CHAPTER 9

GENERAL DISCUSSION
The first aim of this thesis was to gain more insight into the relation between stress and cognitive functioning in younger and older adults. First, we examined whether stressors, childhood and recent negative life events, were associated with cognitive functioning and cognitive decline. Then, we examined the effect of psychological stress, as determined by the appraisal of life events, perceived stress and depression, on cognitive functioning. Next, biological stress, measured by hypothalamic-pituitary-adrenal (HPA)-axis activity, was examined in association with depression and cognitive functioning. Our second aim was to study possible factors impacting on the association between stress and cognitive functioning, namely fatigue, sleep, cognitive interference and genetic vulnerability. In this chapter the findings will be summarized and evaluated in the light of previous literature. In addition, methodological considerations will be discussed. Lastly, implications for clinical practice will be put forward, and ideas for future research will be delineated.

**SUMMARY OF MAIN FINDINGS**

**Table 1.** Summary results of the association between stressors, psychological stress, biological stress and cognitive functioning.

<table>
<thead>
<tr>
<th>Stressors</th>
<th>Chapter</th>
<th>Age group</th>
<th>Processing speed</th>
<th>Memory</th>
<th>Executive functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Working memory</td>
<td>Interference control</td>
<td>Fluency</td>
</tr>
<tr>
<td>Childhood events</td>
<td>2</td>
<td>65-89</td>
<td>0/−*</td>
<td>0/−**</td>
<td>ne</td>
</tr>
<tr>
<td>-Recent life events</td>
<td>2</td>
<td>65-89</td>
<td>+/-***</td>
<td>0</td>
<td>ne</td>
</tr>
<tr>
<td>-Psychological stress</td>
<td>3</td>
<td>18-93</td>
<td>ne</td>
<td>-</td>
<td>ne</td>
</tr>
<tr>
<td>-Life event severity</td>
<td>3</td>
<td>18-93</td>
<td>ne</td>
<td>-</td>
<td>ne</td>
</tr>
<tr>
<td>-Perceived stress</td>
<td>4</td>
<td>64-100</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-Current depression</td>
<td>5</td>
<td>60-93</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-Depression severity</td>
<td>5</td>
<td>60-93</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Biological stress</td>
<td>8</td>
<td>60-93</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>-Cortisol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ne</td>
</tr>
</tbody>
</table>

+=positive association between stress measure and cognitive domain; -=negative association between stress measure and cognitive domain; 0=no significant association between stress measure and cognitive domain; ne=not examined.

* Childhood events were not associated with worse processing speed at baseline, but with faster decline in processing speed only in depressed persons.

** Childhood events were not associated with worse memory at baseline, but showed slower memory decline than persons without childhood events.

*** Life events were associated with poorer processing speed at baseline, but not with faster decline in processing speed.

**Stressors in relation to cognitive functioning**

Table 1 shows a summary of the main results on stressors, stress and cognitive functioning presented in this thesis. In **chapter 2** the association between childhood events, recent negative life events and global cognitive functioning, memory functioning and processing
speed were examined in a population based sample of older adults. In addition, the possible modifying effect of depressive symptoms and ApoE-ε4 on these associations were examined. The experience of childhood events was not associated with poorer cognitive functioning at baseline but a faster decline in processing speed was observed when also depressive symptoms were present. This suggests that childhood adversity may cause a biological or psychological vulnerability, which is associated with both depressive symptoms and cognitive decline in later life. An alternative pathway might be that adverse childhood conditions negatively affect education and occupation, which in turn might be associated with faster decline in cognitive functioning in late life (1-3). However, we did not find evidence for this pathway as education level and occupation prestige was not different for persons with or without childhood adversity.

The experience of more recent negative life events was associated with worse cognitive functioning, which is in line with previous research (4;5). However, we did not observe that recent negative life events were associated with a faster cognitive decline. In addition, depressive symptoms or ApoE-ε4 did not modify the association between recent life events and cognitive functioning. It might be that older persons adjust relatively fast to negative life events because of previous experiences and learned coping strategies (6). The negative recent events might therefore not lead to chronic stress and cognitive decline. Previous studies did observe differential effects of life events, some events were associated with worse cognitive performance/decline while others were associated with better cognitive performance (7;8), which also might be a reason of not finding an overall effect of the number of life events on cognitive decline.

In chapter 3 we focused on the association between recent negative life events and primary memory, episodic memory, and working memory in adults (19-83 years). In addition, we were interested if psychological and behavioural factors might underlie the association between life events and memory functioning. We found that negative life events were associated with poorer primary memory but not with poorer episodic memory and working memory. In addition, although previous research observed that stressors are associated with fatigue, sleep problems, and depression (9-11) and that poor sleep quality and depressive symptoms are associated with cognitive impairments (12-14), a mediating effect of these factors could not be observed in the association between the number of life events and memory functioning.

Perceived stress in relation to cognitive functioning
In addition to the number of negative life events, in chapter 3 we focused also on the appraisal of life events. For any negative life event indicated, participants also rated the
perceived negative impact of that event, for when it occurred (past severity appraisals) as well as currently (current severity appraisals), at the moment of the interview. We expected that life events, even if they were appraised as having a high impact at the time they occurred, would only have negative effects on current cognitive functioning if their effects persist. We observed that the past severity appraisals were associated with poorer primary memory but not with working memory, whereas current severity appraisals were associated both with poorer primary memory and poorer working memory. In addition, sleep, fatigue, depression and cognitive interference proved to be mediators in the association between the current severity appraisals and working memory. When examining these factors together, cognitive interference proved to be the strongest and independent mediator between current severity appraisals and working memory. Different mechanisms might underlie this association. First, repetitive thinking about stressful events may impact on cognitive function by maintaining the physiological effects of chronic stress. Stress-related thoughts can lead to physiological dysregulation and eventually to neuro-cognitive impairment (15). This process is further defined in the preservative cognition theory of stress suggesting that prolonged stress responses only occur when the mental representations of stressors are prolonged for example by repetitive thinking and rumination. This sustains the physiological response of the stressor and might, over time lead to somatic complaints such as cognitive dysfunctioning (16). Second, the attention needed for these stress-related intrusive and avoidant thoughts limits attentional resources required for cognitive performance (17). This might also be the reason why the mediating effect of cognitive interference is especially observed in relation with working memory because the intrusive thoughts might be seen as a distracting task interfering with working memory.

We were also interested if there were differences in the association between stress and cognitive functioning between older and younger adults. In the study described in chapter 3 an adult sample with a wide age range (18-93 years) was included, which gave us the opportunity to study this possible differential age effect. We did not observe a differential association for older and younger persons, suggesting that life event severity impacts on cognitive functioning both in younger and older adults. It might be that aging has a competing influence on this association; on the one hand previous research observed that the ability to inhibit intrusive or avoidant thoughts might diminish with aging (18), which should make older adults more susceptible to the negative effects of stress. On the other hand, older adults might be protected against the effects of stressful events because they are more efficient in emotion regulation and types of coping (6;19). These two mechanisms might have resulted in no different association between older and younger adults. In addition, the number of older persons was relative small in this study sample; 25% of the persons were 65 years or older (n=77), examining a larger sample with a higher age variation might have
led to different results.

In chapter 4 we focused on perceived stress and cognitive functioning in a large sample of older adults (aged 64-100). Perceived stress was defined as the degree to which persons find their lives unpredictable, uncontrollable and overloaded. Some sources of stress which are not measured by listing life events (e.g. stress about future events, stress in the lives of loved ones) are likely to be captured by asking about the global level of perceived stress. In addition to total perceived stress, we examined which sub-dimensions of perceived stress, perceived helplessness or perceived self-efficacy especially impacted on cognitive functioning. We found that higher levels of total perceived stress and lower levels of perceived self-efficacy were associated with worse processing speed, memory, and executive functioning also after taking into account important confounding factors and symptoms of depression and sense of mastery. The sub-dimension perceived helplessness was not consistently associated with cognitive functioning, and showed closer resemblances with symptoms of depression and sense of mastery, indicating that concepts overlap. The results of higher total perceived stress and poorer cognitive functioning are in line with previous research in older adults (5;20;21). In addition, Ezzati and colleagues (21), observed a positive correlation between perceived self-efficacy and memory functioning. In our study we also observed this association for memory functioning, but also for processing speed and executive functioning. The results suggest that focusing on coping strategies such as self-efficacy and mastery, but also on depressive symptoms may lead to lower levels of perceived stress and this may be helpful in the prevention of cognitive dysfunctioning.

Depression in relation to cognitive functioning
Depression can be a psychological consequence of the experience of stressors (10), therefore, in chapter 5, we focused on depression in association with processing speed, episodic memory, working memory, and interference control in older persons. Because late-life depression is a heterogeneous disorder (22;23) we were also interested whether specific aspects of late-life depression were especially important in cognitive dysfunctioning. We observed that persons with a current depression performed significantly worse on all domains of cognitive functioning. We also observed that severity of psychopathology, including depression severity, anxiety severity and symptoms of worrying were associated with poorer cognitive functioning. In addition, when focusing on different symptom dimensions of depression we found that higher scores on mood symptoms and motivational/apathy symptoms were associated with cognitive functioning, which might be explained by deficiencies in mental effort, attention, and motivation. These results are in line with the ‘resource and allocation model’ of Ellis & Ashbrook (24). This model states that stress-related depressive symptoms lead to less attentional resources because of (1) a greater focus on one’s current mood
state, or (2) depressive symptoms lead to an overall decrease in attentional resources (24), resulting in fewer attentional resources available for cognitive processes. This is in line with the idea that intrusive thoughts lead to worse cognitive functioning by depleting attention resources, and it is suggested that intrusive thoughts might also be a mediating mechanism in the association between depressive symptoms and cognitive dysfunctioning (25).

Another aspect of late-life depression, which is highly important, is the use of psychotropic medication. We observed that the use of tricyclic antidepressants (TCAs), serotoninergic and noradrenergic working antidepressants and benzodiazepines was associated with worse cognitive functioning, whereas selective serotonin reuptake inhibitors were associated with faster processing speed. This is in line with previous reviews showing that TCAs and benzodiazepines were consistently associated with impaired cognitive function (26-28).

In chapter 6 we wanted to broaden the knowledge about depression throughout the life span by examining predictors associated with the onset of the first depressive episode. In an adult sample (age range 18-65 years) we observed that a longer duration of symptoms, a personal history of depressive episodes, a serious suicide attempt, childhood events, a family history of depression and neuroticism were associated with an earlier onset of depression. When focusing on depressive symptomatology, especially feelings of sadness, diminished concentration and suicidal thoughts were less prevalent at a higher age of onset, whereas decreased appetite/weight loss was more prominent at a higher age of onset. Some characteristics associated with early onset depression in middle-aged adults were also associated with worse cognitive functioning in older adults (chapter 2,5). These results might suggest that an early onset depression is associated with a more chronic character of depression and a higher personal vulnerability for cognitive dysfunctioning.

**Biological stress in relation to late-life depression and cognitive functioning**

In this thesis we were also interested in the biological stress response, therefore, we focused on HPA-axis functioning in association with depression and cognitive functioning in older adults. Several indicators of HPA-axis functioning were examined whereby the diurnal rhythm of cortisol secretion was taken into account. We assessed morning cortisol, total cortisol secretion over the first hour after awakening (AUCg), changes in cortisol over the first hour after awakening (AUCI), the diurnal slope of cortisol, and the dexamethasone suppression ratio. In chapter 7, HPA-axis activity was described in depressed and non-depressed older adults. We observed that higher morning cortisol levels were observed in depressed older adults. In addition, in depressed older adults cortisol levels remained higher during the day, although not significantly, as compared to non-depressed older persons. Furthermore, we observed that non-depressed persons showed a rise in cortisol levels after
awakening. This rise was less profound in depressed persons, reflected by lower cortisol levels 30 minutes after awakening and a significantly flatter course of the cortisol awakening response, probably suggesting that stress-reactivity might be decreased in depressed older adults. Our results are in line with a recent meta-analysis suggesting that depression in older persons is associated with diurnal elevations in cortisol as compared to non-depressed older persons (29). In addition, some previous studies observed a U-shaped relation with both higher and lower cortisol levels in depressed older persons as compared to non-depressed older persons (30;31). However, these studies were in community based samples with no official depression diagnosis (31) or in which small numbers of persons with a depression diagnosis were included (30). Our findings in a large sample of depressed persons with an official DSM-IV depression diagnosis do not provide support for a U-shaped association between HPA-axis activity and depression.

In chapter 8, the associations between HPA-axis activity and processing speed, episodic memory, working memory, and interference control are described in older adults. No associations between HPA-axis activity and cognitive functioning were observed. Our study sample consisted of a high percentage of depressed persons, therefore the results in the total group were mainly driven by the depressed older adults. In the depressed group only, no associations between any of the cortisol measures and cognition were observed. This suggests that although altered HPA-axis activity was associated with depression as described in chapter 7, cortisol might not be a major factor in the association between late-life depression and cognitive dysfunctioning.

In summary
This thesis provided insight into the relation between stress and cognitive functioning across the life span. Different aspects of stress were examined: stressors, psychological stress and biological stress. Childhood events were associated with worse cognitive functioning and a faster decline in older adults, but the faster decline was only found when depressive symptoms were present. In both younger and older adults, recent negative life events were associated with poorer cognitive functioning. However, we observed no indication of a faster rate of cognitive decline in late life. When we focused on the psychological stress response, perceived stress and depressive symptoms, consistent associations with multiple domains of cognitive functioning were observed both in younger and older adults, suggesting that the psychological impact of stress seems essential in the relation between stress and cognitive dysfunctioning. Furthermore, although altered HPA-axis activity was associated with late-life depression, HPA-axis alterations do not seem to be an important explanation for cognitive dysfunctioning in late-life depression.
METHODOLOGICAL CONSIDERATIONS

Cohort studies
Results in this thesis were based on several cohort studies, the Longitudinal Aging Study Amsterdam (LASA) (chapters 2, 4), the Netherlands Study of Depression and Anxiety (NESDA) (chapter 6), and the Netherlands Study of Depression in older persons (NESDO) (chapters 5, 7, 8).

In all three cohort studies extensive information was collected on different domains of functioning. Therefore, we were able to test and include important variables in our models which may have confounded or explained the studied associations, such as demographics, physical health, mental health, lifestyle factors, and genetic factors. A major strength of the LASA study is the longitudinal design that allowed us to study trajectories of cognitive functioning. In addition to the level of cognitive functioning on a given moment, the rate of cognitive decline over time could be examined, which gives more information about the influence of stress on cognitive decline over multiple years.

Cohort studies also have some limitations. An important limitation is that no definitive conclusions can be given about causality of the findings. It thus remains unclear whether stress leads to poorer cognitive functioning or whether poorer cognitive functioning leads to higher levels of stress. Of course childhood adversity occurred before the age of 18 and logically precedes cognitive functioning in later life. However, there might be other processes, which lead both to the experience of childhood adversity and poorer cognitive functioning, such as prenatal stress factors. In addition, in chapter 3, the past and current life event appraisals were assessed, which included some time effects of the chronicity of stress, and might give some better indication of the causality between stress and cognitive functioning. However, cognitive decline might have a long natural history, which may start years before it is clinically observed, and makes it difficult to achieve a decisive answer about cause and effect in the relation between stress and cognitive decline in observational studies.

Attrition and exclusion
In longitudinal studies attrition is an important issue. In LASA loss to follow up was generally caused by death and to a lesser part by refusal and frailty (32). It was observed that refusal was random, i.e., it was not associated with demographics, and physical or mental health. However, persons who did not participate because of ineligibility (frailty) had a poorer self-rated health, more cognitive problems, were of female sex, and had a higher age (32). Therefore, in the longitudinal data analyses we used linear mixed model analyses, which has as major advantage that the subjects are included regardless of missing values, which
reduces the risk of underestimation because of differential loss to follow-up of the frail older persons. In addition, the included study samples were still large with sufficient power. Still, when we compared the included and excluded persons in our study samples, persons included in the study samples were healthier than excluded persons. They were often older, had lower education, and lower scores on cognitive measures. Moreover, recruitment of depressed persons (chapter 5, 6, 7, 8) was done both in mental health care institutes and general practices, and persons with depression in various developmental and severity stages were included. However, it is expected that the most severely depressed persons may have been unwilling or unable to participate and conclusions can therefore not be generalized to the most severely depressed groups. When the most severely ill/depressed persons might have been under-represented in the study samples this might also have led to underestimation of the found results.

**Measurement of stressors, psychological stress, and biological stress**

By asking about the experience of stressors and psychological stress in the past, recall bias might have been present. In LASA (chapter 2), recent life events were asked every three years, and childhood events were asked retrospectively at the baseline interview. It is likely that some adverse childhood events were not reported because of embarrassment or painful thoughts. This might have led to underreporting of especially traumatic events. Alternatively, persons who experienced more mood problems later in life might have responded more positively to the question if childhood adversity had an impact on the rest of their lives. In line with this, current psychological status might also have led to higher levels of life event severity (chapter 3), which might have resulted in an overestimation of the mediating effects of depression and intrusive and avoidant thinking on the association between life event severity and cognitive functioning. In chapter 6, the age of onset of the first depressive episode was assessed retrospectively. It has been suggested that milder and older episodes are more likely to be underreported (33;34). However, other studies reported high test-retest reliability of self-reported age of onset of major depression (35;36). A strength is that depression diagnoses based on official DSM-IV criteria were used rather than on cut-off points of screening lists, which improves the reliability of the study findings (chapters 5, 6, 7, 8).

Regarding the biological stress response, previous studies often included only one measure of cortisol, whereas we included different cortisol measures reflecting different aspects of HPA-axis functioning, including morning cortisol, evening cortisol and the diurnal slope. Cortisol levels were measured in saliva samples, which has as advantages that it can be done at home, is non-invasive, and can be obtained from large study samples. However, cortisol was collected on one day only, which might have reduced the reliability. Other
research shows that collecting cortisol on 3 days gives the highest reliability for cortisol levels in older adults (37). In addition, cortisol is the end product of HPA-axis activity and does not fully cover HPA-axis functioning. Some studies suggest that other measures might better reflect HPA-axis activity such as adrenocorticotropin (ACTH) or the ratio between dehydroepiandrosterone (DHEA) and cortisol concentrations (38;39).

**Measurement of cognitive functioning**

Unfortunately, we could only focus on the longitudinal association between stressors and cognitive functioning in the LASA study in chapter 2. Chapter 4 was also based on LASA data but because perceived stress was only measured in the last measurement cycle no longitudinal analyses could be performed. In the other chapters cross-sectional associations were examined because cognitive functioning was only available from one measurement cycle, therefore changes in perceived stress, chronicity of stress, depressive symptoms and biological stress could not be linked to cognitive decline. A limitation of previous studies is that they often focussed only on global functioning or few domains of cognitive functioning. We were able to study multiple domains of cognitive functioning including processing speed, memory functioning, and executive functioning (interference control, working memory and fluency). Conclusions about the association between stress and cognitive functioning can therefore be given for specific domains of cognitive functioning.

**IMPLICATIONS FOR CLINICAL PRACTICE**

Problems in cognitive functioning may lead to limitations in multiple domains of functioning (40), therefore, it is important to examine factors associated with cognitive functioning which are modifiable, and might decrease cognitive dysfunctioning.

We observed that the stress associated with the experience of adverse childhood events may cause a biological or psychological vulnerability, which is associated both with depressive symptoms and cognitive decline in later life. In addition, we observed that recent life events, depression, and perceived stress are associated with poorer cognitive functioning. In clinical practice it is important to be alert on situations that might cause perceived stress in the present life of a person, whether the situations are currently experienced, in the past, or maybe even in the future. Although the stressful situations can often not be prevented, the way persons handle these stressful situations or thoughts about the situation might be open for change. In this thesis we observed that especially the psychological response to stress might lead to cognitive dysfunctioning. We observed that low feelings of self-efficacy and mastery, depression, and intrusive and avoidant thoughts might be highly important in decreasing cognitive functioning and might be factors to focus on in treatment strategies.
In essence, most psychological treatments focus on improving coping strategies. However, different conceptual strategies are used in different forms of therapy. Currently, the treatment of psychiatric disorders relies mostly on cognitive behavioural therapy (CBT), which focuses on irrational cognitions leading to dysfunctional behaviour, such as avoidant thoughts. By changing these irrational cognitions, avoidant thoughts might be diminished, which might lead to better cognitive functioning. Another form of therapy, a mindfulness-based training, might also be effective in reducing intrusive and avoidant thoughts and increasing coping strategies. Classical mindfulness finds it origin in Buddhism and is the process of developing bare attention, by repeated and extended practice in awareness and attention. The combination of bare attention and introspective awareness is used to facilitate the observation of adaptive and maladaptive experiences to learn to increase adaptive and decrease maladaptive experiences (41). In 1979 the mindfulness based stress reduction program (MBSR) was developed by Jon Kabat-Zinn and is a modernized version of classical Buddhist mindfulness that focuses specifically on stress reduction. MBSR consists of a 8-week program mindfulness meditation in a group, which is based on a systematic procedure to enhance awareness of moment-to-moment experiences of observable mental processes, which is expected to reduce negative affect and to improve coping strategies (42). A recent study in college students demonstrated that mindfulness training improved working memory capacity, and that this effect was mediated by reduced mind-wandering (43). Also in older adults it was observed that MBSR led to improvements in mindfulness, memory, executive functioning, and reduced worrying (44;45). Although mindfulness training might decrease psychological stress and improve well-being and cognitive functioning, further high quality studies including standardized mindfulness protocols, high trainer expertise, and longer periods of mindfulness training are needed (46;47). MBSR and CBT might thus be helpful in reducing psychological stress, depression, and improving psychological well-being (48), however, more research is needed to show the (long term) effectiveness of these interventions on improving cognitive functioning.

Next to psychological treatment, psychotropic medication might be helpful in reducing psychological stress, especially depressive symptoms. However, in our study we observed that the use of TCAs, SNRIs, and benzodiazepines was associated with worse cognitive functioning. Unfortunately, the cross-sectional nature of the current study limits us to state conclusions about the causality. It might be that especially persons with a complex depression used these anti-depressants and had lower levels of cognitive functioning already before medication treatment. Although no definitive conclusions can be given about the exact effect of antidepressants on cognitive functioning, in clinical practice it is advised to monitor depressive symptoms and cognitive functioning when antidepressant medication is described to prevent cognitive worsening due to antidepressant medication.
FUTURE RESEARCH

**Cumulative stress**
In our studies, in older adults, childhood events and recent life events were examined. However, it is expected that not only stress in childhood or stress in late life contribute to cognitive dysfunctioning but also negative experiences in midlife. Therefore, the cumulative effect of childhood adversity, negative events in midlife and negative events in late-life should be examined in future research to be able to obtain a more complete picture on the effects of cumulative stress during the life span.

Cumulative stress could also be measured biologically; higher cortisol levels might be a biological mechanism resulting in poorer cognitive functioning and faster decline. In this thesis we did not observe an association between cortisol and cognitive functioning in older adults. However, cortisol levels and cognitive functioning were cross-sectionally measured and it might be expected that especially chronically elevated cortisol levels lead to functional and structural brain changes associated with cognitive functioning (49;50). Therefore in future research it is important to examine cortisol levels longitudinally in association with cognitive decline. In addition to collecting saliva samples longitudinally, hair cortisol might be an innovative measure of chronic cortisol excretion. Associations have been observed between hair cortisol and physical and mental diseases (51;52), but studies are scarce and the association with cognitive functioning has only examined once, observing lower hair cortisol concentrations to be associated with worse cognitive functioning (53). Future research should further examine the relationship between hair cortisol and cognitive functioning and cognitive decline.

In addition to the changes in HPA-axis activity, stress might lead to pathophysiological changes in multiple physiological stress systems such as the immuno-inflammatory system, the autonomic nervous system, the metabolic system (54), and higher levels of oxidative stress (55). It is observed that a pro-inflammatory state of the immune-inflammatory system, hyperactivity of the HPA-axis, and dysregulation of the autonomic nervous system are associated with shortening of telomeres, and that cumulative dysregulation of these stress systems is most strongly associated with biological aging (56). The cumulative dysregulation of these biological stress-systems should be further investigated in association with cognitive functioning across the lifespan.

**Resilience**
Although this thesis was more focused on the negative effects of stress, stress might also be associated with better performances on cognitive functioning (7;8;57). We observed that
there are persons who experience childhood adversity or more recent stressors but do not develop health problems, and even perform cognitively slightly better. These persons might be more resilient to the negative effects of stress. In future research it should be examined which factors make these persons more resilient to stress. In clinical practice, these factors might be used in treatment strategies. For example, we observed that low levels of self-efficacy were associated with cognitive dysfunctioning. For treatment purposes, it is then useful to know whether ‘resilient’ persons indeed have higher levels of self-efficacy.

Another aspect that might contribute to the resilience for stress is the presence of specific genes. Genetic predisposition might make persons more resilient to the effects of stress. In this thesis we examined only the presence of the ApoE-ε4 gene, however, we did not observe that persons without the ApoE-ε4 gene showed less effects of stress on cognitive functioning. Nevertheless, other genes can make persons more resilient to stress and should be examined in future research. For example the BDNF gene, related to neurotoxic processes might influence the effect of stress on cognitive functioning in older adults (58).

Field studies

We observed the importance of the psychological reaction to stress in association with cognitive functioning, by examining the appraisal of major life events and perceived stress in the last month. However, next to major life events there are minor daily stressors related to interpersonal tension, work, home, finance, health, and network situations (59), which cannot be measured in observational studies. By using diary methods information about the experiences of stressors in daily lives can be examined. Different approaches to collect daily stressors can be used, such as end-of-day assessments, predetermined intervals during the day, self-report when a stressors occurs, or by an alert of an electronic devices (60). In previous daily diary studies associations are found between daily stressors and increased levels of cortisol (61), daily stressors and more memory complaints (62), and higher emotional distress to daily events and worse cognitive performance (63). Methods using repeated collection of data in real-life are called Ecological Momentary Assessment (EMA) and advantages are reducing recall bias, improving ecological validity, and the possibility to study micro-processes in real-life (64). In future research information about stressors, psychological stress, and biological stress should be integrated in these EMA studies. For example, an electronic device may alert every three hours and asks to enter daily stressors, the appraisal of these stressors, mood levels and intrusive thoughts. In addition, a short cognitive task can be assessed, and biological measures might be collected daily. It can then be examined what the maximum level of cognitive functioning is of a person and how persons deviate from this maximum level. Finally, the role of stressors, psychological, and biological stress on cognitive functioning can be examined.
Age differences
In this thesis we observed that stress was associated with poorer cognitive functioning both in younger and older adults. Although we did not observe difference in this association between younger and older persons, the underlying mechanisms of this association might differ between younger and older adults. It might be hypothesized that brain changes have a greater role in older adults, whereas intrusive and avoidant thoughts might be more important in younger adults. In future research large study samples with a high age variation should be examined to detect possible differences in underlying mechanism between younger and older adults.

CONCLUSION
This thesis shows that stress is associated with poorer cognitive functioning across the life span. Stressors showed negative associations with cognitive functioning both in younger and older adults, but limited evidence was found for a faster decline in cognitive functioning. HPA-axis hyperactivity and decreased stress-reactivity was observed in depressed older adults. However, alterations in cortisol levels did not seem to be an explanation for worse cognitive functioning in depressed older adults. Quoting Hans Selye “It is not stress that kills us; it is our reaction to it”, implicates the importance of the psychological stress response. Depressive symptoms, life event severity, and perceived stress were consistently associated with multiple domains of cognitive functioning. In addition, we observed that intrusive and avoidant thoughts, and ineffective coping strategies might be mechanisms linking stress to cognitive dysfunctioning. Psychological treatment focusing on the development of effective coping strategies is therefore likely to make persons more resilient to the negative effects of stress.
REFERENCE LIST


