- **Master Thesis –**

Cognitive decline in anxious and depressed individuals and the role of significant life events

The Maastricht Aging Study

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ABSTRACT

Background The extent to which cognitive abilities decline over age depends on a lot of different factors and varies considerably between individuals. Among these factors are depression, anxiety and significant life events (SLE's) as possible predictors of individual differences in cognitive aging. *Objective* To investigate the effects of depression and anxiety on cognitive decline and to investigate the role of significant life events in depression, anxiety and cognitive decline. *Methods* 16 participants screened with a depressive disorder and 21 participants screened with an anxiety disorder have been selected from the MAAS Study and compared to matched control participants on compound scores of memory, simple speed and interference to examine possible differences in cognitive impairment (cross-sectional) and cognitive decline (longitudinal), and compared on amount and severity of experienced SLE's. Moreover, a second, experiment has been done with 522 participants from the MAAS study in which depressive and anxious symptoms were investigated as a predictor for cognitive impairment and decline. SLE's were investigated as a predictor for depression and anxiety and for cognitive impairment and cognitive decline as well. *Results* In the first experiment, participants with an anxiety or depressive disorder did not significantly differ from control subjects on measures of cognitive impairment, cognitive decline, or SLE's. In the second experiment, depressive and anxious symptoms had no significant effect on cognitive decline, but there was a significant effect of anxious symptoms on measures of speed and interference cross-sectionally. No effect was found for SLE's as a predictor for depression and anxiety, or for cognitive performance and decline. *Conclusions* Except from some partial support for an effect of anxious symptoms on speed and interference, both experiments failed to find an effect of anxiety and depression on future cognitive decline. Furthermore, this study provides no evidence for SLE's as a predictor for anxiety, depression or future cognitive decline.

Keywords: Depression - anxiety - cognitive decline - significant life events

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1. INTRODUCTION

In recent research it is well established that during aging, not only physical abilities generally decline, but cognitive abilities as well. However, the extent to which these cognitive abilities decline over age varies considerably between individuals. Almost one in every four elderly people, for example, suffers from serious cognitive decline, which is a major risk factor for later development of dementia (Unverzagt et al., 2001). Since the number of elderly people will continue to grow steadily, cognitive decline leading to dementia is likely to become one of the most important medical conditions (Park, O'Connell & Thomson, 2004). It is therefore important to consider which factors can influence individual differences in normal cognitive aging, in order to increase our knowledge of the mechanisms by which cognitive decline occurs. In the literature, individual-difference factors such as life-style (e.g. social activity, exercise), genetics (e.g. the APOE-ε4 allele), health-related variables (e.g. vitamin B deficiency, thyroid disturbance, circulatory disease, diabetes) and personality traits (e.g. neuroticism) have been mentioned (Bäckman, 2004; Rosnick, Small, McEvoy, Borenstein and Mortimer, 2007; Wilson et al., 2006). Three other factors which are thought to influence cognitive decline, namely depression, anxiety and the experience of significant life events will be discussed in more detail below.

1.1 Depression

A factor that is thought to influence individual differences in normal cognitive aging is the presence of depressive symptoms. Recently there has been a growing awareness that mood disorders may be associated with a distinct pattern of cognitive impairment (Austin, Mitchell & Goodwin, 2001). For example, an inverse association between depression and cognitive function has been reported in clinical studies in both younger and elderly samples, with cognitive deficits found on tests of attention (Beats, 1996; King, Cox, Lyness & Caine, 1995; Purcell, Maruff, Kyrios & Pantelis 1997), memory functions (Boone et al., 1995; Elliott & Greene, 1992; King et al., 1995), psychomotor functions (Purcell et al., 1997) and executive functions (Boone et al., 1995, Stordal et al., 2004, Butters et al., 2004).

Recently, Chodosh, Kado, Seeman and Karlamangla (2007) have investigated the hypothesis that depression may even lead to a faster rate of cognitive decline. They investigated the association between depressive symptoms and longitudinal cognitive changes in older adults who were high-functioning at baseline and found that a higher number of baseline depressive symptoms were strongly associated with greater seven-year decline in cognitive performance. They therefore concluded that depressive symptoms independently predict cognitive decline in

previously high-functioning older persons. Sachs-Ericsson, Joiner, Plant and Blazer (2005), in a longitudinal study of community-dwelling elderly persons, found that depressive symptoms were associated with subsequent cognitive decline, even after controlling for baseline cognitive status and demographic and physical functioning variables. This was also found by Chi en Chou (2000) in a study with Hong Kong Chinese older adults.

In order to study the relationship between depression and dementia, Geerling et al. (2000) investigated whether depressed elderly individuals with normal baseline cognition were at increased risk of cognitive decline and Alzheimer's disease. They found that depression increased the risk of Alzheimer's disease and cognitive decline, but only among people with higher levels of education.

In his review, Jorm (2000) stated that depression could be a serious risk factor for dementia and cognitive decline, and offers a few hypotheses. One hypothesis is that depression could be a possible prodrome of dementia, which is supported by studies of patients who are initially diagnosed with a depression and progress to dementia. A possible biological explanation is that depression as a prodrome of dementia could arise from subcortical cerebrovascular disease. A second hypothesis is that depression is an early reaction to cognitive decline, which may occur if people in the earliest stage of dementia have an awareness of their declining cognitive abilities. According to this hypothesis, although it would seem that depression precedes the diagnosis of dementia, it would actually follow early cognitive decline. A third possibility is explained by the threshold hypothesis. Diagnosis of dementia occurs when a threshold is reached where it begins to significantly impair daily life. Depression involves cognitive deficits which may cumulate with those in early dementia, leading to an earlier stage of reaching the threshold. The final possibility is that depression could play a causal role in dementia and is explained by the 'glucocorticoid cascade' hypothesis of Sapolsky (as cited by Jorm, 2000). This hypothesis states that stressors trigger a release of adrenocorticotropic hormone by the pituitary gland which in turn triggers secretion of glucocorticoids from the adrenal glands. The role of the glucocorticoid receptors in the hippocampus is to inhibit further glucocorticoid secretion. Although short term secretion of glucocorticoids is useful, prolonged secretion can have harmful consequences by damaging the hippocampus leading to impairment of feedback inhibition and hippocampal damage. It is indeed found that depression often involves disregulation of the hypothalamic-pituitary-adrenal (HPA) axis and that the hippocampus is atrophied in individuals with Alzheimer's disease.

1.2 Anxiety

Because most epidemiologic studies regarding cognitive deficits have concentrated on depression, less is known about the effects of anxiety on cognitive deficits, and results are mixed. Mantella et al. (2007) studied cognitive functioning in elderly patients with generalized anxiety disorder (GAD), as compared to normal comparison subjects and patients with major depression. They found that, compared to healthy controls, anxious subjects were impaired on measures of short-term and delayed memory. The anxious subjects did not differ significantly from depressed subjects in any measure of cognitive function.

Airaksinen, Larsson and Forsell (2005) examined whether persons diagnosed with an anxiety disorder show neuropsychological impairments relative to healthy controls. They found that anxiety disorders are associated with episodic memory dysfunction in both free and cued recall, but intact verbal fluency and psychomotor speed. In addition, separate analysis indicated that panic disorder and obsessive-compulsive disorder were related to impairments in executive functioning. Persons suffering from a specific phobia and generalized anxiety disorder however, showed no cognitive dysfunction.

In a longitudinal study, Sinoff and Werner (2003) investigated the hypothesis that anxiety in the elderly, secondary to loss of memory, predicts future cognitive decline. The assumption was that a person often becomes anxious as a reaction to memory loss. The participants were 137 elderly subjects with no depression or cognitive impairment. They were then divided into two groups: 61 participants suffering from anxiety and 76 participants in the control group. Results indicated that complaints of memory loss had no direct effect on development of depression or cognitive decline, but anxiety was found to have an indirect effect via depression and a strong direct effect as well on development of cognitive decline. Biringer et al. (2005) however, examined the effects of depressive disorder alone, anxiety disorder alone, or co-morbid depression/anxiety disorder on cognitive functioning. Although they did find an effect of having a co-morbid depression/anxiety disorder or pure depressive disorder on all 3 tasks, no effect was seen for pure anxiety. They therefore stated that the apparent inverse association between anxiety and cognitive function is confounded by depression and that there is no independent effect of anxiety upon cognitive function beyond that of depression.

1.3 Significant Life Events

A third factor that may influence the rate of cognitive decline in normal aging individuals is the presence of one or more experienced (negative) significant life events. Rosnick, Small, McEvoy, Borenstein and Mortimer (2007) examined negative life events in relation to cognitive

performance in the elderly. They stated that life events could have both a positive and a negative effect on cognitive performance, depending on the length of time that the stressor is endured. Although their research was unable to find an association between the total frequency and severity measures of negative life events and cognitive performance, multiple individual negative life events were associated with cognitive performance. Other evidence for an influence of significant life events on cognitive decline was found in an animal study by Brunson et al. (2005), who found that two forms of memory involving the hippocampus were severely but selectively impaired in middle-aged adult rats exposed to fragmented maternal care during the early postnatal period. The authors stated that a period of early-life psychological stress can lead to delayed, progressive impairments of synaptic and behavioural measures of hippocampal function, which could have potential implications to the basis of age-related cognitive disorders in humans. Unfortunately, still little longitudinal research exists concerning significant life events as a causal factor of cognitive decline.

1.4 Aims of the present study and research questions

So far, three factors have been mentioned that could influence the rate of cognitive decline in normal aging: depression, anxiety and significant life events. As described above, depression and anxiety are often thought to cause cognitive decline. However, often depression and anxiety co-occur, which makes it difficult to determine whether having a depression or having an anxiety disorder can independently predict cognitive decline. The present study will therefore examine to what extent anxiety and depression can independently influence cognitive decline, by examining individuals with a depression but without an anxiety disorder, and individuals with an anxiety disorder but without a depression.

The influence of significant life events on cognitive decline will be investigated indirectly, by examining differences in experienced significant life events between individuals with a depressive or anxiety disorder and people without a depressive or anxiety disorder. Several studies have stated that a depression and/or anxiety disorder can be a consequence of the experience of significant life events (e.g. Brilman & Ormel, 2001; De Beurs et al., 2001; Gillespie, Whitfield, Williams, Heath & Martin, 2005; Patton, Coffey, Posterino, Carlin & Bowes, 2003; Waite, Bebbington, Skelton-Robinson & Orrell, 2004; Yaffe et al., 1999). The onset of anxiety disorders and depression appears to be differentially related with life stress of 'threat' and 'loss' respectively (Sandin, Chorot, Santed & Valiente, 2004).

I propose that individuals with an anxiety or depressive disorder (compared to individuals without an anxiety or depressive disorder) experience a greater number of significant life events

as well as more severe significant life events and that these individuals experience a faster rate of cognitive decline. Therefore, data of individuals who participated in a longitudinal population-based study will be investigated over a period of 12 years. The data of these participants on the first measurement and on the measurement 12 years later will be compared to investigate the following research questions:

Research Question 1:

Do people who suffer from an anxiety or depressive disorder perform worse on cognitive tasks at the 12-year follow-up measurement compared to people without an anxiety or depressive disorder (cross-sectional)?

- *Hypothesis 1.1:* People who suffer from an anxiety disorder perform worse on cognitive tasks at the 12-year follow-up measurement compared to people without an anxiety disorder.
- *Hypothesis 1.2:* People who suffer from a depressive disorder perform worse on cognitive tasks at the 12-year follow-up measurement compared to people without a depressive disorder.

Research Question 2:

Do people who suffer from an anxiety or depressive disorder show a faster rate of cognitive decline over a period of 12 years (as measured at baseline and at a 12-year follow-up) compared to people without an anxiety or depressive disorder (longitudinal)?

- *Hypothesis 2.1:* People who suffer from an anxiety disorder show a faster rate of cognitive decline compared to people without an anxiety disorder.
- *Hypothesis 2.2:* People who suffer from a depressive disorder show a faster rate of cognitive decline compared to people without a depressive disorder.

Research Question 3:

Do people who suffer from an anxiety or depressive disorder experience a greater number of significant life events as well as more severe significant life events compared to people without an anxiety or depressive disorder?

- *Hypothesis 3.1:* People who suffer from an anxiety disorder have experienced a greater number of significant life events as well as more severe significant life events compared to people without an anxiety disorder.
    - Sub-hypothesis 3.1.a: People who suffer from an anxiety disorder have experienced a greater number of significant life events compared to people without an anxiety disorder.

- Sub-hypothesis 3.1.b: People who suffer from an anxiety disorder have experienced more severe significant life events compared to people without an anxiety disorder.
- Sub-hypothesis 3.1.c: People who suffer from an anxiety disorder score higher on the combination of number and severity of significant life events compared to people without an anxiety disorder.

- *Hypothesis 3.2*: People who suffer from a depressive disorder have experienced a greater number of significant life events as well as more severe significant life events compared to people without a depressive disorder.
  - Sub-hypothesis 3.2.a: People who suffer from a depressive disorder have experienced a greater number of significant life events compared to people without a depressive disorder.
  - Sub-hypothesis 3.2.b: People who suffer from a depressive disorder have experienced more severe significant life events compared to people without a depressive disorder.
  - Sub-hypothesis 3.2.c: People who suffer from a depressive disorder score higher on the combination of number and severity of significant life events compared to people without a depressive disorder.

Of further interest is whether people who suffer from a depressive or anxiety disorder will also show more anxious or depressive symptoms on the SCL-90, not only at the time of diagnosis itself, but also 12 years earlier, which leads to the final research question:

Research Question 4:

Do people who suffer from an anxiety or depressive disorder at the 12-year follow-up show a higher score on the subscales of the SCL-90 in question compared to people without an anxiety or depressive disorder?

- *Hypothesis 4.1:* People who suffer from an anxiety disorder at the 12-year follow-up score higher on the anxiety scale of the SCL-90 at both baseline and follow-up measurement compared to people without an anxiety disorder.
- *Hypothesis 4.2:* People who suffer from a depressive disorder at the 12-year follow-up score higher on the depression scale of the SCL-90 at both baseline and follow-up measurement compared to people without a depressive disorder.

2. METHODS

2.1 Design and participants

To answer the research questions mentioned above, data of participants of the Maastricht Aging Study (MAAS) have been used in this study. The aim of the MAAS Study is to identify determinants of both successful and pathological cognitive aging (Jolles, Houx, van Boxtel & Ponds, 1995). The 1823 participants in the MAAS programme were selected from the registration network of family practices in the province of Limburg, with age ranging from 24 to 81 years old, and were without medical conditions that could interfere with normal cognitive function. People with chronic neurological pathology, mental retardation, or chronic psychotropic drug use were excluded.

This study started in 1992 and constituted the basis for a longitudinal project in which subjects are re-tested at 6 years intervals (with the exception of participants aged older than 53, who were tested at a 3-year follow-up moment as well). So far, testing scores of the participants are available at baseline (in the MAAS study referred to as F0), at the 6-year follow-up (referred to as F2), and at the 12-year follow-up (referred to as F4). The MAAS Study consists of four separate cross-sectional panel studies, A1 to A4, each involving nearly 500 subjects at baseline. These studies share the same methodology with respect to sample frame, subject inclusion and stratification criteria, and basis measurement protocol. Each subject panel is stratified for age, sex, and an equivalent of general ability (level of occupational achievement).

Of the 1823 participants in the MAAS programme, only participants in the A1 and A2 panel were included for the present study, a total of 944 participants. However, after 12 years a total of 366 participants were lost to follow-up due to death (N = 138), refusal (N = 138), moving to a new home (N = 43), medical reasons (N = *22*), diagnosis of Alzheimer or (vascular) dementia (N = 19), incomplete or unreliable test results (N = 2), or other reasons (N = 4), which means that a total of 578 participants have been re-tested at the 12 year follow-up.

To examine whether having a depressive or anxiety disorder leads to a faster rate of cognitive decline, these participants were assessed for the presence of DSM-IV major and minor depressive disorders and generalized anxiety disorders at the 12-year follow-up, using the Mini International Neuropsychiatric Interview (MINI). A total of 37 participants from the MAAS study have been selected, who either screened positively for a minor or major depressive disorder (N = 16), or a generalized anxiety disorder (N = 21). Participants with both an anxiety and depressive disorder (N = 6) have been excluded, since the aim of this study was to examine anxiety and depression as independent predictors. Furthermore, a same number of matched

controls were included who were matched on sex, age, and education, and compared to the participants with an anxiety or depressive disorder on cognitive measures of memory, simple speed and interference. These control variables were selected because they are thought to influence cognition, with a higher age, a lower education level and being female as predictors of a faster rate of cognitive decline (Letenneur, Gilleron, Commenges, Helmer, Orgogozo & Dartigues, 1999; Vincze et al., 2007).

Thus, the present study consists of 32 participants in the depression group (16 depressive participants and 16 matched controls) and 42 participants in the anxiety group (21 anxious participants and 21 matched controls).

In the anxiety group, age at baseline ranged from 24 to 59, with a mean age of 39.29 years (SD= 9.87) for the anxious participants and a mean age of 39.38 (SD= 9.85) for the control participants. In the depression group, age at baseline ranged from 25 to 71, with a mean age of 46.56 years (SD= 12.61) for the depressive participants and 46.63 (SD= 12.46) for the control participants. Further basic descriptive data are provided in table 1.

Table 1

Descriptive data of the depression and anxiety group

Descriptive Statistics	Depression group				Anxiety group			
	Depression		Controls		Anxiety		Controls	
	N	%	N	%	N	%	N	%
1. Sex								
Female	10	62.5	10	62.5	13	61.91	13	61.9
Male	6	37.5	6	37.5	8	38.09	8	38.1
2. Marital Status								
Single	2	12.5	1	6.25	2	9.52	1	4.76
Married/living together	13	81.25	14	87.5	19	90.48	17	80,95
Divorced	1	6.25	1	6.25	0	0	2	9.52
Widow/widower	0	0	0	0	0	0	1	4.76
3. Education								
Elementary education	2	12.5	1	6.25	0	0	0	0
Lower vocational education	7	43.75	7	43.75	5	23.81	5	23.81
Intermediate secondary education	1	6.25	2	12.5	3	14.29	3	14.29
Intermediate vocational education	4	25	4	25	6	28.57	7	38.33
Higher secondary education	1	6.25	0	0	2	9.52	0	0
Higher vocational education	1	6.25	2	12.5	4	19.05	5	23.81
University education	0	0	0	0	0	0	0	0
Scientific education	0	0	0	0	1	4.76	1	4.76

A small proportion of the participants who were tested at baseline did not participate in re-testing at the 6-year follow-up, but participated in re-testing again at the 12-year follow-up, which means that for these participants, only scores of baseline (F0) and the 12-year follow-up (F4) are available. Because the group sizes are small and excluding these participants would lead to even smaller groups, it was decided only to use testing scores of the baseline measurement (F0) and the 12-year follow-up measurement (F4) in order to be able to analyse all participants.

2.2. Measures

2.2.1 Demographic information

By using matched controls for the participants with an anxiety or depressive disorder, the demographic variables of age, sex and education have been controlled for. Hence, no statistical differences exist between the anxious/depressed participants versus the controls on these variables.

2.2.2 Depression and anxiety

The Mini International Neuropsychiatric Interview (M.I.N.I.): The M.I.N.I. (Sheehan et al., 1998) is a short diagnostic structured interview designed to generate positive diagnosis for the main Diagnostic and Statistical Manual (DSM) Axis 1 disorders and to explore the symptoms of criterion A for Schizophrenia. Total scores on the subscales for generalized anxiety and depressive disorder of the M.I.N.I. (only measured on the 12-year follow-up) have been used to assess which participants met criteria for a generalized anxiety or depressive disorder.

Symptom Check List-90 (SCL-90): The SCL-90 (Derogatis, 1983) is a self-report questionnaire in which respondents are asked to report on a 5-point Likert scale ranging from 0 (not al all) to 4 (extremely) the extent to which they have experienced various psychological symptoms within the past 7 days. The total scores on the depression and anxiety scale of the SCL-90 have been used in the present study.

2.2.3 Cognition

The Verbal Learning Test (VLT): The VLT (Van der Elst et al., 2005; Deelman et al., 1980), an adapted version of a test originally devised by Rey (1964) has been used as a measurement of memory. The test consisted of 15 words which were presented to the participants on 5 trials. The participants were told to memorize as many words as possible. For each trial, after the words had

been presented, immediate recall was tested by asking the participants to recall as many words as possible. After 20 minutes delayed recall was tested by asking the participants to recall all words previously learned.

The Stroop Colour-Word Test (SCWT): The SCWT (Houx, Jolles & Vreeling, 1993; MacLeod, 1991; Van der Elst et al., 2006b) consists of three different stimuli cards, each involving 100 stimuli. The first card contained colour names which the subjects had to read out loud. The second card contained coloured patches that the subjects had to name. The third card contained names of colours printed in an incongruously coloured ink (e.g. the word red was printed in blue ink) and subjects had to name the colour of the ink used. The test has been used to measure simple speed by measuring the time needed for the first two tasks, and to measure interference by comparing the time needed for the first two tasks with the last task (see 2.3 data preparation).

The Concept Shifting Test (CST): The CST (Van der Elst et al., 2006a; Vink & Jolles, 1985) is divided into three different test conditions and a control condition, with 16 small circles grouped in a larger circle. Depending on the condition, these small circles contain digits, letters, both digits and letters, or are empty. The participants had to cross out as quickly as possible the digits in numerical order (condition A), the letters in alphabetical order (condition B), and the letters and digits in alternating order (condition C). In the control condition (condition Zero), the participants had to cross out the empty circles as fast as possible in a clockwise fashion, in order to obtain an estimate of their motor speed. The test has been used to measure simple speed (condition A and B) and interference (see 2.3 data preparation).

2.2.4 Significant life events

In order to measure the significant life events (SLE's) experienced, the participants were asked if they had experienced one or more of the significant life events mentioned below in the last year:

1. Divorce
2. Moving to a new home
3. Serious accident
4. Being fired
5. Death of a loved one
6. Serious illness
7. Seriously ill loved one
8. Start of a new job/study
9. Marriage/living together
10. Retirement
11. Abortion
12. Child leaving elderly home
13. Victim of criminal activity
14. Big financial disappointment
15. Birth of a child
16. Other

The participants could indicate which significant life event(s) they had experienced, with multiple answers allowed, which means that not only the type of SLE's experienced could be explored, but the number of experienced SLE's as well. Because the present study focused on the possibility of a negative effect of significant life events on cognitive performance, data from options number 9 (marriage/living together) and 15 (birth of a child) were excluded from the analyses, because they are believed to have a positive rather than a negative effect on cognitive performance.

2.3. Data preparation

2.3.1 Compound measures of memory, simple speed, and interference

The participants' raw scores have been transformed into standardized Z-scores which have been clustered in three domains (memory, simple speed, and interference) to yield compound cognitive scores for both the baseline measurement and the 12-year follow-up measurement. A compound measure of memory has been created by averaging the z-scores of the total immediate and delayed score of the Auditory Verbal Learning test. A compound measure of simple speed has been created by averaging the z-scores of the first condition of the Stroop Task, and part A, B and null of the concept shifting task. The compound score was then inverted so that a high score would indicate a good performance. A compound measure of interference, finally, has been created by a formula of the raw scores of part A, B and C of the concept shifting task, and a formula of the raw scores of the first, second and third condition of the Stroop Task. These two outcomes then were transformed into Z-scores and averaged. This compound score was inverted as well.

Memory = (ZWLT total + ZWLT recall) / 2

Simple Speed = - (ZCST null + ZCST condition a + ZCST condition b + ZSCWT condition 1) / 4

Interference = - (Z 'formula CST' + Z 'formula SCWT' / 2

Formula interference CST = (CST condition c – ½ * (CST condition a + CST condition b)) / (½ * (CST condition a + CST condition B)) * 100

Formula interference SCWT = (SCWT condition 3 – ½ * (SCWT condition 1 + SCWT condition 2)) / (½ * (SCWT condition 1 + SCWT condition 2)) * 100

2.3.2 Significant life events

To get a measure of the total number of SLE's experienced, the number of reported life events experienced on baseline, on the 6-year follow-up, and the 12-year follow-up have been added together in order to get a more robust sense of experienced SLE's over a longer period. As has been noted earlier in the design section above, several participants have only been tested at baseline and at the 12-year follow-up measurement, and not on the 6-year follow-up measurement. These participants (2 participants from the anxiety group, 1 participant from the depressive group, and their matched controls, so a total of 6 participants) have been excluded for this particular analysis (hypothesis 3).

In order to get a measure of the severity of the SLE's experienced, a questionnaire was given to two independent samples of individuals on which they had to assign numbers to the SLE's according to their severity, so that the events could be ranked on basis of their severity. In the first sample, 60 students participated, of whom 17 were male and 43 were female, with a mean age of 23.1 years. The second sample consisted of 37 older adults with a mean age of 64.2 years, of whom 20 were female and 14 were male (the sex of 3 participants in this sample was missing). Answers from these two samples were combined and 3 life events that scored highest on rankings on severity were selected as most severe life events, with death of a loved one ranked as most severe, followed by being seriously ill and having a seriously ill loved one (see table 2 below). For this measurement of experienced severe SLE's, the total sum of any of these 3 life events reported over 12 year has been calculated.

Finally, a combination variable has been created where each SLE has been given a weighted score, with the most severe SLE weighted with a score of 13, and the least severe SLE weighted with a score of 1. These weighted scores of all SLE's experienced by the participant over a period of 12 years then have been added together.

Table 2

Combined mean and weighted scores of the significant life events of the two samples

Stressful life event	*Combined mean*	*Sequence*	*Weighted score*
Death of a loved one	2.205	1	13
Seriously ill	3.06	2	12
Seriously ill loved one	3.41	3	11
Serious accident	4.37	4	10
Divorce	5.575	5	9
Victim of criminal activity	6.28	6	8
Abortion	6.66	7	7
Financial disappointment	7.785	8	6
Being fired	7.85	9	5
Child leaves elderly home	9.97	10	4
Moving to a new home	11	11	3
New job	11.31	12	2
Retirement	11.435	13	1

2.3.3 Total scores depressive and anxious symptoms SCL-90

To calculate the total depression score of the SCL-90, scores on items 1 through 16 of the depression subscale have been added together. For the subscale anxiety, scores on items 1 through 10 have been added together to calculate a total anxiety score. However, when more than two scores on the individual items were missing for each subscale, the total score has not been calculated but replaced by a missing value.

For the depression group (N = 32), the total depression score of 1 participant (3.1%) was missing at the baseline measurement and total depression scores of 5 participants (15.6%) were missing at the 12-year follow-up measurement. For the anxiety group (N = 42) none of the total anxiety scores were missing at the baseline measurement but total anxiety scores of 8 participants (19%) were missing at the 12-year follow-up measurement. These participants have been excluded for the particular analyses of hypothesis 4.

2.4 Statistical Analyses

2.4.1 Descriptive Analyses

The normal distributions, homogeneity, descriptive statistics and outliers were revealed with the descriptive analyses. The demographic variables age, sex and education were explored to test the assumption that no differences existed between the depressed/anxious participants and the control participants on these variables. To test for differences in age and education between the

participants, a Mann-Whitney U-test has been performed. It was chosen to perform a non-parametrical analysis due to small group sizes. All matched participants had the same sex.

2.4.2 Main analyses

To test whether a difference exists between the depressed/anxious participants versus the control participants at the follow-up measurement, a Mann-Whitney U-test has been used (hypothesis 1), considered the relatively small sample sizes. This test has also been used to measure whether a difference exists between the participants on experienced significant life events (hypothesis 3) and to measure whether scores on the SCL-90 are higher for the depressed and anxious participants compared to the control participants (hypothesis 4). To compare the rate of cognitive decline between groups and within groups (hypothesis 2), 2x2-repeated-measures ANOVA's have been used (separate analyses for the anxious and control participants and separate analyses for the depressed and control participants), with group (depressed/anxious participants versus control participants) as the between subjects factor, and time (cognitive performance at baseline and at the 12-year follow-up) as the within subjects factor. The statistical analyses were performed with SPSS 13.0 for windows.

3. RESULTS

3.1 Descriptive statistics

To explore possible differences between the participants on age and education despite the fact that matched controls have been used, a Mann-Whitney U-test has been conducted to test for age differences and for differences in education. No significant differences have been found between the anxious/depressed participants and the matched controls.

Table 3

Statistics of the control variables age and education for the depressed, anxious and control participants

	Depression Group				Anxiety Group			
	Depression	Controls	U	*p*	Anxiety	Controls	U	*p*
Age at baseline	46.56	46.63	127	.97	39.29	39.38	217.5	.94
Education level	2.88	3.06	118.5	.71	4.05	4.05	219.5	.98

Note: Mean scores are given for age at baseline and level of education. Level of education was defined by 8 categories, see table 1.

3.2 Results of the statistical analyses

For all the hypotheses described below, analyses have been done separately for the depression group (depressed participants versus controls) and for the anxiety group (anxious participants versus controls).

3.2.1 Results hypothesis 1

To test whether people who suffer from an anxiety or depressive disorder perform worse on cognitive tasks at the 12-year follow-up compared to the control participants, a Mann-Whitney U-test has been used. Results (table 4) show that no significant differences exist for the depression group and the anxiety group on the compound scores memory, speed, and interference.

Table 4

12-year follow-up compound scores for the depressed, anxious and control participants

	Depression Group				Anxiety Group			
	Depression	Controls	U	*p*	Anxiety	Controls	U	*p*
Memory	.12	.09	114	.60	-.05	-.06	219	.97
Speed	-.35	-.20	119	.73	.08	.33	159	.12
Interference	-.03	-.38	99	.27	.02	.33	187	.40

Note: the table shows mean Z-scores, U scores and p-values for the compounds.

3.2.2 Results hypothesis 2

To examine the hypothesis that people who suffer from an anxiety or depressive disorder show a faster rate of cognitive decline compared to control participants, a 2x2-repeated-measures ANOVA has been used, with group (depressed participants versus controls and anxious participants versus controls) as the between subjects factor, and time (cognitive performance at baseline and at the 12-year follow-up) as the within subjects factor. As can be seen in table 5, no group differences existed on the compounds scores of memory, simple speed and interference, which suggest that the depressive and anxious participants did not differ significantly from their control participants on the compound scores on baseline or the 12-year follow-up. There was no overall significant decline in performance over time for the compound scores for the depression group (F (1, 30) = 0.61, p = .62) and the anxiety group (F (1, 40) = 0.29, p = .83). Separate analyses of the effect of depression and anxiety on the individual compound scores did not reveal statistical differences in performance over time either, as can be seen in table 5. Furthermore, there was no overall significant time by group interaction on the compound scores of memory, simple speed and interference for the depression group (F (1, 30) = 0.42, p = .74) and the anxiety group (F (1 40) = 0.99, p = .41) which suggests that no difference exists on the rate of cognitive decline between the anxious/depressed participants and the control participants. Again, separate analyses for the individual compound scores did not reveal statistical differences between the participants on the rate of cognitive decline either (see table 5).

Table 5

The longitudinal influence of depression and anxiety on measures of memory, simple speed and interference.

	Depression Group								Anxiety Group							
	Depression	Controls	Group		Time		Time x Group		Anxiety	Controls	Group		Time		Time x Group	
Compounds	M (SD)	M (SD)	F	*p*	F	*p*	F	*p*	M (SD)	M (SD)	F	*p*	F	*p*	F	*p*
Memory			.15	.71	.81	.37	.86	.36			.04	.84	.17	.69	.22	.64
Baseline	-.17 (1.23)	.09 (.69)							-.06 (.81)	.06 (1.05)						
Follow-up	.12 (1.05)	.09 (.81)							-.05 (.87)	-.06 (1.06)						
Simple Speed			.63	.43	.00	.92	.80	.38			.69	.41	.20	.66	2.78	.10
Baseline	-.44 (.88)	-.09 (.67)							.22 (.58)	.25 (.61)						
Follow-up	-.35 (1.18)	-.20 (.96)							.08 (.54)	.33 (.56)						
Interference			2.35	.14	.97	.33	.08	.78			1.82	.19	.59	.45	.00	.97
Baseline	.08 (.74)	-.18 (.56)							-.08 (1.01)	.23 (.70)						
Follow-up	-.03 (.90)	-.38 (.79)							.02 (1.03)	.33 (.61)						

Note: Mean scores refer to the mean Z-scores of the compounds memory, simple speed and interference.

3.2.3 Results hypothesis 3

To investigate possible differences on experienced SLE's for the depression group and the anxiety group, a Mann-Whitney U-test has been performed (see table 6). No statistical differences have been found for the anxiety group or the depression group for the total number of SLE's experienced, total number of severe SLE's experienced, and on the total weighted score of the SLE's.

Table 6

Mean scores of SLE's for the depressed, anxious and control participants over 12 years.

	Depression Group				Anxiety Group			
	Depression	Controls	U	*p*	Anxiety	Controls	U	*p*
Number	2.69	3.25	93.5	.42	3.76	2.38	122	.08
Severity	1.19	2.13	72	.08	1.57	1.00	144.5	.27
Weighted score	19.06	29.75	74.5	.12	27.81	17.43	128	.13

Note: number refers to the total number of SLE's experienced, severity refers to the total number of severe SLE's experienced and weighted score refer to the total sum of weighted scores of every SLE experienced.

3.2.4 Results hypothesis 4

A Mann-Whitney U-test has been conducted to test whether scores on the SCL-90 are higher for the depressed and anxious participants compared to the controls at both baseline and the 12-year follow-up measurement (see table 7 and figure 1). For the depression group, no significant difference has been found for the SCL-90 scores at baseline. At the 12-year follow-up measurement however, depressed participants had significantly higher scores on the SCL-90 compared to the controls (U = 26,000; p = 0,003). For the anxiety group, significantly higher scores have been found for the anxious participants, both at baseline (U= 90,000; p = 0,001) and at the 12-year follow-up (U = 79,500; p = 0,024).

Table 7

Mean SCL-90 scores for the depressed, anxious and control participants on baseline and the 12-year follow-up.

	Depression Group				Anxiety Group			
	Depression	Controls	U	*p*	Anxiety	Controls	U	*p*
Baseline (F0)	24.42	20.48	78	.149	16.24	11.17	90	.001
Follow-up (F4)	33.33	21.50	26	.003	14.71	12.50	79.5	.024

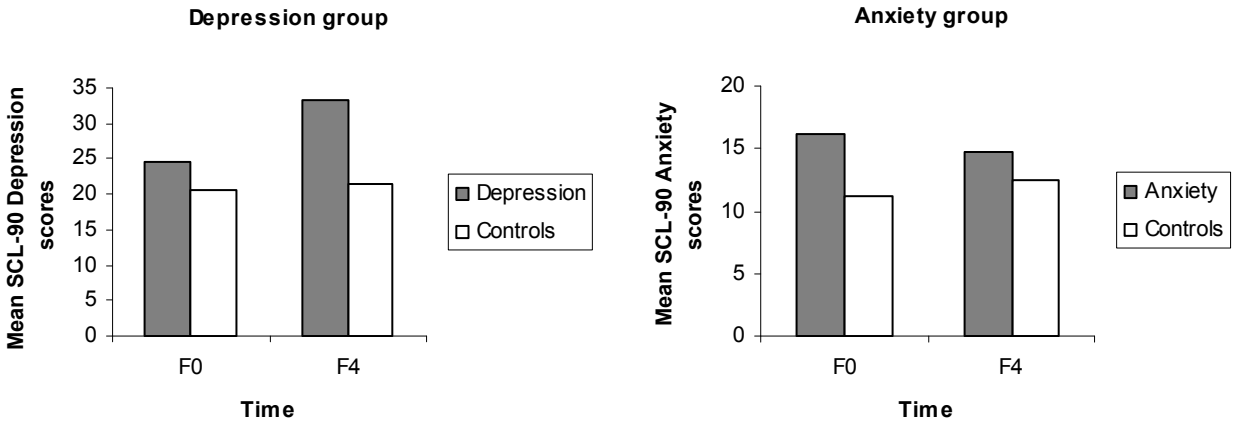

Figure 1. Mean SCL-90 scores for the depression group and the anxiety group at both the baseline and 12-year follow-up measurement. F0 refers to the baseline measurement; F4 refers to the 12-year follow-up measurement.

4. EXPERIMENT 2

As has been shown in the results section above, no significant differences were found between anxious/depressed participants and control participants on either cognitive performance, (cross-sectionally, hypothesis 1) or on cognitive decline (longitudinally, hypothesis 2). Fairly unexpected was the former finding that no cross-sectional differences were found, especially for the depression group, as it is frequently reported that a depressive state has a negative effect on performance on cognitive tasks, especially on interference tasks as the Stroop Colour-Word Test (see for example Lemelin, Baruch, Vincent, Laplante, Everett & Vincent, 1996 and Den Hartog, Derix, van Bemmel, Kremer & Jolles, 2003).

It was hypothesized that a positive diagnosis of depression or anxiety on the 12-year follow-up would mean that these participants had many depressive or anxious symptoms at the baseline measurement as well. However, since screening of depression and anxiety by the M.I.N.I. was only done at the 12-year follow-up, it is unknown whether this is actually true. Although analyses did reveal significant differences in anxious symptoms on the SCL-90 at the baseline measurement for the anxiety group, analyses did not reveal significant differences in depressive symptoms between the depressed and control participants at the baseline measurement, which means that depressive symptoms have emerged at some point during these 12 years between baseline and follow-up. Therefore, to rule out the possibility that significant results have been absent due to the absence of depressive symptoms of these participants at baseline, it was decided to replace the M.I.N.I with the SCL-90 as a screening instrument and independent predictor for anxious and depressive symptoms, because this test was administered not only at the 12-year follow-up, but at the baseline measurement as well. This means that depressive or anxious symptoms at baseline could be examined as a predictor of future cognitive decline. It was decided to investigate scores on the SCL-90 for the whole group of participants of the A1 and A2 panel with available scores, to rule out the possibility that significant results have been absent due to group sizes that were too small. This second experiment makes possible the examination of the direct effect of significant life events on cognitive impairment and cognitive decline as well.

4.1. Differences in participants and design

For this second experiment, the whole group of participants (N = 578) who had been re-tested at the 12-year follow-up was assessed to find out whether an elevated score on the SCL-90 was a good indicator of cognitive decline. For this analysis, people who did not participate on the 6-

year follow-up (but did participate on the 12-year follow-up again) have been excluded (*N* = 51), which means that a total of 527 participants have been analysed.

Of these 527 participants, age at baseline ranged from 24 to 80, with a mean age of 47.2 years (SD = 14.07). Education level was divided into 3 categories: lower education (*N = 160*), intermediate education (*N* = 209), and high education (*N* = 158). The group consisted of 265 men and 262 women. 53 participants were single, 431 participants were married or living together, 18 participants were divorced, 24 participants were widow/widower, and marital status of 1 participant was unknown.

4.2. Differences in statistical analyses

For this second experiment, multiple linear regression analyses (enter model with 2 blocks, see below) have been performed to examine the hypotheses that higher scores on the subscales depression and anxiety of the SCL-90 predict 1) a worse performance on cognitive tasks at the 12-year follow-up measurement and 2) a faster rate of cognitive decline over a period of 12 years. Furthermore, linear regression was performed to examine the hypothesis that having experienced a greater number of significant life events as well as more severe significant life events predicts 3) a higher score on the subscales depression and anxiety of the SCL-90 at the 12-year follow-up, 4) a worse performance on cognitive tasks at the 12-year follow-up measurement and 5) a faster rate of cognitive decline over a period of 12-years, to examine possible longitudinal effects. These variables have been entered in the second block.

For each analysis, age at baseline, gender, and education have been included as independent variables in the first block. These variables have been used as control variables to exclude confounding effects. See table 3 for the independent and dependent variables for each regression model. For each hypothesis, every dependent variable is analysed in a separate regression analyses, which means that there is a total of 14 regression models which have been analysed (see table 8).

4.3. Missing values

For each separate regression analysis, missing values were explored. Participants with missing values on the independent or dependent variables for the analysis in question were excluded for that particular analysis. See table 8 for the number of included participants for each analysis.

Table 8

Dependent and independent variables for each analysis and total number of included participants in analysis.

Hyp.	Dependent variable	Independent variables	Included participants
1.	1. Memory	SCL-90 depression F4, SCL-90 anxiety F4	*N* = 468
	2. Simple speed	SCL-90 depression F4, SCL-90 anxiety F4	*N* = 471
	3. Interference	SCL-90 depression F4, SCL-90 anxiety F4	*N* = 461
2.	1. Memory change	SCL-90 depression F0, SCL-90 anxiety F0	*N* = 507
	2. Simple speed change	SCL-90 depression F0, SCL-90 anxiety F0	*N* = 507
	3. Interference change	SCL-90 depression F0, SCL-90 anxiety F0	*N* = 495
3.	1. SCL-90 depression F4	number, severity, and weighted scores SLE's	*N* = 478
	2. SCL-90 anxiety F4	number, severity, and weighted scores SLE's	*N* = 478
4.	1. Memory	number, severity, and weighted scores SLE's	*N* = 517
	2. Simple speed	number, severity, and weighted scores SLE's	*N* = 517
	3. Interference	number, severity, and weighted scores SLE's	*N* = 502
5.	1. Memory change	number, severity, and weighted scores SLE's	*N* = 517
	2. Simple speed change	number, severity, and weighted scores SLE's	*N* = 517
	3. Interference change	number, severity, and weighted scores SLE's	*N* = 502

Note: each dependent variable represents a separate regression model.

4.4 Results of analyses

In table 9, results are presented of the analysis exploring whether higher scores on the SCL-90 at the 12-year follow-up are a predictor of lower cognitive performance. Besides age, sex, and education as predictors of cognitive performance, none of the subscales of the SCL-90 contribute significantly to a lower performance on the compound score of memory. For the compound scores simple speed and interference, not only age and education are significant predictors of cognitive performance, but the subscale anxiety of the SCL-90 is a significant predictor as well.

Table 9

Hypothesis 1: The cross-sectional influence of depressive and anxious symptoms on cognitive performance.

Variable	Memory		Simple Speed		Interference	
	β-Coefficient	p-value	β-Coefficient	p-value	β-Coefficient	p-value
Age	-.343 (.003)	**.000**	-.594 (.002)	**.000**	-.392 (.002)	**.000**
Sex	.247 (.071)	**.000**	.032 (.047)	.315	.028 (.062)	.479
Education (low)	-.211 (.092)	**.000**	-.227 (.061)	**.000**	-.183 (.081)	**.000**
Education (high)	.144 (.085)	**.001**	.053 (.056)	.134	.039 (.074)	.384
SCL-90 Depression	.033 (.008)	.577	.088 (.005)	.073	.111 (.007)	.077
SCL-90 Anxiety	-.055 (.015)	.362	-.108 (.010)	**.030**	-.177 (.013)	**.005**

Note: compound measures and SCL-90 scores are measured at the 12-year follow-up. Level of education has been examined by the creation of dummy variables, with education (medium) serving as the reference variable.

Results of the prediction that a higher score on the subscales depression and anxiety of the SCL-90 contributes to a faster rate of cognitive decline are shown in table 10. Except for age, no other control variable and none of the subscales of the SCL-90 contribute significantly to a faster rate of cognitive decline.

Table 10

Hypothesis 2: The longitudinal influence of depressive and anxious symptoms on cognitive performance

Variable	Memory Change		Simple Speed Change		Interference Change	
	β-Coefficient	p-value	β-Coefficient	p-value	β-Coefficient	p-value
Age	-.108 (.003)	**.024**	-.272 (.002)	**.000**	-.207 (.003)	**.000**
Sex	-.065 (.071)	.144	.005 (.045)	.906	.003 (.073)	.940
Education (low)	-.094 (.090)	.070	.006 (.057)	.904	-.082 (.093)	.111
Education (high)	-.024 (.084)	.619	-.042 (.053)	.377	-.056 (.086)	.248
SCL-90 Depression	-.053 (.009)	.499	.075 (.006)	.327	-.029 (.009)	.707
SCL-90 Anxiety	.106 (.016)	.175	.051 (.010)	.499	..017 (.016)	.832

Note: compound scores represent the change on memory, simple speed and interference between baseline and 12-year follow-up. Scores of the SCL-90 represent the scores on baseline.

Table 11 shows the results of the hypothesis that experiencing more (severe) SLE's will lead to higher scores on the SCL-90 at the 12-year follow-up. Of the control variables, a low education is the only predictor of higher scores on the subscale anxiety. For the subscale depression, both sex and education are significant predictors of higher scores. No effect was found for the number of SLE's experienced, the number of severe SLE's experienced, or the weighted scores of the SLE's experienced.

Table 11

Hypothesis 3: cross-sectional influence of SLE's on SCL-90 scores

Variable	SCL-90 depression		SCL-90 Anxiety	
	β-Coefficient	p-value	β-Coefficient	p-value
Age	.021 (.026)	.677	.041 (.014)	.409
Sex	.088 (.632)	**.049**	.083 (.334)	.061
Education (low)	.205 (.808)	**.000**	.224 (.427)	**.000**
Education (high)	-.007 (.765)	.892	-037 (.405)	**.**451
Total number of SLE's	.114 (.381)	.304	.065 (.202)	.555
Total severe SLE's	-.169 (.863)	.297	-.215 (.457)	.184
Total weighted score SLE's	.217 (.090)	.337	.244 (.048)	..279

Note: variables of the subscales depression and anxiety of the SCL-90 represent scores at the 12-year follow-up.

Table 12 shows the results for the prediction that having experienced more (severe) SLE's leads to worse performance on cognitive tasks at the 12-year follow-up measurement. As can be seen in the table, besides age and education as a predictor for all compound scores and sex as a predictor of memory, there is no effect of experienced SLE's on cognitive performance.

Table 12

Hypothesis 4: cross-sectional influence of SLE's on cognitive performance

Variable	Memory		Simple Speed		Interference	
	β-Coefficient	p-value	β-Coefficient	p-value	β-Coefficient	p-value
Age	-.383 (.003)	**.000**	-.619 (.002)	**.000**	-.407 (.002)	**.000**
Sex	.236 (.070)	**.000**	.041 (.052)	.183	.037 (.060)	.328
Education (low)	-.206 (.089)	**.000**	-.196 (.067)	**.000**	-.195 (.076)	**.000**
Education (high)	.119 (.085)	**.003**	.034 (.064)	.327	.053 (.072)	.216
Total number of SLE's	.050 (.043)	.592	.072 (.032)	.366	.118 (.037)	.239
Total severe SLE's	.097 (.096)	.461	.158 (.072)	.157	.162 (.083)	.252
Total weighted score SLE's	-.170 (.010)	.365	-.204 (.008)	.199	-.243 (.009)	.226

Note: compound measures represent scores of the 12-year follow-up measurement.

In table 13, results are shown of the last hypothesis that the experience of more (severe) SLE's will lead to a faster rate of cognitive decline. As can be seen in the table, age is a predictor of decline for the compound scores speed and interference. No effect of the other control variables or experienced SLE's was found.

Table 13

Hypothesis 5: longitudinal influence of SLE's on cognitive performance

Variable	Memory Change		Simple Speed Change		Interference Change	
	β-Coefficient	p-value	β-Coefficient	p-value	β-Coefficient	p-value
Age	-.083 (.003)	.090	-.260 (.002)	**.000**	-.218 (.003)	**.000**
Sex	-.048 (.070)	.272	.021 (.045)	.632	.010 (.071)	.820
Education (low)	-.081 (.089)	.118	.041 (.057)	.417	-.077 (.091)	.130
Education (high)	-.033 (.085)	.499	-.042 (.054)	.382	-.060 (.086)	.219
Total SLE's	.136 (.043)	.230	.000 (.028)	.997	.059 (.044)	.607
Total severe SLE's	.059 (.097)	.714	-.148 (.061)	.342	.189 (.099)	.244
Total weighted score SLE's	-.206 (.010)	.364	.203 (.006)	.361	-.260 (.010)	.258

Note: compound scores represent the change on memory, simple speed and interference between baseline and 12-year follow-up.

5. DISCUSSION

The present study examined the effects of depression and anxiety on cognitive decline and examined the possible role of significant life events. Data of the Maastricht Aging Study has been used to reveal if the presence of a depression or anxiety disorder could be a serious risk factor for a faster rate of cognitive decline. Furthermore the relationship between significant life events and depression and anxiety was investigated. 16 participants who screened positively for a DSM-IV depressive disorder and 21 participants who screened positively for a DSM-IV generalized anxiety disorder, by using the Mini Neuropsychiatric Interview (M.I.N.I), were selected from the data and matched to control participants.

The results provided no evidence for an effect of depression or anxiety on cognitive decline. Surprisingly, the assumption that depression or anxiety has an effect on cognitive performance cross-sectionally was not supported either, which suggests that these depressed or anxious participants did not perform worse on cognitive tests of memory, simple speed, or interference compared to healthy control participants. This was especially surprising for the depression group, because cognitive deficits are seen as common features of depressed patients (Baune, Suslow, Engelien, Arolt & Berger, 2006). Furthermore, no evidence was found for a relationship between significant life events and the presence of a depression or anxiety disorder.

The present study did not replicate prior findings by Chodosch, Kado, Seeman and Karlamangla (2007) and by Sachs-Ericsson, Joiner, Plant and Blazer (2005), who found an influence of depression on longitudinal cognitive decline. Findings of Sinoff and Werner (2003), who found that anxiety was a predictor of longitudinal cognitive decline, have not been replicated either. An explanation for this discrepancy might be that none of the studies mentioned above investigated the effects of a pure depressive or pure anxiety disorder. In the present study, besides the 16 participants who screened positively for a depressive disorder and the 21 participants who screened positively for an anxiety disorder, 6 participants had co-morbid anxiety and depressive disorders and were excluded from the analyses. Given that generalized anxiety disorder and depressive disorder are highly co-morbid in both clinical and epidemiological samples (Gorwood, 2004), it is likely that a substantial amount of the participants in the studies mentioned above both had an anxiety and depressive disorder. It is possible that co-morbid depressive and anxiety disorder has a greater influence on the rate of cognitive decline. Basso et al. (2007) found that major depressive disorder corresponds with significant memory impairment, regardless of co-morbid anxiety disorder, but that the presence of a co-morbid anxiety disorder coincides with deficits involving executive function and psychomotor slowing. This was also found by Deluca et

al. (2005), who found evidence that co-morbid generalized anxiety disorder is associated with a greater decline in memory in late-life major depressive disorder. Another difference between the present study and the other studies mentioned above is that their samples consisted of participants of at least 60 years and older. In the present study, no age criterion existed. It could be assumed that this difference in selection may play a role in the effect seen on cognitive decline, since a higher age is strongly believed to be a predictor of the rate of cognitive decline (Letenneur, Gilleron, Commencges, Helmer, Orgogozo & Dartigues, 1999; Vincze et al., 2007). However, since age was controlled for, it is unlikely that this had an influence on the differences in the effects seen in the present study and those of the studies mentioned above.

However, there were some possible limitations to the present study concerning the use of the M.I.N.I., the sample sizes and learning effects that could have prevented the finding of significant effects. Firstly, sample sizes were small. Although control participants have been used who were matched on age, sex, and education, it could be possible that these participants varied significantly on other factors (e.g. MMSE scores, use of medication, neuroticism, medical conditions) that could have influenced cognitive performance.

Secondly, since testing was repeated every 6 years, it might be that the absence of significant differences between the participants on the follow-ups may be due to learning effects. However, most learning effects usually occur at the second time of measurement, which makes a big influence of learning effects on the third time of measurement unlikely. It should be mentioned however, that participants aged 53 and older were tested at a 3-year follow-up measurement as well. Also, in the first experiment, 2 participants with an anxiety disorder and 1 participant with a depressive disorder did not participate at the 6-year follow-up, which both could have obscured the results through different time curves concerning these possible learning effects.

Another limitation concerns the use of the M.I.N.I as a screening instrument for a depressive and generalized anxiety disorder. The M.I.N.I. originally is a short diagnostic structured interview with specific questions for each disorder and is meant to be administered in clinical settings. However, the MAAS study is a population-based study and screening only took place by using these specific questions of the interview, on which participants could answer yes or no, instead of having a more detailed structured interview. This of course gives less certainty about the justification of a positive diagnosis. Moreover, the M.I.N.I has been administered by a lot of different raters, which could lead to differences in interpretation and diagnosis. These shortcomings could explain the discrepancy in prevalence of depression and generalized anxiety in our study and the estimated prevalence of these disorders in the Netherlands by the RIVM

(Schoemaker, Poos & Balkom, 2005; Schoemaker, Poos & Spijker, 2005); in the present study, 3.8% of the participants screened positively for a depressive disorder and 4.7% screened positively for a generalized anxiety disorder, while the estimated prevalence of depression and generalized anxiety by the RIVM is 6,3% and 2.8% respectively.

Finally, the M.I.N.I has only been administered at the 12-year follow-up measurement. Therefore, it is uncertain whether these participants had a depression or anxiety disorder at the baseline measurement as well. For this reason, a fourth hypothesis was included which stated that these participants would not only have an elevated score (compared to the control participants) on the SCL-90 at the 12-year follow-up, but on the baseline measurement as well, since the SCL-90 was used at both time measurements. Support for this hypothesis was only partially found. The participants who screened positively for an anxiety disorder indeed had an elevated score on both baseline and 12-year follow-up measurement. For the participants who screened positively for a depression however, an elevated score was only found on the 12-year follow-up measurement, but was absent on the baseline measurement.

Two explanations for these findings could be given. One possible explanation is that anxiety could be a more stable trait and that depression could be seen as more fluctuating across the life span. This might explain the fact that the anxious participants had an elevated score 12-years earlier while the depressed participants had not. Another possible and more likely explanation could be given by the fact that participants with a known depression to the general practitioner have been excluded from the MAAS Study and hence never entered the study. This means that a great number of individuals with a depression on baseline may have been excluded, only leaving in an unknown number of participants with a depression not known to the general practitioner and participants with more moderate levels of depressive symptoms instead of a full depression. Of course, this could have influenced the extent to which effects could be found for the present study, since possible effects could be suppressed by the exclusion of the extreme cases. This could be supported by the fact that we found a higher percentage of participants with a generalized anxiety in our study compared to participants with a depressive disorder, although the estimated prevalence in the Netherlands for a depressive disorder is higher.

For this reason, it was decided to conduct a second experiment in which the M.I.N.I. as an independent predictor was replaced with the SCL-90. This test was not only administered at the 12-year follow-up, but at the baseline measurement as well, which means that depressive or anxious symptoms at baseline could be examined as a predictor of future cognitive decline. Instead of a selection of depressed and anxious participants, the scores on the SCL-90 were investigated for all participants with available data ($N = 527$) left in the MAAS Study, in order to

reveal if an elevated score on the SCL-90 subscales of depression or anxiety was a predictor of cognitive decline. Furthermore, the experience of significant life events was used as an independent predictor for cognitive impairment/decline and anxious and depressive symptoms as well.

Again, no significant effect of depressive or anxious symptoms was found for cognitive decline. Nevertheless, some cross-sectional effects were found. Although there was no effect for depressive symptoms on cognitive performance, there was a negative relationship between anxious symptoms and performance on simple speed and interference, which indicates that a higher score on the subscale anxiety resulted in lower performance on simple speed and interference. No effect of significant life events was found on cognitive impairment, cognitive decline, or on depressive or anxious symptoms.

Although possible limitations of the M.I.N.I. as a screening instrument for depression and anxiety and small group sizes have been resolved in the second experiment, several other possible limitations of both experiments should be considered. Firstly, both studies used data from the MAAS study, a population based study in which only normal ageing individuals without a known depression participated. As has been mentioned earlier, this may have suppressed possible effects.

Secondly, there was little information available regarding the significant life events experienced by the participants. No data was gathered concerning the experienced severity of each SLE experienced by the participants individually. Instead, severity of the SLE's has been examined by two other independent samples, in order to assess which significant life events were commonly rated as most severe. However, it is unknown to what extent these experienced SLE's have had an impact on the participants themselves. Moreover, on each measurement, SLE's which have happened in the past year have been reported by the participants. The participants have been re-tested at 6 years intervals (baseline, 6-year follow-up and 12-year follow-up), which means that of every six year, only the experienced SLE's of the year prior to the follow-up measurement have been reported and used as an indicator of total significant life events experienced.

A third possible limitation may originate from a certain trend in dropouts. It is possible that a substantial amount of the dropouts were participants with problems of anxiety, depression, or (worries about) noticeable declining cognitive performance which started to take off during the years after the first measurement. This could have obscured the results as well.

A recommendation for further research is to investigate participants who have a clear depression or anxiety disorder at the start of the experiment. These participants could then be

followed closely in a longitudinal study and compared to healthy control subjects to examine the rate of cognitive decline. Another recommendation for further research is to obtain a more useful measurement of experienced significant life events, which could reveal information about experienced severity of each significant life event for all individual participants. It could be effective to examine the influence of certain specific individual significant life events as well.

In conclusion, although partial support was found for an effect of anxious symptoms on cognitive performance concerning speed and interference, both experiments failed to find an effect of depression and anxiety on cognitive decline over a period of 12 years. Furthermore, no support was found for the relationship between significant life events and anxiety/depression, cognitive performance or cognitive decline.

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