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ORIGINAL ARTICLE

The influence of negative life events on hippocampal and amygdala volumes in old age: a life-course perspective

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Background. Psychosocial stress has been related to changes in the nervous system, with both adaptive and maladaptive consequences. The aim of this study was to examine the relationship of negative events experienced throughout the entire lifespan and hippocampal and amygdala volumes in older adults.

Method. In 466 non-demented old adults (age range 60–96 years, 58% female), hippocampal and amygdala volumes were segmented using Freesurfer. Negative life events and the age at which these events occurred were assessed by means of a structured questionnaire. Using generalized linear models, hippocampal and amygdala volumes were estimated with life events as independent variables. The statistical analyses were adjusted for age, gender, intracranial volume, lifestyle factors, cardiovascular risk factors, depressive symptoms, and cognitive functioning.

Results. Total number of negative life events and of late-life events, but not of early-life, early-adulthood, or middle-adulthood events, was related to larger amygdala volume. There were interactions of early-life events with age and gender. Participants who reported two or more early-life events had significantly smaller amygdala and hippocampal volumes with increasing age. Furthermore, smaller hippocampal volume was found in men who reported two or more early-life events, but not in women.

Conclusions. These results suggest that the effect of negative life events on the brain depends on the time when the events occurred, with the strongest effects observed during the critical time periods of early and late life.

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Key words: Ageing, amygdala, hippocampus, MRI, psychosocial stress.

Introduction

Inter-individual differences in brain structure and function are partly due to environmental factors (Davidson & McEwen, 2012). Psychosocial stress is one such factor that may lead to neural changes, and these alterations can have both adaptive and maladaptive consequences (McEwen & Gianaros, 2011). Although most people show resilience to psychosocial stress (Gillespie *et al.* 2009), the experience of stress may result in traumatic memories and development of neuropsychiatric disorders (Kessler *et al.* 1997; Wang *et al.* 2012). Furthermore, psychosocial stress can lead to long-term morphological and functional changes in the brain (Bremner, 2006; Tottenham *et al.* 2010), which may underlie cognitive and behavioural symptoms observed in mood and anxiety disorders.

Two limbic brain regions that are thought to be particularly vulnerable to psychosocial stress are the hippocampus (McEwen, 2007) and the amygdala (Roozendaal *et al.* 2009). Experimental animal studies have shown opposing effects of chronic stress on these two structures: after the experience of a stressor, the hippocampus shows impaired neurogenesis and atrophy or remodelling of the apical dendrites of pyramidal neurons in the CA3 region (McEwen, 2001), whereas the same stressor causes dendritic growth in basolateral amygdala (Vyas *et al.* 2002). In humans, smaller hippocampal volume is a recurrent finding in

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post-traumatic stress disorder (PTSD; Bremner *et al.* 2008) and in young and middle-aged adults who experienced stressful events during childhood (Teicher *et al.* 2012). With regard to amygdala volume, inconsistent findings have been reported, where both smaller (Woon & Hedges, 2009; Morey *et al.* 2012) and larger (Tottenham *et al.* 2010; Kuo *et al.* 2012) volumes have been observed in patients with PTSD and in relation to psychosocial stress.

There is increasing evidence that the timing of a stressor determines how much impact it will have on the brain (Teicher *et al.* 2006). Experience of stress is thought to have a detrimental effect on the brain especially during stages of life when the brain undergoes major changes, i.e. development in early life and deterioration in late life (Wolkowitz *et al.* 2010). Moreover, the effect of childhood stress can influence the brain well into adulthood, although only a few studies have investigated such long-term associations (van Harmelen *et al.* 2010).

Finally, stress may have different neural effects in men and women. As psychiatric disorders are more common in women than in men, it has been proposed that women are more vulnerable to the negative effects of stress (Troisi, 2001). Contrary to this assertion, however, some studies have found that men show greater structural brain effects after the experience of psychosocial stress than women (De Bellis, 2001), whereas others have failed to find such gender differences (Woon & Hedges, 2011).

The current study aims to explore (*a*) the effect of stressful life events experienced from childhood to late life on hippocampal and amygdala volumes in a large cohort of non-demented older adults, (*b*) whether the experience of stressful life events has different effects on the brain in men and women and (*c*) whether the experience of stressful life events exacerbates age-related volume differences of the hippocampus and amygdala.

Method

Study sample

The study population consisted of a sample of 555 persons who were recruited to participate in a Magnetic Resonance Imaging (MRI) study, from the larger Swedish National Study of Ageing and Care in Kungsholmen (SNAC-K), a longitudinal, multidisciplinary study on ageing and health initiated in 2001 that included 3363 participants aged ⩾60 years at baseline (Lagergren *et al.* 2004). In short, the SNAC-K samples were stratified by age and year of assessment. Eleven age cohorts were chosen with different retest intervals: 6 years for the younger cohorts (age 60–72 years), and 3 years for the older cohorts (age ⩾78 years) due to more rapid changes and higher attrition in older ages. During the baseline examination, 555 individuals were randomly selected from all non-institutionalized and non-disabled participants to undergo a MRI examination. Individuals with severe cerebral diseases that affect brain integrity were excluded (e.g. stroke, $n = 21$). Participants with a clinical diagnosis of depression or an anxiety disorder and/or who used antidepressant medication were excluded from the analyses ($N = 45$). Full brain and skull coverage was required for the MRI datasets and detailed quality control was carried out on all MR images, according to established criteria (Simmons *et al.* 2011). After exclusion of bad-quality MR images ($n = 25$), complete data were available for 466 non-demented subjects.

MRI acquisition

MRI scanning was undertaken on a 1.5 T scanner (Philips Intera, The Netherlands) on which 3D FFE (fast-field echo) T1, axial SE (spin echo) proton density/T2, axial FLAIR (fluid-attenuated inversion recovery) and axial DTI (diffusion tensor imaging) were acquired. In this study, the 3D FFE T1 images (TR = 15 ms, TE = 7 ms, flip angle = 15°, number of axial slices = 128, thickness = 1.5 mm, in-plane resolution = 0.94 × 0.94 mm, no gap, field of view = 240 × 240, matrix = 196 × 256) were used for assessment of hippocampal and amygdala volumes.

Image processing

The T1-weighted images were segmented into grey matter, white matter, and cerebrospinal fluid (CSF) in native space using the unified segmentation approach (Ashburner, 2007), as implemented in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Segmentation accuracy was carefully verified and intracranial volume (ICV) was computed by adding grey matter, white matter, and CSF volumes, which included all structures inside the inner table of the skull (total brain tissue, ventricles and extraventricular CSF, brain stem, and cerebellum).

Automatic segmentation of amygdala and hippocampal volumes

Automatic subcortical volumetric segmentation was performed using the Freesurfer image analysis suite (v. 5.0.1, Martinos Center for Biomedical Imaging, Harvard-MIT, Boston, USA; http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures have been described previously (Fischl *et al.* 2002). Briefly, this fully automated process includes motion correction, removal of non-brain tissue, automated Talairach transformation, segmentation of

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subcortical white-matter and deep grey-matter volumetric structures (including hippocampus, amygdala, caudate, putamen, and ventricles), intensity normalization, and cortical reconstruction.

This segmentation procedure assigns a neuroanatomical label to every voxel in the MR image volume. The method is based on probabilistic information estimated from a manually labelled training set. Markov Random Field Theory is applied, where the probability of a label at a given voxel is computed not just in terms of the greyscale intensities and prior probabilities at that voxel, but also as a function of the labels in the neighbourhood around the voxel in question. This feature is important for correct separation of hippocampus and amygdala, which have similar greyscale values.

Psychosocial stress measures

Psychosocial stress was represented by negative life events and measured using a structured questionnaire consisting of 18 pre-defined events (Miller & Rahe, 1997). For each event, participants indicated whether it had happened and, if so, the age at which it happened (Table 1). Some events could have occurred more than once over the life course; each occurrence was counted as a single event. The reported negative life events were summed to create a total life-events score.

Age of events

To examine the effect of age at which events occurred, we computed the following variables: early-life events (events that occurred at or before 18 years); early-adulthood events (events that occurred between 18 and 40 years); middle-adulthood events (events that occurred between 40 and 65 years) and late-life events (events that occurred at or after 65 years).

Covariates

Data on demographics (age, gender, education) were collected through interviews according to standardized protocols by trained nurses. Educational level was measured by the maximum years of formal schooling and recoded into eight levels, from not finishing primary school (1) to having a PhD degree (8). In our sample the mean level of education was 5, which corresponds to having a community college degree. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Arterial blood pressure was measured twice by trained nurses with a sphygmomanometer and the mean of the two measurements was used. Smoking and alcohol use were assessed using self-reports. Other vascular and psychiatric disorders at baseline were identified through the inpatient register system, including depression, anxiety disorders, PTSD, diabetes, heart disease, and stroke (International statistical Classification of Diseases and related health problems – 10th revision; ICD-10 codes). Cognitive screening was performed by a physician using the Mini-Mental State Examination (MMSE; Folstein *et al.* 1975). Depressive symptoms were assessed using the Montgomery–Åsberg scale (Montgomery & Asberg, 1979).

Data analysis

Volumes for left and right hippocampus ($r = 0.84$, $p < 0.001$) and left and right amygdala ($r = 0.77$, $p < 0.001$) were highly related, and aggregated into total volumes for both regions. Hippocampal and amygdala volumes were positively related ($r = 0.70$, $p < 0.001$), the association did not differ across hemispheres All analyses were conducted in separate models for hippocampal and amygdala volumes.

Before summing all events in stress variables, we ensured that there were no effects of specific single life events, by examining the relationship between each category of life events (e.g. widowhood, severe illness, etc.) and hippocampal and amygdala volumes, in linear regression models, adjusted for age, gender and ICV.

To investigate the effects of the computed stress variables on hippocampal and amygdala volumes we conducted the following analysis:

First, we conducted a linear regression with total number of events reported as determinant of brain volumes. Second, we investigated the relationship between age of negative life events occurrence and brain volumes by creating generalized linear models with reported stress in each age period (early-life, early-adulthood, middle-adulthood, and late-life events) as independent variables.

To test for the interactive effect of stressful life events with age and gender on the brain, in a third step, interaction terms of the stress variables with age and with gender were added to the models. In case of significant interactions, analyses were repeated in separate groups (e.g. men *v.* women or events *v.* no events).

All analyses were adjusted for age, gender, educational level, ICV, BMI, alcohol use, current smoking, diabetes mellitus, systolic and diastolic blood pressure, depressive symptoms, and MMSE score.

To ensure that the effects of life events were selective for amygdala and hippocampal volumes we repeated all analyses with caudate nucleus volume and total brain volume as outcome.

Results

Data were available for 466 subjects (age range 60–96 years), of whom 58% were female. Compared to

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subjects who were excluded from the study ($n = 89$), the study sample was younger, had lower BMI and larger hippocampal volumes ($p < 0.05$), but no differences were found on any other variable (Table 2). The mean number of total reported stressful life events was five, with a maximum of 14 (Table 1). None of the single-event categories was associated with hippocampal or amygdala volumes (all $p > 0.05$).

Association between stressful life events and amygdala volume

In the total sample, total number of life events was positively associated with amygdala volume ($F_{2,450} = 3.259$, $p = 0.017$) (Fig. 1*a*). When the separate stress measures per lifespan period were examined, we found that larger amygdala volume was related to late-life events ($F_{2,443} = 3.946$, $p = 0.020$), but not to early- or middle-adulthood events ($F < 1.5$, $p > 0.2$ (Fig. 1*b*). There was no interaction between the life-events measures and gender for amygdala volume ($p > 0.1$).

Association between stressful life events and hippocampal volume

None of the age of event measures was associated with hippocampal volume ($F < 1.5$, $p > 0.2$). There was trend-level association between number of early-life events and hippocampal volume ($F_{2,443} = 2.04$, $p = 0.10$), where Fisher's least significant difference *post-hoc* testing showed that subjects who reported two or more early-life events had smaller hippocampal volume than subjects who reported no early-life events [mean hippocampal volume difference: −198.3 µl; 95% confidence interval (CI) −2.8 to −393.7, $p = 0.05$].

Association between stressful life events and 'control' brain areas

Total brain volume and caudate nucleus volume were not associated with any of the life-event variables ($F < 1.5$, $p > 0.2$).

Interaction between gender and stress variables

We found an interaction between gender and early-life events for hippocampal volume ($B = 27.6$, 95% CI 17.7–37.6, $p < 0.001$). To trace the source of this interaction, we repeated the analyses separately for men and women. We found smaller hippocampal volume in men who reported ⩾2 early-life events compared to men who reported none or one event ($F_{2,180} = 6.688$, $p = 0.002$). This effect was not seen for early-adulthood, middle-adulthood or late-life events, and there were no effects for women (all $F < 1.5$, $p > 0.2$) (Fig. 2).

Interaction between age and stress variables

We found an interaction between age and early-life events for amygdala volume ($B = -4.14$, 95% CI −8.08 to −0.19, $p = 0.04$) and a borderline significant interaction for hippocampal volume ($B = -8.43$, 95% CI −17.44 to 0.56, $p = 0.06$). To trace the source of this interaction, we plotted the estimated amygdala and hippocampal volumes against age with separate lines for persons who reported no early-life events, one early-life event and ⩾2 early-life events (Fig. 3). This finding was specific for early-life events, as we found no interaction with adulthood, mid-life or late-life events (all p for interactions > 0.05).

Compared to persons who reported none or only one early-life event, persons with ⩾2 early-life events showed smaller amygdala volume (B for difference = −18.03, 95% CI −34.11 to −1.95, $p = 0.03$) and smaller hippocampal volume (B for difference = −36.42, 95% CI −71.72 to −1.117, $p = 0.04$) with increasing age.

Because of the observed interaction between gender and early-life stress, we examined whether there was a significant three-way interaction between early-life stress, gender and age, but none of these interaction terms reached significance ($p > 0.05$).

Discussion

In this large sample of adults aged ⩾60 years, self-reported negative life events, particularly late-life events, were associated with larger amygdala volume in both men and women, whereas smaller hippocampal volumes were associated only with early-life events and in men. Furthermore, we found that ⩾2 early-life events exacerbated the age-related volume decline in both the hippocampus and the amygdala.

The experience of stress triggers the activation of the hypothalamic–pituitary–adrenal axis and the end product of this activation is the secretion of glucocorticoids and catecholamines (adrenaline and noradrenaline). Adrenergic receptors are abundant in the amygdala, a region critical to fear processing and memory for emotional information (Roozendaal *et al.* 2009). From an evolutionary perspective, increases in amygdala volume in response to stress may lead to enhanced detection of threatening stimuli and increased survival probability. Experimental studies with animals show that the experience of acute stress strengthens the structural basis of synaptic connectivity, manifested by newly formed spines in the basolateral portion of the amygdala (Vyas *et al.* 2002). If the same acute stress is repeated for several days, it eventually leads to more extensive spinogenesis. This strengthening of the structural basis of synaptic connectivity could even lead to persistent dendritic elongation (Zhang & Rosenkranz,

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Table 1. *Frequencies of reported negative life events per age category*

Type of event	Early-life	Early-adulthood	Middle-adulthood	Late-life	Total events
Death of mother	19	84	260	37	400
Death of father	46	142	237	7	432
Parents' divorce	41	14	2	0	57
Physical abuse	10	16	5	0	31
Poverty while growing up	60	2	0	0	62
Pregnancy loss	1	58	11	0	70
Handicapped child	0	8	0	0	8
Death of child	0	10	9	10	29
Divorce	0	97	101	4	202
Death of partner	0	5	48	42	95
Death of best friend	7	25	66	57	155
Severe illness, self	18	34	61	30	143
Severe illness, friend/family	17	59	160	52	288
Forced move to special care facility	0	1	3	10	14
Loss of job	2	7	49	0	58
Large financial losses	1	7	29	9	46
Legal problems	0	3	10	1	14
Retirement	0	0	162	166	328
Total events	222	572	1213	425	2432

2012). However, in other nuclei of the amygdala, such as the medial and central portions, these stress-related effects have not been observed (Bennur *et al.* 2007). These opposing effects within the amygdala might explain why both larger and smaller amygdala volumes have been reported in human studies on stress and stress-related disorders (Woon & Hedges, 2009; Tottenham *et al.* 2010; Kuo *et al.* 2012; Morey *et al.* 2012). Although the current amygdala findings are consistent with some animal work, higher spatial resolution in MRI (e.g. 7 T) is needed to unravel the differential effects of stress on the subnuclei of the amygdala.

The hippocampus is important in regulating stress responses and a major feedback site for glucocorticoids. This structure is also highly sensitive to neurotoxic effects of increased glucocorticoid levels (Knoops *et al.* 2010). Loss of hippocampal neurons due to stress exposure has been reported in animal studies (Sapolsky, 2003) and in neuropsychiatric disorders, such as PTSD (Bremner *et al.* 2008) and major depressive disorder (Macqueen & Frodl, 2011). Neural development early in life undergoes many phases and it has been suggested that brain structures differ in the age at which they are fully developed (Andersen & Teicher, 2008). For instance, trauma experienced between the ages of 3 and 5 has been associated with much more decreased hippocampal integrity than similar events experienced at other ages (Andersen *et al.* 2008). Exposure to stressful events during the developmental period may increase secretion of glucocorticoids, which could interfere with the transcriptional mechanisms that control the expression of brain-derived neurotrophic factor and thereby increase vulnerability to attrition, resulting in volume loss (Nestler *et al.* 2002). Accordingly, there are more studies reporting a detrimental effect of early-life stress (Frodl *et al.* 2010; van Harmelen *et al.* 2010; Teicher *et al.* 2012) than of late-life stress (Yehuda *et al.* 2007) on hippocampal volume. Unfortunately, we were not able to examine the effect of different age categories early in life due to the relatively low number of reported early-life events. To get a better understanding of the exact sensitive periods early in life, future studies should examine in more detail the age at which stressful events occur early in life.

In addition, our findings suggest that the effect of stress experienced early in life on hippocampal volume persists into old age in men, but not in women. Many previous studies on the effects of psychosocial stress on the brain reported no gender differences (Frodl *et al.* 2010; van Harmelen *et al.* 2010; Teicher *et al.* 2012). However, these studies were all conducted in younger adult populations and used other methods to investigate brain volumes (e.g. voxel-based morphometry) making it difficult to compare findings to those obtained in the present study. Other studies examining gender differences in the effects of stress on brain structures found results similar to those observed in the current study. A review of the rodent literature indicates that, in female rats, stress failed to produce dendritic

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Table 2. *Subjects' characteristics*

	Men	Women	Total sample
N	190	276	466
Age, years, mean (S.D.)	70 (10)	71 (9)	71 (9)
Educational level, years, mean (S.D.)	5.6 (1.8)	5.0 (1.7)	5.2 (1.8)
Body mass index, mean (S.D.)	26 (3)	26 (4)	26 (4)
Systolic blood pressure, mean (S.D.)	144 (18)	142 (19)	143 (20)
Diastolic blood pressure, mean (S.D.)	83 (11)	82 (10)	83 (11)
Diabetes, %	11	5	8
Current smoker, %	14	15	15
Alcohol use %			
Never	6	8	7
1–3 times a week	66	73	70
⩾4 times a week	28	18	23
Intracranial volume, ml, mean (S.D.)	1616 (129)	1407 (108)	1492 (157)
Hippocampal volume, µl, mean (S.D.)			
Right	3856 (534)	3614 (446)	3713 (498)
Left	3940 (557)	3652 (467)	3769 (525)
Amygdala volume, µl, mean (S.D.)			
Right	1504 (221)	1301 (173)	1383 (218)
Left	1490 (223)	1248 (184)	1347 (233)
Mean number of negative life events (range)	5.1 (0–13)	5.8 (0–14)	5.5 (0–14)
One or more early-life events, %	33	33	33
One or more early adulthood events, %	65	76	71
One or more adulthood events, %	82	83	82
One or more late-life events, %	59	57	58
One or more recent events, %	75	78	77
One or more events 10–25 years ago, %	81	75	77
One or more events 25–50 years ago, %	67	73	71
One or more events >50 years ago, %	36	38	38
Median depressive symptoms (10–90%)[a]	1 (0–6)	1 (0–7)	1 (0–6)
Median MMSE score (10–90%)[a]	29 (27–30)	29 (28–30)	29 (28–30)

[a] Medians with 10–90% range in Mini-Mental State Examination (MMSE) score and MADRS depressive symptoms were reported because of non-normally distributed data.

retraction in hippocampus, whereas in male rats clear atrophic effects of chronic stress were observed (McLaughlin *et al.* 2009). Relatedly, in human studies smaller cerebral volumes and corpus callosum regions in PTSD boys as well as larger lateral ventricular volume in maltreated boys with PTSD than in maltreated girls with PTSD have been observed (De Bellis & Keshavan, 2003). Furthermore, men have greater stress-hormone responses to experimentally induced stress than women (Kirschbaum *et al.* 1999) and high levels of cortisol predicted poorer memory performance in men, but not in women (Wolf *et al.* 2001). Taken together, these findings suggest that men may show a greater response to stress than women.

The observed gender differences may also reflect a protective effect of oestrogen on stress-related influences on hippocampal integrity (Takuma *et al.* 2007). Expression of growth hormones is greater in the hippocampus in female than in male rats and growth hormones are sensitive to the presence of oestrogen (Tanapat *et al.* 1999). Although the women in the current study were post-menopausal, the observed gender differences in the influence of stress on hippocampal volume were seen for events occurring in early life, a period in which there are marked gender differences in oestrogen levels (McEwen *et al.* 2012).

Besides the gender difference, we also found an interaction between early-life events and age at which the brain volumes were assessed. Both amygdala and hippocampal volumes decrease with age, but in the group who reported ⩾2 early-life events we observed a much steeper decline of volume as a product of age. Even though our study has a cross-sectional design, the results suggest that the effect of early-life stress becomes more apparent with increasing age. Possibly, persons with a history of early-life stress are at greater risk for pathological ageing effects on the brain (e.g. neurodegenerative disorders).

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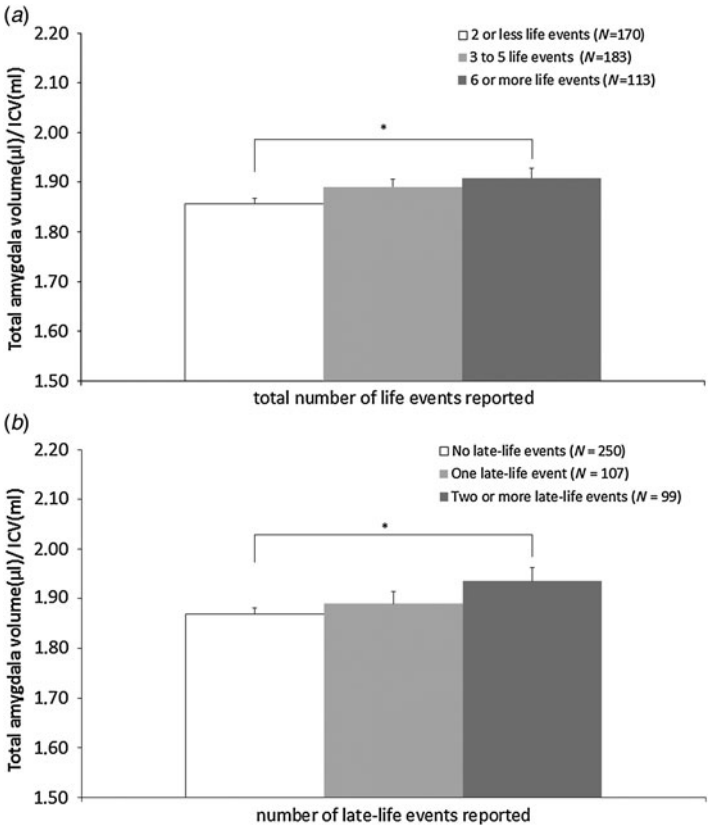

Fig. 1. Adjusted amygdala volume in relation to total number of negative life events over the lifespan (*a*) and number of late-life events (*b*). Error bars represent standard errors (*$p < 0.05$). Adjusted for age, gender, educational level, intracranial volume (ICV), body mass index, alcohol use, current smoking, diabetes mellitus, systolic and diastolic blood pressure, depressive symptoms, and Mini-Mental State Examination score.

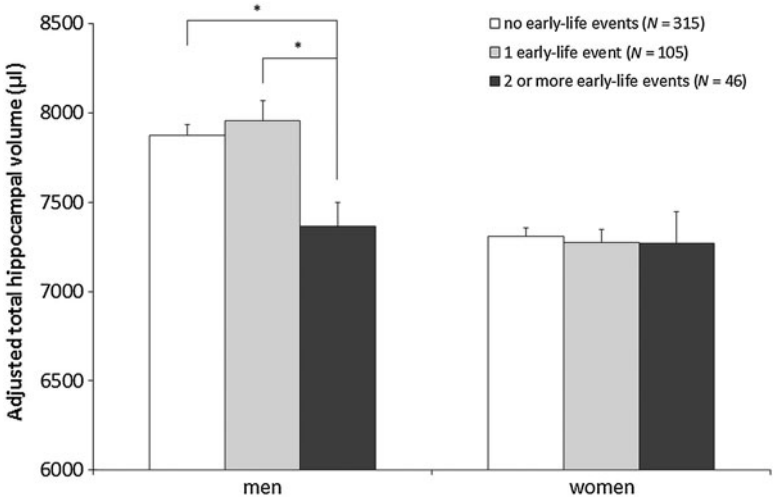

Fig. 2. Mean ICV-adjusted hippocampal volume in relation to number of early-life events by gender. Error bars represent standard errors (*$p < 0.05$). Adjusted for age, educational level, intracranial volume, body mass index, alcohol use, current smoking, diabetes mellitus, systolic and diastolic blood pressure, depressive symptoms, and Mini-Mental State Examination score.

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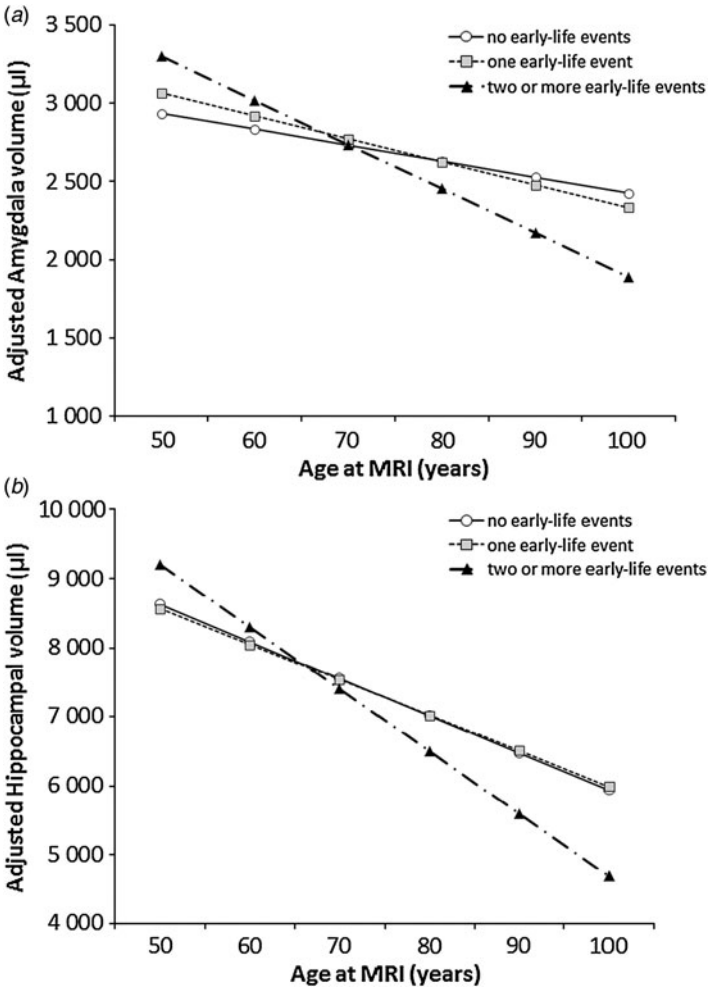

Fig. 3. Estimated volume differences with age in (*a*) amygdala and (*b*) hippocampus for early-life stress groups. Adjusted for gender, educational level, intracranial volume, body mass index, alcohol use, current smoking, diabetes mellitus, systolic and diastolic blood pressure, depressive symptoms, and Mini-Mental State Examination score.

All our findings taken together, there was a clear effect of timing of stressor on the brain, with stronger effects observed for events reported in early and late life. Because of morphological changes occurring in the brain during these stages, it is plausible that environmental factors have a greater influence on the brain than during more stable stages of life, especially on stress-responsive regions such as the hippocampus and amygdala (Lupien *et al.* 2009). Moreover, the fact that the hippocampus and amygdala were differentially affected by early- and late-life stress suggests that the hippocampus is more vulnerable to early detrimental effects, whereas the amygdala is more reactive to stressful events occurring during later stages of life.

Even though the current findings fit well with past research (McEwen, 2001; Bremner, 2006; Yehuda *et al.* 2007; Tottenham *et al.* 2010), the possibility of reversed causality cannot be excluded. For instance, individuals with smaller hippocampal volume and larger amygdala volume might report more negative life events as a result of impaired emotion regulation (Gerritsen *et al.* 2012). Longitudinal studies are needed to substantiate these intriguing timing differences.

A major strength of the current study is the large number of participants, in which hippocampal volume, amygdala volume, and stressful events throughout the entire lifespan were measured. Limitations of the study include assessment of life events by means of self-report, which may have resulted in underreporting of the actual stress experienced. Selection bias may be present, because the MRI sample was slightly younger, more educated, and cognitively advantaged compared to the remaining participants of the SNAC-K study. Further, we excluded people with dementia and those with large brain infarcts. Moreover, survival bias may be operating due to the cross-sectional nature of the study. That said, both the

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possible underreporting of stress-related events and selection biases may, if anything, have resulted in an underestimation of the actual effects.

In summary, our findings support the view that, depending on the timing of a negative life-event occurrence, stress affects amygdala and hippocampal volumes differently and the detrimental effects of early-life stress is not only maintained into old age but also exacerbates age-related volume decline.

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Declaration of Interest

None.

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