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Summary and general discussion

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Human ageing is characterized by a gradual decline in cognitive and physical performance strongly determining someone's functional abilities and quality of life. Insights into these age-related changes and most importantly their interactions might be suggestive for potential causal mechanisms, which is required for an effective clinical assessment, development and application of interventions. The aim of this thesis was to enhance this understanding by assessing the interactions of cognitive and physical performance across different groups of calendar and biological age, i.e. the person's rate of ageing, which might deviate from its calendar age. Therefore, four different study populations were included: three large population based longitudinal cohorts and one cross-sectional study of elderly outpatients. The interactions were assessed across global measures representing functioning on several cognitive or physical domains and domain specific measures. Furthermore, the sensitivity of these measures to calendar and biological age were assessed. For the assessment of physical performance, instrumented measures were introduced to assess their additional value for the identification of age-related changes in physical performance and understanding of the influence of underlying determinants.

Main findings

In the **chapters two and three** we showed that the association of calendar age with domain specific measures of cognitive and physical performance is already observable from middle age, supporting the current literature¹⁻⁴. Higher calendar age was associated with worse performances on memory and executive tasks, sit-to-stand transfers and steady-state 25-meter walking speed. More complex cognitive tasks were sensitive for biological age, which was indicated by a better performance of offspring of nonagenarian siblings, who are enriched for familial factors of longevity, compared to their partners of similar calendar age. The assumed younger biological age of the offspring of nonagenarian siblings could not be detected by differences in physical performance. These findings indicate the early onset of age-related changes in cognitive and physical performance and the role cognitive performance might have in healthy ageing.

Furthermore, we showed in **chapter three** that instrumented measures of physical performance have similar sensitivity to calendar age as standard clinical measures. Instrumented measures showed strongest associations with calendar age for physical tasks requiring a good balance control; the extension and flexion phase of sit-to-stand and stand-to-sit transfers, respectively, and gait stability and symmetry in especially mediolateral direction during walking across a steady-state 25-meter course. These results indicate that instrumented measures can be used for the identification of age-related changes in physical performance from middle age and may be of additional value in getting insight into the influence of potential underlying determinants.

In the **chapters four to six** we showed that across two populations of different calendar and biological age, i.e. healthy middle-aged to older adults and elderly outpatients, a consistent cross-sectional relationship was found of poor global cognitive function and memory function with low 4-meter walking speed. For other physical domains such as standing balance and steady-state longer distance walks, associations were only found in the population of elderly outpatients. These findings suggest that independent of calendar and biological age, especially the initiation of movements, i.e. the start from standing position in the 4-meter walk, requires cognitive control, with memory function more in specific.

Moreover, we showed in **chapter four** that the presence of cerebral microbleeds and lacunar infarcts, as potential common underlying determinant of cognitive and physical performance, was associated with lower steady-state 25-meter walking speed independent of cognitive performance at middle age. These findings suggest that the influence of brain structure and cognitive performance on physical performance are two independent processes and emphasize the clinical relevance of identifying each of these possible underlying determinants of physical performance in order to develop targeted therapies.

In **chapter seven**, we showed that the temporal relationship between cognitive and physical performance differs across domains and calendar age, suggesting a specific rather than a general relationship. Across the age range of 55 to 90 years, lower executive function was associated with a stronger decline in 6-meter walking speed. From the age of 85 years, this relationship was found for the different measures of cognitive and physical performance that were tested, i.e. global cognitive function, memory and executive function, 6-meter walking speed and handgrip strength. An inverse relationship was found from the age of 65 years, with lower 6-meter walking speed being associated with a stronger decline in global cognitive function and across all measures of cognitive performance in the age range of 75 to 85 years. The findings in this study emphasize the importance of repeated measurements on different cognitive and physical domains and encourage further research to the development of domain and age specific interventions.

Reflection

Interactions between cognitive and physical performance

According to the influence of calendar age, consistent interactions between cognitive and physical performance were found across the entire age range of 45 to 90 years covered by the four study populations that were included. The influence of cognitive performance on physical tasks was found from the age of 55 years, supporting the findings of functional imaging studies showing that already from middle age, several additional brain areas are recruited during the performance of physical tasks when compared to younger adults^{5,6}. In the age range of 75 to 85 years, there seems to be a window with influences of physical performance on cognitive performance, while from the age of 85 years the influence of

cognitive performance is more prominent again with more elaborate interactions between different cognitive and physical domains compared to younger age groups. From the age of 85 years, associations with both low and high complex tasks, i.e. handgrip strength and walking, respectively, were found, while in younger age groups only associations with high complex tasks were observed. These more consistent interactions between different cognitive and physical domains above the age of 75 years might indicate a more significant role of cognitive and physical performance as compensating mechanisms of each other. A possible explanation for that might be the deterioration of other underlying systems such as the central and peripheral nervous, musculoskeletal and cardiovascular system, which are likely to be more affected in higher age groups^{7,8}.

Our specific findings for calendar age on the temporal relationship between cognitive and physical performance in chapter seven, might explain the inconsistent results according to the direction of this relationship in the current literature. They support the findings of longitudinal studies on broad age ranges showing bidirectional relationships and the findings of unidirectional relationships of longitudinal studies including a specific age range⁹⁻¹². The dependence of the interaction between cognitive and physical performance on specific domains, which was observed for both cross-sectional and temporal relationships, might explain the inconsistencies between studies even more. Furthermore, these findings indicate that different cognitive domains are incorporated in the performance of physical tasks instead of one in particular. Our results support the important role of executive function in walking, which has been frequently reported in literature, and also the less frequently studied influence of memory function¹³⁻¹⁵. Thereby, we showed that memory function might especially be of influence on the initiation of movements. However, future studies focusing on the role of different cognitive domains on these specific phases of physical tasks are needed to further explore this.

With respect to the effect of biological age, the association of cognitive performance with both low and high complex physical tasks was also found for a clinically relevant population of elderly outpatients (mean age (standard deviation) 82 (7) years). In this population, poor global cognitive function was associated with a lower ability to maintain standing balance and 4-meter walking speed, representing physical tasks of low and high complexity, respectively. These findings underpin the idea of cognitive performance as compensating mechanism for the deterioration of several other underlying determinants of physical performance^{8,16}.

For the assessment of physical performance, we showed that instrumented measures can be used for the identification of age-related changes in physical performance from middle age and may be of additional value in getting insights into the influence of underlying determinants. In addition to our findings of standard clinical measures showing longer durations on the performances of sit-to-stand transfers and a steady-state 25-meter walk at

higher calendar age, the findings of instrumented measures suggested that this might especially be the influence of balance control as one of the underlying determinants of these tasks. These more refined observations of performances on physical tasks using instrumented measures might provide insights into the relation with specific cognitive domains as well. Some studies already showed that more specific instrumented measures of walking, instead of walking speed as standard clinical measure, are associated with particular cognitive domains such as executive function^{17,18}. It was not possible to further explore this with the available data in this thesis, due to the minimal number of strides which is required for a reliable determination of instrumented measures of walking¹⁹. Within the study populations with available instrumented measures, only associations of cognitive performance with relatively short distance walks were found. This also shows a limitation of the use of instrumented measures, especially in clinical settings, where the practical realization of longer distance walks is sometimes difficult. More elaborate research on different and long enough physical tasks for a reliable estimation of instrumented measures across a wide range of calendar and biological age is needed to further investigate their additional value as sensitive marker of age-related changes and influence of underlying determinants in particular.

Potential causal mechanisms

One of the hypotheses for the co-occurrence of age-related changes in cognitive and physical performance is the presence of common underlying causes^{9,20}. The findings in chapter seven showing that age-related changes in cognitive and physical performance are present in both directions at the same time, whereby the effect sizes were similar, support this hypothesis. Brain pathology, at least at middle age, as a common underlying cause is less likely due to the independence of the association between brain structure and physical performance on cognitive performance we showed in chapter four. However, longitudinal studies covering a broader age range and including repeated measures of brain structure are needed to get more insight into this.

Besides brain pathology, other biological aspects of ageing have been suggested as common underlying causes of age-related changes in cognitive and physical performance. For example, an increased number of senescent cells, i.e. cells with a permanently arrested cell cycle, has been shown to be associated with age-related pathologies including decline in both cognitive and physical performance²¹. Furthermore, the potential role of metabolites, i.e. the intermediate and endpoint products of metabolism, in the ageing process has been shown by the age-dependence of metabolic profiles^{22,23}. Differences according to these important indicators of biological age have been shown between offspring of nonagenarian siblings and their partners, indicating a younger biological age of the offspring²⁴⁻²⁶. The better cognitive performance which was found for the offspring of nonagenarian siblings compared to their partners in this thesis encourage the idea of the

potential role of these biological aspects as underlying causal mechanisms. Together with the findings of a bidirectional temporal relationship between cognitive and physical performance, the findings in this thesis emphasize the need for ongoing research on these more general aspects of ageing.

Clinical implications and future directions

The interactions between cognitive and physical performance shown in this thesis support the potential effectiveness of cognitive and physical interventions to delay physical and cognitive decline, respectively. Especially on the effectiveness of physical interventions several studies have been performed showing reduced risks on cognitive decline and dementia²⁷⁻²⁹. Because the relationship of baseline physical performance on cognitive performance was found in particular between 75 and 85 years, interventions might be most effective in this age range. In the age range of 85 to 90 years, future studies on the effectiveness of cognitive interventions may be interesting because of the more prominent role of cognitive performance indicated in this thesis.

The already available interventions and promising results for the development of more specific ones encourages the early assessment of cognitive and physical performance. Based on the results in this thesis, we showed that age-related changes in cognitive and physical performance are already observable from middle age in the absence of overt diseases. Thereby, the presence of temporal relationships between cognitive and physical performance in each of the directions indicates the clinical relevance of measuring both; in patients with poor cognitive performance, a poor and faster change in physical performance should be considered and vice versa, in patients with poor physical performance a poor and faster change in cognitive performance should be considered. Because of the dependence of the interaction between cognitive and physical performance on specific domains, inclusion of these domain specific measures besides global measures is recommended.

According to the assessment of physical performance, instrumented measures can be used for the identification of age-related changes and thereby showed promising results in giving additional insights into potential underlying determinants. Moreover, some instrumented measures have the advantage of enabling measurements outside clinical settings providing a more complete observation of the patient. Future studies are however needed to investigate the potential of instrumented measures in characterizing groups of individuals based on deterioration of specific underlying determinants, like deterioration of the sensory system (including vision and the vestibular and proprioceptive systems), low muscle mass or strength and cognitive impairment. This will enable the development of more refined and patient specific interventions.

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