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Prospective reports of chronic life stress predict decreased grey matter volume in the hippocampus

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Abstract

Chronic stress in non-human animals decreases the volume of the hippocampus, a brain region that supports learning and memory and that regulates neuroendocrine activity. In humans with stress-related psychiatric syndromes characterized by impaired learning and memory and dysregulated neuroendocrine activity, surrogate and retrospective indicators of chronic stress are also associated with decreased hippocampal volume. However, it is unknown whether chronic stress is associated with decreased hippocampal volume in those without a clinical syndrome. We tested whether reports of life stress obtained prospectively over an approximate 20-year period predicted later hippocampal grey matter volume in 48 healthy postmenopausal women. Women completed the Perceived Stress Scale repeatedly from 1985 to 2004; in 2005 and 2006, their hippocampal grey matter volume was quantified by voxel-based morphometry. Higher Perceived Stress Scale scores from 1985 to 2004—an indicator of more chronic life stress—predicted decreased grey matter volume in the right orbitofrontal cortex and right hippocampus. These relationships persisted after accounting for age, total grey matter volume, time since menopause, use of hormone therapy, subclinical depressive symptoms, and other potentially confounding behavioral and age-related cerebrovascular risk factors. The relationship between chronic life stress and regional grey matter volume—particularly in the hippocampus and orbitofrontal cortex—appears to span a continuum that extends to otherwise healthy individuals. Consistent with animal and human clinical evidence, we speculate that chronic-stress-related variations in brain morphology are reciprocally and functionally related to adaptive and maladaptive changes in cognition, neuroendocrine activity, and psychiatric vulnerability.

Keywords

chronic life stress; hippocampus; orbitofrontal cortex; voxel-based morphometry

Stressful experiences can be both constructive and destructive to the body and brain. In the short term, acute stressful experiences mobilize adaptive changes in physiology and behavior that help to meet the demands of environmental challenges and protect against threats to internal homeostasis (Sapolsky et al., 2000; Selye, 1956). Over the long term, however, chronic

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stressful experiences can lead to maladaptive changes in physiology and behavior that undermine health, cognition, mood, and longevity (McEwen, 1998). Chronic stressful experiences can also damage the structural integrity of multiple bodily and brain systems, which may play a role in the pathophysiology of several stress-related psychiatric syndromes (Yehuda and McEwen, 2004). One brain system that is particularly sensitive to the effects of chronic stressful experiences is the hippocampus (Fuchs and Flugge, 1998; Lee et al., 2002; McEwen, 1999; Miller and O'Callaghan, 2005; Sapolsky, 1999).

In nonhuman animals, chronic psychosocial stress leads to cellular changes in subregions of the hippocampus that decrease its overall volume. In the rat, tree shrew, and monkey, chronic stress decreases the length and branching complexity of apical dendrites in the CA3 subfield (Magariños and McEwen, 1995; Magariños et al., 1996; Sapolsky et al., 1990; Uno et al., 1994). Chronic stress also inhibits the proliferation and survival of new granule neurons in the dentate gyrus (Czeh et al., 2001; Fuchs et al., 2004). These cellular changes are mediated in part by the cumulative exposure of hippocampal sub-regions to a chronic-stress related increase in glucocorticoids and excitatory amino acids and a corresponding decrease in neurotrophic factors (Fuchs and Flugge, 1998; Lee et al., 2002; McEwen, 1999; Miller and O'Callaghan, 2005; Sapolsky, 1999). By these and other mechanisms, chronic stress may impair the cognitive, neuroendocrine, and emotional functions that the hippocampus supports: learning and remembering declarative and spatial information, regulating the hypothalamic-pituitary-adrenal axis, and processing the contextual aspects of emotional events (Conrad, 2006; McEwen and Magariños, 1997; Sapolsky, 2003).

With noted exceptions, chronic stressful experiences are also associated with a decreased volume of the hippocampus and with impaired hippocampal-dependent functions in humans with stress-related psychiatric syndromes, including major depressive disorder and post-traumatic stress disorder (Campbell et al., 2004a; Geuze et al., 2005; Kitayama et al., 2005; Smith, 2005). Specific findings from clinical MRI studies agree with animal models of chronic stress and hippocampal atrophy. First, among individuals with major depression, a longer lifetime experience of untreated and recurrent depressive episodes predicts a decreased volume of the hippocampus (MacQueen et al., 2003; Sheline et al., 2003; Sheline et al., 1999; Sheline et al., 1996). Second, among individuals with post-traumatic stress disorder, longer-term exposure to traumatic events beginning earlier in life also predicts a decreased volume of the hippocampus (Bremner et al., 2003; Gurvits et al., 1996; Kitayama et al., 2005; Vythilingam et al., 2002). As in animal models of chronic stress, the underlying cellular changes that decrease hippocampal volume in individuals with stress-related psychiatric syndromes could partly mediate impaired hippocampal-dependent learning and memory and dysregulated neuroendocrine activity (Bremner, 2001; Manji et al., 2000; Vermetten et al., 2003; Vythilingam et al., 2004).

As yet, however, it is unknown whether chronic stress is associated with a decreased hippocampal volume among those without a psychiatric or clinical syndrome. By available evidence, it is possible that decreased hippocampal volume in stress-related psychiatric syndromes is associated with more extreme forms of chronic psychological stress and trauma that are not experienced by most individuals. Alternatively, it is possible that the association between chronic stress and decreased hippocampal volume lies along a continuum that extends to individuals without a clinical syndrome.

To test the latter possibility, we examined the relationship between chronic perceived stress, as prospectively tracked over an approximate 20-year period, and later grey matter volume in the hippocampus. Participants were healthy postmenopausal women without a history of a psychiatric, neurological, or major medical disorder. As part of their participation in a prospective epidemiological study (Matthews et al., 1989), women underwent detailed medical

evaluations and used a standardized scale (Cohen et al., 1983) to provide self-reports of perceived stress every 1 to 3 years from 1985 to 2004. In 2005 and 2006, they underwent high-resolution structural brain imaging. Hippocampal grey matter volume was determined by an automated and rater-independent method: optimized voxel-based morphometry (Ashburner and Friston, 2000; Good et al., 2001). In our analyses, we also accounted for factors that could possibly confound the relationship between chronic perceived stress and regional brain tissue volume: namely, chronological age (Good et al., 2001), use of hormone therapy (Erickson et al., 2005), alcohol consumption (Geuze et al., 2005), smoking status (Seshadri et al., 2004), resting blood pressure (Gianaros et al., 2006), body mass index (Ward et al., 2005), educational attainment (Raz et al., 2005), depressive symptoms (MacQueen et al., 2003; Sheline et al., 2003; Sheline et al., 1999; Sheline et al., 1996), and the severity of age-related ischemic white matter lesions (Wen et al., 2006). In this way, we tested whether a prospective indicator of chronic perceived stress uniquely predicted an indicator of hippocampal grey matter volume.

Method

Participants

Participants were 50 postmenopausal women (M age = 67.98, SD = 1.38) from the Pittsburgh Healthy Women Study (Matthews et al., 1989). In 1983 and 1984, 541 women were recruited by random sampling from driver's license lists provided by the Department of Transportation in Allegheny County, PA, USA. Women were eligible at study entry if they were between 42 and 50 years old; had menstruated in the past 3 months; were not on hormone supplements; were not hypertensive (defined as a diastolic blood pressure > 100 mmHg or on antihypertensive medication); were not postmenopausal; were not taking psychotropic medication; and were not taking medications to regulate blood lipids, insulin, or thyroid metabolism.

In 2005 and 2006, eligible Pittsburgh Healthy Women Study participants were invited to participate in a brain imaging protocol. As determined by standardized interviews and a review of medical records dating to 1983, women were eligible if they did not have any history of (a) a cardiovascular or cerebrovascular disease (including hypertension, coronary artery disease, angina, transient ischemic attacks, blood clotting, a prior myocardial infarction, and congestive heart failure); (b) a stroke or prior cerebrovascular incident involving a loss of consciousness; (c) claustrophobia; (d) Type I or II diabetes; (e) cancer; and (f) a psychiatric or neurological disorder (including dementia or suspected Alzheimer's disease). Women were also ineligible if they were hospitalized or had major surgery in the past 3 years, if they had used any psychotropic medication in the past, or if they had a metallic implant. All women provided informed consent; the University of Pittsburgh Institutional Review Board approved all procedures.

The participant characteristics in Table 1 indicate that this was a relatively healthy sample of postmenopausal women. Most women (n = 40) attended college or completed advanced training after high school; the remaining 10 women completed high school or attained a general education diploma. The majority was right-handed (n = 47). Most never smoked tobacco (19 former and 2 current smokers). Most women (n = 44) classified themselves as Caucasian non-Hispanic, 3 as African-American, and 3 as Asian-Pacific Islander. Approximately half (n = 24) never used hormone therapy after menopause, 16 were former users, and 10 were current users. Among former and current users of hormone therapy, the mean duration of use was 4.81 years (SD = 6.17). At entry into the Healthy Women Study, the average age of the present sample was 47.50 (SD = 1.36), and the average number of years between menopause and brain imaging was 15.45 years (SD = 2.48).

Study procedures

When women were pre-menopausal in 1983–1984, they received a medical evaluation and began reporting their menstrual status monthly. Women were classified as postmenopausal when they ceased menstruating for 12 consecutive months or when they ceased menstruating and used hormone therapy for a total of 12 months. At the time of postmenopausal classification, women underwent another medical evaluation. Women then completed follow-up evaluations every 1 to 3 years. In 2005–2006, the 50 women of the present sample were recruited for a two-part protocol. The first part involved a laboratory visit to verify eligibility, obtain demographic information and a health history, measure resting blood pressure, and record cardiovascular responses to laboratory stressors. The second part was comprised of a structural and functional brain imaging session (functional imaging results concerning blood pressure responses to an acute psychological stressor in this sample are reported in Gianaros et al., in press). The laboratory and imaging sessions were separated by a median of one week. Two women completed the laboratory session, but did not complete the imaging session. The final sample size for statistical analyses of structural brain imaging data was $n = 48$.

Assessment of chronic perceived stress

At each postmenopausal evaluation, women completed the 4-item Perceived Stress Scale (Cohen et al., 1983). This standardized scale assesses the extent to which an individual appraises life situations as unpredictable, uncontrollable, and overloading—core components of the stressful experience. The scale asked women to respond to four items that follow the question stem: “In the last two weeks, how often have you felt that you were…” The items following this stem were (1) unable to control the important things in your life? (2) confident about your ability to handle your personal problems? (3) that things were going your way? (4) that difficulties were piling up so high that you could not overcome them? Women responded to each item using a 5-point scale, anchored by 1 = “never” and 5 = “very often.” Perceived Stress Scale scores were obtained by summing responses to all items, after reverse-scoring items 2 and 3; the maximum possible score was 20.

The means and standard deviations of Perceived Stress Scale scores for each postmenopausal evaluation are shown in Table 2. The internal consistency of the scale’s items was high at each evaluation (range of Chronbach alpha values = 0.80 – 0.85). The variance of the Perceived Stress Scale scores from the four evaluations was homogenous (Levene’s test statistic = 0.04, $P = 0.98$). A repeated measures ANOVA showed no difference between scores across assessments, $F = 0.27$, $P = 0.85$. All Perceived Stress Scale scores from years 1985 to 2004 were thus averaged for each woman to compute an indicator of chronic perceived stress (Cohen et al., 1983).

Assessment of depressive symptoms

Depressive symptoms were assessed at each post-menopausal evaluation and at the brain imaging session to account for their potential relationship with regional grey matter volume. At each post-menopausal evaluation, women completed the Beck Depression Inventory (BDI; Beck, 1978). At the time of the brain imaging protocol, women also completed the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). None of the women in this sample exceeded a CES-D score of 16, which indicates suspected clinical depression. And, the mean CES-D score ($M = 4.35$, $SD = 3.02$) was below this value, $t = 13.11$, $P < 0.001$ by one-sample t-test.

Assessment of confounding variables

We assessed additional demographic and health-related variables that were used as covariates in statistical analyses. These variables included age; educational attainment (number of school

years completed); number of years from menopause to brain imaging; use of hormone therapy (0 = never, 1 = former, 2 = current); body mass index (BMI; weight in kg / height in m^2); smoking status (0 = nonsmoker, 1 = former smoker, and 2 = current smoker); alcoholic beverage consumption (defined as the number of single-serving alcoholic beverages consumed per week). At the laboratory and MRI sessions, we measured three auscultatory blood pressure levels according to the protocol of the Multiple Risk Factor Intervention Trial (Dischinger et al., 1986). After discarding the first blood pressure measurement to allow for adaptation, the average of the remaining two measures combined across the sessions was taken as an estimate of seated resting blood pressure. The remaining covariates were the severity of age-related ischemic white matter lesions (indicated by white matter grade) and total grey matter volume (see below).

Brain imaging protocol

Structural magnetic resonance images were acquired with a 3-Tesla Signa scanner (GE Medical Systems, Milwaukee, WI) and a standard birdcage radiofrequency head coil. Regional grey matter volume was assessed from coronal structural images acquired with a T_1-weighted 3D spoiled gradient recalled (SPGR) acquisition sequence (TE = 5 msec; TR = 25 msec; flip angle = 40º; NEX = 1). SPGR images provided 124 slices (1.5 mm thick; 0 mm spacing between slices; matrix size = 256 x 192 pixels; FOV = 24 x 18 cm). Before analysis, SPGR images were re-sampled to contain 1 mm^3 isotropic voxels, and they were reoriented to the axial plane of the anterior and posterior commissures. White matter hyperintensities were assessed from axial images obtained with a T_2-weighted fast spin-echo inversion recovery (FSEIR) sequence (effective TE = 160 msec; TR = 10004 msec; TI = 2250 msec; NEX = 2). FSEIR images were acquired in the plane of the anterior and posterior commissures (5 mm slice thickness; 1 mm spacing between slices; matrix size = 256 x 192 pixels; FOV = 20 x 20 cm).

Assessment of regional grey matter volume by optimized voxel-based morphometry

Optimized voxel-based morphometry (Ashburner and Friston, 2000; Good et al., 2001) was used to quantify regional and total grey matter volume. All voxel-based morphometry processing steps were implemented in statistical parametric mapping software (SPM2; Wellcome Trust Centre for the Study of Cognitive Neurology) with Matlab scripts co-authored by John Ashburner and Christian Gaser (available from http://dbm.neuro.uni-jena.de/vbm.html).

For optimized voxel-based morphometry, grey matter, white matter, and cerebrospinal fluid were first segmented from each woman's T_1-weighted SPGR image with a mixture model cluster analysis. For tissue segmentation, the mixture model used customized Bayesian prior probability maps (templates) that were created from all SPGR images of the present sample. Segmented grey matter images were then normalized to the standard anatomical space of the International Consortium for Brain Mapping (CBM) 152 template (Montreal Neurological Institute; MNI) with our study-specific grey matter template. For spatial normalization, affine transformations and linear combinations of smooth basis functions were used to minimize the sum of global (and nonlinear) squared differences between individual grey matter images and the grey matter template. Spatial normalization parameters were then re-applied to the original, non-segmented SPGR images (in their native space) to optimize tissue segmentation; this step minimizes the contribution of non-brain voxels and tissue misclassification (partial volume effects) to the final voxel-wise volume estimates (Good et al., 2001). Segmented and spatially normalized images were then multiplied (modulated) by the Jacobian matrix determinants derived from spatial normalization. With this modulation step, the volume change that was applied to each voxel during nonlinear spatial normalization was incorporated into each voxel value. As a result, modulated images provide relative voxel-wise grey matter volume values in milliliters.

Before statistical analyses, modulated grey matter volume images were smoothed with an 8 mm FWHM isotropic Gaussian kernel. Spatial smoothing was done to accommodate between-participant differences in brain morphology and to meet the distribution assumptions of the general linear models that were used to examine voxel-wise grey matter volume in relation to chronic perceived stress (Friston et al., 1996; Friston et al., 1995).

Assessment of ischemic white matter lesions

MRI indicators of white matter hyperintensities in the periventricular and subcortical white matter areas indicate the presence of age-related ischemic lesions and correlate with lower regional grey matter volume in older adults (e.g., Wen et al., 2006). To estimate the severity of white matter hyperintensities, two readers graded films of the T_2-weighted FSEIR images by the protocol of the Cardiovascular Health Study (Longstreth et al., 1996). Both readers were blind to participant characteristics and the study purpose. Using an atlas of predefined visual standards, each reader graded the T_2 images for white matter with a 9-point scale anchored by 0 = minimal and 8 = extensive. As determined by intra-class correlation coefficients (ICCs), the readers showed high inter-rater agreement for periventricular white matter grades (ICC = 0.94) and subcortical white matter grades (ICC = 0.92). White matter grades were thus averaged across the two readers. Also, because rater-averaged periventricular and subcortical white matter grades were highly correlated ($\underline{r} = 0.92$), these two grades were averaged to compute a composite indicator of white matter severity. Compared to population-based norms for older individuals (Longstreth et al., 1996), the present sample had minimal white matter grades (Table 1). Further, none of the participants showed signs of gross brain pathology or a prior stroke, as determined by consensus evaluations between our readers and a neuroradiologist.

Data analysis

To determine whether a history of chronic perceived stress predicted decreased grey matter volume in the hippocampus, we conducted a regression analysis in SPM2 using the framework of the general linear model (Friston et al., 1995). For this analysis, we tested for a negative relationship between the average of all postmenopausal perceived stress scores from 1985–2004 and voxel-wise grey matter volume using a hypothesis-driven region-of-interest approach. This was done using the standard MNI anatomical mask of the hippocampus from the Wake Forest University Pick-Atlas (anatomical boundaries detailed in Maldjian et al., 2003). The family-wise error rate (FWE) was used to correct $\underline{P}$-values for conducting multiple voxel-wise statistical tests within the hippocampus (Nichols and Hayasaka, 2003). In a supplementary whole-brain exploratory analysis, we tested for a negative relationship between chronic perceived stress and grey matter volume using an uncorrected voxel-wise statistical significance level of $\underline{P} \leq 0.001$ and a voxel-extent threshold of 130 voxels (~1/2 the extent of the right hippocampal cluster described in the Results). In both regressions, age and total grey matter volume were treated as covariates.

In subsequent 2-step hierarchical regression analyses, we tested whether chronic perceived stress predicted decreased regional grey matter volume in the hippocampus or in areas identified in the exploratory whole-brain analysis independently of additional confounding factors. For these 2-step regressions, we extracted the sum of the volume values from all voxels that were contiguous with the voxel of peak correlation between chronic perceived stress and regional grey matter volume. Summed grey matter volume values, which were imported into Statistical Package for the Social Sciences 11.0 (SPSS, Chicago, IL for Mac OSX, Apple Computers, Cupertino, CA), were then used as dependent variables in the 2-step regressions. In step 1, we entered age, educational attainment, time since menopause, use of hormone therapy, body mass index, smoking status, alcohol use, resting systolic blood pressure, white matter grade, and total grey matter volume, and subclinical depressive symptoms, as assessed by the average of all postmenopausal BDI scores and the current CES-D score. In step 2, we

entered the average of all postmenopausal Perceived Stress Scale scores (our indicator of chronic stress). The unique percentage of variance in regional grey matter volume explained by chronic perceived stress was evaluated by the change in R^2 (ΔR^2) in step 2. For the post-hoc regressions that were conducted for areas identified in the exploratory (whole-brain) analysis, we considered Step 2 results statistically significant at $P < 0.008$ by Bonferroni-correction for 6 unplanned analyses (to maintain the Type I family-wise error rate at $P = 0.05$).

Results

Region-of-interest analysis for the hippocampus

Higher chronic perceived stress predicted decreased grey matter volume in the right, but not left, hippocampus (Figure 1). This result was revealed by a multiple regression analysis of voxel-wise grey matter volume in the bilateral hippocampus. In this region-of-interest regression analysis, the primary explanatory variable was the average of all historical scores on the Perceived Stress Scale completed after menopause (see Table 2); the additional covariates were total grey matter volume and age. For the right hippocampus, the MNI coordinates for the peak correlation between chronic perceived stress and grey matter volume were x = 35, y = −34, & z = −9, $t = 3.18$, $z = 3.00$, $P_{ROI.FWE\text{-}corrected} = 0.025$; cluster size = 261 voxels. As shown in Fig. 1, chronic perceived stress accounted for ~30% of the variance in right hippocampal grey matter volume, after controlling for age and total grey matter volume, $P < 0.001$.

Unique relationship between chronic perceived stress and hippocampal grey matter volume

Potential confounding variables failed to explain the relationship between chronic perceived stress and right hippocampal grey matter volume. In a 2-step hierarchical regression analysis, chronic perceived stress accounted for 8% of the variance in right hippocampal grey matter volume above-and-beyond all of the following step 1 covariates ($\Delta R^2 = 0.08$, $F_{1, 34} = 6.35$, $P = 0.02$): age, total grey matter volume, time since menopause, use of hormone therapy, smoking status, alcohol consumption, resting systolic blood pressure, body mass index, educational attainment, white matter hyperintensity grade, and historical and current depressive symptoms (see supplementary Table 1 on the NeuroImage website for individual step 1 and 2 regression coefficients). Of note, only total grey matter volume uniquely correlated with right hippocampal grey matter volume in step 1 (semi-partial $r^2 = 0.17$, $P = 0.002$); all other step 1 semi-partial r^2 values < 0.048, Ps > 0.08. However, total grey matter volume did not correlate with chronic perceived stress, $r = -0.05$, $P = 0.75$.

Exploratory analysis

An exploratory whole-brain regression analysis showed that in addition to the right hippocampus, higher chronic perceived stress predicted decreased grey matter volume in Brodmann area 47 of the right orbitofrontal cortex, area 11 of the left orbitofrontal cortex, area 7 of the left postcentral gyrus, area 6 of the right pre-central gyrus, and the right cerebellum after controlling for age and total grey matter volume (see supplementary Figure 1 and supplementary Table 2 the NeuroImage website). In post-hoc 2-step regression analyses with Bonferroni Type I error correction, higher chronic perceived stress predicted decreased grey matter volume only in right orbitofrontal area 47 ($\Delta R^2 = 0.12$, $F_{1, 34} = 11.29$, $P = 0.002$) after step 1 control for all covariates that were used in the hierarchical hippocampal regression analysis detailed above (see supplementary Table 3 on the NeuroImage website). For illustration, Figure 2 shows that a history of chronic perceived stress accounted for ~25% of the variance in the grey matter volume of right orbitofrontal area 47, after controlling for age and total grey matter volume ($P < 0.001$).

Discussion

Chronic perceived stress, which was prospectively tracked in healthy postmenopausal women over an approximate 20-year period, predicted decreased grey matter volume in the right hippocampus. This main finding agrees with those from prior animal studies (Fuchs and Flugge, 1998; Kim and Diamond, 2002; McEwen, 1999; Miller and O'Callaghan, 2005) and human clinical MRI studies (Campbell et al., 2004; Geuze et al., 2005; Kitayama et al., 2005; Smith, 2005) indicating that chronic stress is associated with a decreased volume of the hippocampus. To our knowledge, this is the first report of a relationship between a prospectively measured indicator of chronic life stress and hippocampal grey matter volume among otherwise healthy individuals. Our primary conclusion is that the relationship between chronic life stress and hippocampal grey matter volume appears spans a linear continuum. Taken together with prior animal and human clinical findings, we speculate that chronic-stress-related variations in regional brain morphology likely express both reciprocal and functional relationships with adaptive and maladaptive changes in cognition, neuroendocrine activity, and psychiatric vulnerability over the lifespan.

Among individuals with stress-related psychiatric syndromes, surrogate and retrospective indicators of chronic stress, such as longer illness duration, are associated with decreased hippocampal volume (e.g., Sheline et al., 1999). These clinical findings are taken to suggest that chronic stress may be associated with decreased hippocampal volume by mechanisms that are similar to those delineated in animal models of chronic stress and hippocampal atrophy (Bremner, 2001; Campbell and MacQueen, 2004, 2006; Charney and Manji, 2004; Manji, 2000; McEwen, 2004; Sapolsky, 2000; Sheline, 1996). These mechanisms include a retraction and debranching of apical dendrites in CA3 pyramidal neurons, a decrease in the proliferation of new neurons in the dentate gyrus, a decrease in hippocampal cell body size, and a decrease in expressed dendrite spines (Fuchs et al., 2004; Fuchs and Flugge, 1998; McEwen, 1999; McEwen, 2001; Sapolsky, 2000).

The present findings build on prior clinical MRI findings in several ways. First, chronic stress was assessed directly from aggregated reports of perceived stress that were prospectively tracked over an extended period of life. This prospective assessment minimized potential retrospective memory biases that are inherent to recalling multi-year levels of life stress. Second, perceived stress was assessed using a standardized inventory, permitting comparisons with prior studies. In point, women in the present study did not report extreme levels of perceived stress as compared with prior studies using this inventory (Cohen et al., 1983). As shown in Table 2, their perceived stress scores did not vary significantly over time, and their averaged stress scores ($\underline{M}$ = 8.75) were below the mid-point of the maximum possible score of 20 on this inventory. Thus, the perceived stress reported by women in the present study can be taken to reflect relatively stable and modest levels of life stress, which were consistent with concurrently minimal reports of depressive symptoms.

The present study also demonstrated that chronic perceived stress continued to predict lower right hippocampal grey matter volume after accounting for potentially confounding factors related to age and health. Further, none of the women in the present study had a co-morbid medical condition that could likely have affected reports of perceived stress or regional grey matter volume. We note, however, that because of our selection criteria, the present sample may not represent the general population, particularly older postmenopausal women who may have one or more medical conditions. Further, it is possible that chronic-stress may relate to structural changes in the hippocampus and other areas in an age-dependent fashion. In the tree shrew, for example, chronic psychosocial stress decreases cell proliferation in the dentate gyrus of the hippocampus more strongly in older compared to younger animals (Simon et al., 2005)—although extrapolating such findings to humans should be made cautiously.

Nevertheless, it will be important for future studies to determine whether chronic stress predicts decreased hippocampal grey matter volume in younger individuals.

A secondary finding of the present study was that chronic perceived stress predicted decreased grey matter volume in the right orbitofrontal area of the prefrontal cortex, an area that supports a range of emotional and cognitive processes and that participates in the negative feedback regulation of neuroendocrine activity (McEwen, 2005; Sullivan and Gratton, 2002). It is noteworthy that chronic stress in animal models results in structural changes in orbitofrontal and other prefrontal areas that are comparable to those in the hippocampus (Radley and Morrison, 2005). Recent clinical studies also demonstrate that individuals with the stress-related psychiatric syndrome, major depressive disorder, show a decreased grey matter volume in the orbitofrontal cortex (Campbell and MacQueen, 2006; Cotter et al., 2005; Lai et al., 2000; Rajkowska et al., 1999). Moreover, a postmortem study recently demonstrated that individuals who had major depressive disorder showed a focal reduction in neuronal size and in neuronal and glial cell densities specifically in Brodmann area 47 (Rajkowska et al., 1999). Thus, it is possible that chronic-stress related variations in the regional morphology of the orbitofrontal cortex, in addition to the hippocampus, may be associated with symptom expression or other functional impairments in emotion, cognition, or neuroendocrine activity characteristic of psychiatric syndromes. Although paralleling prior animal and clinical evidence, however, we regard our secondary finding on chronic life stress and decreased grey matter volume in the orbitofrontal cortex as preliminary and in need of replication before firmer speculations on the functional significance of this finding can be made.

At present, it is unclear why chronic perceived stress specifically predicted a right-lateralized decrease in hippocampal and orbitofrontal grey matter volume. Right-lateralized decreases in hippocampal volume are observed in major depressive disorder (O'Brien et al., 2004) and in post-traumatic stress disorder (Bremner et al., 1995), although the mechanisms explaining these unilateral findings are unknown (Campbell et al., 2004; Kitayama et al., 2005; Smith, 2005; Van Petten, 2004). One speculation (Bremner et al., 1995), with some support from the animal literature (Sullivan and Gratton, 2002), is that an asymmetric concentration of stress-related neurotransmitters, such as serotonin, may partly mediate right-lateralized chronic-stress related changes in the structure and function of the hippocampus and related circuitry. There is evidence from animal models of psychosocial stress and hippocampal remodeling that neurotransmitters such as serotonin act synergistically with glucocorticoids and excitatory amino acids to affect the branching complexity and length of apical dendrites in the CA3 region; however, lateralized effects of chronic stress on hippocampal structure and function are not often reported in the animal literature (Conrad, 2006). Another possibility is that in otherwise healthy individuals without a clinical syndrome, the morphology of the right hippocampus and networked brain areas, including sub-regions of the orbitofrontal cortex, are more closely related than left-lateralized areas to indicators of moderate chronic life stress. By extension, it is possible that with higher levels of chronic perceived stress, more widespread (bilateral) relationships with regional grey matter volume could be detected. In support of this possibility, supplementary analyses of the present data suggested a trend-level decrease in left hippocampal grey matter volume as a function of increasing chronic life stress (see supplementary Figure 2 on the NeuroImage website). Future studies specifically examining the factors that may account for the laterality of chronic-stress-related variations in regional brain morphology are thus warranted.

Further study is also needed to determine whether there is a functional relationship between chronic life stress, hippocampal grey matter volume, and hippocampal-dependent cognitive and neuroendocrine functions. In animal models, chronic stress impairs hippocampal-dependent memory and disrupts neuroendocrine regulation by prefrontal cortex and hippocampus (Fuchs and Flugge, 1998; Kim and Diamond, 2002; McEwen and Magariños,

1997; Sapolsky, 2003). Further, decreased hippocampal volume is frequently, but not always (Van Petten, 2004), associated with poorer performance on tests of hippocampal-dependent learning and memory, which may be mediated in part by stress-related changes in neuroendocrine activity (Conrad, 2006; Lupien et al., 2005). Over the lifespan, it is thus likely that chronic stress-related changes in hippocampal volume would be related to ongoing or later disruptions in learning, memory, and neuroendocrine activity.

We close by noting that the relationship between chronic life stress and decreased grey matter volume in the hippocampus—and possibly in an area of the orbitofrontal cortex—appears to span a continuum that extends to otherwise healthy individuals. As in animal models, it is plausible that chronic life stress contributes to adverse changes in regional grey matter volume and other indicators of brain morphology. However, without serial longitudinal assessments of structural brain images along with concurrent reports of perceived stress, we cannot exclude the possibility that changes in regional grey matter volume (e.g., in the hippocampus) preceded (or co-occurred with) individual differences in stress perceptions over time (cf. Gilbertson et al., 2002). Thus, it is important for future longitudinal studies to address this issue.

Another future research goal will be to determine the genetic factors that interact with environmental sources of chronic life stress to predict changes in regional brain morphology over the lifespan. Recent human evidence, for example, shows that carriers of the methionine (met) allele of the valine(val)^{66}met brain-derived neurotrophic factor (BDNF) polymorphism express lower grey matter volume in the hippocampus and prefrontal cortex compared with carriers of the val/val allele (Pezawas et al., 2004). In animal models, chronic stress is known to down-regulate BDNF, contributing in part to cellular remodeling in the hippocampus (Charney, 2004; Duman, 2002). Given that the met allele is associated with relatively reduced activity-dependent secretion and intracellular trafficking of pro-BDNF, it could plausibly affect the contribution of BDNF to signaling cascades mediating synaptic plasticity and, potentially, neurogenesis in response to environmental demands and stressors. Our ongoing work is thus testing whether functional polymorphisms, such as BDNF val^{66}met, modify the expression of stress-related variations in hippocampal and cortical morphology that are associated with resiliency and vulnerability to maladaptive conditions affecting neuroendocrine activity, cognition, and mood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Ashburner J, Friston KJ. Voxel-based morphometry--the methods. NeuroImage 2000;11:805–821. [PubMed: 10860804]

Beck, AT. Depression Inventory. Philadelphia: Center for Cognitive Therapy; 1978.

Bremner JD. Hypotheses and controversies related to effects of stress on the hippocampus: an argument for stress-induced damage to the hippocampus in patients with posttraumatic stress disorder. Hippocampus 2001;11:75–81. [PubMed: 11345127]

Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, Delaney RC, McCarthy G, Charney DS, Innis RB. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am J Psychiatry 1995;152:973–981. [PubMed: 7793467]

Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A, Khan S, Vaccarino LV, Soufer R, Garg PK, Ng CK, Staib LH, Duncan JS, Charney DS. MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. Am J Psychiatry 2003;160:924–932. [PubMed: 12727697]

Campbell S, MacQueen G. An update on regional brain volume differences associated with mood disorders. Curr Opin Psychiatry 2006;19:25–33. [PubMed: 16612175]

Campbell S, MacQueen G. The role of the hippocampus in the pathophysiology of major depression. J Psychiatry Neurosci 2004;29:417–426. [PubMed: 15644983]

Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: A meta-analysis. Am J Psychiatry 2004;161:598–607. [PubMed: 15056502]

Charney DS, Manji HK. Life stress, genes, and depression: multiple pathways lead to increased risk and new opportunities for intervention. Sci STKE 2004;225:re5. [PubMed: 15039492]

Charney DS. Psychobiological mechanisms of resilience and vulnerability: Implications for successful adaptation to extreme stress. Am J Psychiatry 2004;161:195–216. [PubMed: 14754765]

Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Beh 1983;24:385–396.

Conrad CD. What is the functional significance of chronic stress-induced CA3 dendritic retraction within the hippocampus? Behav Cogn Neurosci Rev 2006;5:41–60. [PubMed: 16816092]

Cotter D, Hudson L, Landau S. Evidence for orbitofrontal pathology in bipolar disorder and major depression, but not in schizophrenia. Bipolar Disord 2005;7:358–369. [PubMed: 16026489]

Czeh B, Michaelis T, Watanabe T, Frahm J, de Biurrun G, van Kampen M, Bartolomucci A, Fuchs E. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc Natl Acad Sci USA 2001;98:12796–12801. [PubMed: 11675510]

Dischinger P, DuChene AG. Quality control aspects of blood pressure measurements in the Multiple Risk Factor Intervention Trial. Control Clin Trials 1986;7:137S–157S. [PubMed: 3802839]

Duman RS. Synaptic plasticity and mood disorders. Mol Psychiatry 2002;7 (suppl):S29–S34. [PubMed: 11986993]

Erickson KI, Colcombe SJ, Raz N, Korol DL, Scalf P, Webb A, Cohen NJ, McAuley E, Kramer AF. Selective sparing of brain tissue in postmenopausal women receiving hormone replacement therapy. Neurobiol Aging 2005;26:1205–1213. [PubMed: 15917105]

Friston KJ, Holmes A, Poline JB, Price CJ, Frith CD. Detecting activations in PET and fMRI: levels of inference and power. NeuroImage 1996;4:223–235. [PubMed: 9345513]

Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RS. Statistical parametric maps in functional imaging: A general approach. Human Brain Mapp 1995;2:189–210.

Fuchs E, Czeh B, Kole MH, Michaelis T, Lucassen PJ. Alterations of neuroplasticity in depression: the hippocampus and beyond. Eur Neuropsychopharmacol 2004;14(suppl 5):S481–490. [PubMed: 15550346]

Fuchs E, Flugge G. Stress, glucocorticoids and structural plasticity of the hippocampus. Neurosci Biobehav Rev 1998;23:295–300. [PubMed: 9884123]

Geuze E, Vermetten E, Bremner JD. MR-based in vivo hippocampal volumetrics: 2. Findings in neuropsychiatric disorders. Mol Psychiatry 2005;10:160–184. [PubMed: 15356639]

Gianaros PJ, Greer PJ, Ryan CM, Jennings JR. Higher blood pressure predicts lower regional grey matter volume: Consequences on short-term information processing. NeuroImage 2006;31:754–765. [PubMed: 16488626]

Gianaros PJ, Jennings JR, Sheu LK, Derbyshire SWG, Matthews KA. Heightened functional neural reactivity to psychological stress covaries with exaggerated blood pressure reactivity. Hypertension. in press

Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci 2002;5:1242–1247. [PubMed: 12379862]

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. NeuroImage 2001;14:21–36. [PubMed: 11525331]

Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, Orr SP, Kikinis R, Jolesz FA, McCarley RW, Pitman RK. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biol Psychiatry 1996;40:1091–1099. [PubMed: 8931911]

Kim JJ, Diamond DM. The stressed hippocampus, synaptic plasticity and lost memories. Nat Rev Neurosci 2002;3:453–462. [PubMed: 12042880]

Kitayama N, Vaccarino V, Kutner M, Weiss P, Bremner JD. Magnetic resonance imaging (MRI) measurement of hippocampal volume in posttraumatic stress disorder: a meta-analysis. J Affect Disord 2005;88:79–86. [PubMed: 16033700]

Lai T, Payne ME, Byrum CE, Steffens DC, Krishnan KR. Reduction of orbital frontal cortex volume in geriatric depression. Biol Psychiatry 2000;48:971–975. [PubMed: 11082470]

Lee AL, Ogle WO, Sapolsky RM. Stress and depression: possible links to neuron death in the hippocampus. Bipolar Disord 2002;4:117–128. [PubMed: 12071509]

Longstreth WT, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, O'Leary D, Enright PL, Fried L. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people: The Cardiovascular Health Study. Stroke 1996;27:1274–1282. [PubMed: 8711786]

Lupien SJ, Fiocco A, Wan N, Maheu F, Lord C, Schramek T, Tu MT. Stress hormones and human memory function across the lifespan. Psychoneuroendocrinology 2005;30:225–242. [PubMed: 15511597]

MacQueen GM, Campbell S, McEwen BS, Macdonald K, Amano S, Joffe RT, Nahmias C, Young LT. Course of illness, hippocampal function, and hippocampal volume in major depression. Proc Natl Acad Sci USA 2003;100:1387–1392. [PubMed: 12552118]

Magariños AM, McEwen BS. Stress-induced atrophy of apical dendrites of hippocampal CA3 neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors. Neuroscience 1995;69:89–98. [PubMed: 8637636]

Magariños AM, McEwen BS, Flugge G, Fuchs E. Chronic psychosocial stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews. J Neurosci 1996;16:3534–3540. [PubMed: 8627386]

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage 2003;19:1233–1239. [PubMed: 12880848]

Manji HK, Moore GJ, Rajkowska G, Chen G. Neuroplasticity and cellular resilience in mood disorders. Mol Psychiatry 2000;5:578–593. [PubMed: 11126389]

Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. N Engl J Med 1989;321:641–646. [PubMed: 2488072]

McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med 1998;338:171–179. [PubMed: 9428819]

McEwen BS. Stress and hippocampal plasticity. Annu Rev Neurosci 1999;22:105–122. [PubMed: 10202533]

McEwen BS. Plasticity of the hippocampus: adaptation to chronic stress and allostatic load. Ann N Y Acad Sci 2001;933:265–277. [PubMed: 12000027]

McEwen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann N Y Acad Sci 2004;1032:1–7. [PubMed: 15677391]

McEwen BS. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. Metabolism 2005;54:20–23. [PubMed: 15877308]

McEwen BS, Magariños AM. Stress effects on morphology and function of the hippocampus. Ann N Y Acad Sci 1997;821:271–284. [PubMed: 9238211]

Miller DB, O'Callaghan JP. Aging, stress and the hippocampus. Ageing Res Rev 2005;4:123–140. [PubMed: 15964248]

Nichols TE, Hayasaka S. Controlling the familywise error rate in functional neuroimaging: A comparative review. Stat Methods Med Res 2003;12:419–446. [PubMed: 14599004]

O'Brien JT, Lloyd A, McKeith I, Gholkar A, Ferrier N. A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. Am J Psychiatry 2004;161:2081–2090. [PubMed: 15514410]

Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, Egan MF, Meyer-Lindenberg A, Weinberger DR. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. J Neurosci 2004;24:10099–10102. [PubMed: 15537879]

Radley JJ, Morrison JH. Repeated stress and structural plasticity in the brain. Ageing Res Rev 2005;4:271–287. [PubMed: 15993654]

Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Applied Psychological Measurement 1977;1:385–401.

Rajkowska G, Miguel-Hidalgo JJ, Wei J, Dilley G, Pittman SD, Meltzer HY, Overholser JC, Roth BL, Stockmeier CA. Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. Biol Psychiatry 1999;45:1085–1098. [PubMed: 10331101]

Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, Dahle C, Gerstorf D, Acker JD. Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. Cerebral Cortex 2005;15:1676–1689. [PubMed: 15703252]

Sapolsky RM. Glucocorticoids, stress, and their adverse neurological effects: relevance to aging. Exp Gerontol 1999;34:721–732. [PubMed: 10579633]

Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 2000;57:925–935. [PubMed: 11015810]

Sapolsky RM. Stress and plasticity in the limbic system. Neurochem Res 2003;28:1735–1742. [PubMed: 14584827]

Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev 2000;21:55–89. [PubMed: 10696570]

Sapolsky RM, Uno H, Rebert CS, Finch CE. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. J Neurosc,i 1990;10:2897–2902.

Selye, H. The stress of life. New York: McGraw-Hill; 1956.

Seshadri S, Wolf PA, Beiser A, Elias MF, Au R, Kase CS, D'Agostino RB, DeCarli C. Stroke risk profile, brain volume, and cognitive function: the Framingham Offspring Study. Neurology 2004;63:1591–1599. [PubMed: 15534241]

Sheline YI. Hippocampal atrophy in major depression: a result of depression-induced neurotoxicity? Mol Psychiatry 1996;1:298–299. [PubMed: 9118352]

Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. Am J Psychiatry 2003;160:1516–1518. [PubMed: 12900317]

Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci 1999;19:5034–5043. [PubMed: 10366636]

Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci USA 1996;93:3908–3913. [PubMed: 8632988]

Simon M, Czeh B, Fuchs E. Age-dependent susceptibility of adult hippocampal cell proliferation to chronic psychosocial stress. Brain Res 2005;1049:244–248. [PubMed: 15950198]

Smith ME. Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: a meta-analysis of structural MRI studies. Hippocampus 2005;15:798–807. [PubMed: 15988763]

Sullivan RM, Gratton A. Prefrontal cortical regulation of hypothalamic-pituitary-adrenal function in the rat and implications for psychopathology: side matters. Psychoneuroendocrinology 2002;27:99–114. [PubMed: 11750772]

Uno H, Eisele S, Sakai A, Shelton S, Baker E, DeJesus O, Holden J. Neurotoxicity of glucocorticoids in the primate brain. Horm Behav 1994;28:336–348. [PubMed: 7729802]

Van Petten C. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. Neuropsychologia 2004;42:1394–1413. [PubMed: 15193947]

Vermetten E, Vythilingam M, Southwick SM, Charney DS, Bremner JD. Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. Biol Psychiatry 2003;54:693–702. [PubMed: 14512209]

Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, Brummer M, Staib L, Vermetten E, Charney DS, Nemeroff CB, Bremner JD. Childhood trauma associated with smaller hippocampal volume in women with major depression. Am J Psychiatry 2002;159:2072–2080. [PubMed: 12450959]

Vythilingam M, Vermetten E, Anderson GM, Luckenbaugh D, Anderson ER, Snow J, Staib LH, Charney DS, Bremner JD. Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. Biol Psychiatry 2004;56:101–112. [PubMed: 15231442]

Ward MA, Carlsson CM, Trivedi MA, Sager MA, Johnson SC. The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. BMC Neurololgy 2005;5:23.

Wen W, Sachdev PS, Chen X, Anstey K. Gray matter reduction is correlated with white matter hyperintensity volume: a voxel-based morphometric study in a large epidemiological sample. NeuroImage 2006;29:1031–1039. [PubMed: 16253521]

Yehuda R, McEwen BS. Protective and damaging effects of the biobehavioral stress response: cognitive, systemic and clinical aspects: ISPNE XXXIV meeting summary. Psychoneuroendocrinology 2004;29:1212–1222. [PubMed: 15219646]

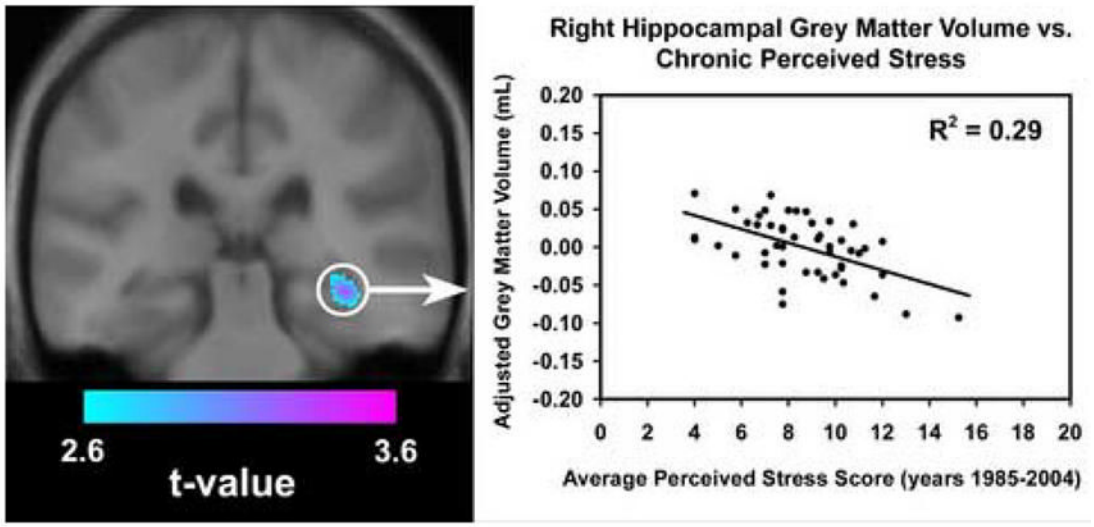

Figure 1.

Higher chronic perceived stress among 48 healthy postmenopausal women predicted decreased grey matter volume in the right hippocampus. Left panel: Profiled with color-scaled t-values (legend beneath the coronal image) is a cluster of right hippocampal voxels where chronic perceived stress predicted decreased grey matter volume after controlling for age and total grey matter volume in a region-of-interest analysis. Right panel: Plotted along the y-axis is the grey matter volume from the cluster of hippocampal voxels profiled at left; these volume estimates are adjusted for age and total grey matter volume. Plotted along the x-axis is the average Perceived Stress Scale score from 1985–2004, which was used to define chronic stress.

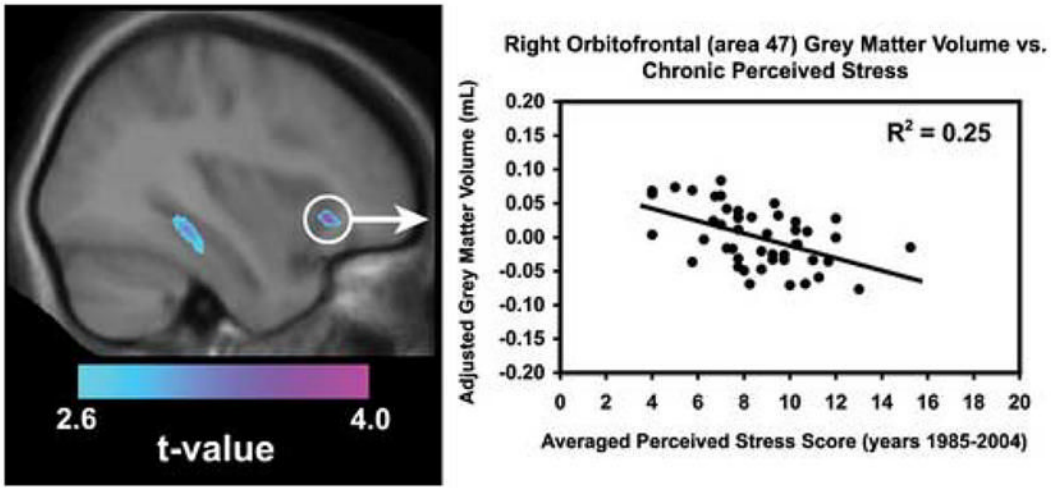

Figure 2.

Left panel: Illustrated with color-scaled t-values (legend beneath the sagittal image) is an area of the right orbitofrontal cortex where higher chronic perceived stress predicted decreased grey matter volume after controlling for age and total grey matter volume in an exploratory whole-brain analysis. The MNI coordinates for the peak correlation in this orbitofrontal area were x = 32, y = 33, & z = −8, $\underline{t} = 3.98$, $\underline{z} = 3.66$, $\underline{P}_{\text{uncorrected}} < 0.001$; cluster size = 294 voxels. The right hippocampal area in which chronic perceived stress predicted decreased grey matter volume is also visible in this sagittal image. Right panel: Plotted along the y-axis is the grey matter volume of the orbitofrontal area profiled at left (adjusted for age and total grey matter volume). Plotted along the x-axis is the average score on the Perceived Stress Scale.

Table 1

Characteristics of 48 Postmenopausal Women

Characteristics	Mean	Standard Deviation
Age (years)	67.98	1.37
Number of school years completed	15.48	1.57
Number of years since menopause[a]	18.30	.77
Alcoholic beverages consumed / week	2.37	3.69
Height (in)	63.38	3.02
Weight (lbs)	154.34	22.09
Body mass index (kg/m^2)	27.09	4.17
Systolic blood pressure (mmHg)	125.45	12.80
Diastolic blood pressure (mmHg)	74.57	6.81
CES-D (concurrent with MRI Scan)	4.35	3.02
White matter hyperintensity grade (0–8 scale)	1.91	1.24
Total grey matter volume (mL) [a]	571.04	45.57

Note.

[a]Indicates number of years between onset of menopause and brain imaging; CES-D = Center for Epidemiological Studies Depression Scale; MRI = magnetic resonance imaging.

Table 2

Mean (SD) Perceived Stress Scale (PSS) Scores and Beck Depression Inventory (BDI) Scores for Each Postmenopausal Assessment (N = 48)

Assessment Number	PSS Score	BDI Score
1	8.96 (2.97)	4.74 (3.95)
2	8.91 (3.10)	5.67 (5.53)
3	8.58 (2.92)	4.43 (3.66)
4	8.58 (2.97)	4.18 (3.24)
Average	8.75 (2.44)	4.82 (3.60)

Note. The 4-item Perceived Stress Scale and the Beck Depression Inventory were completed from 1985 to 2004. The mean number of years between assessments 1–2 = 1 year (SD = 0.28); between 2–3 = 3.18 years (SD = 0.98); and between 3–4 = 3.01 years (SD = 0.60). At bottom are averaged PSS and BDI scores computed for each participant.