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Negative life stress and longitudinal hippocampal volume changes in older adults with and without depression

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Abstract

Major depressive disorder is associated with smaller hippocampal volumes but the mechanisms underlying this relationship are unclear. To examine the effect of environmental influences, we examined the relationship between self-reported stressors and two-year change in hippocampal volume. Seventy elderly nondepressed subjects and eighty-nine elderly depressed subjects were followed for two years. The number of negative stressful life events (nSLE), perceived stress levels, and cranial MRI were obtained at baseline and at the two-year assessment. For secondary analyses, subjects provided blood for *5-HTTLPR* polymorphism genotyping. After controlling for covariates including presence or absence of depression, greater numbers of baseline nSLEs were significantly associated with greater baseline hippocampal volumes bilaterally. Greater numbers of baseline nSLEs were also associated with reduction in hippocampal volume over two years in the right but not the left hemisphere. Neither perceived stress levels nor changes in stress measures were significantly associated with hippocampal volume measures. However, in secondary analyses, we found that increases in perceived stress over time was associated with volume reduction of the left hippocampus, but only in *5-HTTLPR* L/L homozygotes. Our findings suggest different short- and long-term effects of negative life stressors on hippocampal volumes in older adults. These effects appear independent on the presence or absence of depression. Furthermore, these effects may be moderated by genetic polymorphisms in key neurotransmitter systems. These novel findings have important implications for understanding environmental influences on brain aging.

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Keywords

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1. Introduction

Most studies show a relationship between major depressive disorder (MDD) and smaller hippocampal volumes (Sheline et al., 1996; Videbech & Ravnkilde, 2004), but there is considerable debate about the temporal direction and mediating mechanisms of this relationship (Sheline, 2011). The neurotoxicity hypothesis posits that chronic hyperactivity of the stress system in MDD leads to decreased neurogenesis, augmented neuroinflammation, dendritic retraction, and accelerated apoptosis (Lucassen et al., 2006; Sorrells et al., 2009). Supporting this hypothesis, a longer duration of depression is associated with smaller hippocampal volumes in depressed subjects (Bell-McGinty et al., 2002; Sheline et al., 2003; Videbech & Ravnkilde, 2004). However, there is evidence to support the opposite causal direction (Sheline, 2011) as smaller hippocampal volumes can be present at the onset of MDD and may predispose to the development of the disorder (Chen et al., 2010; Cole et al., 2011).

One parameter not examined in much of this literature is the effect of psychosocial stressors. Stressful life events (SLE) are a major risk factor for the development of MDD (Kendler et al., 1999) and are associated with lower odds of remission (Zannas et al., 2012). Moreover, greater numbers of SLE and higher levels of chronic perceived stress predict hippocampal volume reductions in nondepressed adults (Gianaros et al., 2007; Papagni et al., 2011). The hippocampus itself exerts an inhibitory effect on the stress system (Jacobson & Sapolsky, 1991) and smaller hippocampal volumes correlate with heightened response to stressors (Lyons et al., 2001). Therefore, hippocampal atrophy may confer vulnerability to SLEs and contribute to a predisposition to the development of MDD. This may lead to further hippocampal shrinkage and greater vulnerability to subsequent SLE, establishing a bidirectional relationship between hippocampal atrophy and MDD.

The relationship between the hippocampus and environmental stressors may be moderated by genetic factors. The serotonin-transporter-linked polymorphic region (*5-HTTLPR*) has been shown to moderate the relationship between SLE and depression (Caspi et al., 2003), and is associated with smaller hippocampal volumes in adult (Eker et al., 2011) and elderly depressed subjects (Taylor et al., 2005). However, few studies have examined the effects of gene-by-stress interactions on the hippocampus. In young subjects, the *5-HTTLPR* polymorphism was shown to interact with childhood adversity to predict hippocampal volumes (Everaerd et al., 2012). Similarly, a previous study examining elderly subjects found that *5- HTTLPR* genotype did not interact with SLE but interacted with waking cortisol levels to predict hippocampal volumes (O'Hara et al., 2007).

The relationship between stress, hippocampal volume changes, and depression may be particularly important in elderly populations. Studies in elderly depressed subjects have found an association between smaller hippocampal volumes and subsequent cognitive decline (Steffens et al., 2011). Additionally, hippocampal volume changes and cognitive decline may be reversible in some elderly patients with antidepressant treatment (Hou et al., 2012). To our knowledge, no studies have examined the longitudinal effects of life stress on hippocampal volumes in late-life depression (LLD).

To better elucidate the relationship between stress and the hippocampus, we examined negative SLE (nSLE) and perceived stress severity as predictors of both baseline hippocampal volumes and longitudinal two-year change in hippocampal volumes. Given clinical associations between hippocampal volume loss and cognitive decline, we examined these relationships in an elderly cohort consisting of individuals with LLD and nondepressed comparison subjects. Based on existing evidence, we a priori hypothesized that greater self-reported stress would be associated with smaller baseline hippocampus and with greater two-year reduction in hippocampal volumes. Finally, in secondary analyses we examined the moderating effects of *5-HTTLPR* genotype on these relationships by testing for interactive effects of genotype and stress on hippocampal volume measures.

2. Methods

2.1. Participants

Participants enrolled in this longitudinal study through several mechanisms at Duke University Medical Center. Starting in 1994, participants began enrolling in the National Institute of Mental Health (NIMH)-sponsored Mental Health Clinical Research Center for the study of Depression in Later Life and its longitudinal sister study. In 2001, these programs transitioned to the newly established Conte Center for the Neuroscience of Depression in the Elderly and the companion Neurocognitive Outcomes of Depression in the Elderly (NCODE) longitudinal study.

Eligible depressed subjects were aged 60 years or older and met diagnostic criteria for MDD. Diagnosis was based on the NIMH Diagnostic Interview Schedule (DIS) (Robins et al. 1981) and confirmed by clinical interview. Exclusion criteria included: 1) other major psychiatric illnesses; 2) substance abuse or dependence; 3) primary neurologic illnesses, including dementia; and 4) contraindications for magnetic resonance imaging (MRI).

Nondepressed comparison subjects were recruited through the Center for Aging Subject Registry at Duke University. Eligible comparison subjects were age 60 years or older, had a nonfocal neurologic examination, no self-report of neurologic disease or depressive disorder, and no evidence of depression based on DIS (Robins et al. 1981).

The study was approved by the Duke University Medical Center Institutional Review Board. All study participants provided written informed consent prior to enrollment. We have previously published results from this cohort examining the relationship between two-year change in hippocampal volume and subsequent cognitive decline (Steffens et al., 2011). The current study has three less subjects than the prior study as those three subjects did not provide data on life stress.

2.2. Clinical evaluation and treatment

Clinical assessments were performed every three months and when clinically indicated. At baseline, a study geriatric psychiatrist interviewed each depressed subject and completed standardized assessments, including the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979). All participants completed the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) at baseline, and individuals who scored below 25 were excluded from the study.

Depressed subjects were treated according to the Duke Somatic Treatment Algorithm for Geriatric Depression (Steffens et al., 2002a). This algorithm engages a stepwise approach that allows broad use of commercially available antidepressant modalities. Although the majority of depressed subjects were prescribed sertraline on study entry, the antidepressant regimen differed across the sample based on depression severity, past treatments, medication

tolerability, and response. Switching antidepressant medications and augmentation strategies were allowed as necessary for subjects who did not respond to initial treatment. Although not routinely recommended to all subjects, psychotherapy and electroconvulsive therapy were also treatment options.

Life stress was measured at baseline and at the 2-year assessment with a self-report questionnaire (Hays et al., 1997; Zannas et al., 2012). This 20-item questionnaire assesses a variety of SLE that occurred over the last year, including physical illness or injury, separation from a loved one, marriage or divorce, new members in the family or loss of family members, relocation, work-related difficulties, legal problems, improvement or deterioration of financial situation, new employment or retirement, and others. Each item has a sub-specifier which asks whether subjects experienced the respective SLE as positive, negative, or neutral. SLE with “negative” as a sub-specifier were summed to form the nSLE variable. Additionally, there is an item for evaluation of perceived stress severity (coded as “average stress”), which asks participants to rate, on a scale of 1 to 10, the subjective severity of life stress over the last 6 months. Based on our prior work showing that nSLE and perceived stress are the stress measures that best predict depression outcome (Zannas et al., 2012), we a priori elected to examine only these two measures for this study.

2.3. MRI acquisition and analysis

After screening all subjects for contraindications, cranial MRI was performed using a 1.5 Tesla, whole-body MRI system (Signa, GE Medical Systems, Milwaukee, WI). Alignment was confirmed by a rapid sagittal localizer scan and then two dual-echo, fast spin-echo acquisitions were obtained: the first in the axial plane for morphometry of cerebral structures and the second in a coronal oblique plane for morphometry of the hippocampus. Our MRI acquisition protocol has been previously described (Payne et al., 2002; Steffens et al., 2000).

Image processing was performed by the Duke Neuropsychiatric Imaging Research Laboratory (NIRL). Tissue segmentation and measurement of total cerebral volume was performed using previously described methods (Payne et al., 2002). Total cerebral volume included total white and gray matter and ventricle volumes in both hemispheres.

The hippocampus was quantified using the NIRL-developed GRID program and was delineated according to a previously described semi-automated method (Steffens et al., 2000). Beginning with the most posterior coronal slice and moving anteriorly, analysts measured the hippocampus on each side where the pulvinar nucleus of the thalamus obscured the crura fornicis. Both the fimbria and the thin strip of gray matter along the medial border of the hippocampus were cut at their narrowest points. Tracing continued around the hippocampal body to the starting point. The amygdala-hippocampal transition zone appeared as a diffuse area of gray matter between the anterior portion of the hippocampus and the posterior portion of the amygdala, and was also transected at its narrowest point. The anterior border of the hippocampus was defined as the slice on which the inferolateral ventricle appeared horizontally without any body of gray matter visible below it.

All analysts received extensive training. Reliability was established by repeated measurements separated by at least a week on multiple MRIs before raters were approved to process study data. Intraclass correlation coefficients were: left hippocampus=0.8; right hippocampus=0.7; and total cerebral volume=0.997.

2.4. Genotyping

Genotyping for the *5-HTTLPR* polymorphism was performed using a previously described method and its modifications (Steffens et al., 2002b). Genomic DNA was extracted from

fresh or frozen samples of peripheral blood by standard procedure (Puregene D-50K DNA Isolation Kit, Gentra, Minneapolis, Minn). Subsequently, polymerase chain reaction amplification was used to generate either a 484- or a 528-bp fragment, corresponding to the short and long alleles of the polymorphism. Subjects were either homozygous for the long allele (L/L genotype), heterozygous (L/S genotype), or homozygous for the short allele (S/S genotype). Genotyping efficiency above 95% was required before data submission.

2.5. Statistical analysis

All statistical tests were conducted using SAS version 9.2 (Cary, NC, USA). Missing values were handled by excluding subjects from the respective analyses. Demographic and clinical variables were compared between the two diagnostic groups at baseline, by using χ^2 tests for categorical variables, pooled two-sample *t* tests for continuous variables with equal variances, and Satterthwaite *t* tests for variables with unequal variances.

Primary analyses included three sets of models examining relationships between: A) baseline stress measures and baseline hippocampus volumes; B) baseline stress measures and change in hippocampus volumes; and C) change in stress measures and change in hippocampus volumes. Each set included four models, examining left and right hippocampus volumes separately, and nSLE and perceived stress severity separately. To determine statistical significance for these models, we adjusted the initial alpha of 0.05 to account for the twelve multiple comparisons, resulting in a Bonferroni-adjusted alpha of 0.0042.

All multivariable linear regression models examined hippocampal volumes or changes in volumes as the dependent variables. Stress measures were included as independent variables, while also controlling for age, sex, diagnostic cohort (depressed / nondepressed), and baseline cerebral volume. Models examining change in hippocampal volume further included baseline hippocampal volume as a covariate, while models examining change in stress measures included the baseline stress measure.

Several exploratory analyses were also conducted. For the three sets of models described above, we tested for interactive effects between stress measures and diagnostic cohort. We also incorporated *5-HTTLPR* genotype into these as an additional independent variable, while also examining an interaction term between each stress measure and genotype. For these potential interactions, in order to minimize the number of statistical comparisons we planned to perform subgroup analyses only if the interaction term was statistically significant in the entire sample. To avoid the effects of population stratification, we limited analyses involving genetic data to the cohort of Caucasian subjects. Given the small frequency of *5-HTTLPR* S allele homozygotes, we dichotomized this cohort in L allele homozygous (L/L genotype) and S allele carriers (L/S or S/S genotypes). Although exploratory, we also further adjusted the alpha to account for these additional twelve comparisons, resulting in an adjusted alpha = 0.0021.

3. Results

3.1. Sample characteristics

Study analyses included 159 subjects (89 depressed and 70 nondepressed) with longitudinal clinical and neuroimaging data. As compared with the non-depressed group, the depressed group had a significantly lower proportion of women, a lower average level of education, and significantly higher nSLE and perceived stress scores (Table 1).

3.2. Stress measures as predictors of hippocampal volumes

Initial models examined baseline hippocampal volumes as the dependent variables, while examining baseline nSLE and perceived stress as independent variables. Baseline nSLE but not perceived stress severity were significantly positively associated with both baseline left and right hippocampal volume (Table 2), so greater numbers of nSLE over the preceding twelve months predicted larger bilateral hippocampal volumes. These associations remained significant after adjustment for multiple comparisons. In subsequent models, there were no statistically significant interactions between stress measures and diagnostic cohort (data not shown).

We next examined the effects of baseline stress measures on two-year change in hippocampal volume. In these models (Table 2), there was a statistically significant relationship only between nSLE and change in right hippocampal volume, wherein greater baseline nSLE were associated with greater right hippocampal volume reduction. However, this association did not retain statistical significance after Bonferroni correction. Again, there were no statistically significant interactions between stress measures and diagnostic cohort (data not shown).

Finally, we examined the relationship between change in stress measures and change in hippocampal volume over two years. In these analyses, we found no evidence to support a direct association between change in stress and change in hippocampal volume (Table 2), nor did we find statistically significant interactive effects between change in stress and diagnostic cohort. Since none of the interaction terms between stress measures and diagnostic cohort reached statistically significance, we did not perform subgroup analyses.

3.3. Interactions between stress measures and 5-HTTLPR genotype as predictors of hippocampal volumes

In subsequent secondary analyses, we examined if *5-HTTLPR* genotype moderated the effects of stress on hippocampal volume observed above. The same demographic differences observed in the larger cohort (Table 1) were also present in this smaller cohort of 125 Caucasian subjects (comparisons not shown). Genotype frequency did not significantly differ from Hardy-Weinberg equilibrium in either diagnostic cohort.

For these analyses, we added *5-HTTLPR* genotype and a genotype-stress interaction term as independent variables to the three sets of models described above. None of these interactions reached statistical significance (data not shown), except for the model examining the effect of genotype and two-year change in perceived stress severity predicting two-year change in left hippocampal volume. In this model, the interaction between genotype and change in perceived stress was statistically significant ($N = 121$, $F_{1,111} = 10.20$, $p = 0.0018$) even under the Bonferroni-adjusted alpha.

To characterize this interaction further, we stratified the sample based on genotype and ran models separately for each genotype group, examining the effects of change in perceived stress severity on change in left hippocampal volume. In these models, change in perceived stress was negatively correlated with change in left hippocampal volume only in L/L homozygotes ($F_{1,38} = 10.21$, $p = 0.0032$). In this genotype group, an increase in perceived stress severity over time was associated with a decrease in left hippocampal volume. The interaction between genotype and change in perceived stress was not statistically significant in the S allele carrier group ($F_{1,81} = 1.82$, $p = 0.1811$).

4. Discussion

To our knowledge, this study is the first to examine the longitudinal effects of life stress on hippocampal volumes in a cohort of elderly adults with and without LLD. After correcting for multiple comparisons, we found that at baseline, greater numbers of nSLE are associated with larger bilateral hippocampal volumes. More baseline nSLE also predicted two-year decrease in the right hippocampal volume, although this was not statistically significant after correction for multiple comparisons. Additionally, in *5-HTTLPR* L/L homozygotes, changes in perceived stress severity were negatively associated with two-year change in left hippocampal volume. Taken together, our findings suggest that negative life stressors may have different short- and long-term effects on hippocampus morphology. As we did not find a relationship between hippocampal volume change and change in nSLE over the study interval, this further suggests that effects of stress on hippocampal structure is not immediate but delayed. However, changes in perceived stress are associated with concomitant changes hippocampal volume, but this varies by *5-HTTLPR* genotype.

Contrary to our a priori hypothesis, we found a positive relationship between baseline numbers of SLE and baseline hippocampal volumes, which remained significant after correction for multiple comparisons. Our initial hypothesis was based on past observations that stress-driven activation of the HPA axis and proinflammatory pathways may affect hippocampal structure (Lucassen et al., 2006; Sorrells et al., 2009). Indeed, many animal studies show decreased neurogenesis and accelerated apoptosis in the hippocampus with both acute and chronic stress (Lucassen et al., 2006). However, these effects vary by stressor intensity, duration, and frequency; for example, some have reported that repeated intermittent restraint stress increases neurotrophin-3 mRNA expression and granule cell survival in the hippocampus (Smith et al., 1995; Snyder et al., 2009). It is also possible that these relationships vary for different ages and developmental stages. For instance, while smaller hippocampus is widely associated with higher cortisol levels, in young healthy men larger hippocampal volume has been associated with stronger cortisol reactivity in response to stress and awakening (Pruessner et al., 2007). Finally, the positive relationship observed in our study may be explained by the temporal effects of the reported stressors. Given the hippocampus's role to inhibit the stress response (Jacobson et al., 1991), it may be possible that our findings represent a compensatory transient hypertrophy of the hippocampus in response to environmental nSLE. In other words, for intermediate stressors that are not yet chronic, this structural finding may reflect a functional effort to inhibit the stress response.

While this positive relationship was observed for baseline hippocampal volumes, baseline numbers of SLE also predicted two-year decrease in the right hippocampal volume that was nonsignificant under the adjusted alpha. At the same time, we found no association between change in stress measures and change in hippocampal volumes over the study period. These findings were consistent with our a priori hypothesis but should be viewed cautiously as they did not survive corrections for multiple comparisons. However, this may represent differences in short- versus long-term effects of nSLE. In other words, there appears to be a delay between life changes – either increased stress, or the relief of stress – and observable changes in hippocampal volume. Temporal factors are crucial when examining the effects of stress on brain structures. Stress has been reported to have short-lived positive effects on hippocampal granule cell survival (Snyder et al., 2009) and delayed negative effects on hippocampal volumes (Isgor et al., 2004). The exact mechanisms of these temporal effects on the hippocampus are currently unknown and factors other than neuronal or glial changes, including reversible fluid shifts and changes in extracellular space and vasculature have been speculated (Czéh & Lucassen, 2007).

Although changes in stress measures did not predict hippocampal volume changes in *5-HTTLPR* S allele carriers, two-year changes in perceived stress severity negatively correlated with left hippocampal volume changes in L/L homozygotes. In other words, only subjects homozygous for the more active (L) allele of the serotonin transporter exhibited significant increases or decreases in hippocampal volume with respective decreases or increases in perceived stress. Serotonin has been shown in animal studies to enhance hippocampal neurogenesis and to activate the stress system (Gould, 1999; Heisler et al., 2007). Similarly, presence of the *5-HTTLPR* S allele appears to moderate the relationship between stress and depression (Karg et al., 2011). Therefore, one may speculate that impaired function of the serotonin transporter may moderate the responsivity of the stress system and the effects of stress on hippocampal neurogenesis while superior or intact serotonin transporter function may be necessary for the deleterious effects of stress on neural circuits to reverse once the stress has improved or resolved. Clearly more work is needed to elucidate the mechanisms via which genetic variation in the serotonin system may moderate stress-induced changes in the hippocampus.

The findings of this study should be viewed in the context of its strengths and limitations. Among studies examining the effects of life stress on human hippocampal volumes (Cohen et al., 2006; Everaerd et al., 2012; Ganzel et al., 2008; Gianaros et al., 2007; O'Hara et al., 2007; Papagni et al., 2011), to our knowledge this is the largest prospective study and the only one that includes elderly depressed subjects. In this large cohort, we observed several significant associations after controlling for factors known to affect hippocampal morphology; however, we did not control for all possible factors. Importantly, there is the potential confounder of antidepressant treatment. All depressed participants started a naturalistic pharmacologic antidepressant algorithm on study entry, but we do not have data on antidepressant use prior to enrollment. Also, given substantial variability in treatments, durations, and doses received over the study period, it was not feasible to assess for medication effects over the study period. Finally, even with treatment there is substantial variability in depression severity across study subjects over a two-year period. Thus it is not clear how either treatment or response to treatment may have influenced our results. Notably, the proportion of females was significantly larger in the nondepressed group; however, sex was included as a covariate in all regression models and it is unlikely that this difference influenced our findings. Furthermore, stress was assessed using self-report questionnaires, a measure that is subject to recall bias. We did not measure biological markers of stress responsivity, such as waking cortisol levels which have been shown to predict hippocampal volumes in elderly subjects (O'Hara et al., 2007). Finally, we limited our analyses to the relationship between stress and the hippocampus. Previous studies in humans have linked different stress measures with differences in a range of brain structures, including amygdala, anterior cingulate cortex, parahippocampal gyrus, prefrontal cortex, insula, and caudate nucleus (Cohen et al., 2006; Ganzel et al., 2008; Gianaros et al., 2007; Papagni et al., 2011).

Despite these limitations, our findings suggest that stressful events have significant effects on the aging hippocampus, effects that may vary with time and are independent of depression diagnosis. While further research is required to characterize these processes, our findings have important implications both for future research and clinical practice. Future studies should explore the structural and functional effects of stress on networks in the aging brain. Such studies should perform longitudinal measurements of brain regions and life stress, using both stress questionnaires and biological markers of stress responsivity. Given the association of hippocampal volume reduction with worse antidepressant outcomes and subsequent cognitive decline (Hsieh et al., 2002; Steffens et al., 2011), elevated stress measures may be a useful marker for the identification of elderly depressed patients who are at increased risk of cognitive decline and poor clinical outcomes. Finally, given the potential

reversibility of hippocampal volume changes and associated cognitive decline (Hou et al., 2012), stress measures may be useful for targeting early psychosocial interventions and intensive treatment modalities to susceptible elderly individuals.

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Table 1

Characteristics and demographic data of participants by diagnostic cohort

Demographic variables (N = 159)	Depressed (N = 89)	Non-depressed (N =70)	Test Statistic	P value
Age, years	69.91 (6.9)	69.14 (6.0)	$t_{157} = 0.73$	0.4637
Sex, female	55 (61.8)	56 (80.0)	$\chi^2 = 6.16$, 1 df	**0.0131**
Race, caucasian	75 (84.3)	62 (88.6)	$\chi^2 = 0.61$, 1 df	0.4355
Education, years	14.29 (2.8)	15.50 (1.6)	$t_{146} = 3.40$	**0.0009**
Baseline MADRS score	26.48 (6.7)	-	-	-
MMSE score	28.55 (1.8)	28.83 (1.2)	$t_{150} = 1.15$	0.2502
nSLE	1.61 (1.5)	0.31 (0.5)	$t_{114} = 7.61$	<**0.0001**
Perceived stress severity	6.55 (1.9)	2.68 (1.5)	$t_{155} = 14.03$	<**0.0001**
Left hippocampal volume, ml	2.98 (0.4)	2.96 (0.4)	$t_{157} = 0.31$	0.7599
Right hippocampal volume, ml	3.09 (0.4)	3.09 (0.4)	$t_{157} = 0.02$	0.9877
Total cerebral volume, ml	1158.50 (134.1)	1135.60 (111.6)	$t_{157} = -1.15$	0.2528
***5-HTTLPR* genotype** L/L L/S or S/S	N = 72 24 (33.3) 48 (66.7)	N = 53 15 (28.3) 38 (71.7)	$\chi^2 = 0.36$, 1df	0.5485

Continuous measures are presented as mean (SD). Categorical measures are presented as N (%). All analyses examined 159 subjects, except for analyses examining MMSE (N=154) and perceived stress (N=157) where there were missing data. *5-HTTLPR* analyses included 125 Caucasian subjects. All analyses of continuous variables used pooled, two-tailed t-tests, except for analyses of education, nSLE, and perceived stress severity, where the Satterthwaite t-test was used for unequal variances.

Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; MMSE, Mini-Mental State Exam; N, number of observations; NA, not available; nSLE, the number of negative stressful life events over the last year; Perceived stress severity, the subjective severity of life stress over the last 6 months, as rated by the subject on a scale of 1 to 10

Table 2

Main effects of stress measures on hippocampal volumes

Baseline stress measures	**Baseline left hippocampal volume**			**Baseline Right hippocampal volume**		
	N	**F statistic value**	**P value**	**N**	**F statistic value**	**P value**
nSLE	159	12.44	**0.0006** *	159	9.96	**0.0019** *
Perceived stress severity	154	2.15	0.1443	154	0.22	0.6394
Baseline stress measures	**2-year change in left hippocampal volume**			**2-year change in right hippocampal volume**		
nSLE	159	1.88	0.1727	159	4.12	**0.0441**
Perceived stress severity	154	1.69	0.1951	154	0.03	0.8592
2-year change in stress	**2-year change in left hippocampal volume**			**2-year change in right hippocampal volume**		
Change in nSLE	159	0.02	0.8998	159	0.24	0.6256
Change in perceived stress severity	154	0.03	0.8598	154	0.00	0.9485

*Statistically significant after adjusting for multiple comparisons with the Bonferroni method, resulting in an adjusted alpha = 0.0042.

All subjects had longitudinal data on nSLE. 5 subjects had no longitudinal data on perceived stress severity and were excluded from the respective analyses. Therefore, as shown above, analyses involving nSLE had N of 159, whereas analyses involving perceived stress had N of 154. All models controlled for age, sex, diagnostic cohort (depressed or nondepressed), and baseline cerebral volume. Models examining two-year change in hippocampal volume also controlled for baseline hippocampal volume. Models examining change in stress measures also controlled for the respective baseline stress measure.

Abbreviations: N, number of subjects included in each regression model; nSLE, the number of negative stressful life events over the last year; Perceived stress severity, the subjective severity of life stress over the last 6 months, as rated by the subject on a scale of 1 to 10