3) CoV Stride time (%)	$\text{CoV} = \frac{\text{Standard deviation}}{\text{mean}} * 100\%$	The Coefficient of Variation of stride time is the standardized measure of dispersion of the average stride time.
(4) Root Mean Square	$\text{RMS} = \frac{\sqrt{x^1+x^2+\dots+x^n}}{n}$	The RMS quantifies the magnitude of amplitude variability.
(5) Step- and stride regularity	$\text{AC}(t) = \frac{1}{N- t } \sum_{i=1}^{N- t } x_i x_{i+t}$	Step and stride regularity indicate the regularity of steps and strides, respectively. Autocorrelation refers to the correlation of a time series with its own past and future values. Perfect regular steps or strides will adopt a value of 1 [15].
(6) Multi-scale Sample Entropy	$\text{MSE}(N, m, \tau, \gamma) = -\ln \left[\frac{A^{m+1}(\gamma)}{A^m(\gamma)} \right]$	Mscale-En reflects the degree of predictability of a gait pattern. A complete predictable signal has a Mscale-En value of 0 [26].
(7) Maximal Lyapunov Exponent	$\lambda_i = \lim_{n \rightarrow \infty} \frac{1}{n} \log_2 \frac{p_i(t)}{p_i(0)}$	Maximal Lyapunov Exponent indicates local dynamic stability, i.e., the ability to resist perturbations. A larger λ_{\max} reflects a less local dynamic stability [31].

RESULTS

Nineteen patients were followed for 14.4±6.6 months (age 80.0±5.8; 63% women). Based on average RCI-scores of MMSE and 7MS, 7 of 19 patients (37%) showed significant cognitive decline over time and were retrospectively classified as the 'Cognitive Decline' group (average follow-up time was 11.3±2.0 months). The other 12 patients remained cognitively stable or slightly increased in cognitive function and formed the 'Cognitive Stable' group (average follow-up time was 16.2±1.7 months). At baseline, the groups were comparable in terms of age, height, weight, BMI, CCI, the number of medication used, MMSE-score, and 7MS-score (all $p>0.05$). At follow-up, the groups only differed in MMSE ($p=0.05$) and 7MS ($p=0.01$). The MMSE ($p=0.05$) and the 7MS scores ($p=0.01$) decreased in the 'Cognitive Decline' group but not in the 'Cognitive Stable' group (MMSE: $p=1.0$; 7MS: $p=0.83$). Other outcomes did not significantly change ($p>0.05$) in either group (Table 2).

Table 2. Patient demographics (mean±SD) by final cognitive state. Differences were evaluated with the Mann-Whitney's U test, with significant differences between groups indicated in bold.

	Baseline			<i>p</i>	Follow-up		
	'Cognitive Decline' (n=7)	'Cognitive Stable' (n=12)			'Cognitive Decline' (n=7)	'Cognitive Stable' (n=12)	<i>p</i>
Age	80.9 ± 6.4	79.5 ± 5.6	0.37	NA	NA		
Height (cm)	166 ± 7.3	165 ± 9.2	0.53	NA	NA		
Weight (kg)	65.3 ± 10.7	69.7 ± 14.4	0.55	NA	NA		
BMI	23.6 ± 2.3	25.9 ± 5.6	0.40	23.8 ± 2.3	25.9 ± 5.9	0.35	
CCI	3.3 ± 1.5	2.2 ± 1.3	0.13	3.3 ± 1.5	2.5 ± 1.7	0.24	
Medication	6.1 ± 3.4	6.2 ± 3.3	0.93	5.0 ± 4.2	6.1 ± 4.1	0.40	
MMSE	25.7 ± 3.7	26.3 ± 2.8	0.83	22.3 ± 6.2	26.4 ± 3.4	0.05*	
7MS	8.3 ± 16.7	0.0 ± 4.6	1.00	16.1 ± 23.9	0.3 ± 4.3	0.01*	

* $p < 0.05$.

BMI = Body Mass Index; CCI = Charlson Comorbidity Index; MMSE = Mini Mental State Examination; 7MS = Seven Minute Screen; NA = Not Applicable.

Relationship between baseline gait and future cognitive change

Table 3 presents correlations between baseline gait outcomes and changes in cognitive function 14 months later. Stride-related outcomes (gait speed, stride time, CoV of stride time) did not correlate with changes in cognition ($p < 0.3$). Trunk outcomes showed modest correlations with changes in cognition, with a decline in cognition corresponding to more regular steps ($\rho = 0.579^*$) and strides ($\rho = 0.347$), and a more predictable gait ($\rho = -0.484^*$). Figure 2 shows the correlations between gait outcomes (Step regularity, Stride regularity, and Multi-scale sample entropy) and changes in cognition in each group. Correlations between baseline gait and cognition in MMSE and 7MS separately were in the same direction, in which some gait outcomes related more to change in MMSE, while others were more closely linked to change in 7MS. For example, stride regularity correlated more strongly with Δ MMSE ($\rho = 0.339$) than with Δ 7MS ($\rho = 0.230$), while Multi-Scale Sample Entropy correlated more strongly with 7MS ($\rho = -0.509^*$) as compared to MMSE ($\rho = -0.321$).

Table 3. Spearman's Rho (ρ) correlations between baseline gait and future change in cognition in 19 geriatric patients. The degree of decline in cognition is expressed using the Reliable Change Index (RCI), combining MMSE and 7MS-scores.

	<i>Change in cognition</i> (Average of MMSE and 7MS)
<i>Stride-related outcomes</i>	
Gait Speed	0.073
Stride Time	0.051
Coefficient of Variation of Stride Time	-0.260
<i>Trunk outcomes</i>	
Root Mean Square	-0.065
Step Regularity	0.579*
Stride Regularity	0.347
Multi-Scale Sample Entropy	-0.484*
Maximal Lyapunov Exponent	0.196

* $p < 0.05$.

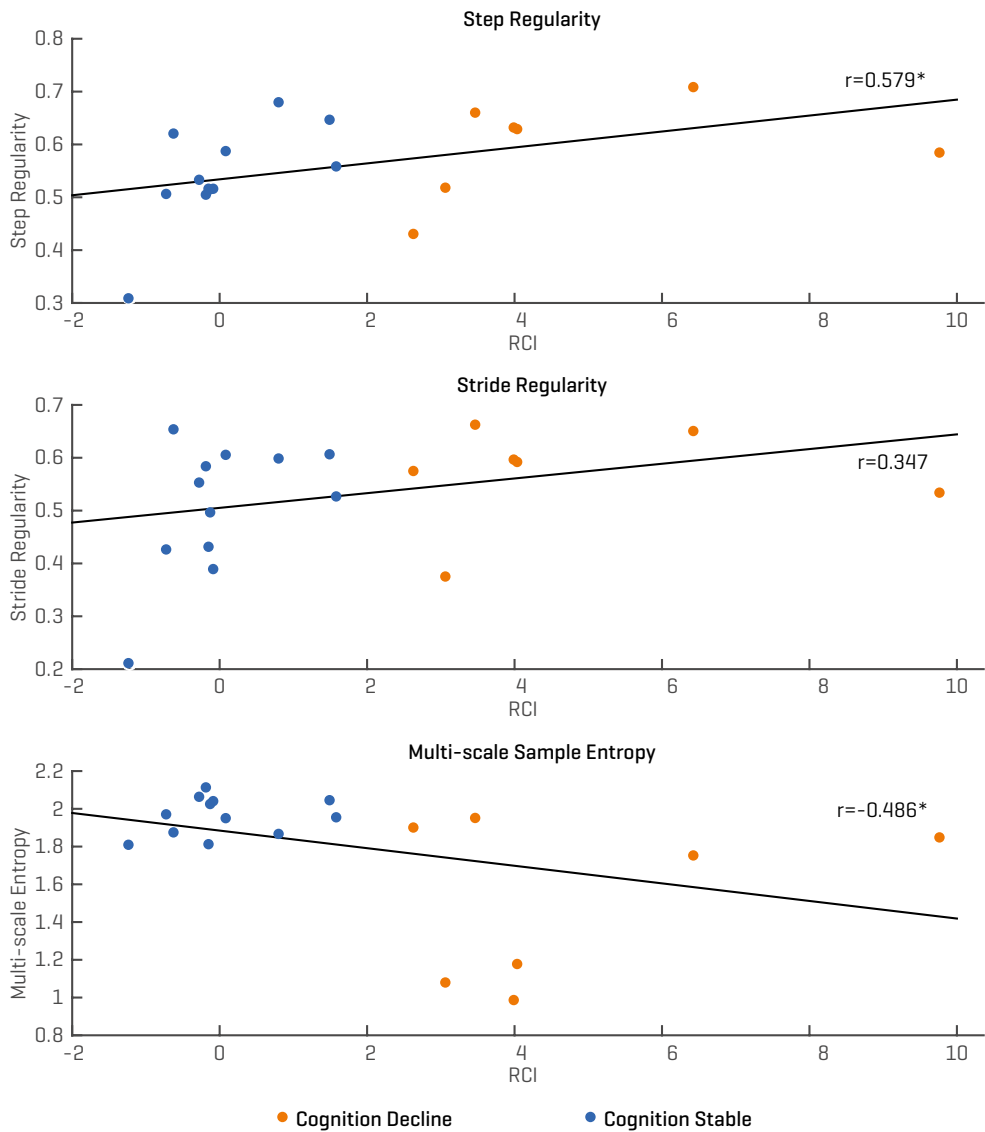


Figure 2. Correlations between baseline gait outcomes and future decline in cognition (MMSE+7MS). The degree of cognitive change was quantified with the Reliable Change Index (RCI), with an RCI>1.96 indicating significant cognitive change over time ($p<0.05$). Each symbol denotes an individual patient. Patients whose MMSE and 7MS decreased are coloured in orange ($n=7$) and those patients who remained cognitively stable are coloured in blue ($n=12$).

DISCUSSION

The present prospective pilot study examined whether baseline gait characteristics predicted changes in cognition 14.4±6.6 months later in 19 geriatric patients (mean age 80.0±5.8). The results revealed that a more regular and predictable gait pattern correlated with future cognitive decline in geriatric patients admitted to an outpatient diagnostic clinic. We discuss these results from a theoretical perspective in terms of the 'loss of complexity' hypothesis, and from a clinical perspective in terms of how smart devices that extract gait details could possibly facilitate the prediction of cognitive decline and the development of early tailored interventions.

While population-based studies reported that gait speed predicts cognitive decline [2, 22], the present analyses did not confirm these results. Patient characteristics may account for the discrepant data. While previous studies focused on relatively young and healthy old adults with a mean age around 65, our geriatric patients had a mean age of 80. Geriatric syndromes that are also linked to gait slowing (e.g., muscle weakness, polypharmacy, falling, osteoporosis-related factors) [23, 24], may have caused a slower gait, also in the group that remained cognitively stable. Gait speed alone might thus not be specific enough to predict future cognitive decline in geriatric patients that suffer from multi-system degeneration [24]. These results are in agreement with a recent population study that concluded that a slow baseline gait speed was only modestly related to future cognitive decline, and provided no early marker of clinical progression to dementia [25]. The short follow-up period in the present study could also account for the discrepancies relative to previous studies, as our average follow-up time vs. the average follow-up time of a systematic review were 1.2 and 4.5 years, respectively.

Cognitive decline over time correlated with a more regular (higher autocorrelation coefficients) and more predictable (lower multi-scale sample entropy) baseline gait pattern. Because increases in stride regularity and predictability during gait reflect a decline in gait complexity [26], we confirm our hypothesis that the 'loss of complexity hypothesis' [10] could provide a theoretical framework to relate those findings to health status. The LOC theory suggests that a deterioration in age-related and pathological physiological functioning leads to a breakdown of system elements, causing a decline in variability and overall complexity [10]. This loss of complexity in turn relates to a reduced adaptive capacity and most likely relate to poor functional outcomes such as an increased fall risk [11]. Our results are in agreement with postural control studies that reported a reduced complexity of postural fluctuations (as quantified by the multi-scale sample entropy) in older adults with sensory impairments as compared to age-matched controls [27]. A sample of frail and pre-frail older adults (who closely compare to the present sample of geriatric patients) exhibited less postural complexity as compared to non-frail controls [28]. Physiological decline related to cognitive loss possibly adds to this loss of complexity and the association between cognitive decline and higher gait regularity and predictability might thus reflect a loss of complexity of the aging system. Although increased regularity and predictability may seem beneficial, such a strategy reduces the ability to resist and recover from perturbations and may actually promote gait instability and increase the risk of falling [9]. The latter is in agreement with studies that reported a decline in gait stability in old adults with dementia



as compared to age-matched controls [17]. However, given the limited sample size and explorative nature of the present study, the results should be taken with caution and need replication in larger cohorts.

The finding that trunk outcomes vs. more traditional gait outcomes (i.e., gait speed) were more closely correlated to future cognitive decline provides support for the use of wearable sensors in clinics. Indeed, the compact size, relatively low-cost, and ease of operation facilitate the incorporation of sensor technologies in gait analysis. Based on the present preliminary results, it seems that the use of dynamical systems in gait analyses could make prediction of cognitive decline more accurate as compared to the use of traditional gait outcomes such as gait speed. Except for its use in the prediction of cognitive decline, monitoring gait dynamics is encouraged because such details also relate to one's ability to act independently and autonomously. Intervention strategies could in turn specifically tailor gait functions in an aim to remain activities of daily living and to reduce fall risk. Although studies that examined the effects of exercise on gait and cognition showed contradictory results, a recent population-based study highlighted that transitions in gait as well as in cognitive function were mutable and reversible over a 9-year period, even in the oldest-old [29]. However, despite technological and clinical advantages of incorporating gait analysis derived from wearable sensors, future studies should confirm the clinical utility and the predictive ability of such technologies, and applications should be built to translate gait details to clinical outcomes.

Procedures at the MC Slotervaart hospital are highly patient-oriented. While this provided us with an extensive characterization of this vulnerable population in terms of demographic, physical, and social information, standard procedures at the hospital also placed some difficulties. For example, even though the protocol for a follow-up appointment is set to be at 1 year, the actual follow-up period always depends on organizational and patient factors. This resulted in a large variation in follow-up time between patients (follow-up period is 14.4 ± 6.6 months), which can be considered a limitation of the present study. For the same reasons, we were unable to measure gait function at follow-up. Because there is a clear theoretical and experimental basis for the relationship between gait and cognitive impairment [2, 7], we expected that gait would have been changed in the patient group who presented with significant cognitive decline over time, and that correlations between gait and cognition would have become stronger. A recent study highlighted the sensitivity of changes in gait speed over a follow-up period of 1 year in healthy old adults aged 75. This study showed that 25% of healthy old adults showed a gait speed decline of more than 0.1 m/s per year [30]. We therefore expected that those changes in mobility may also be reflected in elements of mobility that underlie gait speed, i.e., gait dynamics. Finally, the small sample size places a limitation of the present study.

In conclusion, the present pilot study revealed that a more regular and predictable gait pattern was correlated with future cognitive decline in geriatric patients admitted to an outpatient diagnostic clinic. Those results could reflect a loss of complexity of the aging NMSS. In addition to traditional outcomes such as gait speed, trunk outcomes derived from wearable sensors are promising indicators of cognitive as well as physical decline. Hence, we recommend the incorporation of a non-invasive detailed gait analysis in predicting,

diagnosing, and monitoring health status in vulnerable geriatric patients. However, our results and interpretations are preliminary and need replication in larger cohorts, as for now our conclusions are based on a small sample size and a relatively short follow-up period.

CONFLICT OF INTEREST

None.

DESCRIPTION OF AUTHORS' ROLES

CJC, TH, NV, and LHJK created the concept and design of the study. LHJK collected the data. BA and JPvC were responsible for clinical aspects such as patient inclusion, diagnoses and ethical issues. LHJK analysed the data, and the results were interpreted by CJC, TH, and LHJK. LHJK wrote a draft of the full manuscript. CJC, TH, NV, BA, JPvC critically revised the manuscript and approved the final version.

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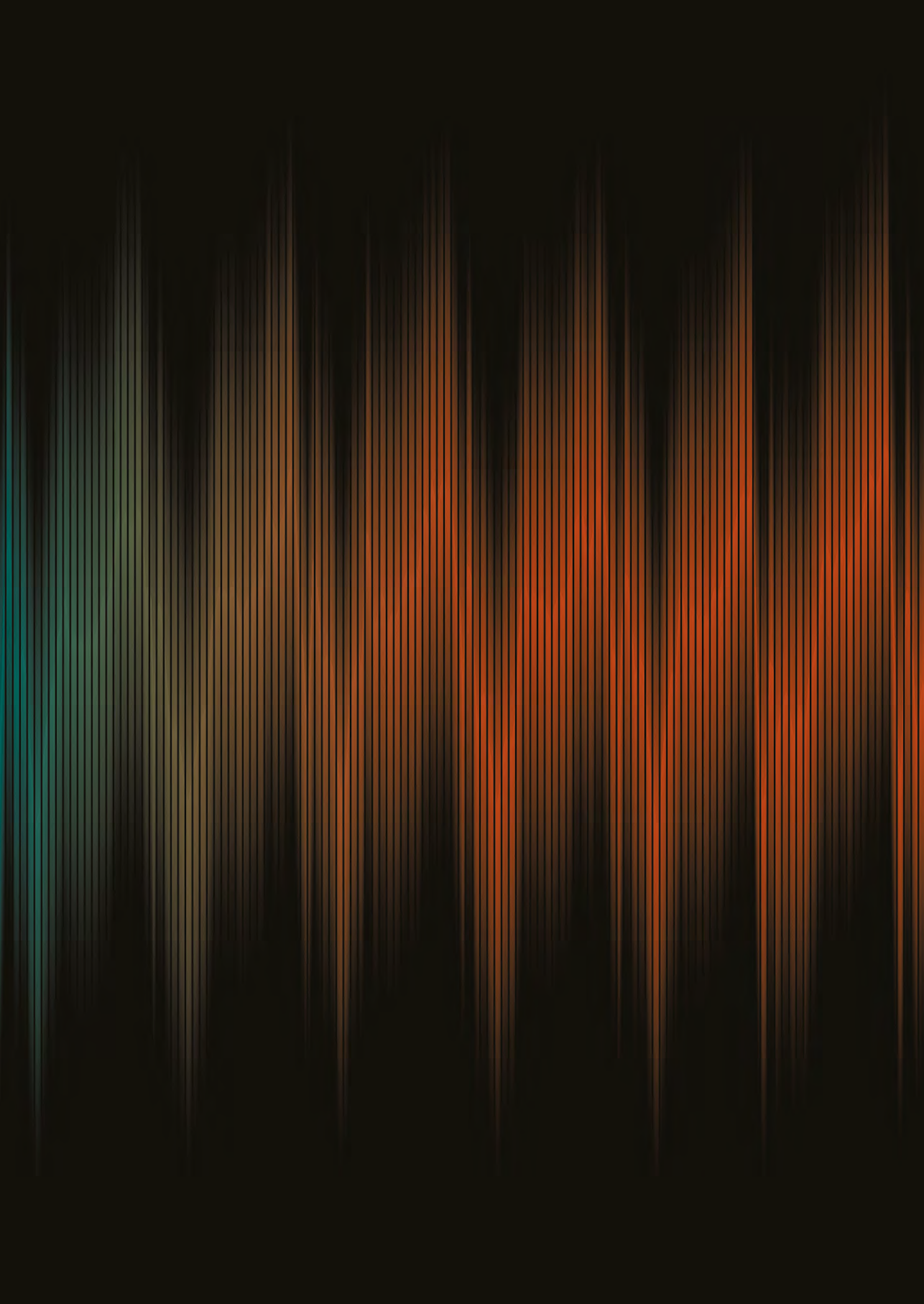
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6

GENERAL DISCUSSION



An 80-year old woman walks down the hallway of the hospital. She has recently noticed that she regularly experiences confusion, struggles with finding the right words, and sometimes does not remember why she entered a particular room. A fall last week was 'the straw that broke the camels' back', and her family encouraged her to make an appointment with her general practitioner. The general practitioner referred her to the geriatric diagnostic day clinic for a comprehensive screening of physical, cognitive, and mental health. Now she walks back and forth for 3 minutes, while an iPod attached to her lower back registers accelerations of her trunk. She voluntarily participates in a study that investigates the relationship between gait and cognition in geriatric patients. Acceleration signals derived from a simple, non-invasive walking test contain a wealth of specific information about her gait, reflecting not only mobility-, but also cognitive functioning. The presence of (pre-clinical stages of) cognitive impairment may thus be reflected in the way she walks. How is her gait pattern characterized? (How) can gait characteristics add to usual screening tests to identify cognitive impairment and/or an increased fall risk? The present thesis aimed to answer those research questions, shed light on methodological challenges with regards to an accurate gait analysis in geriatric patients, and discussed clinical perspectives of a gait analyses as part of comprehensive geriatric assessments.

Main findings

In 2015, a systematic literature search identified 20 longitudinal studies (including data from 24.368 old adults aged over 65) that examined associations between baseline gait function and future cognitive decline. The review discussed the current knowledge and gaps in the literature on this topic, and therefore provided the basis of this thesis. Eighteen out of 20 studies documented gait speed as main outcome, and a slow gait speed was associated with future decline in MMSE score and specific cognitive functions such as executive functioning. Moreover, a slow gait speed increased the risk for MCI and dementia (maximal odds and hazard ratios of 10.4 and 11.1, respectively). The results also emphasized methodological inequalities and inaccuracies in the 20 studies, and projected that future research could increase the specificity of the gait-cognition link by indexing gait and cognition in more detail (Chapter 2). From this perspective, a more extensive cognitive evaluation (MMSE, memory, and executive functioning) and fine-grained, dynamic gait outcomes were complemented to a usual fall-risk screening. The overall classification accuracy of fallers and non-fallers increased from AUC=0.86 to AUC=0.93. The specificity of the fall-classification model increased from 60% to 72% when cognitive outcomes were added, and from 72% up to 80% when gait dynamics were added to the model. The results underscored the need for a multifactorial approach in fall risk assessment in geriatric patients, including a detailed evaluation of cognitive- and gait functions (Chapter 3). To explore what gait characteristics are most susceptible to cognitive decline, the next study scrutinized the relationship between multiple gait outcomes and cognitive impairment in geriatric patients. Outcomes related to gait speed, regularity, predictability, and stability revealed with the highest discriminative power for single- and dual-tasking (average VIP-score of 1.12, with a VIP-score>1 indicating a high discriminative power). Geriatric patients walked slower, less regular, and less stable than healthy old controls. However, the discrimination of geriatric patients with- and without cognitive impairment based on gait outcomes alone was poor, with 57% (single-task) and 64% (dual-task) of the patients being misclassified (Chapter 4). Gait outcomes with the highest discriminative power in

chapter 4 were then studied in a prospective pilot study. Significant cognitive decline over 14.4 months on average correlated with a more regular ($\rho=0.579^*$) and a more predictable ($\rho=0.486^*$) gait at baseline, but not with baseline gait speed ($\rho=0.073$). The increased gait regularity and predictability most likely reflected a loss of gait complexity and this may thus signify future cognitive decline in geriatric patients. Yet, the quantification of gait dynamics (including complexity outcomes) in geriatric patients provided a non-invasive mobility measure that could be added to routine geriatric assessments and potentially facilitates the identification of cognitive impairment in this vulnerable population (Chapter 5).

A broader perspective on gait and cognition via the 'Loss of Complexity' theory

Researchers have been using gait speed extensively as a comprehensive index of old adults' locomotor performance [1]. Even natural aging entails a pyramid of alterations in neuromuscular and neurophysiological functions that engender declines in muscle structure and function, resulting in a slower gait [2]. Considering the sizable body of literature that suggests that gait speed further slows with cognitive impairment [3-10], we expected but did not find associations between gait speed and cognitive impairment. Differences in patient characteristics may account for the discrepant results between our and previous findings, as most studies recruited old adults from the community, who were healthier and younger than our geriatric patients who are 80 years on average. In addition to age-related declines, geriatric patients presented with 1.8 co-existing chronic conditions (e.g., pulmonary disease, tumours, diabetes) on the Charlson Comorbidity Index [11]. Furthermore, they on average met the criteria for polypharmacy (>4 medication), and 63% of the patients were frail or pre-frail according to Fried's definition [12]. Finally, conditions typically present in geriatric patients (e.g., vision impairment, pain, thoracic kyphosis, polypharmacy, sarcopenia) have been associated with a gait slowing [13-16]. Such conditions may already have substantially slowed a patients' gait, causing a 'floor-effect' so that gait speed did not slow further when cognitive impairment added to the symptoms [16].

Fine-grained, dynamic gait outcomes described features of gait not apparent in gait speed. Because geriatric patients show multi-system degeneration, the gait-cognition link was placed in a theoretical framework to better understand the coupling and coordination between elements of the aging neuro-musculo-skeletal system (NMSS), for which the 'loss of complexity' (LOC) theory was considered [17]. As derived from the field of cardiology, complexity could be defined as 'irregular (variable) fluctuations that appear in healthy physiological rhythms which take the form of chaos' [18]. Similar to sinus rhythm in heartbeats, human gait is a highly rhythmic movement, which is why several studies speculated that the gait pattern would also be characterized by a complex type of variability, and if it is, that alterations in complexity reflect disease-related aging. Because pathological conditions such as sensory impairment [19], frailty [20], recurrent falling [21], and Huntington's disease [22] have been associated with a loss of gait complexity, in this thesis the hypothesis was that cognitive impairment may also induce a loss of gait complexity. A loss of gait complexity could become manifested through an increased gait regularity and an increased gait predictability. Although preliminary, the results of Chapter 5 underscored this hypothesis by revealing correlations between a more regular and more predictable baseline gait and reliable cognitive decline over time, reflecting a loss of gait complexity [23].



Gait complexity is often interpreted and discussed in terms of gait variability. Several studies examined the ability of gait variability, quantified by the coefficient of variation, to identify and predict cognitive impairment or dementia syndromes [10, 24, 25]. A quite robust finding from this literature is that a higher gait variability signifies cognitive pathology. Those findings, however, cannot explain the observation that highly complex activities (e.g., Epke Zonderland doing his exercise on the rings) are usually performed in a variable, infinite number of ways, while performance remains stable or even improves. According to this view, and in line with findings of the present thesis, variability increases rather than decreases in a 'healthy system', and decreases with aging and pathology [18, 26-28]. The contrasting results reported in the literature could be explained by the way gait variability is quantified in most studies. Traditional variability measures typically quantify the magnitude of variability by delineating outcomes such as the standard deviation or the coefficient of variation. Such linear statistical tools treat every step as being independent, averaging data over multiple strides. However, variability of how gait evolves over time, i.e., the structure of gait variability, is best described by non-linear statistical tools that presume steps being not independent but instead temporally interdependent: previous steps affect subsequent steps [23, 28-32]. The increased magnitude of variability and the decreased structure variability thus represent different characteristics of gait functioning and are mutually not exclusive. While a relatively large number of studies were designed to clarify changes in magnitude variability, the functional meaning and implications of changes in structure variability, i.e., a loss of gait complexity, are poorly studied and understood.

A consistent finding from previous studies is that a loss of complexity in physiological systems results in more rigid, more regular, and less flexible systems, reducing the ability to adapt to stimuli arising from the ever-changing environment [17, 33-36]. From this perspective, Stergiou and colleagues developed a model that explained how gait complexity could relate to health [18]. This model proposed that there is an optimal amount of complexity so that too little complexity results in a more rigid system and too much complexity results in a noisy and unstable system. Both situations significantly affect the capacity to adapt to perturbations. The authors directly associated this reduced adaptive capacity with a lack of health [18]. With respect to gait function, it remains however unknown whether a loss of gait complexity actually translates to a reduced adaptive capacity to overcome potential perturbations during walking. A possible way to study this is to examine geriatric patients with and without a loss of gait complexity and to compare the effects of unexpected perturbations to their adaptive responses. A more challenging walking environment or task would be required for such a study design. Because a loss of gait complexity has been linked to an increased fall risk [27, 28], it seems likely that this relationship is mediated through reductions in ones' adaptive capacity to perturbations during walking.

A conceptual model of gait characteristics in geriatric patients with- and without cognitive impairment, as compared to healthy old controls

Based on the findings and corresponding interpretations of the experimental studies presented in Chapters 4 and 5, figure 1 illustrates a conceptual model that shows how gait is possibly characterized in cognitive intact geriatric patients and in cognitive impaired geriatric patients, as compared to relatively young and healthy old controls. Lines visualize the trajectory of how gait may change with 'geriatric aging' and with the development of

cognitive impairment. Gait speed declined from healthy old controls to cognitive intact geriatric patients, but did not further decline with diagnosed cognitive impairment (solid line). Gait regularity and predictability decreased from healthy old controls to cognitive intact geriatric patients, but increased when cognitive impairment added to geriatric conditions. The increase in gait regularity and predictability most likely come with a gradual loss of gait complexity and a decline in gait stability (dashed lines).

The combination of gait characteristics per population is caused by many underlying factors such as age and other patient demographics, and should therefore not be viewed as a functional capacity, but rather as an emerging, dynamic system. The high gait regularity observed in healthy old adults and geriatric patients with cognitive impairment, for example, results from different underlying factors and are therefore not comparable. While the higher gait regularity in healthy old adults may be beneficial in terms of for example metabolic cost, the high gait regularity in geriatric patients with cognitive impairment may come with a loss of gait complexity and a decline in gait stability.

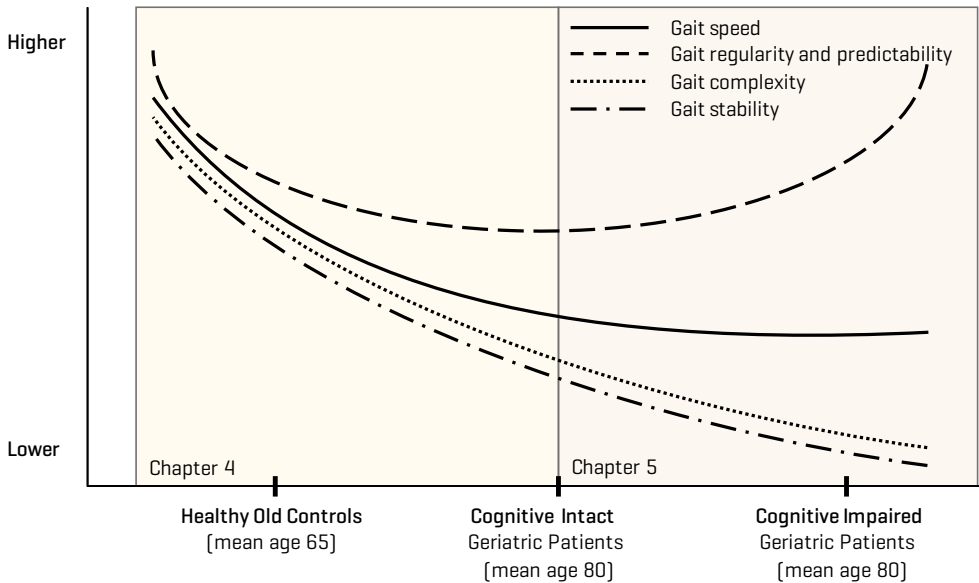


Figure 1. A conceptual model that shows how gait is possibly characterized in cognitive intact geriatric patients and in cognitive impaired geriatric patients, as compared to relatively young and healthy old controls. Lines visualize the trajectory of how gait may change with 'geriatric aging' and with the development of cognitive impairment.

How can the assessment of gait function contribute to the identification of cognitive impairment and falls in geriatric patients?

A consistent finding in this thesis was that gait dynamics added to widely used gait outcomes such as gait speed. Adding gait dynamics to usual diagnostics increased the specificity of a fall-classification model (Chapter 3). Similarly, gait regularity, predictability, and stability presented with the highest power to discriminate patient groups (Chapter 4). Additionally,



cognitive decline over time correlated with baseline gait regularity and predictability, but not with baseline gait speed (Chapter 5). Notwithstanding the attractiveness of gait speed as a simple summary index of mobility, the assessment of gait speed alone may lack specificity because many clinical and non-clinical conditions induce a gait slowing. In geriatric patients, typical conditions such as vision impairment, pain, thoracic kyphosis, the use of multiple medications, and sarcopenia all have been associated with a decline in gait speed [13-16]. Therefore, gait speed can be viewed as a marker for global health, but perhaps not as a cognition-specific marker. Dynamic gait outcomes enable to extract additional information about someone's gait in terms of for example gait coordination, complexity, and stability. However, even though gait dynamics could complement gait speed, a detailed gait analysis on its own was not sufficient to identify cognitive impairment. Geriatric patient groups with- and without cognitive impairment could not be discriminated, with 57% (single-task) and 64% (dual-task) of the patients misclassified. Those findings are interpreted to mean that an accurate identification of falls and cognitive impairment necessitates a multifactorial approach, including patient characteristics (e.g., geriatric conditions), and a comprehensive evaluation of cognitive- and gait function.

Challenges posed by analysing a geriatric patients' gait

As highlighted by the scoping review in Chapter 2, several methodological weaknesses complicate an accurate gait analysis in old adults. For example, some studies used very short distances such as 8 feet (~2.4 meters) to compute average gait speed, while it is recommended to exclude the first 2.5 meters of the gait pattern in frail old adults because of acceleration and deceleration phases [37]. Another study recommended extracting at least 30 steps and preferably 50 steps to accurately determine temporal-spatial gait outcomes (e.g., gait speed, step length, step width, swing time, stance time) in patients with Parkinson's disease [38]. One requirement for reliable estimates of gait outcomes derived from non-linear dynamics is that the length of the acceleration signal should be long. Despite the fact that the exact length depends on the gait outcome to be calculated, the signal should contain enough input to be able to quantify time-dependent fluctuations. For example, extracting gait regularity and symmetry outcomes using autocorrelation procedures has found to be reliable when at least 40 steps [39] or 40 meters [40] are included in the analysis.

Another challenge to accurately examine gait in geriatric patients comes from outcomes that rely on step detection methods. In a healthy gait pattern, steps are reflected in clear and smooth peaks in the anterior-posterior acceleration signals of the lower trunk [41]. Nevertheless, peak detection in healthy old adults already achieved an error rate of 7.4%, and this rate is expected to increase with gait slowing and gait shuffling [42]. In contrast to healthy old adults, geriatric patients not only walk (much) slower, but also typically present with a shuffling gait and/or a stooped posture. Such conditions can result in abnormalities in acceleration signals such as the presence of extra peaks, and thus complicate the automatic detection of steps from trunk acceleration signals. Unreliable step detection in turn substantially affects gait outcomes [43]. The use of gait outcomes that are independent of step detection is therefore essential in this vulnerable population.

Finally, an unexpected finding of this thesis was that dual-tasking did not identify cognitive impairment better than single-task walking (Chapters 4, and 5). While dual-task paradigms

are often used to highlight motor-cognitive interactions [9, 44-47], recent dual-task studies reported no increased sensitivity of dual-tasking vs. single-tasking to detect cognitive impairment, and shed light on concerns and difficulties of dual-task paradigms [48, 49]. For example, the majority of studies do not report the dual-task effect on the cognitive task, nor do these studies report the performance for the cognitive single-task. Therefore, it is possible that patients ignored the secondary task and only performed the gait task, or vice versa. Furthermore, the taxing effect of the cognitive task on gait functioning strongly depends on the nature and complexity of the cognitive task, instructions about task prioritizing, distractions of the environment, and baseline gait and cognitive function of the patient [50]. Those difficulties particularly arise in cognitive impaired geriatric patients, as cognitive impairment could affect their ability to follow task instructions. As a consequence, there is a lack of clear recommendations on how to use and interpret dual-task paradigms in different patient groups, which limits its implementation in clinical practice [50]. Taken together, it remains questionable whether and how a motor-cognitive dual-task paradigm in a heterogeneous sample of geriatric patients actually improves the detection of cognitive impairment, or poses additional uncertainties with regards to an accurate interpretation of the data. To increase its validity, recent studies suggested tailoring the cognitive task specifically to the cognitive domain that is predominantly affected by cognitive pathologies [48].

Clinical perspectives

Gait assessment as used throughout the present thesis is an easy and non-invasive measure, taking clinicians only minutes to assess. Today's rapid development in technologies facilitates the use of an extensive gait analysis in clinics and research. Wearable sensors (phones, iPods, or accelerometers) become more and more incorporated in healthcare sectors [51], and are nowadays standardly equipped with Inertial Measurement Units (IMU) such as gyroscopes, accelerometers, and magnetometers. Furthermore, those wearable sensors are widely-available, easy to operate, low-cost, and of compact size [52].

In addition to its potential to identify cognitive impairment and fall-status, dynamic gait outcomes identified subtle gait disturbances [27, 28, 53, 54]. Intervention strategies can be specifically tailored to reduce fall risk, and to maintain independent living. A promising finding from a recent population study was that transitions in gait disorders as well as cognitive impairment were mutable and reversible over a 9-year period, even in the oldest-old [55]. While there is abundant evidence that walking ability has the capacity to pick-up changes in physical as well as in mental health-related quality of life, a mobility measure is usually not part of standard assessments in geriatric diagnostic clinics. A recent study therefore recommended healthcare professionals to focus on screening procedures and intervention strategies to maintain mobility in old adults in order to preserve and/or increase their health-related quality of life [56].

In summary, there are multiple technological and clinical advantages of incorporating a 3-minute gait assessment into standard clinical routine evaluations. Future studies should confirm the clinical utility and the predictive ability of such technologies, and norm-scores and cut-off scores need to be determined for different population groups. Ultimately, an application that translates the technical gait details to clinical outcomes, integrates gait and other diagnostics could be built, and ultimately provides a multifactorial risk profile for cognitive decline and falling.



Future directions

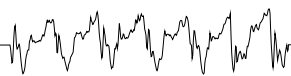
Future studies are urged to study multiple gait outcomes that reflect different aspects of the gait pattern in a larger sample of old adults to disentangle the trajectory of how gait changes with healthy aging, with geriatric aging, with cognitive impairment, and with falling. Because an increase in age is often accompanied by the presence of comorbidities, the effect of such conditions should be documented and taken into account in the analysis. In addition, future studies are encouraged to improve the sub-typing of cognitive impairment (e.g., amnesic MCI, non-amnesic MCI, multiple-domain MCI). For example, patients with amnesic MCI presented with less gait rhythm and more gait variability as compared to patients with non-amnesic MCI [57]. A recent report from the GOOD (Gait, cOgnitiOn, and Decline) initiative, including data from 7 countries, presented distinct gait characteristics from the earliest to the latest stages of dementia, depending on the type of dementia [58]. In line with this recommendation, concepts and definitions of dementia-related diagnoses should be improved, as they are still in evolution [59]. Although much effort has been devoted to the field of dementia during the last decade, the uptake of the use of MCI is still premature, and clinicians as well as researchers use inconsistent criteria for diagnoses [59]. In addition, even though 15% of the patients with MCI yearly convert to dementia syndromes [60], MCI is not always a precursor of dementia. Several causes of MCI (e.g., depression) are of transient nature, and approximately 40% of the patients with MCI actually convert back to normal cognition within 2 to 3 years [61]. Furthermore, there is a need to develop guidelines that standardize gait protocols (e.g., procedures, instructions, analyses, type of task) for single- as well as for dual-task walking. Examining neural correlates of gait dynamics could help to underpin the neural control of gait, and is therefore recommended in the neuroscientific field. Finally, while there is a clear theoretical and experimental basis for the use of dynamic gait outcomes in the identification of cognitive impairment, multifactorial models should examine whether incorporating gait outcomes in prediction models actually significantly improves the prediction accuracy of cognitive status.

Conclusions

This thesis contributed to our understanding of the relationship between gait and cognition in geriatric patients. In line with the hypothesis, the results revealed that the presence of cognitive impairment in the geriatric population possibly becomes manifested through an increased gait regularity and predictability, reflecting a loss of gait complexity. Against the hypothesis and in contrast to previous research, the results revealed no associations between cognitive impairment and gait speed as a summary index of mobility. Hence, gait outcomes related to gait complexity could increase the specificity of the gait-cognition link, and gait dynamics can therefore be considered promising indicators of cognitive impairment and falls. However, clinicians and researchers should be aware of the effects of multiple, co-existing, conditions in geriatric patients that interact with each other and with gait function. An accurate identification of cognitive impairment and falls thus most likely necessitates a multifactorial approach in this vulnerable population, including physical, cognitive, pharmacological, and behavioural measures. Because smart devices such as smartphones are nowadays routinely equipped with IMU's (e.g., accelerometers), the assessment of gait function provides a cheap and non-invasive mobility measure that in the near future could be added to routine geriatric assessments. However, future studies are encouraged to replicate our findings in larger cohorts, and to reduce methodological weaknesses in gait- and cognitive measurements that complicate an accurate gait analysis in geriatric patients.

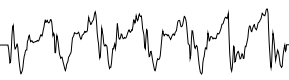
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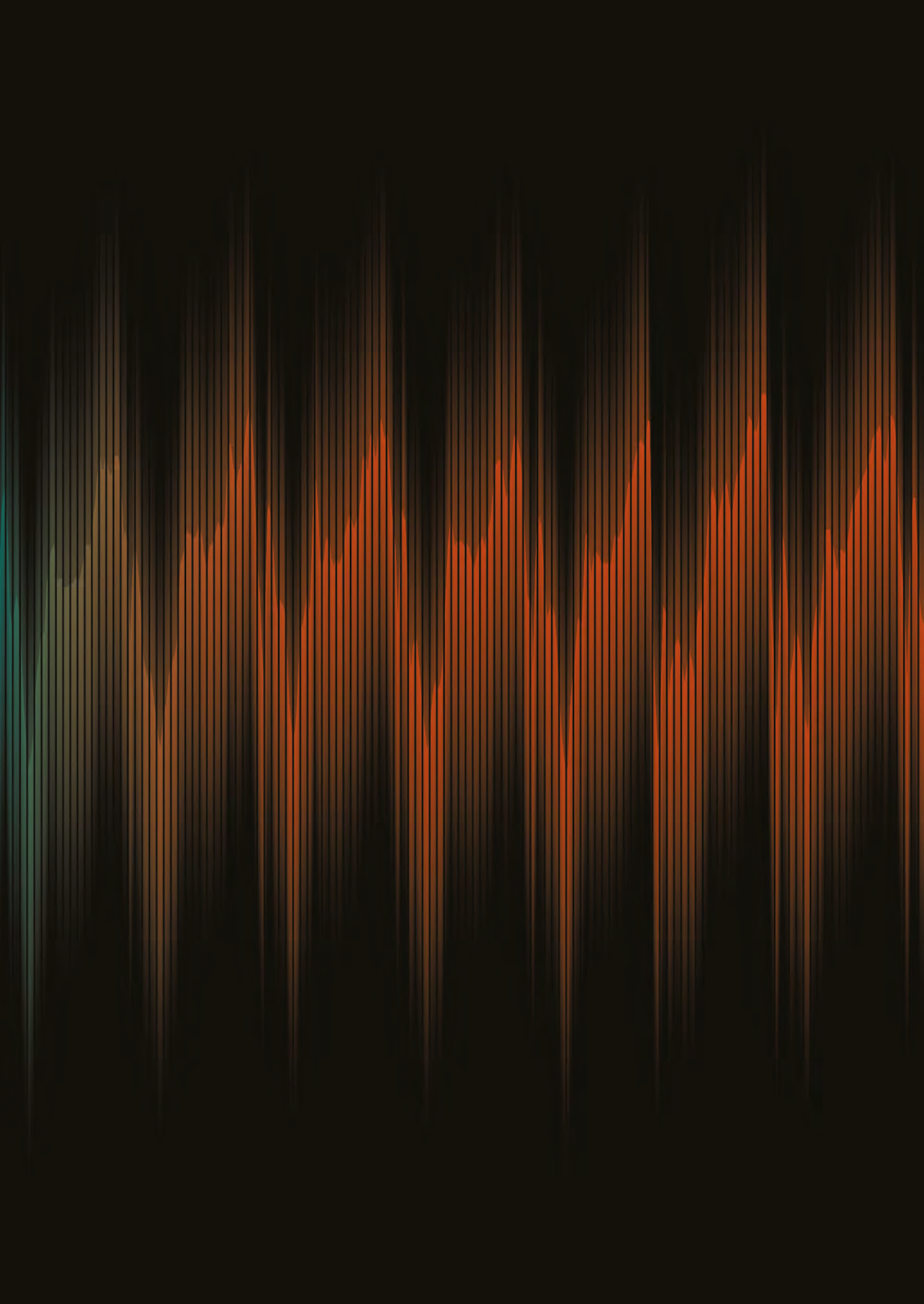


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7

THÈSE EN FRANÇAIS



Introduction générale

La société vieillissante

Comme la sagesse et l'expérience augmentent avec l'âge, les personnes âgées sont précieuses pour leurs familles, les communautés locales et la société en général. À présent, on constate une augmentation considérable au niveau de la durée de vie des populations dans la plupart des pays. Ce phénomène aboutit à une proportion accrue de personnes âgées de plus de 65 ans au niveau mondial [1]. Le bénéfice personnel et social d'une vie prolongée dépend apparemment largement de la question suivante: est-ce que les personnes concernées peuvent s'attendre à des années en bonne santé où doivent-elles s'attendre à des années de souffrance? D'après l'Organisation mondiale de la santé, il y a donc un grand défi à relever: il ne faut pas se limiter à ajouter des années à la vie; il faut veiller à ajouter des années pleines de santé.

'Le vieillissement en bonne santé' par rapport au 'vieillissement gériatrique'

Personne n'échappe aux changements liés à l'âge à long terme. Même 'le vieillissement en bonne santé' entraîne toute une série de changements physiologiques, psychologiques et sociaux dans le temps [2]. Lorsque le degré du déclin des fonctions physiques et/ou psychologiques dépasse le degré de déclin attendu à cause du vieillissement seul, on adresse les personnes âgées en général à des gériatres ou à d'autres spécialistes ayant de l'expérience avec le traitement d'affections et de maladies gériatriques [3]. Parmi les affections gériatriques typiques on trouve la sarcopénie, le délire, la perte de poids, la déficience cognitive, l'ostéoporose et les chutes récurrentes. De telles affections se caractérisent souvent par des facteurs étiologiques et des mécanismes pathogènes interdépendants [4]. La définition suivante s'applique donc aux patients gériatriques: un segment vulnérable de personnes âgées chez lesquelles la moindre affection risque d'aboutir à une catastrophe.

La population étudiée dans la présente thèse

Les études expérimentales incluses dans cette thèse (chapitres 3-5) portent sur des patients gériatriques qui ont été recrutés parmi les patients admis à l'hôpital MC Slotervaart à Amsterdam pendant la période de 2014 à 2017. Ces patients se sont présentés à la clinique de jour spécialisée en diagnostic gériatrique pour une évaluation des fonctions physiques, cognitives et psychologiques. Les patients gériatriques qui se présentaient au service de gériatrie avaient env. 80 ans en moyenne et une espérance de vie moyenne d'env. 4 ans.

Déficience cognitive de la population gériatrique

Parmi les causes majeures de l'invalidité des patients gériatriques, il faut citer les déficiences cognitives du fait qu'elles affectent la mémoire, la réflexion, le comportement, les émotions et/ou les facultés de perception [5]. Les études au niveau de la population montrent des taux de prévalence de déficiences cognitives de 5% à 29% chez les personnes âgées de plus de 65 ans qui vivent dans la collectivité [6]. Les déficiences cognitives émergentes sont souvent considérées comme précurseurs de démence. Même s'il n'y a pas de remède permettant de guérir voire d'inverser la neurodégénérescence cognitive, des interventions sur mesure (médication, psychothérapie, psychoéducation, modifications de l'environnement, activité physique) peuvent ralentir la progression de la maladie et réduire les symptômes [5].

Les caractéristiques de la démarche comme indicateurs d'une déficience cognitive

Les modèles actuels ont recours à des variables démographiques, génomiques, vasculaires, comportementales et neuropsychologiques pour prédire la pathologie liée à la démence [7]. Du fait que ces modèles ne distinguent pas suffisamment entre les patients à risque et les patients sans risque (aire sous la courbe comprise dans une plage de AUC=0.50 à AUC=0.87) [8], on a besoin de marqueurs supplémentaires. Outre les prédicteurs courants, la présente thèse étudiait les caractéristiques de la démarche comme indicateurs potentiels non invasifs de déficiences cognitives chez des patients gériatriques.

Des études de nombreux domaines scientifiques soulignent l'interdépendance entre les fonctions motrices et cognitives. Exemple: le cerveau fonctionne mieux et le risque de développer des troubles neurodégénératifs baisse lors d'une augmentation de la condition physique [9, 10]. En outre, les troubles neurodégénératifs comme la démence et le syndrome de Parkinson entraînent souvent une forte perte de poids [11].

L'interdépendance entre les fonctions motrices et cognitives se traduit également dans la démarche humaine. La marche exige l'exécution d'actions ciblées. C'est donc un processus qui s'appuie fortement sur la mémoire et la fonction exécutive pour anticiper et interpréter l'environnement et le comportement d'autrui. La démarche et la cognition montrent des structures associatives distinctes dans ce processus [12, 13]. Des études impliquant l'imagerie neurologique ont confirmé le lien entre la démarche et la cognition du fait d'illustrer que la marche sollicite des régions cérébrales qui assurent des fonctions exécutives, des fonctions de mémoire et des fonctions visuo-spatiales ainsi que des régions motrices comme le cortex moteur, le cervelet et les noyaux gris centraux [14]. Les régions cérébrales impliquées dans la fonction de démarche et la fonction cognitive se recoupent donc partiellement. On peut alors s'attendre à des changements au niveau de la démarche lors du début d'une déficience cognitive.

Le lien entre la démarche et la cognition à la lumière de la théorie de la 'Perte de Complexité'

Comme les patients gériatriques montrent des dégradations dans des systèmes interdépendants multiples, le lien entre la démarche et la cognition peut être placé dans un contexte théorique pour augmenter la compréhension du couplage et de la coordination entre les éléments du système neuro-musculo-squelettique (NMSS) (c.-à-d. la démarche et la cognition). Eu égard à cette idée, on considérerait un phénomène clé du NMSS vieillissant, à savoir la 'perte de complexité' (LOC). La théorie de la LOC relève du domaine des dynamiques non-linéaires et présume que même le vieillissement en bonne santé est associé à une défaillance (neuro)-physiologique d'éléments qui cause une perte de complexité générale [15]. Dans la présente thèse, on a établi l'hypothèse que le déclin (neuro)-physiologique causé par le déficit cognitif se traduisait également dans la démarche. Une perte de complexité au niveau de la démarche devrait donc se caractériser par une augmentation de la régularité et de la prévisibilité [16]. Les résultats seront détaillés dans les paragraphes qui suivent.

La nature dynamique de la marche: Qu'est-ce que la démarche traduit?

La vitesse de démarche est le paramètre le plus documenté de la démarche [17]. Une observation omniprésente d'études précédentes est la baisse de la vitesse de démarche liée à l'âge. Une vitesse de démarche de moins de 1.0 m/s indique la présence d'affections



cliniques comme des troubles de mobilité, des chutes récurrentes, une perte d'indépendance et très probablement une faible fonction cognitive. L'importance de la mesure de la vitesse de démarche chez des personnes âgées est donc soutenue davantage et la vitesse de démarche a même été proposée comme 'sixième signe vital' [18]. C'est par ailleurs un test utilisé dans les cliniques de gériatrie [17, 19].

À côté de la vitesse de démarche comme indice global de la mobilité, des paramètres de démarche dynamiques finement grainés décrivent des caractéristiques qui ne se manifestent pas dans la vitesse de démarche. La quantification d'une telle dynamique de démarche peut être obtenue lorsqu'on considère la démarche comme tâche dynamique. La marche exige en effet des interactions permanentes entre les différents segments du corps, le corps et l'environnement et nécessite des réponses tant préventives que réactives. Nous parvenons facilement à marcher sur des surfaces différentes, à prévoir le trafic arrivant, à éviter des obstacles qui bloquent la route et à assurer le contrôle et la coordination des parties du corps en mouvement comme les jambes, les bras, le torse et la tête [20].

L'analyse des fluctuations dépendant du temps, c.-à-d. la manière dont la démarche évolue dans le temps peut révéler les causes d'une démarche lente en termes de coordination de la marche et des réactions à des perturbations [16, 20-24]. La corrélation des séries temporelles entre les événements constituant de la démarche peut montrer des troubles ou des pathologies de démarche sous-jacentes. Le recours aux mesures traditionnelles de la démarche comme la vitesse et (le coefficient de la variation de) l'avancée peut masquer l'interdépendance temporelle entre les étapes successives du fait que ces mesures ne moyennent que les informations relatives aux étapes dans le temps. La quantification des fluctuations dépendant du temps qui surviennent pendant la marche pourrait augmenter notre compréhension de la relation entre la démarche et le déficit cognitif et aider à étayer le contrôle neural de la démarche.

La théorie des systèmes dynamiques propose des outils et des concepts pour la quantification des fluctuations dépendant du temps survenant pendant la démarche [16, 21-23, 25, 26]. Le monitoring continu du type de démarche d'un patient est nécessaire pour saisir ces fluctuations dépendant du temps. Il y a toute une série de méthodes permettant la surveillance continue de la démarche (exemples: les systèmes optoélectroniques, les essais sur une plateforme de force). L'avantage de l'accélérométrie réside pourtant dans le fait que la marche est largement sans contrainte et peut être mesurée en dehors du laboratoire sur des distances et des durées de marche prolongées [27]. Comme on sait que la régulation de l'équilibre pendant la marche se traduit par des signaux d'accélération du bas du torse (à cause de sa proximité du centre de gravité du corps) [28], les accélérations du torse traduisent exactement le comportement du centre de gravité pendant la démarche [27]. Sur la base des signaux d'accélération du torse, des paramètres de démarche dynamiques, qui quantifient les fluctuations et schémas dépendant du temps pendant le cycle de démarche [16, 21-23, 25, 26], peuvent être saisis. Dans cette thèse, le terme 'dynamique de démarche' est employé pour désigner les aspects dynamiques de la marche. En général, la dynamique de démarche indique la coordination, la capacité d'adaptation et la faculté de réagir à des perturbations en général.

Une approche multivariée

Le grand nombre de comorbidités exige une approche multivariée pour étudier le lien entre la démarche et la cognition chez des patients gériatriques. Comme nous venons de mentionner, de telles affections se caractérisent souvent par des facteurs étiologiques et des mécanismes pathogènes interdépendants [4]. Ces affections gériatriques sont probablement inter-reliées. Exemple: des affections typiquement présentes chez des patients gériatriques sont connues pour leur interaction avec la performance de démarche, comme la posture voûtée [29], la faiblesse musculaire [30], et la poly-pharmacie [31]. Par ailleurs, les caractéristiques de démarche semblent corrélées entre elles. Outre le fait que les hypothèses statistiques ne sont pas remplies, les analyses à une variable pour chaque paramètre individuel risquent de masquer des clusters/dépendances dans les données. De ce fait, des analyses à variables multiples basées sur la Régression par les Moindres Carrés Partiels (PLS) ont été effectuées [32] dans les chapitres 3 et 4. La PLS combine des caractéristiques de l'analyse en Composantes Principales et de l'analyse de la régression courante. Des structures de covariance ont été modélisées; les clusters latents sous-jacents ont été extraits.

Objectifs et schémas scientifiques

La plupart de la littérature existante sur la relation entre la démarche et la déficience cognitive se concentre sur des personnes âgées relativement jeunes et en bonne santé, tandis que les patients gériatriques de notre échantillon sont plus âgés et présentent de nombreuses comorbidités qui sont connues pour leur interaction avec la fonction de démarche. Par ailleurs, les études précédentes se concentraient en premier lieu sur la vitesse de démarche comme indicateur de déficit cognitif, tandis que des paramètres de démarche dynamiques finement grainés sont susceptibles d'augmenter la spécificité du lien entre la démarche et la cognition et peuvent aider à étayer le contrôle neural de la démarche. De ce fait, l'augmentation de notre compréhension de la relation entre la démarche et la cognition dans des patients gériatriques constituait l'objectif principal de la thèse. Des analyses à variables multiples ont à cet effet été employées pour étudier des paramètres de démarche multiples en relation avec le statut cognitif. En fin de compte, les caractéristiques de démarche pourraient servir d'indicateurs non invasifs d'une déficience cognitive chez cette population vulnérable. Pour arriver à ce but principal, un double sous-objectif a été établi: (1) définir le type de démarche de patients gériatriques avec et sans déficit cognitif par rapport à des personnes âgées relativement jeunes et en bonne santé, et (2) étudier si et dans quelle mesure les caractéristiques de démarche peuvent contribuer à l'identification et/ou à la prédiction d'une déficience cognitive et de chutes. On a établi l'hypothèse que les patients gériatriques souffrant d'une déficience cognitive présentaient un type de démarche plus lent, plus régulier et moins complexe par rapport aux patients gériatriques cognitivement intacts. Par ailleurs, on s'attendait à ce que les paramètres de démarche dérivés d'une analyse de démarche exhaustive pouvaient contribuer aux diagnostics habituels servant à identifier/prévoir une déficience cognitive et des chutes.

L'illustration 1 montre le protocole de démarche et les mesures employées dans les chapitres 3-5. Outre les procédures de dépistage courantes employées au MC Slotervaart hospital, les patients marchaient pour 3 minutes pendant un test à tâche simple ou à double-tâche. Les accélérations du torse exprimées en signaux des sens suivants: antérieur-postérieur (AP),



médio-latéral (ML) et vertical (V) étaient extraits d'un Ipod touch 4G. L'illustration montre l'exemple d'un signal d'accélération brute dans le sens AP qui servait de base pour le calcul en 3D des paramètres du torse, c.-à-d. de la dynamique de démarche. Compte tenu de la nature exploratoire des études, des paramètres de démarche multiples ont été quantifiés. Tandis que tous les paramètres reflètent la nature dynamique de la démarche, ils quantifient différents aspects du schéma de démarche en se basant sur différentes propriétés du signal d'accélération (ex. l'amplitude, la fréquence, les cadres temporels, l'espace de phases).

Schéma de la thèse

Pour arriver à une vue d'ensemble de la littérature existante sur la relation entre les caractéristiques de démarche et le déficit cognitif chez des personnes âgées, on a systématiquement révisé les preuves fournies par des études longitudinales qui révélaient des associations entre la fonction de démarche et le déclin cognitif dans le chapitre 2. Dans le chapitre 3, on a étudié la contribution d'une évaluation exhaustive de la cognition et de la démarche en ce qui concerne l'exactitude de la classification de patients chuteurs et de patients non chuteurs. Dans le chapitre 4, on a examiné les caractéristiques de démarche et leur pouvoir distinctif chez des individus témoins en bonne santé et chez des patients gériatriques avec et sans déficit cognitif. Les paramètres de démarche qui montraient le plus grand pouvoir distinctif ont alors été étudiés dans une conception prospective dans le chapitre 5. Cette étude pilote servait à examiner la manière dont les paramètres de démarche initiaux corrélaient avec le déclin cognitif future.

Résultats principaux et discussion générale

En 2015, une recherche littéraire systématique permettait d'identifier 20 études longitudinales (y compris les données de 24.368 personnes âgées de plus 65 ans) qui examinaient les associations entre la fonction de démarche initiale et le déclin cognitif futur. La révision discutait les connaissances actuelles et les lacunes présentes dans la littérature à ce sujet et servait donc de base à la présente thèse. Dix-huit sur 20 études citaient la vitesse de démarche comme paramètre principal: une vitesse de démarche lente était associée au déclin futur dans le score MMSE et à des fonctions cognitives spécifiques comme le fonctionnement exécutif. Par ailleurs, une vitesse de démarche lente augmentait le risque pour un MCI et la démence (odds et hazard ratios maximaux de 10.4 et de 11.1 respectivement). Les paramètres ont également souligné les inégalités et inexactitudes méthodologiques dans les 20 études et montraient que la recherche future pourrait augmenter la spécificité du lien entre la démarche et la cognition par une indexation plus détaillée de la démarche et de la cognition (chapitre 2). Sous cette optique, une évaluation cognitive plus exhaustive (MMSE, mémoire, fonctionnement exécutif) et des paramètres de démarche finement grainés ont été ajoutés à un dépistage chute-risque courant. L'exactitude globale de la classification des patients chuteurs et patients non chuteurs passait d'une valeur AUC=0.86 à une valeur AUC=0.93. La spécificité de ce modèle de classification des chutes passait de 60% à 72% lorsque les paramètres cognitifs étaient ajoutés et de 72% à 80% avec l'ajout des paramètres de démarche dynamiques au modèle (illustration 2). Les résultats soulignaient la nécessité d'une approche multifactorielle dans l'évaluation du risque de chute chez des patients gériatriques, y compris une évaluation détaillée des fonctions cognitives et de démarche (chapitre 3). Afin de déterminer quelles caractéristiques de démarche sont les plus sensibles au déclin cognitif, l'étude suivante

examinait la relation entre des paramètres de démarche multiples et le déficit cognitif chez des patients gériatriques. Les paramètres relatifs à la vitesse de démarche, la régularité, la prévisibilité et la stabilité montraient le plus grand pouvoir distinctif au niveau de la simple tâche et de la double tâche (score VIP moyen de 1.12 avec un score VIP>1 indiquant un important pouvoir distinctif). Les patients gériatriques montraient une démarche plus lente, moins régulière et moins stable que les individus témoins en bonne santé (illustration 3). Quoi qu'il en soit, la distinction entre les patients avec et sans déficit cognitif sur la seule base des paramètres de démarche était insuffisante, avec 57% (simple tâche) et 64% (double tâche) des patients ayant été incorrectement classés (illustration 4) (chapitre 4). Les paramètres de démarche avec le plus grand pouvoir distinctif du chapitre 4 ont été étudiés dans le cadre d'une étude pilote prospective. Déclin cognitif significatif pendant une période de 14.4 mois en moyenne corrélé avec une démarche initiale plus régulière ($\rho=0.579^*$) et plus prévisible ($\rho=0.073$), mais pas avec la vitesse de démarche initiale ($\rho=0.073$) (illustration 5). La régularité et la prévisibilité de démarche reflètent très probablement une perte de complexité de démarche et peuvent donc indiquer un déclin cognitif futur chez des patients gériatriques. La quantification de la dynamique de démarche (y compris les paramètres de complexité) chez des patients gériatriques apportait pourtant une mesure de mobilité non-invasive qui pourrait être ajoutée aux évaluations gériatriques de routine où elle pourrait éventuellement faciliter l'identification d'une déficience cognitive chez cette population vulnérable (chapitre 5).

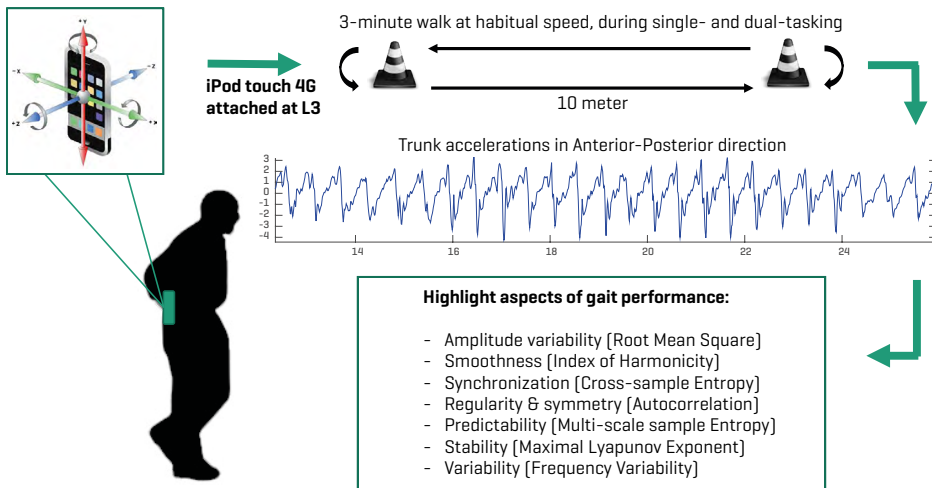


Illustration 1. Le protocole de démarche et les mesures employées dans les chapitres 3-5.

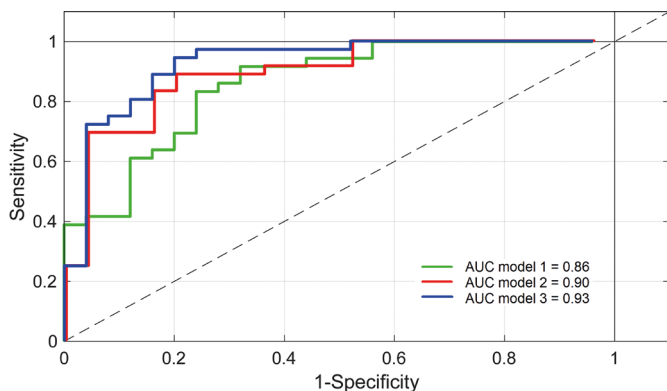


Illustration 2. Obtention de caractéristiques de fonctionnement - courbes pour les trois modèles de classification de chutes Modèle 1 = caractéristiques du patient; Modèle 2 = caractéristiques du patient + paramètres cognitifs; modèle 3 = Caractéristiques du patient + paramètres cognitifs + paramètres de démarche. AUC = région sous la courbe.

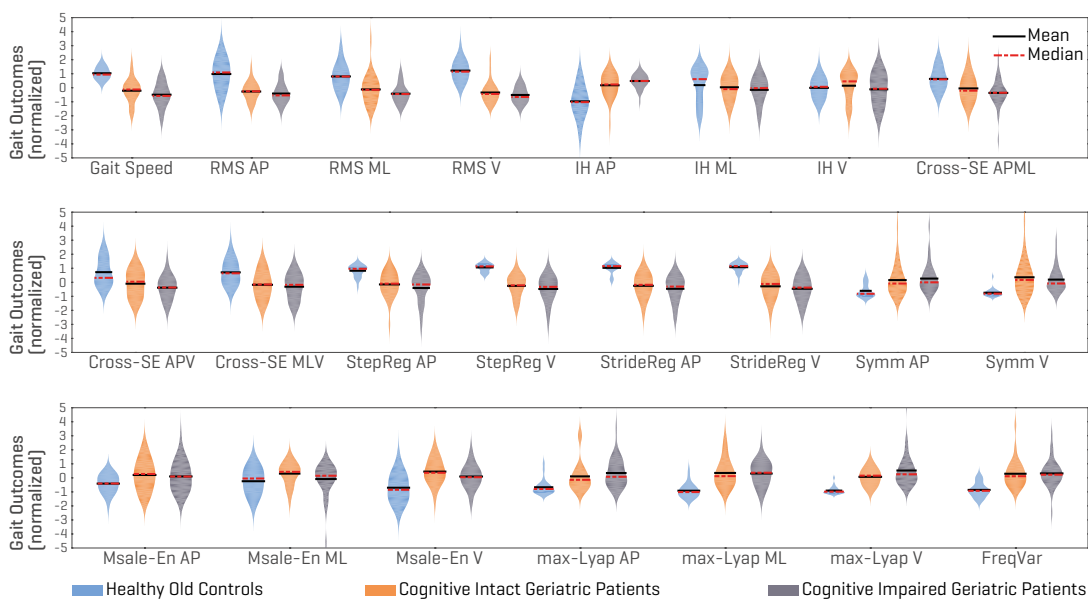


Illustration 3. Des diagrammes en violon basés sur l'estimation par noyau indiquent la répartition des paramètres de démarche. Les diagrammes en violon montrent les paramètres de démarche pour des personnes âgées en bonne santé (n=25), des patients gériatriques cognitivement intacts (n=31) et des patients atteints d'un déficit cognitif (n=36) pendant un test de marche à tâche simple. Un noyau plus compact et moins allongé indique une densité et une homogénéité plus élevées à travers les paramètres de marche. Les lignes noires et les lignes rouges pointillées indiquent des valeurs moyennes et médianes respectivement. Les paramètres sont normalisés en une variance au carré aux fins du traçage uniquement. RMS = Moyenne quadratique; IH = Indice d'harmonicité; Cross-SampEn = Entropie croisée Mscale-En = Entropie multi-échelle; max-Lyap = Exposant de Liapounov maximal; FreqVar = Variabilité de fréquence; AP = Antérieur-Postérieur; ML = Médio-Latéral; V = Vertical.

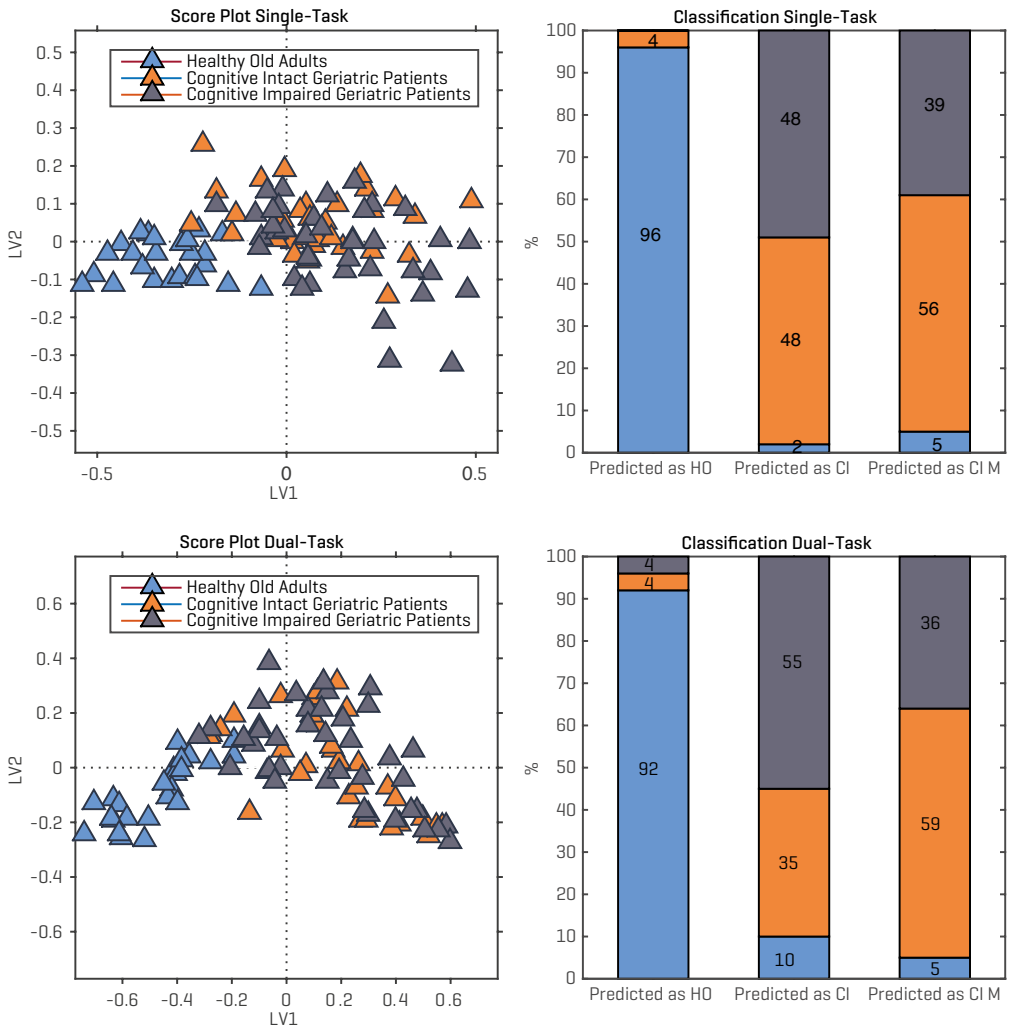


Illustration 4. Tracés de scores et exactitude de classement. Les tracés de scores (tableau gauche) illustrent les scores des participants individuels et montrent la relation entre les paramètres de marche et les participants de chaque groupe compte tenu des deux premières variables latentes pour la simple tâche (tableau du haut) et la marche à double tâche (tableau du bas). Les personnes âgées en bonne santé se trouvent dans un cluster clairement délimité tandis que 57% et 64% des patients gériatriques cognitivement intacts (CI) et des patients atteints d'une déficience cognitive (CIM) sont incorrectement classés pour la simple tâche et la double tâche respectivement (tableau droit).

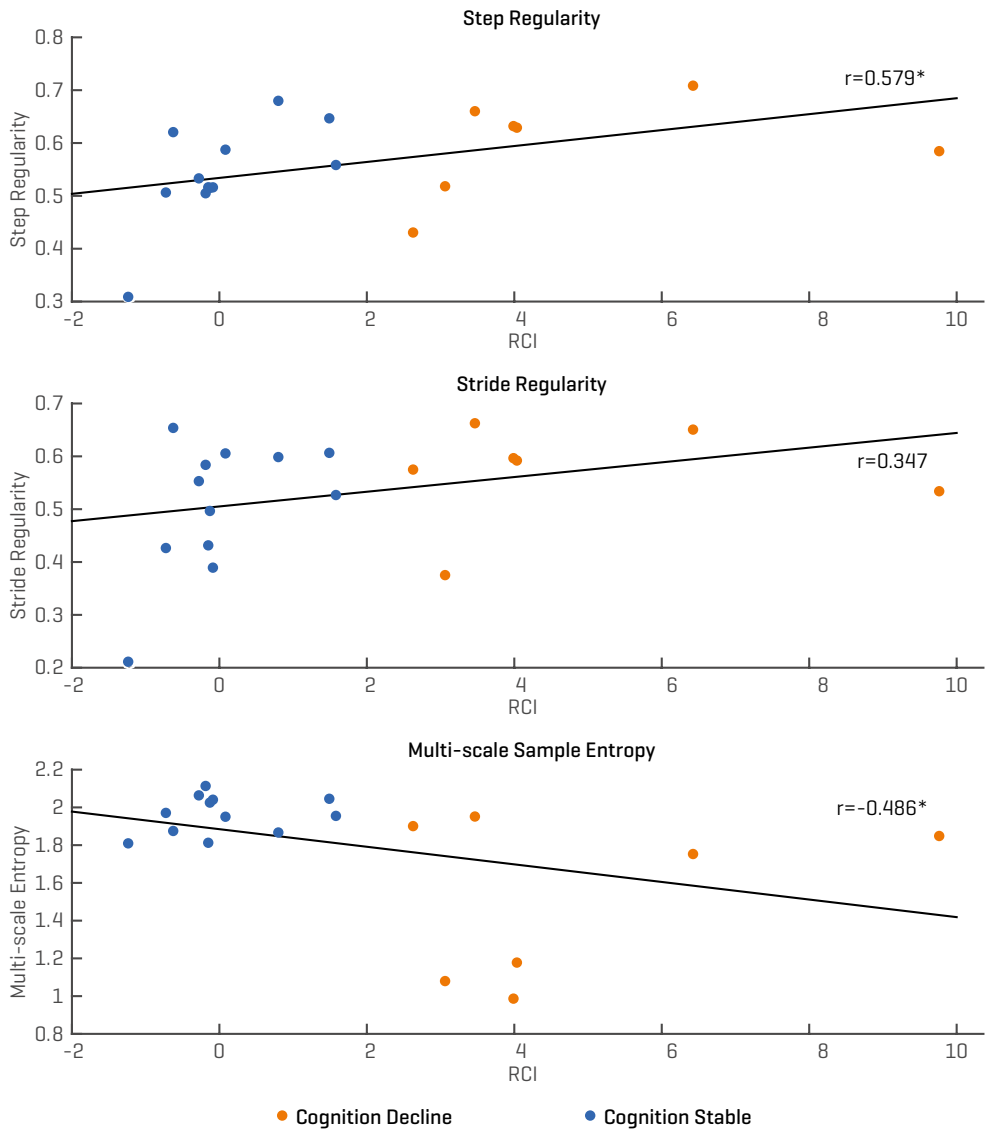
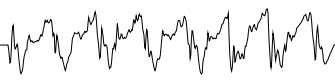
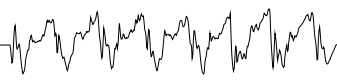


Illustration 5. Corrélations entre les paramètres de démarche initiaux et le déclin cognitif futur (MMSE+7MS) Le degré du changement cognitif a été quantifié par l'Indice de Changement Fidèle (RCI) où un RCI>1.961 indique un changement cognitif considérable dans le temps ($p<0.05$). Chaque symbole désigne un patient individuel. Les patients chez lesquels les valeurs MMSE et 7MS ont baissé sont marqués en orange ($n=7$) et les patients qui restaient cognitivement stables sont marqués en bleu ($n=12$).

Une perspective plus large sur la démarche et la cognition obtenue par le biais de la théorie de la 'Perte de Complexité'

La vitesse de démarche est le paramètre le plus documenté dans le domaine de la mobilité [17]. Même le vieillissement naturel entraîne toute une série d'altérations au niveau des fonctions neuro-musculaires et neuro-physiologiques qui aboutissent à un déclin de la structure et de la fonction musculaire et donc à une démarche plus lente [33]. Compte tenu de la littérature abondante qui dit que la vitesse de démarche baisse davantage avec la déficience cognitive [34-41], nous avons espéré trouver des associations avec la vitesse de démarche et le déficit cognitif mais en vain. Les différences au niveau des caractéristiques des patients pourraient expliquer les résultats divergents entre nos constatations et les constatations précédentes du fait que la plupart des études recrutaient des personnes âgées de la communauté qui étaient en meilleure santé et plus jeunes que nos patients gériatriques qui ont 80 ans en moyenne. À côté du déclin lié à l'âge, les patients gériatriques présentaient un score de 1.8 sur l'indice de comorbidités de Charlson (affections pulmonaires, tumeurs, diabète) [42]. Par ailleurs, ils remplissaient en moyenne les critères d'une poly-pharmacie (>4 médicaments) et 63% des patients étaient fragiles ou pré-fragiles selon la définition de Fried [43]. En fin de compte, les conditions typiquement présentes chez des patients gériatriques (comme la déficience visuelle, les douleurs, la cyphose thoracique, la poly-pharmacie, la sarcopénie) ont été associées au ralentissement de la démarche [29, 44-46]. De telles affections peuvent déjà avoir causé un ralentissement considérable de la démarche d'un patient et un 'effet de plancher' de manière à ce que la vitesse de démarche ne pouvait pas baisser davantage au moment où le déficit cognitif venait s'ajouter aux symptômes [46].

Les paramètres de démarche dynamiques finement grainés décrivaient des caractéristiques de démarche qui ne se manifestaient pas dans la vitesse de démarche. Du fait que les patients gériatriques montrent des dégénérescences multi-systèmes, le lien entre la démarche et la cognition a été placé dans un cadre théorique pour augmenter la compréhension du couplage et de la coordination entre les éléments du système neuro-musculo-squelettique vieillissant (NMSS) pour lesquels la théorie de la 'Perte de complexité' (LOC) a été prise en considération [15]. Tel qu'il ressort de la cardiologie, la complexité pourrait être définie comme fluctuations 'irrégulières (variables) qui se présentent dans des rythmes physiologiques saines qui aboutissent à une forme de chaos' [47]. Tel le rythme sinusal dans les battements du cœur, la démarche humaine est un mouvement hautement rythmique. C'est pour cette raison que différentes études prétendaient que le schéma de démarche était également caractérisé par un type de variabilité complexe et que, dans l'affirmative, les altérations au niveau de la complexité reflétaient le vieillissement lié à des maladies. Du fait que les affections pathologiques comme le déficit sensoriel [48], la fragilité [49], les chutes récurrentes [50] et le syndrome de Huntington [51] ont été associés à une perte de complexité de démarche, cette thèse partait de l'hypothèse que la déficience cognitive pouvait également induire une perte de complexité de démarche. Bien que préliminaires, les résultats du chapitre 5 étayaient cette hypothèse du fait de révéler des corrélations entre une démarche initiale plus régulière et prévisible et un déclin cognitif fiable dans le temps où la régularité et la prévisibilité accrues de la démarche reflètent une perte de complexité de démarche [16].



Une constatation cohérente des études précédentes est le fait qu'une perte de complexité dans les systèmes physiologiques aboutit à des systèmes plus rigides, réguliers et moins flexibles. La faculté de s'adapter à des stimulations de l'environnement en évolution constant est donc réduite [15, 52-55]. Dans cette perspective, Stergiou et collègues ont développé un modèle qui expliquait la manière dont la complexité de démarche pouvait être liée à la santé [47]. Selon ce modèle, il y a une quantité optimale de complexité: un manque de complexité se traduit donc dans un système plus rigide tandis qu'une complexité excessive aboutit à un système bruyant et instable. Les deux situations affectent la capacité de s'adapter à des perturbations de manière considérable. Les auteurs ont directement associé cette capacité d'adaptation réduite à un manque de santé [47]. En ce qui concerne la fonction de démarche, on ignore pourtant toujours si une perte de complexité de démarche aboutit vraiment à une capacité d'adaptation réduite qui est nécessaire pour maîtriser les perturbations potentielles pendant la marche. L'étude de patients gériatriques avec et sans perte de complexité de démarche et la comparaison des effets de perturbations inattendues sur leurs réponses adaptatives constitue une possibilité d'examiner ce phénomène. Un environnement de marche ou une tâche plus exigeante seraient nécessaires pour un tel scénario d'étude. Du fait qu'une perte de complexité de démarche a été mise en relation avec un risque de chute accru [21, 56], il paraît probable que cette relation est induite par les réductions de la capacité d'adaptation à des perturbations pendant la marche.

Un modèle conceptuel des caractéristiques de démarche de patients gériatriques avec et sans déficience cognitive par rapport à des individus témoins en bonne santé.

Sur la base des constatations et des interprétations correspondantes des études expérimentales présentées dans les chapitres 4 et 5, l'illustration 6 montre un modèle conceptuel qui indique la manière dont la démarche se distingue probablement chez des patients gériatriques cognitivement intacts et des patients souffrant d'une déficience cognitive par rapport à des individus témoins relativement jeunes et en bonne santé. Les lignes illustrent l'évolution du changement probable de la démarche avec le 'vieillessement gériatrique' et avec le développement d'une déficience cognitive. La vitesse de démarche diminuait lors du passage d'individus témoins en bonne santé à des patients gériatriques cognitivement intacts. Elle ne diminuait pourtant pas davantage avec les patients souffrant d'une déficience cognitive diagnostiquée (ligne pleine). La régularité et la prévisibilité de démarche diminuaient lors du passage d'individus témoins en bonne santé à des patients gériatriques cognitivement intacts. Les deux augmentaient pourtant au moment où une déficience cognitive venait s'ajouter aux conditions gériatriques. Cette augmentation de la régularité et de la prévisibilité survient probablement avec la perte progressive de la complexité de démarche et un déclin de la stabilité de démarche (lignes pointillées).

La combinaison des caractéristiques de démarche par population est due à de nombreux facteurs sous-jacents comme l'âge et d'autres données démographiques des patients. La combinaison ne devrait donc pas être considérée comme capacité fonctionnelle mais plutôt comme système dynamique émergent. La grande régularité de démarche qu'on peut observer chez des personnes âgées en bonne santé et des patients gériatriques atteints d'une déficience cognitive p. ex. provient de différents facteurs sous-jacents. La comparaison est impossible de ce fait. Tandis qu'une régularité de démarche plus importante peut être bénéfique chez des personnes âgées en bonne santé en termes du coût métabolique p. ex.,

la grande régularité de démarche chez des patients gériatriques atteints d'une déficience cognitive peut être accompagnée d'une perte de complexité de démarche et d'un déclin au niveau de la stabilité de démarche.

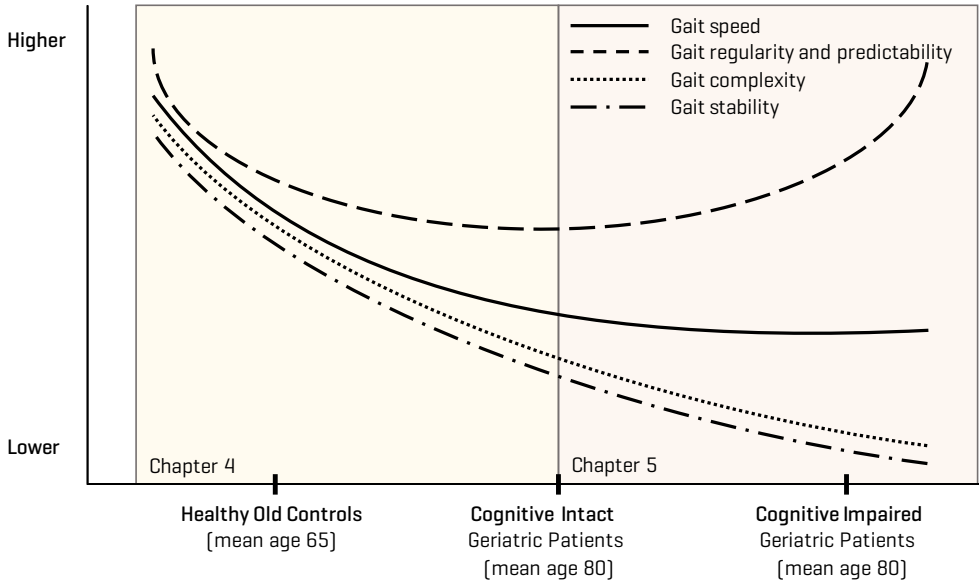



Illustration 6. Un modèle conceptuel qui montre la manière dont la démarche se distingue probablement chez des patients gériatriques cognitivement intacts et chez des patients gériatriques atteints d'une déficience cognitive par rapport à des individus témoins relativement jeunes et en bonne santé. Les lignes illustrent l'évolution du changement probable de la démarche avec le 'vieillesse gériatrique' et avec le développement d'une déficience cognitive.

Comment est-ce que l'évaluation de la fonction de démarche peut contribuer à l'identification de déficits cognitifs et de chutes chez des patients gériatriques?

Une constatation cohérente de cette thèse indique que la dynamique de démarche pouvait compléter des paramètres de marche largement utilisés comme la vitesse de démarche. L'ajout de la dynamique de démarche aux diagnostics courants augmentait la spécificité d'un modèle de classification de chutes (chapitre 3). Par ailleurs, la régularité de démarche, la prévisibilité et la stabilité présentaient le plus grand pouvoir distinctif au niveau des groupes de patients (chapitre 4). De plus, le déclin cognitif dans le temps corrélait avec la régularité de démarche et la prévisibilité initiales mais pas avec la vitesse de démarche initiale (chapitre 5) Bien que la vitesse de démarche puisse se prêter comme simple indice global de mobilité, l'évaluation de la vitesse de démarche seule ne présente pas forcément la spécificité suffisante du fait que de nombreuses affections cliniques et non cliniques induisent un ralentissement de démarche. Chez les patients gériatriques, les affections typiques comme la déficience visuelle, les douleurs, la cyphose thoracique, l'utilisation de nombreux médicaments et la sarcopénie ont toutes été associées à un déclin au niveau de la vitesse de démarche [29, 44-46]. De ce fait, la vitesse de démarche peut être considérée comme marqueur de la santé globale mais probablement pas comme marqueur spécifique



de la cognition. Les paramètres de démarche dynamiques permettent l'extraction d'informations supplémentaires sur la démarche d'une personne en termes de coordination, de complexité et de stabilité de démarche p. ex. Par contre, même si la dynamique de démarche peut compléter la vitesse de démarche, une analyse détaillée de la démarche seule est insuffisante à l'identification de déficiences cognitives. La distinction entre les groupes de patients gériatriques avec et sans déficit cognitif n'était pas possible, du fait que 57% (simple tâche) et 64% (double tâche) de patients avaient été incorrectement classés. Ces constatations sont interprétées dans le sens qu'une identification exacte des chutes et des déficiences cognitives exige une approche multifactorielle y compris les caractéristiques des patients (affections concomitantes) et une évaluation globale de la fonction cognitive et de la fonction de démarche.

Perspectives cliniques

L'évaluation de la démarche telle qu'utilisée pour la présente thèse est une mesure facile et non-invasive qui prend juste quelques minutes aux médecins. Le progrès rapide au niveau des technologies facilite le recours à une analyse exhaustive de la démarche dans les milieux cliniques et de recherche. Les capteurs portables (téléphones, iPods ou accéléromètres) sont de plus en plus présents dans le secteur de la santé [57]. De nos jours, ces appareils sont par défaut équipés d'unités de mesure d'inertie (IMU) comme les gyroscopes, les accéléromètres et les magnétomètres. Par ailleurs, ces capteurs portables sont largement disponibles, faciles à opérer, peu chers et de taille compacte [58].

Outre le potentiel d'identifier des déficiences cognitives et le statut de chutes, les paramètres de démarche dynamiques permettent d'identifier des perturbations de démarche subtiles [21, 56, 59, 60]. Des stratégies d'intervention sur mesure peuvent être élaborées pour réduire le risque de chutes et pour maintenir la vie indépendante. Une constatation prometteuse d'une récente étude de population montrait que les transitions concernant des troubles de démarche ainsi que la déficience cognitive étaient mutables et réversibles pendant une période de 9 ans même chez les personnes les plus âgées [61]. Tandis qu'il y a des preuves abondantes disant que la capacité de marche permet de mesurer les changements au niveau de la qualité de vie liée à la santé tant physique que mentale, une mesure de mobilité ne fait en général pas partie des évaluations standards dans les cliniques de diagnostic gériatrique. Une étude récente conseille donc aux professionnels de la santé de se concentrer sur des procédures de dépistage et des stratégies d'intervention permettant de maintenir la mobilité des personnes âgées afin de préserver et/ou d'augmenter la qualité de vie liée à la santé [62].

En résumé, l'incorporation d'une évaluation de démarche de 3 minutes dans les évaluations cliniques de routine présente des avantages techniques et cliniques multiples. D'autres études devront confirmer l'utilité clinique et la capacité prédictive de telles techniques; des scores de norme et des scores seuil doivent être établis pour différents groupes de populations. Finalement, une application qui traduit les détails techniques de la démarche en paramètres cliniques, qui incorpore par ailleurs des diagnostics de démarche et d'autres pourrait être conçue et finalement fournir un profil de risque multifactoriel pour le déclin cognitif et les chutes.

Conclusions

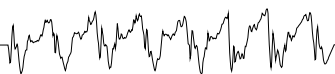
La présente thèse contribuait à notre compréhension de la relation entre la démarche et la cognition chez des patients gériatriques. Les résultats montraient que la présence d'une déficience cognitive chez la population gériatrique se manifeste probablement à travers une régularité et une prévisibilité de démarche augmentées et reflète une éventuelle perte de complexité de démarche. Comme les résultats n'ont pas révélé des associations avec la vitesse de démarche en tant qu'indice globale de la mobilité, les paramètres dynamiques pourraient augmenter la spécificité du lien entre la démarche et la cognition. La dynamique de démarche peut donc être considérée comme indicateur prometteur du déficit cognitif et des chutes. Les médecins et les chercheurs devraient toutefois être conscients des effets d'affections multiples concomitantes chez des patients gériatriques qui peuvent interagir entre elles et avec la fonction de démarche. Une identification exacte du déficit cognitif et des chutes exige très probablement une approche multifactorielle chez cette population vulnérable et devrait inclure des mesures physiques, cognitives, pharmacologiques et comportementales. Du fait que les appareils intelligents comme les smartphones sont de nos jours par défaut équipés d'IMU (comme les accéléromètres), l'évaluation de la fonction de démarche fournit une mesure de mobilité avantageuse et non-invasive qui pourrait bientôt être ajoutée aux évaluations gériatriques de routine. Il convient pourtant que des études futures reproduisent nos constatations avec des cohortes plus larges et réduisent les faiblesses méthodologiques au niveau des mesures de la démarche et de la cognition qui compliquent l'analyse exacte de la démarche chez des patients gériatriques.



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APPENDICES

SUMMARY

RÉSUMÉ [SHORT SUMMARY IN FRENCH]

SAMENVATTING [SHORT SUMMARY IN DUTCH]

ACKNOWLEDGEMENTS

CURRICULUM VITAE

SUMMARY

The rising life expectancy will result in an increased number of 'older old adults' who will need specialized geriatric care to slow functional decline. Cognitive impairment is a major cause of disability in geriatric patients. Even though there is no cure yet to reverse neurodegeneration, tailored interventions can slow disease progression and reduce symptoms. Because of the abundant evidence from experimental, neuroscientific, and behavioral studies that underscored the close link between motor- and cognitive function, the present thesis proposed to use gait characteristics as non-invasive indicators of cognitive impairment and falls in geriatric patients. The main objective therefore was to increase our understanding of the relationship between gait and cognition in this vulnerable population, in which gait outcomes were calculated from 3D-acceleration signals of the lower trunk that were collected with an iPod Touch 4G. The 'Loss of Complexity' hypothesis provided a theoretical framework. Multivariate analyses were applied to dynamic gait outcomes in relation to cognitive- and fall-status (**Chapter 1**).

Chapter 2 presents a systematic literature review including 20 longitudinal studies that examined associations between baseline gait function and future cognitive decline. A slow gait speed was associated with future decline in global cognition and in specific cognitive functions, and with an increased risk for Mild Cognitive Impairment (MCI) and dementia (maximal odds and hazard ratios of 10.4 and 11.1, respectively) in 4.5 years on average. The review projected that future research could increase the specificity of the gait-cognition link by indexing gait and cognition in more detail.

From this perspective, **Chapter 3** examined whether an extensive cognitive evaluation (global cognition, memory, and executive functioning) and fine-grained, dynamic gait outcomes could add to a usual fall-risk screening. The overall classification accuracy of fallers and non-fallers increased from Area Under the Curve (AUC) =0.86 to AUC=0.93. The specificity of the fall-classification model increased from 60% to 72% when cognitive outcomes were added, and from 72% up to 80% when gait dynamics were added to the model. The results underscored the need for a multifactorial approach in fall risk assessment in geriatric patients, including a detailed evaluation of cognitive- and gait function.

Chapter 4 explored what gait outcomes are most susceptible to change with cognitive decline, and examined multiple gait outcomes in relation to cognitive impairment. Outcomes related to gait speed, regularity, predictability, and stability revealed with the highest discriminative power, indicated by the Variable Importance in Projection (VIP)-values for single- and dual-tasking (average VIP-score of 1.12, with a VIP-score>1 indicating a high discriminative power). Geriatric patients walked slower, less regular, and less stable than healthy old controls. However, the discrimination of geriatric patients with- and without cognitive impairment based on gait outcomes alone was poor, with 57% (single-task) and 64% (dual-task) of the patients being misclassified.

In **Chapter 5**, the gait outcomes with the highest discriminative power in chapter 4 were studied in a prospective pilot study. Significant cognitive decline (in global cognition, memory, and executive functioning) over 14.4 months on average correlated with a more

regular ($\rho=0.579^*$) and more predictable ($\rho=0.486^*$) gait at baseline, but not with baseline gait speed ($\rho=0.073$). The increased gait regularity and predictability reflected a loss of gait complexity and this loss of gait complexity may thus predict future cognitive decline in geriatric patients.

The results are summarized and discussed in **Chapter 6** of this thesis. Cognitive impairment in the geriatric population possibly becomes manifested through increased gait regularity and predictability, reflecting a loss of gait complexity. Therefore, dynamic gait outcomes could increase the specificity of the gait-cognition link, and can be considered promising indicators of cognitive impairment and falls. Ultimately, the assessment of gait function provides a cheap and non-invasive mobility measure that in the future could be added to routine geriatric assessments. However, clinicians and researchers should be aware of the effects of multiple, co-existing, conditions in geriatric patients that interact with each other and with gait function. An accurate identification of cognitive impairment and falls thus most likely necessitates a multifactorial approach in this vulnerable population.

RÉSUMÉ

Le déficit cognitif est une cause majeure de handicap de la personne âgée. Du fait de l'augmentation de la durée de vie, le nombre de personnes âgées qui pourraient bénéficier d'une prise en charge spécialisée dans le but de ralentir leur perte fonctionnelle va croître. En dépit de traitement validé qui stoppe le processus neurodégénératif, des interventions spécifiques peuvent en ralentir les manifestations. De nombreuses études expérimentales, neuroscientifiques et comportementales ont démontré la relation étroite entre cognition et motricité.

Ce travail doctoral propose d'explorer si certaines caractéristiques de la marche sont des biomarqueurs non-invasifs d'un trouble cognitif et des chutes, et de mieux comprendre les relations entre la cognition et le contrôle de la marche. Le cadre théorique était l'hypothèse de la « Perte de Complexité ». Des analyses multivariées ont été appliquées aux critères de jugement dynamiques de marche en relation avec le statut cognitif-et-chute (Le **Chapitre 1**).

Le **Chapitre 2** est une revue systématique de la littérature. Nous avons recensé 20 études longitudinales de prédiction de trouble de la marche et de déficit cognitif. La vitesse de marche était associée à la cognition, son ralentissement était un prédicteur de la perte cognitive. Cette revue a aussi mis en évidence la nécessité d'améliorer la mesure des phénomènes concernés

L'objectif du **Chapitre 3** était de déterminer ce qu'apportait l'évaluation cognitive (MMSE, mémoire et fonctions exécutives) et des paramètres dynamiques précis de la marche, au bilan habituel du risque de chute. La précision de la classification entre chuteurs et non-chuteurs a augmenté avec l'ajout de la cognition et des paramètres de marche de AUC=0.86 à AUC=0.93. La spécificité du modèle de classification a, quant à elle, augmenté de 60% à 72% avec l'ajout des mesures cognitives, et de 72% à 80% avec l'ajout des paramètres dynamiques de la marche. Dans leur ensemble, ces résultats montrent l'intérêt d'une approche multidimensionnelle incluant l'évaluation des fonctions cognitives et de la marche, dans la prédiction du risque de chute chez la personne âgée.

Le **Chapitre 4** détermine les paramètres de marche les plus associés au déclin cognitif. La vitesse de marche, la régularité, la prévisibilité et la stabilité ont montré que les simples et doubles-tâches étaient les plus discriminantes (score VIP moyen de 1.12). La marche des patients avec troubles cognitifs est plus lente, moins régulière et moins stable que celle de personnes âgées saines. Cependant, les résultats montrent également que la discrimination des patients âgés avec et sans déficit cognitif, fondée sur l'exploitation des paramètres de marche uniquement, est faible, avec 57% (simple tâche) et 64% (double-tâche) des patients classés de manière erronée.

Le **Chapitre 5** présente une étude pilote prospective dans laquelle les paramètres de marche les plus discriminants du Chapitre 4 ont été étudiés. Les résultats ont montré qu'un déclin cognitif significatif observé après 14.4 mois en moyenne était corrélé avec une marche plus régulière ($\rho=0.579^*$) et plus prévisible ($\rho=0.486^*$) mesurée pendant les mesures de ligne de base, mais pas avec la vitesse de marche de la ligne de base ($\rho=0.073$). Une augmentation

de la régularité et de la prévisibilité de la marche est le reflet d'une perte de la complexité de la marche, témoin d'une détérioration future des fonctions cognitives chez les patients âgés.

Les résultats de ce travail doctoral sont résumés et discutés dans le **Chapitre 6**. Le déficit cognitif chez la population gériatrique se manifeste par une augmentation de la régularité et la prévisibilité de la marche, reflétant une perte de la complexité de la marche. Par conséquent, des paramètres dynamiques de marche pourraient augmenter la spécificité de la relation marche-cognition, et être considérés comme des marqueurs du déficit cognitif et des chutes chez les patients gériatriques. L'évaluation de la marche est un test de mobilité bon marché et non-invasif qui pourrait avantageusement compléter les bilans de routines en gériatrie. Cependant, cliniciens et chercheurs doivent être conscients de l'effet des pathologies multiples co-existants qui interagissent entre elles ainsi que sur le contrôle de la marche dans cette population. En définitive, l'identification fiable et précise du déficit cognitif et des chutes nécessite donc une approche multifactorielle chez cette population vulnérable.

SAMENVATTING

'Ouder worden komt met gebreken'. Met andere woorden: Met de leeftijd neemt het aantal comorbiditeiten en chronische condities toe. Met het stijgen van de levensverwachting kunnen we daarom verwachten dat het aantal ouderen dat gespecialiseerde geriatrie zorg nodig heeft ook zal stijgen. Geriaters richten zich op deze kwetsbare populatie, en hebben als doel om ziektes te behandelen en functies van het dagelijks leven zoveel mogelijk te behouden. Cognitieve achteruitgang (zoals vormen van dementie of milde cognitieve problematiek (MCI)) heeft een desastreus effect op het dagelijks functioneren van ouderen. Ondanks dat medische behandelingen cognitieve achteruitgang nog niet kunnen 'genezen', blijken doelgerichte interventies het ziekteproces wel te vertragen.

Omdat er een duidelijk verband is aangetoond tussen motorisch- en cognitief functioneren in verschillende takken van wetenschappelijk onderzoek (e.g., neurowetenschappen en gedragswetenschappen), veronderstelt het huidige proefschrift dat karakteristieken van het lopen kunnen dienen als non-invasieve indicatoren van cognitieve achteruitgang in geriatrie patiënten. Het overkoepelende doel van dit proefschrift was daarom om meer inzicht te verkrijgen in de relatie tussen lopen en cognitie in geriatrie patiënten, waarbij een breed scala aan loopvariabelen is berekend uit 3D-acceleraties van de onderrug (gerelateerd aan loopsnelheid en de dynamica van het lopen). De 'Loss of Complexity' hypothese heeft gefungeerd als theoretisch kader. Multivariate analyses zijn vervolgens gebruikt om loopvariabelen te relateren aan cognitieve- en val-status (**Hoofdstuk 1**).

Volgend op de algemene introductie presenteert **Hoofdstuk 2** een systematisch literatuuronderzoek. Het review analyseerde 20 longitudinale studies welke de relatie tussen karakteristieken van het lopen en verandering in cognitieve functies over de tijd hebben onderzocht. Een lagere loopsnelheid tijdens de baseline meting werd geassocieerd met een achteruitgang in globale en specifieke cognitieve functies, en met een verhoogd risico op het ontwikkelen van MCI en dementie (met maximale odds en hazard ratio's van respectievelijk 10.4 en 11.1) over gemiddeld 4.5 jaar. Het review veronderstelde dat toekomstige studies de relatie tussen lopen en cognitieve achteruitgang wellicht verder kunnen specificeren door het lopen en cognitieve functies in meer detail te kwantificeren.

Voortbordurend op deze bevindingen is in **Hoofdstuk 3** onderzocht of een meer gedetailleerde beschrijving van cognitie (globale cognitie, geheugen, en executief functioneren) en van het lopen (dynamische loopvariabelen) het voorspellen van vallen kon verbeteren ten opzichte van alleen een reguliere valrisico-screening. De classificatie-nauwkeurigheid van vallende en niet-vallende ouderen steeg van Area Under the Curve (AUC) =0.86 naar AUC =0.93. De specificiteit van het val-classificatiemodel steeg van 60% naar 72% wanneer cognitieve uitkomsten werden toegevoegd aan de reguliere screening, en van 72% naar 80% wanneer dynamische loopuitkomsten werden toegevoegd aan het model. De resultaten onderstrepen dat een accurate identificatie van val-gevaarlijke ouderen hoogstwaarschijnlijk een multivariate evaluatie aanpak vereist, waarbij cognitieve- en loopvariabelen toe kunnen voegen aan de huidige diagnostiek.

In **Hoofdstuk 4** is onderzocht welke loopvariabelen het sterkst gerelateerd zijn aan cognitieve achteruitgang. Loopsnelheid, en variabelen gerelateerd aan de regelmatigheid, voorspelbaarheid, en stabiliteit van het looppatroon hadden het hoogste vermogen om groepen van elkaar te onderscheiden, aangeduid met de 'Variable Importance in Projection' (VIP)-waarden (met een gemiddelde VIP-waarde van 1.12, waarbij een VIP-waarde van >1 een hoog discriminatief vermogen aanduidt). Geriatrie patiënten liepen langzamer, minder regelmatig en minder stabiel dan relatief jonge en gezonde ouderen. Echter, geriatrie patiënten met- en zonder cognitieve achteruitgang konden niet onderscheiden worden op basis van de loopvariabelen alleen, waarbij respectievelijk 57% en 64% van de geriatrie patiënten verkeerd werden geclassificeerd tijdens enkel- en dubbel-taak.

De loopvariabelen met het hoogste discriminatieve vermogen uit hoofdstuk 4 zijn vervolgens onderzocht in een longitudinale pilotstudie in **Hoofdstuk 5**. Significante cognitieve achteruitgang (globale cognitie, geheugen, en executief functioneren) over gemiddeld 14.4 maanden correleerde met een meer regelmatig ($\rho=0.579^*$) en meer voorspelbaar ($\rho=0.486^*$) looppatroon tijdens de basismeting. Deze hogere regelmatigheid en voorspelbaarheid van het looppatroon reflecteerde een afname van complexiteit, wat in dit hoofdstuk verklaard met behulp van de 'Loss of Complexity' hypothese. De afname van de complexiteit van het looppatroon kan daarom mogelijk dienen als voorspeller van cognitieve achteruitgang in geriatrie patiënten.

De resultaten zijn samengevat en bediscussieerd in **Hoofdstuk 6** van dit proefschrift. Cognitieve achteruitgang in geriatrie patiënten kenmerkt zich mogelijk door een verhoogde regelmatigheid en voorspelbaarheid van het looppatroon, wat verband houdt met een afname van complexiteit. Als toevoeging op veelgebruikte variabelen zoals de loopsnelheid, kunnen dynamische loopvariabelen (zoals uitkomsten gerelateerd aan de regelmatigheid, voorspelbaarheid, complexiteit, en stabiliteit van het lopen) de relatie tussen lopen en cognitie verder specificeren, en deze dynamische loopvariabelen kunnen daarom mogelijk dienen als indicator van cognitieve achteruitgang en vallen in geriatrie patiënten. Een uitgebreide analyse van het looppatroon is een niet-invasieve en goedkope diagnostische maat, en zou toegevoegd kunnen worden aan de huidige screening van geriatrie patiënten. Echter, geriateren en andere clinici moeten zich bewust zijn van de effecten van de vele comorbiditeiten en chronische condities in geriatrie patiënten, welke met elkaar en met het lopen interacteren. Een nauwkeurige identificatie van cognitieve achteruitgang en vallen in deze kwetsbare populatie vereist daarom hoogstwaarschijnlijk een multifactoriële aanpak, waaronder algemene patiënt karakteristieken, comorbiditeiten, en een uitgebreide analyse van het cognitief als wel het motorisch functioneren.

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Hora Finita.
Lisette



CURRICULUM VITAE

I was born on New Year's Day 1990 in Hoogeveen, the Netherlands. In 2008, I moved to Groningen to study Human Movement Sciences, and specialised in 'Healthy Aging' during the 2-year master program. The following 3 years I worked on my PhD-project, which was an international collaboration, 'a co-tutelle', between the Université Grenoble Alpes and the University of Groningen. I was registered at two graduate schools: research institute School of Health Research (SHARE; Groningen) and L'Ecole Doctorale Ingénierie pour la Santé, la Cognition et l' Environnement (EDSICE; Grenoble). The project resulted in two theses on the same topic.

As a human movement scientist specialized in Healthy Aging I am highly motivated to improve health and maintain quality of life of individuals. I have been intrigued by the medical world since I was a child, and I am still fascinated by the endless complexity of the human body and brain. Although I originally wished to study Medicine, I have come to realize that studying Human Movement Sciences significantly contributed to my knowledge of medical, biological, technical, and behavioural aspects of human health. My PhD-project therefore perfectly suited my interests and competences, as it combined applied clinical science with technological innovations.

Currently, I am looking forward to continue my career at ProScoop in Zwolle, where I will start as junior advisor on March ^{1st}, 2018. Proscop is a non-profit organisation that gives independent healthcare advice, initiates new collaborations between healthcare facilities, and connects different stakeholders.

SCIENTIFIC OUTPUT

Walking ability to predict future cognitive decline in old adults: A scoping review.

Lisette H.J. Kikkert, Nicolas Vuillerme, Jos P. van Campen, Tibor Hortobágyi, Claudine J.C. Lamoth.

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Gait Dynamics to Optimize Fall Risk Assessment in Geriatric Patients Admitted to an Outpatient Diagnostic Clinic.

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Fall risk factors in frail geriatric patients: how can we optimize fall risk assessment?

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