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Gait characteristics as indicators of cognitive impairment in geriatric patients

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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 (ρ=0.579*) and a more predictable (ρ=0.486*) gait at baseline, but not with baseline gait speed (ρ=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 Frieds´ 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.

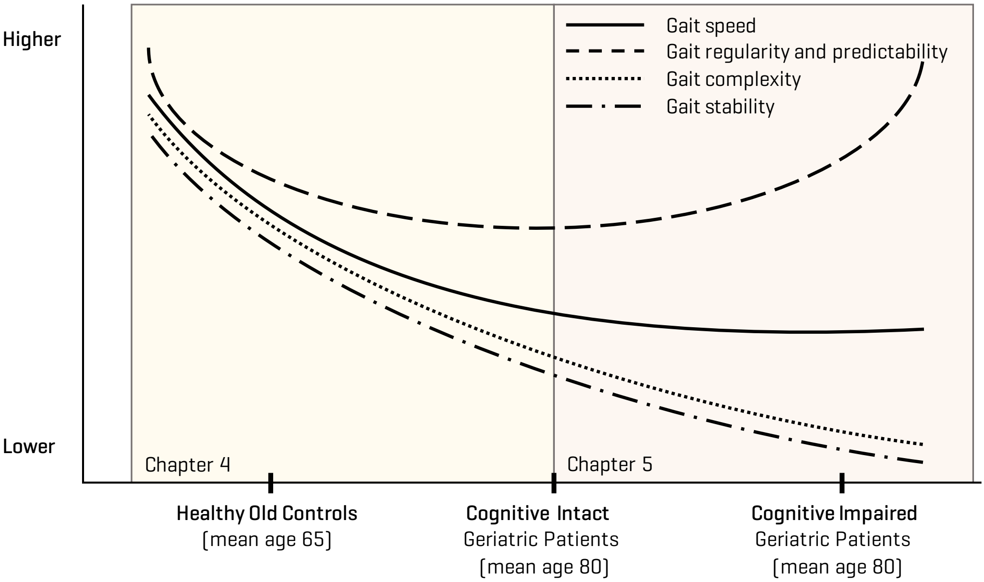

Figure 1. A conceptual model that shows how gait is possibly characterized in cognitive intact geriatric patients and in cognitive impaired geriatric patients, as compared to relatively young and healthy old controls. Lines visualize the trajectory of how gait may change with 'geriatric aging' and with 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 co-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., amnestic MCI, non-amnestic MCI, multiple-domain MCI). For example, patients with amnestic MCI presented with less gait rhythm and more gait variability as compared to patients with non-amnestic 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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