CHAPTER 1

GENERAL INTRODUCTION
Cognitive functioning
Cognitive functioning is important for our daily living. Intact cognitive abilities are needed for planning activities, remembering important things, focusing attention to strenuous efforts and shifting between different tasks (1). Poorer cognitive functioning is associated with functional limitations, decreases in physical performance, increased feelings of loneliness and use of healthcare services (2). Persistent declines in cognitive function can ultimately lead to dementia, and as societies are aging the prevalence and incidence of persons with cognitive impairment and dementia are growing (3-5).

Aging is associated with physiological changes and declines in brain volume, especially in the frontal cortex and hippocampus which may be the cause of age-related cognitive decline (1). Not all cognitive functions are equally vulnerable to aging; cognitive domains that most prominently decline in older age are processing speed, episodic memory and executive function (6;7). Processing speed is the ability to rapidly process incoming information from basic stimuli, which is needed to perform higher order tasks without difficulty. Episodic memory is memory for personal information closely related to time and location. Executive functioning consists of more complex tasks such as inhibition of irrelevant stimuli, working memory, set-shifting of attention, doing similar tasks at the same time, taking initiative and planning actions. To gain a more comprehensive insight into processes of cognitive aging it is important to examine these different cognitive domains.

The rate of cognitive decline varies highly between individuals, some persons stay relatively stable, some show a temporary decline, and others a progressive cognitive decline (8). It is suggested that differences in cognitive decline are determined by an interplay between genetic and environmental factors (8). However, the exact mechanisms are still unclear and need to be examined thoroughly.

This thesis will focus on stress as possible risk factor for poorer cognitive functioning and faster cognitive decline. Determining the role of stress on cognitive functioning is relevant because some aspects of stress might be amenable to change through e.g. psychosocial support or psychosocial interventions, and might thus be treatable factors in the prevention of cognitive dysfunctioning.

Stress, stressors and the stress-response
Already in the beginning of the 20\textsuperscript{th} century concepts of stress were introduced. In 1930 one of the founders of stress research, Hans Selye, defined stress as ‘a non-specific response of the body to any demand made on it’ (9). This definition focused mainly on the physical reaction of the body to stress. To distinguish between the cause and the effect of stress Selye included the term stressor as the factor causing stress. He termed the physiological
responses to stressors the general adaptation syndrome, which he later renamed as the stress response. Lazarus & Cohen (10) further defined the term stressors as ‘demands made by the internal or external environment that upset balance, thus affecting physical and psychological well-being and requiring action to restore balance’. In this definition attention is broadened to the psychological consequences of stressors.

In recent decades McEwen & Steller (11) proposed the theory of allostasis and allostatic load to explain the relationship between stress and physical and psychological health. When stress is experienced physiological responses occur with changes in cardiovascular, neural, autonomic, immune, and metabolic activity. These responses are needed to maintain the body in a state of homeostasis and serve an adaptive function. However, if these responses persist over longer time periods, as is the case in chronic stress, this creates a ‘wear-and-tear’ on the body (12-14). This wear-and-tear is defined as allostatic load and is proposed as the key factor in the development of physical diseases such as hypertension and diabetes. McEwen (15) suggests that allostatic load might also play an important role in cognitive consequences of stress.

![Figure 1. Schematic overview of the concepts of stress and cognitive functioning.](image)

In epidemiological research different aspects of stress can be examined (Figure 1). Life events can be used as a measure of the number of stressors experienced. The psychological experience of stress can be measured by the amount of perceived stress or depressive
symptoms. The biological stress response can be measured for instance by determining cortisol levels in saliva. As shown in Figure 1 these concepts of stress are expected to be related amongst each other. For example, depression is likely to be associated with biological stress, and perceived stress is expected to be associated with depression.

**Stress and cognitive functioning across the life span**

The relationship between stress and cognitive functioning might be different for younger and older adults. Aging might influence the stress response by changes in biological systems such as increased hypothalamic-pituitary-adrenal (HPA)-axis activity (16;17). In addition, older adults might be more vulnerable to the effects of stress on cognitive functioning because of losses in social and personal resources, such as diminished attentional resources to inhibit stress-related intrusive information (18;19). However, on the other hand older adults may be protected against adverse effects of stress because of previous experiences and learned coping strategies (20;21). Thus, the effect of stress might have different effects on cognitive functioning throughout the life span. Therefore in this thesis the association between stress and cognitive functioning will be examined both in younger and older adults.

**Life events in relation to cognitive functioning**

Stressful life events include acute as well as ongoing stressful situations, such as the death of a close relative, a severe disease of a beloved one, and serious conflicts (22). In addition to negative events that are currently experienced, events that have occurred in childhood might still have negative effects on cognitive functioning in later life. Adverse childhood events might result in dysregulation of one of the most important stress systems, the HPA-axis, causing prolonged increased levels of cortisol, which might lead to changes in the developing brain, resulting in cognitive impairments even in late life (23;24). In addition, adverse events in childhood might affect education, occupation, life style factors, and mental health, which in turn might be associated with decrements in cognitive functioning in late life (25-27).

Regarding the association between life events and cognitive functioning in late-life, some studies found that the number of recent negative life events was associated with a worse cognitive performance (28;29), whereas other studies did not observe an effect of the total number of life events experienced (30;31) but observed differential effects. Some events had negative effects on cognitive functioning and others positive or no effects (30-34). Inconsistencies might be the result of differences in sample characteristics, such as age, sex, life event severity, and small sample sizes. The longitudinal association between negative life events and cognitive functioning is not often studied yet. Longitudinal studies are important, because they will give more information about the trajectory of cognitive
functioning. In addition to the influence of stressors on cognitive performance on a given moment, longitudinal studies allow examination of the rate of cognitive decline over time. This will give more evidence if stressors influence cognitive decline over multiple years.

Perceived stress in relation to cognitive functioning

Some life events might be more stressful than others. For example, the death of a partner is likely to be more stressful than the illness of a relative. Alternatively, the death of a partner might also be a ‘relief’ when this was associated with long-lasting illness, and the chronic care of an ill relative might be associated with high levels of stress. Thus in addition to the number of stressors, the amount of stress experienced by a person from the life events can be used as measure of psychological stress. In middle-aged and older adults it was observed that persons who experienced more daily stressors performed better on fluid cognitive tasks (35;36). However, higher psychological distress due to these daily events was associated with worse cognitive performance, suggesting that the appraisals and emotional responses to events may be especially important in predicting cognitive functioning.

Moreover, there are other sources of stress that are not measured by assessing a list of negative life events. For example stress about ongoing circumstances, expectations of what will happen in the future, and negative events in the lives of loved ones. Therefore a global measure of perceived stress based on the way persons rate their lives as unpredictable, uncontrollable or overloaded will give more insight into the association between stress and cognitive functioning. In older adults perceived stress was associated with worse cognitive performance and cognitive decline (29;37;38). However, some limitations were small sample sizes and limited adjustment for confounding variables.

Depression in relation to cognitive functioning

There is a considerable amount of evidence that stressors, such as death of partner, death of children, and childhood adversity lead to depressive symptoms (39;40). In older adults, the association between depression and cognitive impairment is extensively investigated and decrements in processing speed, memory and executive functioning are consistently observed (41). However, late-life depression is a heterogeneous disorder, and specific aspects of late-life depression may have a closer association with cognitive functioning than others. Furthermore, inconsistencies are observed in studies examining different aspects of late-life depression in relation to cognitive functioning, possibly due to the lack of adjustment for factors confounding this association, such as age, sex, education, alcohol use, and chronic diseases. Studying different characteristics of depression and cognitive functioning may provide a better understanding of the link between psychological stress and cognitive functioning.
In addition, focusing on the time of onset of the first depressive episode and studying the association between depression and biological stress might further broaden our knowledge about depression throughout the lifespan.

**Biological stress and cognitive functioning**

Biological aspects of stress are likely to show an association with cognitive functioning. When stress is experienced the hypothalamic-pituitary-adrenal (HPA)-axis is activated and cortisol is secreted. The hypothalamus releases corticotropin releasing hormone (CRH), which in turn triggers the pituitary gland to release adrenocorticotropic hormone (ACTH). These increases in ACTH are detected by the adrenal cortex, and in the final step there is a secretion of glucocorticoids (cortisol) by the adrenal cortex. The system has many feedback loops to maintain homeostasis. Cortisol follows a diurnal rhythm, with a cortisol peak in the morning at awakening and a gradual decrease during the day. Cortisol can cross the blood-brain barrier and can cause adverse changes to the hippocampus, amygdala, and frontal lobes. These changes may affect different cognitive functions such as memory, processing speed and executive functioning (42). Cortisol can be measured in saliva during the day and a range of cortisol measures reflect various aspects of HPA-axis functioning and might be differentially associated with cognitive functioning. The cortisol awakening response (CAR) reflects the natural response of the HPA-axis to awakening, while evening cortisol reflects the basal cortisol levels. Cortisol levels after dexamethasone intake reflect the negative feedback system of the HPA-axis. When the feedback system is working adequately, cortisol levels are suppressed after dexamethasone intake.

In community-based studies of older adults higher cortisol levels are often associated with worse cognitive functioning (43-48). However, in depressed older adults this research is scarce and inconsistent with some showing no association (49;50) and others showing a positive association (51). Inconsistencies in the association between cortisol and cognitive functioning might be the result of methodological limitations and differences between studies. Sample sizes were often small and the diurnal rhythm of cortisol is not always taken into account because often only one measure of cortisol was included.

**Factors influencing the association between stress and cognitive functioning**

When studying the association between stress and cognition it is important to take some possible underlying factors into account. In this thesis the following factors are examined: fatigue, sleep, cognitive interference, and genetic vulnerability.

Behavioral or psychological processes following stress, including drinking, smoking, overeating, worrying, symptoms of anxiety and depression might lead to fatigue and
sleep problems (13). Sleep problems and fatigue are found to be associated with impaired cognitive function (52;53). Given these results, fatigue and sleep disturbances might be plausible mediators in the association between life events and cognitive function.

Another possible mechanism in the association between stress and cognitive functioning might be stress-related cognitive interference. Cognitive interference may occur when stress is experienced and includes, ruminating, and repetitive, intrusive and avoidant thinking (54). It is shown that the experience of stress results in intrusive thoughts, as well as in the avoidance of intrusive thoughts (55;56). These processes of intrusive and avoidant thinking may interfere with the attentional resources used for cognitive tasks and result in cognitive impairments. Several studies observed that cognitive interference was associated with impairments in cognitive functioning both in younger and older adults (56-58). However, cognitive interference as an underlying factor on the relation between stress and cognitive functioning has as far as we know not been examined before.

Genetic vulnerability may also play a role in the association between stress and cognitive functioning. The response to stress varies widely among persons and might be associated with specific genetic vulnerability, which may predispose some individuals to cognitive decline when stress is encountered and others not. A candidate gene in this association is ApoE-ε4, which increases the risk for Alzheimer’s disease (59) and it is also suggested that ApoE-ε4-carriers have stronger responses to stress than non-ApoE-ε4 carriers (60). It might be that ApoE-ε4 also increases the vulnerability of the negative effects of stress on cognitive functioning and cognitive decline.

**Aims of the thesis**

The general aims of this thesis are:

1. To examine whether stressors, psychological stress and biological stress are associated with cognitive functioning both in younger and older adults
2. To study which factors mediate or modify the association between stress and cognitive functioning.

**Studies used in this thesis**

*The Longitudinal Aging Study Amsterdam (LASA)*

LASA is an ongoing longitudinal population-based study focusing on physical, social, emotional and cognitive functioning in late-life (61). The initial sample (aged 55 to 85 years) was recruited in 1992 in 11 municipalities in areas in the West, Northeast and the South of the Netherlands, thereby representing variation in religious background and urbanicity, with an oversampling of older people and older men in particular. At baseline 3,107 participants
were enrolled, and every three years participants were interviewed in their homes. More information about sampling and data collection is extensively described elsewhere (62). Chapters 2 and 4 are based on LASA-data.

The Netherlands Study of Depression and Anxiety (NESDA)
NESDA is a multi-site cohort study designed to study the course and consequences of depression and anxiety in adults (63). At baseline, in 2004, 2,981 persons (aged 18 to 65 years) were included from the general population, general practices, and mental health organizations. Of the 2,981 participants 22% were healthy controls, 21% had a prior history of depression and/or anxiety and 57% had a current depressive and/or anxiety disorder. For this thesis, data on depressed persons from the baseline measurement was used. Chapter 6 is based on NESDA-data.

The Netherlands Study of Depression in Older adults (NESDO)
NESDO is a multi-site cohort study of 378 depressed and 132 non-depressed older adults aged 60 through 93 (64). In 2010, depressed older adults were recruited from both mental health care institutes and general practices. Non-depressed older adults were recruited from general practices. Participants were again interviewed after 2 years and 4 years. For this thesis, data from the baseline measurement was used. Chapters 5, 7, and 8 are based on NESDO-data.

Finally, a sample of 324 adults between 19 and 83 years of age were recruited between 2008 and 2010 in Syracuse, New York. Participants were recruited by advertisement in local newspapers, flyers in community centers and other public venues, and through referrals from community leaders. The sample was age stratified (by decade) which created an approximately uniform age distribution. Participants were interviewed in two sessions scheduled one week apart. During the two in-lab sessions, respondents completed cognitive tasks and health measurements. In between the two sessions, respondents filled out self-reported questionnaires assessing health behaviors and life experiences. Chapter 3 is based on these data.

The outline of the thesis
Chapter 2 describes the association between recent life events and childhood events with cognitive functioning and cognitive decline in a population based study of older adults. We also study the role of depression and ApoE-ε4 in this association. In chapter 3 we examine the association between life events, and the severity appraisal of life events, and cognitive functioning in an adult sample. In addition, the mediating role of sleep, fatigue, depression, and cognitive interference is reported. In chapter 4 we concentrate on the association
between perceived stress and cognitive functioning, and we also examine whether these associations are independent of depressive symptoms and feelings of mastery. In chapter 5 we focus on the heterogeneity of late-life depression, by addressing the issue to what extent different depression characteristics and symptom dimensions are associated with cognitive functioning. In chapter 6 the heterogeneity of depression is explored by examining differences in symptomatology, characteristics and risk factors for early versus late onset depression in young and middle aged adults. Chapter 7 reports on the association between cortisol and depression and chapter 8 on the association between cortisol and cognitive functioning. In chapter 9 the main findings are summarized and discussed within the framework of previous studies. Methodological considerations and clinical implications are addressed and directions for future studies are identified.
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