Chapter 1

GENERAL INTRODUCTION
1.1 INTRODUCTION

Slowing announces end of life in many species. In worms and in rats mobility remains stable until late life after which it declines rapidly.\textsuperscript{1-3} Also in humans slowing predicts mortality.\textsuperscript{1,4} The uniform signalling capacities of slowing in many living species possibly makes it a valuable marker to predict health outcomes in aging people. For instance, both psychomotor slowing and cognitive slowing are core-features of depression in late life. In this thesis I will examine the relationship between different aspects of slowing, depression and pain, cognitive decline, falls and mortality.

1.2 Depressive Symptoms in Old Age

Geriatric patients suffer by definition from multiple somatic morbidities at the same time. In addition to these co-morbidities depressive symptoms are frequently seen. Depressive symptoms in late-life interfere heavily with the patient’s quality of life and their social and medical wellbeing.

About 8 to 16% of older people living in the community suffer from clinically relevant depressive symptoms not necessarily meeting Diagnostic and Statistical Manual (DSM) criteria for major depression or dysthymia.\textsuperscript{5} Depressive symptoms are associated with worsened quality of life, increased use of health services and cognitive impairment.\textsuperscript{5} Depressive symptoms are also associated with worsened outcomes of medical conditions. Associations are described with slower recovery of hospitalized rehabilitation patients,\textsuperscript{4,6} a higher risk to develop coronary heart disease\textsuperscript{7,8} and cancer.\textsuperscript{9} Moreover, higher mortality rates are described in older people with depressive symptoms in combination with specific medical conditions, such as diabetes mellitus, renal failure and stroke.\textsuperscript{5} With regard to the neuropsychiatric domain, depressive symptoms are associated with cognitive impairment\textsuperscript{2} and dementia.\textsuperscript{10} Also, older people who suffer from depressive symptoms have a 2.4 fold increased risk of developing an episode of major depression over three years’ time, when compared to non-depressed peers.\textsuperscript{11} Depressive symptoms in late life often run a chronic course, with remission rates over a period of one year ranging from 4% to 52%, with a median of 27%\textsuperscript{5}.

Clearly, there is a need for clinical markers signalling risk of chronicity of depression in late life. These markers may improve our understanding of the underlying disease process and also, may guide towards more personalized treatment strategies that can prevent chronicity of depression.
1.3 Slowing

In humans movement slows with aging by as much as 15–30%. It can be seen in a number of tasks and one of these tasks is gait speed. Clear associations have been demonstrated between gait speed and disability, institutionalization and mortality in old and in very old (85+) humans.

When studying age-related aspects in humans, the incorporation of a measure of biological aging over chronological age can yield important information. Apart from its potential as measure of slowing, gait speed is also used as marker of biological aging as it has a strong correlation with frailty in community based samples of older adults.

Slowing is not restricted to gait speed or the motor system only. Slowing in aging humans can also be seen in a number of domains of cognitive functioning. Processing speed is a leading indicator of cognitive change in aging. Changes in processing speed have an impact on other cognitive domains, a phenomenon referred to as ‘the processing speed hypothesis’. As is true for gait speed, processing speed is regarded as a measure of biological aging. It is associated with first-time stroke, heart disease, Alzheimer’s disease and like gait speed, it is associated with mortality.

1.4 Slowing and Depression

Psychomotor slowing, including slowed thinking and slowed gait speed, is a part of depression as a syndrome as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM, ‘psychomotor retardation; by others observable slowed down behaviour’). In adult depressed patients the co-occurrence of psychomotor slowing is seen in at least 40% of the cases while figures in late life are even larger. Depressive symptoms as well as slowing symptoms are associated with adverse health outcomes. The clinical and pathophysiological significance of psychomotor symptoms in depression is a central theme of the first part of this thesis.

In healthy adults with depression, psychomotor slowing is considered an indicator of a more severe subtype with a less favourable outcome. Knowledge about the predictive abilities of slowing symptoms in late life however is scarce. Studies addressing the role of slowed processing speed in relation to the natural course of depression in old age are rare and show conflicting results, while the role of slowed gait in late life depression has not been addressed.
The strong association between slowing symptoms and depressive symptoms in late life might result from a number of age related determinants (Figure 1). In particular, late life depression has been shown to be related to vascular brain damage and repeatedly a close association with medical burden is reported. Furthermore, a characteristic of the aging immune system is a state of chronic low-level inflammation in the absence of overt infection. This low-level inflammation is associated with late life depression. Each of these factors has been associated with slowing of thought and/or slowing of gait in other studies.

1.5 Pain, Depression and Gait Speed

Population-based studies among older people consistently demonstrate that both pain and depression are highly prevalent in late life. Cross-sectional studies have shown that these two phenomena frequently co-occur, that patients with comorbid depression experience more intense pain and are more likely to have persistent pain. The interaction between pain and depression has been labelled as the depression-pain dyad. Very little is known about the influence or consequences of aging with regard to this depression-pain dyad, while a better understanding of this link may identify factors suitable for prevention or improved treatment outcomes in late life. Introducing gait speed as a measure of biological aging enables the study of age-effects of the pain depression dyad in more detail. The putative association between gait speed, depressive symptoms and pain are added in Figure 1.

Figure 1. Slowing, Pain and Depressive Symptoms in Late Life; Possible Associations and Underlying Mechanisms.
1.6 Motor and Cognitive Slowing, Geriatric Health Outcomes and Depressive Symptoms

Since both slowed gait speed and slowed processing speed predict morbidity and mortality, one may suppose that there is a reasonable overlap between these slowing symptoms in their ability to predict future health outcomes. However, their combined potential as markers of adverse health outcomes has not been addressed before. This will be investigated in the last part of this thesis. The role of depression in such an association is unclear. On the basis of their frequent co-occurrence and phenomenological overlap, an explanatory role of depressive symptoms can be assumed, for instance on basis of a similar underlying mechanisms.

1.7 Aim of the Thesis

This thesis investigates the relationship between processing speed, gait speed, depressive symptoms and adverse health outcomes in old age.

The five empirical chapters included in this thesis are based upon three main subjects:
1. To ascertain and understand the ability of processing speed and gait speed to predict the onset and natural course of depressive symptoms.
2. To investigate the effect of age and aging on the association between pain and depressive symptoms and to clarify whether this association is driven by somatic and/or psychological factors.
3. To investigate the association of gait speed and processing speed with adverse health outcomes and to examine whether depressive symptoms influence this association.

1.8 Longitudinal Aging Study Amsterdam

For this research project data from the Longitudinal Aging Study Amsterdam (LASA) were used. LASA is an ongoing population based cohort study on predictors and consequences of changes in autonomy and well-being in the aging population. In a prospective design, data have been gathered on four components of functioning: social, emotional, cognitive and physical functioning.

The LASA cohort is based on a nationally representative sample of older adults aged 55–85 years (years of birth 1908–37), based in three geographic regions in The Netherlands. These three regions were selected so that an optimal representation of the older Dutch population would be achieved, with respondents from the protestant north, the catholic south and secular parts of The Netherlands and from both urbanized
and rural areas within each of these regions. To ensure large enough numbers of the most frail, men and older people were oversampled.

For reasons of economy, the sample was used in two studies. Respondents were first interviewed for the NESTOR study on living arrangements and social networks of older adults (response 62.3%). About 10 months later, between September 1992 and September 1993, 3,107 men and women (response= 81.7%) enrolled in the LASA study. Every three years participants were re-interviewed. The first follow-up measurement was performed in 1995/1996 (n=2545). Since 1992, there have been eight LASA measurement waves to date. At the seventh measurement wave, approximately 20 years after the start of LASA, a total of 763 respondents of the original sample was retained.

A selection of respondents (n=277) have been followed more regularly across a span of 6 years to capture in more detail the natural course of depression. The first two papers of this thesis were based on these data. During every main cycle, amongst other measurements, several cognitive tests, depressive symptoms and gait speed were assessed, enabling the study of the longitudinal course of these parameters. These data were used for the studies described in chapter 4 to 6.

Falls represent an important health problem in older individuals because they frequently occur in older people and because they can result in major injuries. For this reason, in LASA falls were assessed in a detailed, prospective and retrospective way. Mortality data have been obtained through linkage with municipality registers. The falls and mortality data were used to study the association between the slowing symptoms and adverse health outcomes in chapter 6.

1.9 Outline of This Thesis

In chapter two it is hypothesized that several domains of cognitive functioning including slowed processing speed are associated with chronicity of depressive symptoms in late life. Additionally, it is hypothesized that the associations are explained by risk factors for vascular brain damage. In chapter three it is hypothesized that slowed gait speed predicts chronicity of depressive symptoms in late life. It will be tested whether such an association is independent from processing speed and whether a number of possible underlying pathologies explain the association, such as somatic co-morbidity and low-grade inflammation.
In chapter four we hypothesize that there is a bidirectional association between the incidence of depressive symptoms and gait speed impairment, and that these associations share common risk factors. Finding shared risk factors can reveal a common underlying pathology for slowed gait speed and depressive symptoms in late life.

In chapter five we investigate the effect of calendar aging (operationalised as chronological age) and biological aging (frailty, operationalised as gait speed) on the longitudinal association between pain and depression. We hypothesize that this association will become stronger with age and frailty, and that it is mainly driven by somatic and psychological factors.

In chapter six it is hypothesised that processing speed and gait speed are associated with a number of geriatric adverse health outcomes. It is hypothesized that depressive symptoms explain the association between slowing symptoms and adverse health outcomes, which would suggest that slowing symptoms and depressive symptoms both act through the same causal path in their association with adverse health outcomes.

In chapter seven results will be summarized and overall (clinical) consequences will be discussed.
REFERENCES


