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Accumulated and Differential Effects of Life Events on Cognitive Decline in Older Persons: Depending on Depression, Baseline Cognition, or ApoE ε4 Status?

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Objectives. The study examined the accumulated as well as the differential influence of negative life events on cognitive decline in older persons, and whether this association was different for persons with normal and poor cognitive functioning, and for ApoE ε4 carriers and noncarriers.

Methods. We used data from the Longitudinal Aging Study Amsterdam (N = 1,356). Data were analyzed using linear mixed models.

Results. We found differential associations for different negative life events with cognitive decline none of which were mediated by depressive symptoms. The death of a child or grandchild, which may be considered a highly stressful event, was associated to a higher rate of cognitive decline, whereas more chronic stressors, such as the illness of a partner or relative, or serious conflicts, were associated with better cognitive function. The associations between life events and cognitive function were stronger in ApoE ε4 carriers compared with noncarriers, suggesting that this gene plays a role in the association between stress and cognitive function.

Discussion. Highly stressful events seem to be associated with a higher rate of cognitive decline, whereas mild chronic stressors may have an arousing function that stimulates cognitive performance.

Key Words: ApoE—Cognition—Cognitive decline—Life events.

OLDER persons are frequently exposed to various stressors. It has been estimated that about 25% of healthy older persons experience at least one stressful life event within a 3-month period (Ormel, Oldehinkel, & Brilman, 2001). Life events include acute as well as ongoing stressful situations, such as the death of a close relative, a severe disease of a beloved one, and relocation, and are important contributors to reduced well-being and the development of psychopathology, especially depression (Van Praag, De Kloet, & Van Os, 2005). Former research also suggests that life events may have an adverse effect on cognitive function, especially in old age (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007; Vondras, Powless, Olson, Wheeler, & Snudden, 2005), although no association or enhanced cognitive performance has also been found (Deeg, Huizink, Comijs, & Smid, 2005; Rosnick, Small, McEvoy, Borenstein, & Mortimer, 2007; Ward, Mathias, & Hitchings, 2007).

Stressors generally induce a physical reaction that is expected to form the biological foundation for the association between stressors and cognitive function. In response to stressors, the hypothalamic–pituitary–adrenal axis is activated and the stress hormone cortisol is secreted. Cortisol may influence cognitive function because it can easily cross the blood–brain barrier and access the brain, where it binds to receptors, localized in various brain regions, such as the hippocampus, amygdala, and frontal lobes, all brain structures known to be involved in learning and memory (Lupien et al., 2007; McEwen, 2007; Van Praag et al., 2005). In a review, De Kloet, Oitzl & Joëls (1999) suggest that the effect of cortisol on cognitive performance depends on the levels of circulating cortisol in the brain. Mildly elevated levels of cortisol can enhance cognitive function, whereas high levels may result in cognitive impairment. Based on this suggestion, differential effects from life events on cognitive function may be expected, depending on the amount of stress it induces in an individual (Lupien et al., 2007).

Research on the effect of life events on cognition has been focused on the accumulated and the differential effects of life events. Thus far, the results from studies that examined the accumulated effects of life events are conflicting. In cross-sectional analyses, Vondras and colleagues (2005) found that the accumulation of negative events was associated with lower scores on measures for episodic memory, whereas Rosnick and colleagues (2007) did not find such an association. Several studies examined the effects of specific negative life events on cognitive functions. Rosnick and colleagues found that the injury or illness of a friend was associated with recalling a greater number of words, faster performance on psychomotor speed tasks, and better performance on attention tasks. However, having less money to live on and being a victim of a crime was associated with slower performance on psychomotor speed tasks. Longitudinal analyses in a previous study from our research group

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showed that older persons who lost a spouse showed greater cognitive decline in memory function over a period of 6 years than those who remained married (Aartsen, Van Tilburg, Smith, Comijs, & Knipscheer, 2005). This association was not mediated by the levels of depressive symptoms. These findings are in line with the findings from Xavier, Ferraz, and Trentini (2002) and van Gelder and colleagues (2006) but are in contrast with the findings from Ward and colleagues (2007), who found that poor cognitive performance in persons who lost their partner was due to depressive symptoms. Very few longitudinal studies have focused on the effects of other negative life events on cognition, although it is generally assumed that life events, such as the loss of children or serious illness of the partner, may have an effect on cognition as well.

The conflicting results with respect to the accumulated and differential effects of life event on cognition may be due to differences in design. For instance, most studies were cross-sectional and thus reflect the level of cognitive performance but not cognitive decline as a consequence of the life events (Rosnick et al., 2007; Vondras et al., 2005; Ward, Mathias, & Hitchings, 2007; Xavier et al., 2002). In addition, the characteristics of the study samples varied widely between studies. Vondras and colleagues included a mixed age-group of younger and older adults, whereas van Gelder and colleagues (2006) included only men, aged 70 years and older. In addition, when examining the association between life events and cognitive decline, it is important to take into account that some individuals may be more vulnerable to cognitive decline when stress is encountered than others. For instance, persons at increased risk for Alzheimer's disease may be particularly vulnerable to the effects of elevated levels of cortisol in the hippocampus resulting from high levels of stress. The already existing hippocampal loss in these patients may change the impact of cortisol on hippocampal function and therefore on cognitive function. It might also be expected that the genetic factor ApoE ε4 increases the vulnerability to the adverse effects of stress on cognition because this allele increases the risk for Alzheimer's disease (Lee et al., 2008). Thus far, there is little research on the role of ApoE ε4 or poor cognitive functioning in the association between life events and cognitive decline. Only Peavy and colleagues (2007) examined this issue and found that older persons with the combination of high chronic stress and at least one ApoE ε4 allele performed worse on memory tests compared with older persons with high stress and no ε4 allele. They also found that mild cognitive impairment (MCI) may be an important vulnerability factor for the adverse effect of stressors on cognition (Peavy et al., 2009).

In the current study, we examine whether negative life events are associated with cognitive decline in older persons from a community-based sample. Both the accumulated and the differential influence of the life events on cognitive decline are investigated and we will examine whether this association is explained by depressive symptoms. As previous research showed that the association between life events and cognition may be different for specific cognitive domains, we perform a series of separate analyses for general cognitive performance, as measured with the Mini-Mental State Examination (MMSE), speed of information processing, learning, and retention. Furthermore, we investigate whether the association between life events and cognitive decline is different for persons with normal and poor cognitive function, and for ApoE ε4 carriers and noncarriers. We hypothesize that negative life events are associated with increased levels of stress and may have differential effects on several cognitive domains; mild stressors may lead to better cognitive performance, whereas severe stressors may lead to cognitive decline. We further hypothesize that a greater accumulation of negative life events lead to more cognitive decline and that the association between negative life events and cognitive decline will be stronger in persons with poor cognitive status compared with persons with normal cognitive function, and in ApoE ε4 carriers compared with non carriers.

Methods

Study Sample

The study was conducted using the Longitudinal Aging Study Amsterdam (LASA; http://www.lasa-vu.nl), an ongoing population-based prospective cohort study among persons initially aged 55–85 years in the Netherlands (Deeg, Van Tilburg, Smit, & De Leeuw, 2002). Longitudinal Aging Study Amsterdam is based on a random sample, stratified for age and sex, drawn from the population registries of 11 municipalities in the Netherlands. In total, 3,107 participants were enrolled in the baseline LASA interview, which took place between September 1992 and September 1993 (T1). The second measurement cycle of LASA was performed in 1995/1996 (T2; n = 2,545; 81.7%). Loss to follow-up was mainly due to mortality, and to a lesser extent due to refusal or serious illness, or because persons could not be located. Because we were specifically interested in the association between life events and cognitive decline in older persons, we included persons 65 years and older at T2 (n = 1,951). Data on cognitive function was available from both LASA measurements (T1 and T2), and recent life events were available from the second measurement cycle (T2). For the present study, persons were included if data on life events at T2 and data on memory performance on T1 and T2 were available, resulting in a sample of 1,356 persons. Excluded persons (n = 595) were older, more often men, had more chronic diseases and depressive symptoms at baseline, and also had lower scores on cognitive measures at baseline (for all $p < .05$). With respect to life events, excluded persons reported less frequently illness of their partner and death of a relative, and more frequently having

a conflict with others compared with persons who participated in the study (all *p*s < .05).

Measures

Dependent variables.—Cognitive function was assessed with a set of widely used cognitive tests that are sensitive to aging-related decline. The tests were administered during T1 and T2. The following cognitive domains were assessed: general cognitive function, episodic memory, and information processing speed.

General cognitive performance was measured with the MMSE (Folstein, Folstein, & McHugh, 1975), a frequently used screening instrument for global cognitive dysfunction. Scores range from 0 to 30, a higher score indicating better performance.

Information processing speed was measured by an adapted version of a letter substitution task, the Alphabet Coding Task-15 (Piccinin & Rabbitt, 1999; Savage, 1984). In this task, two rows of characters were shown. Each character in the first row belongs to a character in the second row. Participants had to complete as many character combinations as possible by verbally naming the corresponding character. This test was repeated over three trials of 1 min each. The maximum score of one of the three trials is included in the present study.

Episodic memory was measured by means of the adapted Dutch version of the Auditory Verbal Learning Test (AVLT; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2005). This test consists of 15 words, which had to be learned during three trials. The total number of words the respondent had learned during the three presentations is the *learning* score, which ranges from 0 to 45. The ratio of the highest score out of three trials (immediate recall) and delayed recall is defined as the *retention* score. This reflects the percentage of words that the respondent still remembered after a distraction period relative to the learning phase. During the second measurement cycle, a parallel version of the AVLT was used. The parallel versions have been validated and tested on parallelism.

Independent variables.—Recent stressful life events were assessed retrospectively covering the 3-year time interval prior to T2 with a structured questionnaire. Respondents were asked whether the following events had occurred in the 3-year time interval prior to the interview: widowhood, divorce, severe illness of partner, death of a relative, death of a child, relocation, severe conflicts, or being a victim of a crime. The questions were adapted from the life event inventory developed by Tennant and Andrews (1976) with the aim of assessing the stress of life events. The items used in the LASA data collection were selected on the following criteria: the event is likely to occur relatively frequent in the population, and the event scores relatively high on the distress and life changes scales (de Beurs et al., 2001).

Depressive symptoms were measured by means of the Dutch translation of the Center for Epidemiological Studies-Depression scale (CES-D; Beekman et al., 1997; Radloff, 1977). We used the continuous CES-D scores (range 0–60), a higher score indicating more depressive symptoms.

The *ApoE phenotype* was determined by isoelectric focusing of delipidated serum samples, followed by immunoblotting (Havekes et al., 1987). Obtained serum samples were frozen at −80°C until actual ascertainment. The distribution of ApoE phenotypes was in Hardy–Weinberg equilibrium (ApoE ε2/2: 0.7%; ε2/3: 11.7%; ε3/3: 60.5%; ε2/4: 3.0%; ε3/4: 21.3%; ε4/4: 2.9%; Dik et al., 2000). ApoE status was classified as ε4 carriers for participants with the ApoE ε4 isoform (phenotypes ε2/4, ε3/4, and ε4/4) and as ε4 noncarriers for participants without the ApoE ε4 isoform (phenotypes ε2/2, ε2/3, and ε3/3).

Covariates.—Several variables may be related to life events as well as cognitive decline and consequently could confound the associations examined. Therefore, the following covariates were included in the analyses. Sociodemographic variables included age, sex, and level of education. Information on health status included questions about he presence of the following chronic diseases or disease events: cardiac disease (including myocardial infarction), peripheral artherosclerosis, stroke, diabetes mellitus, COPD (asthma, chronic bronchitis, or pulmonary emphysema), arthritis (rheumatoid arthritis or osteoarthritis), and cancer. Answers were coded as either "yes" or "no" for each of these diseases. Compared with general practitioner information, the accuracy of self-reports of these diseases was shown to be adequate and independent of cognitive impairment (Kriegsman, Penninx, Van Eijk, Boeke, & Deeg, 1996). Benzodiazepine use was assessed by having the interviewer record information on type and dose of medication from the drug containers provided by the respondents. Drug use was classified in categories according to the Anatomic Therapeutic Chemical classification (Sonnenberg, Beekman, Deeg, & Van Tilburg, 2003).

Statistical Analyses

Data were analyzed using linear mixed models in which cognitive performance on a specific neuropsychological test at both measurements was the outcome measure. With linear mixed models, we are able to perform regression analyses with repeated measures data (Blackwell, Mendes de Leon, & Miller, 2006). This method takes into account the dependency of the repeated observations obtained from the same individual over time. To fulfill the assumption of normality, MMSE scores were transformed (ln [31-MMSE score]) to obtain a near-normal distribution.

First, the association between the number of life events and cognitive decline was examined in a series of three models. To start, the association between the number of life events and cognitive decline was examined in a full factorial model with the number of life events, time, and the interaction of the Number of Life Events × Time as independent variables. In this model, the main effect for life events reflects the cross-sectional association between life events and cognitive performance over time and the interaction term reflects the longitudinal association and thus the rate of decline. When the *p* value of the association between the number of life events or the interaction term and cognitive decline was smaller than .10, the second model was adjusted for age, sex, education level, chronic diseases, and benzodiazepine use obtained from both measurements, and the third model was additionally adjusted for depressive symptoms. The probability of a nonlinear association was tested by entering a number of life events-squared term to the fully adjusted models. A nonlinear association was considered to be present when the *p* value for the life events-squared term was below .05. Next, we investigated whether the associations between the number of life events and the rate of cognitive decline was different for persons with normal cognitive functioning (MMSE score ≥24) and poor cognitive functioning (MMSE score <24) at baseline, and for ApoE ε4 carriers and noncarriers by entering the three-way product terms of these variables and the number of life events (Life Events × Time × MMSE or ApoE ε4) into the fully adjusted models. The interaction with MMSE was only examined in the models for memory and speed of information processing. An interaction was considered statistically significant when the *p* value for the interaction term was below .05. If a significant interaction was found, the subsequent analyses were stratified for different groups.

Second, the association between the separate life events and cognitive decline was examined in the same subsequent multivariate models as described for the number of life events. However, in order to investigate the interaction with, respectively, MMSE and ApoE ε4 for the separate life events, the prevalence of the life event in low-MMSE groups or in the ApoE ε4 carriers had to be large enough ($n > 20$) to allow analyses. The unstandardized regression coefficients (*B*), their 95% confidence intervals (CIs), and the *p* values are presented.

Results

The descriptives of the study sample are presented in Table 1. The mean age at T2 was 75.6 years and ranged from 64.8 to 88.3 years. Over 74% of the study sample experienced at least one life event in the previous 3 years. The number of events varied from one (40%) to three or more (11%). Serious illness of a close relative (45.1%) and the death of a close relative (29.4%) were the most frequently reported life events. The mean scores on the MMSE and information processing speed decreased a little over the 3 years, whereas the mean memory scores increased, most probably due to the recollection of the procedure.

Table 1. Descriptives of the Study Sample

	T1	T2
Background characteristics		
Age in years, *M* (SD)	72.50 (6.58)	75.56 (6.58)
Female, *n* (%)	695 (51.3)	
Education, *M* (SD)	3.50 (2.00)	
No. of chronic diseases, *M* (SD)	1.39 (1.18)	1.74 (1.27)
Benzodiazepine users, *n* (%)	177 (13.1)	194 (14.3)
CES-D score, *M* (SD)	7.51 (7.35)	8.05 (7.62)
ApoE ε4[a], *n* (%)		
No ApoE ε4 carrier	890 (73)	
ApoE ε4 carrier	329 (27)	
Cognitive scores		
MMSE score, *M* (SD)	27.32 (2.25)	26.77 (2.96)
Speed of information processing, *M* (SD)	25.90 (7.34)	25.13 (7.46)
Memory, learning score, *M* (SD)	18.33 (5.79)	18.97 (6.31)
Memory, retention score, *M* (SD)	61.39 (25.29)	66.64 (26.77)
Negative life events		
Any life event in past 3 years, *n* (%)		1,009 (74,4)
No. of life events in past 3 years, *n* (%)		
0		347 (25.6)
1		542 (40.0)
2		318 (23.5)
≥3		149 (11.0)
Death/divorce partner, *n* (%)		91 (6.7)
Death (grand)child, *n* (%)		45 (3.3)
Death close relative, *n* (%)		398 (29.4)
Illness partner/spouse, *n* (%)		185 (13.6)
Illness relative(s), *n* (%)		594 (45.1)
Victim of crime, *n* (%)		53 (4.0)
Serious conflict with others, *n* (%)		100 (7.6)
Relocation, *n* (%)		184 (13.6)

Notes: CES-D = Center for Epidemiological Studies-Depression scale; MMSE = Mini-Mental State Examination.
[a]*n* = 1,219.

Accumulated Influence of Life Events

First, the association between the number of life events and cognitive decline was examined by means of linear mixed models (see Table 2). We found no linear associations between the number of events and any of the cognitive measures. The presence of a nonlinear association was tested by entering a number of life events-squared term to the adjusted models, but in none of the models a nonlinear association was significant. Next, we examined whether the associations between the number of life events and the rate of cognitive decline was different for persons with normal cognitive function (MMSE score ≥24) and poor cognitive function (MMSE score <24). This was only true for the retention score (interaction term: $p = .035$). A negative association between the number of life events and decline in retention was only present in persons with poor cognitive function ($B = -7.75$; 95% CI: −13.282 to −2.223; $p = .007$), indicating that these persons scored relatively better after 3 years on this

Table 2. The Association Between Life Events and Cognitive Decline (linear mixed models)

	Model 1		Model 2		Model 3	
	B	95% CI	*B*	95% CI	*B*	95% CI
MMSE						
No. of life events	0.009	−0.025 to 0.044				
No. of Life Events × Time	0.005	−0.028 to 0.038				
Death/divorce partner	0.100	−0.037 to 0.236				
Death/Divorce Partner × Time	−0.032	−0.163 to 0.099				
Death (grand)child	0.404	0.214 to 0.594***	0.215	0.042 to 0.388**	0.222	0.050 to 0.394*
Death (grand)Child × Time	−0.193	−0.375 to −0.012*	−0.195	−0.377 to −0.013*	−0.195	−0.377 to −0.012*
Death close relative	0.094	0.019 to 0.168*	0.032	−0.036 to 0.100	0.042	−0.026 to 0.110
Death Close Relative × Time	−0.011	−0.082 to 0.061				
Illness partner	−0.098	−0.202 to −0.006*	−0.114	−0.210 to −0.019**	−0.118	−0.213 to −0.022*
Illness Partner × Time	0.145	0.044 to 0.245**	0.146	0.045 to 0.247**	0.151	0.050 to 0.253**
Illness relative(s)	−0.047	−0.116 to 0.022				
Illness Relative(s) × Time	0.028	−0.039 to 0.095				
Victim of crime	−0.068	−0.245 to 0.108				
Victim of Crime × Time	−0.053	−0.223 to 0.117				
Conflict with others	−0.089	−0.218 to 0.041				
Conflict With Others × Time	−0.058	−0.183 to 0.067				
Relocation	0.187	0.087 to 0.287***	0.128	0.037 to 0.219**	0.100	0.007 to 0.192*
Relocation × Time	−0.050	−0.145 to 0.046				
Speed of information processing						
No. of life events	−0.379	−0.783 to 0.025	−0.049	−0.381 to 0.283	−0.075	−0.406 to 0.256
No. of Life Events × Time	0.075	−0.126 to 0.276				
Death/divorce partner	−0.632	−2.231 to 0.967				
Death/Divorce Partner × Time	0.254	−0.535 to 1.044				
Death (grand)child	−6.162	−8.395 to −3.929***	−3.335	−5.187 to −1.483***	−3.429	−5.265 to −1.593***
Death (grand)Child × Time	0.069	−1.063 to 1.202				
Death close relative	−1.394	−2.270 to −0.518**	−0.358	−1.081 to 0.365	−0.437	−1.156 to 0.280
Death Close Relative × Time	−0.200	−0.638 to 0.237				
Illness partner	0.279	−0.898 to 1.456				
Illness Partner × Time	0.145	−0.431 to 0.720				
Illness relative(s)	0.132	−0.675 to 0.940				
Illness Relative(s) × Time	0.123	−0.276 to 0.522				
Victim of crime	0.146	−1.912 to 2.205				
Victim of Crime × Time	0.091	−0.934 to 1.112				
Conflict with others	1.218	−0.298 to 2.734				
Conflict With Others × Time	0.970	0.218 to 1.722*	0.977	0.225 to 1.730*	0.976	0.223 to 1.729*
Relocation	−2.461	−3.637 to −1.285***	−1.627	−2.596 to −0.657**	−1.482	−2.450 to −0.514**
Relocation × Time	0.277	−0.316 to 0.871				
Memory, learning						
No. of life events	−0.198	−0.523 to 0.127				
No. of Life Events × Time	−0.117	−0.380 to 0.146				
Death/divorce partner	−0.648	−1.937 to 0.640				
Death/Divorce Partner × Time	−0.272	−1.316 to 0.771				
Death (grand)child	−2.478	−4.273 to −0.683**	−0.665	−2.225 to 0.896	−0.699	−2.249 to 0.851
Death (grand)Child × Time	−0.394	−1.851 to 1.062				
Death close relative	−0.976	−1.682 to −0.269**	−0.284	−0.897 to 0.329	−0.358	−0.969 to 0.253
Death Close Relative × Time	0.078	−0.494 to 0.651				
Illness partner	0.138	−0.825 to 1.100				
Illness Partner × Time	−0.157	−0.965 to 0.652				
Illness relative(s)	0.706	0.057 to 1.355*	0.641	0.080 to 1.201*	0.653	0.092 to 1.212*
Illness Relative(s) × Time	−0.516	−1.047 to 0.016	−0.508	−1.041 to 0.025	−0.515	−1.049 to 0.019
Victim of crime	−0.013	−1.659 to 1.633				
Victim of Crime × Time	0.137	−1.212 to 1.486				
Conflict with others	1.065	−0.155 to 2.285	0.150	−0.910 to 1.210	0.315	−0.748 to 1.378
Conflict With Others × Time	−1.183	−2.182 to −0.184*	−1.203	−2.203 to −0.202*	−1.220	−2.221 to −0.219*
Relocation	−2.585	−3.520 to −1.650***	−1.944	−2.756 to −1.133***	−1.812	−2.634 to −0.991***
Relocation × Time	1.156	0.397 to 1.916**	1.099	0.334 to 1.863**	1.106	0.325 to 1.887**
Memory, retention						
No. of life events	0.651	−0.747 to 2.049				
No. of Life Events × Time	−0.559	−2.093 to 0.974				
Death/divorce partner	2.339	−3.199 to 7.877				
Death/Divorce Partner × Time	2.994	−3.091 to 9.078				

(Table 2 continues)

Table 2. The Association Between Life Events and Cognitive Decline (linear mixed models) (*Continued*)

	Model 1		Model 2		Model 3	
	B	95% CI	*B*	95% CI	*B*	95% CI
Death (grand)child	−5.195	−12.933 to 2.542				
Death (grand)Child × Time	−1.133	−9.626 to 7.361				
Death close relative	0.175	−2.870 to 3.220				
Death Close Relative × Time	−2.096	−5.435 to 1.243				
Illness partner	0.991	−3.136 to 5.119				
Illness Partner × Time	1.861	−2.733 to 6.456				
Illness relative(s)	2.010	−0.785 to 4.801				
Illness Relative(s) × Time	−0.176	−3.265 to 2.913				
Victim of crime	1.998	−5.093 to 9.088				
Victim of Crime × Time	−0.426	−8.247 to 7.395				
Conflict with others	4.875	−0.371 to 10.120	2.921	−2.101 to 7.943	3.124	−1.928 to 8.176
Conflict With Others × Time	−5.671	−11.466 to 0.125	−5.750	−11.560 to 0.060	−5.778	−11.592 to 0.035
Relocation	−7.642	−11.678 to −3.607***	−6.110	−9.973 to −2.247**	−5.952	−9.877 to −2.027**
Relocation × Time	2.476	−1.964 to 6.917				

Notes: CI = confidence interval; MMSE = Mini-Mental State Examination. Scores were transformed [ln (31-MMSE score)] to obtain a near-normal distribution. Model 1 = full factorial model with life event variable and time; Model 2 = Model 1 adjusted for age, education level, gender, chronic diseases, and benzodiazepine use; Model 3 = Model 2 with additional adjustment for depressive symptoms.

*$p < .05$; **$p < .01$; ***$p < .001$.

memory task when they experienced more life events, whereas the persons with normal cognitive function did not show such an accumulated effect (see Figure 1). We found also an interaction effect between ApoE ε4 and the number of life events on decline on the coding task. ApoE ε4 carriers showed more decline on the coding task when they experienced life events, but this association was not significant in stratified analyses.

Differential Influence of Life Events

The differential association between life events and cognitive decline was examined in subsequent multivariate models (see Table 2). In the first model, the transformed MMSE scores were associated with the death of a (grand) child, the death of a close relative, illness of the partner, and relocation. In the adjusted Model 2, the associations with the death of a (grand)child, the illness of the partner, and relocation remained significant. Additional adjustment for depressive symptoms did hardly change the strength of these associations. Significant interactions with time were found for the death of a (grand)child and illness of the partner; both interactions stayed significant after adjustment for confounders and depression. As the MMSE scores were transformed and therefore difficult to interpret, we looked into the original MMSE scores to clarify these outcomes. These results show that persons who lost a (grand)child had lower MMSE scores at baseline (0.8 points) and declined more (mean decline 1.78) compared with persons who did not lose a (grand)child (mean decline 0.51). In contrast, persons who were confronted with illness of their partner had also somewhat lower scores at baseline (0.13) but showed less decline on the MMSE scores (mean decline 0.04) than the persons who had no ill partner (mean decline 0.46). With regard to relocation, compared with persons who were not relocated, those who were relocated had lower MMSE scores at baseline (26.8 vs. 27.4) and follow-up (25.9 vs. 26.9) but showed no faster decline.

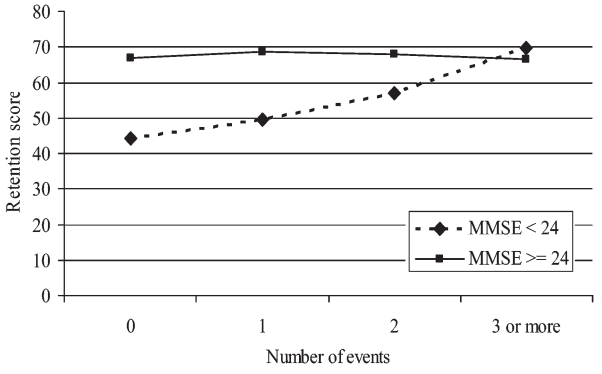

Figure 1. The adjusted means of the retention scores at T2 in relation to the number of events in persons with poor and good cognitive functioning. MMSE = Mini-Mental State Examination.

Regarding information processing speed, we found negative associations with death of a (grand)child), death of a close relative, and relocation, with lower mean scores for the persons who experienced these events. Faster decline in information processing speed was only found in persons who reported having a serious conflict with others (mean decline 1.88; persons who had no conflict: mean decline 0.91). This association remained significant after adjustment for confounders and depressive symptoms.

Learning new information was negatively associated with death of a (grand)child, death of a close relative, and relocation, and positively with illness of a relative. In the adjusted models, only the negative associations with relocation remained significant, with lower mean scores (mean difference between groups 1.42) for persons who were relocated. Also, the positive association with illness of

a relative remained significant, meaning that persons who reported the illness of a relative had higher mean learning scores (mean difference between groups 0.19). In addition, significant associations between the negative events and the rate of decline were found for having a serious conflict with others and relocation. Persons who had a conflict improved more on the learning scores (mean increase 1.74) than persons who reported no conflict (mean increase 0.56). Persons who had relocated declined on the learning scores (mean decline 0.36), whereas persons who had not moved to another house had higher scores (mean increase 1.00). Additional adjustment for depression did not change the strength of these associations.

Memory retention scores were only associated with relocation also in the adjusted models, meaning that persons who had relocated showed lower mean retention scores (56.92%) than those who were not relocated (62.09%). There were no associations between the life events and the rate of decline on the retention.

Differential Influence of Individual Life Events Across Subgroups

The prevalence of the life event in low-MMSE groups had to be large enough ($n \geq 20$) to justify analyses across subgroups of persons who are at risk for dementia. This was possible for death of a close relative, illness of a close relative, and relocation. In examining whether the associations between these life events and cognitive decline were different for persons with normal cognitive function (MMSE scores ≥24) and poor cognitive function (MMSE scores <24), we found no significant interactions in the fully adjusted models.

Finally, we investigated whether the associations between specific life events and cognitive decline were different for ApoE ε4 carrier and noncarriers. The number of persons in the subsamples (combination of life events and ApoE ε4 carrier) was large enough ($n > 20$) to do so for the following life events: the death or divorce from the partner, the death of a close relative, serious illness of the partner, illness of a close relative, having a serious conflict with others, and relocation. We found significant three-way interaction terms in the fully adjusted analyses for (a) all life events and coding; (b) for the death or divorce from the partner, the death of a close relative, and having a serious conflict with others and the MMSE; and (c) for serious illness of the partner and learning. In subsequent stratified analyses in the ApoE ε4 carriers and in noncarriers, just one of the associations between life events and cognition reached significance; persons who had a serious conflict with others showed more decline on the coding task (mean decline 3.0; b_{adj} = 1.550; 95% CI: 0.085–3.023; p = .038) than persons who did not report having a conflict (mean decline 1.3; b_{adj} = 0. 590; 95% CI: −0.357 to 3.023; p = .228). Although the other associations between the life events and decline on the coding task were not significant in stratified adjusted analyses, there is a tendency that the decline in cognitive function in ApoE ε4 carriers seem to be stronger than in noncarriers, which explains the significant interaction terms.

Discussion

Cognitive decline is a common condition in older persons and is a major risk factor for dementia. The rate of cognitive decline varies highly between individuals, and is determined by an interplay between genetic and environmental factors. In the present study, we examined whether negative life events were associated with decline in general cognitive performance, speed of information processing, learning, or retention. In our sample of 1,356 older persons, as many as 3 of 4 experienced at least one negative life event in the previous 3 years. About half of the participants experienced more than one life event. The most frequently reported events included serious illness and death of close relatives (45.1% and 29.4%, respectively), followed by illness of the partner and relocation (both 13.6%).

We did not find a cumulative negative effect of life events on decline in any of the cognitive domains in the full sample. When we examined the individual life events, we found a differential effect of the type of event on cognitive decline —meaning that some life events were associated with less decline or even improvement in cognitive function, whereas others were associated with cognitive decline. Experiencing the death of a partner and being a victim of a crime were not associated with any measure of cognitive decline. Compared with persons without these events, persons who reported illness of a partner showed less decline in general cognitive performance, whereas illness of a relative or having a serious conflict with others showed less decline in learning new information. Persons who had relocated or had lost a (grand) child showed more decline in general cognitive performance and learning compared with those who did not report such events. These findings are in line with the study by Rosnick and colleagues (2007) who also did not report an association between the accumulated events and also found differential effects for the individual life events. These differential effects may be due to the amount of stress these events generate. Illnesses and conflicts are often ongoing stressful situations causing mild levels of chronic stress for a longer period of time. Our data suggest that this might have an arousing function that stimulates cognitive performance. This is in line with the suggestion made by De Kloet and colleagues (1999) that the effect of cortisol on cognitive performance depends on the levels of circulating cortisol in the brain and that mildly elevated levels of cortisol can enhance cognitive function, whereas high levels may result in cognitive impairment. In a previous study from our group, we have found such an arousing effect also for exposure to disaster and for moderate levels of anxiety symptoms, whereas severe anxiety symptoms had an adverse effect on

cognitive performance (Bierman, Comijs, Van Leeuwen, Jonker, & Beekman, 2005, Deeg et al., 2005). Thus, the death of a child or grandchild may cause very high levels of stress, leading to a higher rate of cognitive decline.

We found no support for the assumption that the associations between life events and cognitive decline were explained by depressive symptoms. This is in line with some former research (Aartsen et al., 2005; Xavier et al., 2002) but is in contrast with the findings of Ward and colleagues (2007), who found that the association between bereavement and cognitive functioning was mediated by depressive symptoms. This difference may the due to differences in design; Ward and colleagues used a cross-sectional design and had a very small sample size ($N = 50$), which makes it difficult to adjust the analyses for all relevant confounders. In addition, our results seem not in line with the findings of van Gelder and colleagues (2006), who found that men who lost their partners, were unmarried, or started to live alone showed a twofold increased risk for cognitive decline, measured with the MMSE. However, their focus was not alone on the effect of life events of cognitive decline and their sample consisted only of men, which makes comparison limited.

It must be noted that the direction of the association between relocation and cognitive decline may also be the other way around, for persons who had relocated had already somewhat lower scores on the memory tasks at baseline. Also, 23% of the persons who had relocated were moved into a residential or nursing home (21.2% and 2.1%, respectively). So, it is most likely that the relocation is the consequence of cognitive decline.

In the whole sample, the negative life events seemed especially to be associated with memory function and general cognitive performance (MMSE), whereas speed of information processing was only associated with a life event in ApoE ε4 carriers. An association with memory was expected because the stress hormone cortisol binds to receptors in brain regions known to be involved in learning and memory (Lupien et al., 2007; McEwen, 2007; Van Praag et al., 2005). The MMSE includes several memory items and is therefore probably also associated with negative life events. Speed of information processing, however, is generally considered one of the most sensitive measures for early Alzheimer's. So, our finding that speed of information processing was only associated with a life event in ApoE ε4 carriers seems in line with our hypothesis that the association between negative life events on cognitive decline would be stronger in persons who are at risk for Alzheimer's disease. We found many significant interaction terms between life events, time, and ApoE ε4. Inspection of the data suggest that in ApoE ε4 carriers, decline in memory and general cognitive performance as a consequence of a negative life event is stronger than in noncarriers. However, only having a serious conflict reached significance with faster rate of decline in speed of information processing in ApoE ε4 carriers. Nevertheless, these findings support the assumption that this gene plays a role in the association between stress and cognitive function (Peavy et al., 2007), but further research in larger samples is needed to further clarify this issue. In contrast with these findings, we found that persons with poor cognitive function showed less cognitive decline or even improvement in cognitive function when experiencing more life events compared with persons with normal cognitive function. This is not in line with Peavy and colleagues (2009), who found an adverse effect of psychosocial stress on cognitive decline in persons who already had MCI and not in cognitively intact persons. This contradiction may be caused by the selection of the groups. We used the MMSE to identify persons with poor cognitive function, whereas Peavy and colleagues (2009) identified persons with MCI according to the Petersen criteria (Petersen et al. 1999) and probably included persons who were already in an early phase of Alzheimer's disease.

Strengths and Limitations

Some methodological aspects of our study need to be addressed. We have performed a series of separate analyses on the various life events and several cognitive domains, which raise the possibility of increasing chance findings (Type I error), which raises the possibility of increasing chance findings (Type I error). By choosing a p value of .05 in 1 in 20 statistical tests, the test may show an association while in fact there is none. Using the Bonferroni method, the p value of each individual test is adjusted downward to ensure that the overall risk for a number of tests remains .05. However, there is a serious drawback. If the chance of incorrectly producing an association, making a Type I error, on an individual test is reduced, the chance of making a Type II error is increased, meaning that no association is declared, while in fact there is an association. Thus, by reducing for individual tests the chance on Type I errors, the chance on Type II errors is increased. In that case, the Bonferroni correction is too conservative (Perneger, 1998). Therefore, we did not perform Bonferroni adjustments but show the levels of significance as well as the 95% CIs.

An important strength of our study is that we used a large representative cohort of older persons with data on a wide range of variables and longitudinal data on cognitive performance in several cognitive domains. This gave us the opportunity to investigate cognitive decline and to adjust analyses for potential confounders and to look into the role of cognitive status and ApoE ε4. However, there are also some limitations that need to be addressed. First, despite the large sample, some life events were experienced by only few participants, thus limiting the power of our analyses. Second, both attrition due to mortality and exclusion based on incomplete data were related to cognitive function, age, psychological and physical health, and some of the life events. Thus, the frailest older people ended up being

excluded from the analyses, while those persons may be most vulnerable for the adverse effects of life events on cognitive decline. Third, in our study we included general cognitive performance, information processing speed, and memory function because these are cognitive domains that decline in older age. However, executive function is also a cognitive domain that declines when people grow old. Unfortunately, in LASA we have no information about this cognitive domain. In addition, the data on memory function could suffer from practice effects: several participants had better scores during the second measurement, even though parallel version of the memory test was used. Inspection of the data showed, however, that persons with real cognitive problems are likely to show less increase or even decrease in memory scores than person with normal cognitive functioning. This indicates that—even though some practice effects may exist—less improvement on this task may be considered as a negative outcome. Fourth, we had no information about the exact date of occurrence and the duration of the events. Life events were assessed by asking whether they had occurred in the period of 3 years between the two measurements. Some of the events may have happened 2 years prior to the second measurement and others just a few weeks. This has probably led to an underestimation of the association between life events and cognitive decline. We also had no information about the levels of stress related to the events, so we do not know whether the reported events were also experienced as being stressful or traumatic. Finally, in the present study we only examined negative life events, whereas it might be expected that positive life events also cause increased levels of stress and probably influence cognitive performance. Future research is necessary to focus on the effects of positive life events on cognitive performance.

In conclusion, we found a differential association between negative life events and cognitive decline. None of these associations were mediated by depressive symptoms. The death of a child or grandchild, which may be considered a highly stressful event, was associated with a higher rate of cognitive decline, whereas more chronic stressors, such as the illness of a partner or relative, or serious conflicts, were associated with better cognitive function. The associations between life events and cognitive function were stronger in ApoE ε4 carriers compared with noncarriers, suggesting that this gene plays a role in the association between stress and cognitive function. More research is needed to further clarify these findings and should examine the effects of life events and levels of stress and cortisol on cognitive decline in more detail. It is also important to investigate whether cognitive decline as a consequence of an event is reversible after stress levels due to the event are back to normal.

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