Self-esteem, locus of control, hippocampal volume, and cortisol regulation in young and old adulthood

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Self-esteem, the value we place on ourselves, has been associated with effects on health, life expectancy, and life satisfaction. Correlated with self-esteem is internal locus of control, the individual's perception of being in control of his or her outcomes. Recently, variations in self-esteem and internal locus of control have been shown to predict the neuroendocrine cortisol response to stress. Cumulative exposure to high levels of cortisol over the lifetime is known to be related to hippocampal atrophy. We therefore examined hippocampal volume and cortisol regulation, to investigate potential biological mechanisms related to self-esteem. We investigated 16 healthy young (age range 20– 26 years of age) and 23 healthy elderly subjects (age range 60–84 years). The young subjects were exposed to a psychosocial stress task, while the elderly subjects were assessed for their basal cortisol regulation. Structural Magnetic Resonance Images were acquired from all subjects, and volumetric analyses were performed on medial temporal lobe structures, and whole brain gray matter. Standardized neuropsychological assessments in the elderly were performed to assess levels of cognitive performance, and to exclude the possibility of neurodegenerative disease. Self-esteem and internal locus of control were significantly correlated with hippocampal volume in both young and elderly subjects. In the young, the cortisol response to the psychosocial stress task was significantly correlated with both hippo-campal volume and levels of self-esteem and locus of control, while in the elderly, these personality traits moderated age-related patterns of cognitive decline, cortisol regulation, and global brain volume decline.
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Introduction

Self-esteem is a broadly defined personality variable referring to the degree to which an individual values and accepts him- or herself. Low self-esteem has been associated with a host of negative life outcomes, including substance abuse, delinquency, unhappiness, depression, eating disorders, and worsened recovery after illnesses (see Hoyle et al., 1999; Leary and McDonald, 2003). High self-esteem has been associated with positive characteristics such as initiative, strong coping skills, persistence in the face of challenges, happiness, and longevity (Baumeister et al., 2003). In geriatric research, the suggestion has been made that a positive self-concept may play a key role in the model of successful aging, predicting independence, cognitive stability, and general health in old age (Baltes and Baltes, 1990; Markus and Herzog, 1991).

Little is known about possible biological mechanisms underlying self-esteem, or underlying the association between self-esteem, and health and disease. One likely candidate is the set of structures and systems relating to people's reactions to stress. Low self-esteem is associated with greater amounts of perceived daily hassles and chronic stressors, even after correcting for environmental factors, occupation, age, and gender. Conversely, high self-esteem tends to be strongly associated with internal locus of control, or the confident perception that one's outcomes are determined by one's actions (DeLongis et al., 1988; Lo, 2002; Petrie and Rotheram, 1982; Whisman and Kwon, 1993). These personality variables have been found to be predictive of people's neuroendocrinological reactions to stressful social situations. In a previous study, we demonstrated the importance of self-esteem in the cortisol stress response by showing that in a mental challenge task only the subjects with low self-esteem and low levels of internal locus of control exhibited a significant cortisol response (Pruessner et al., 1999b). We further found that these personality variables predicted the ability to habituate to repeated psychosocial stress, with subjects with low levels of self-esteem and low internal locus of control showing continuous high cortisol stress responses (Kirschbaum et al., 1995).

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In the current research, we sought to investigate a central nervous system (CNS) characteristic possibly related to cortisol and personality variables, by examining the hypothesis that individuals with low self-esteem and low internal locus of control would have smaller hippocampal volumes. Previous findings have demonstrated that across the lifetime, high stress loads can impair health, with a specific effect on the CNS via the "allostatic load" model (McEwen, 1998; Schulkin et al., 1998). Briefly, chronic perceived stress can lead to poor habituation of the hypothalamic–pituitary–adrenal (HPA) axis and dysregulation of glucocorticoid (i.e., cortisol) release. Documented effects of stress include impairment and damage to specific brain structures via the action of neurotoxic glucocorticoids (Sapolsky, 1996; Watanabe et al., 1992; Woolley et al., 1990). Glucocorticoids further disrupt the cellular metabolism, via excitatory amino acids and glutamate accumulation. They also affect neuronal tissue by disruption of BDNF expression (Nibuya et al., 1995; Schaaf et al., 2000). Over time, dysregulation of glucocorticoid release, in conditions such as chronic pain or burnout, can take the form of a distorted diurnal pattern involving reduced cortisol response upon wakening but increased reactivity to threat. The hippocampus is the brain structure that appears particularly susceptible to damage as a result of chronic stress, due to a high density of receptors for glucocorticoids. We therefore examined the correlation between hippocampal volume, basal glucocorticoid regulation, and self-esteem and locus of control, in a sample of healthy elderly subjects, selecting individuals across a relatively wide age range to investigate the long-term relationship between self-esteem, locus of control and hippocampal volume. We also assessed the association between hippocampal volume and both self-esteem and locus of control in a sample of young subjects, to determine the relationships among these variables earlier in life. In the young subjects, we assessed acute rather than basal glucocorticoid regulation, by conducting psychosocial stress testing with accompanying cortisol assessment.

We hypothesized that in healthy elderly subjects, low self-esteem and low internal locus of control would be linked to smaller hippocampal volume, and signs of cortisol dysregulation. We assessed the cortisol response to awakening in the elderly, which has been recently reported to be associated with HC integrity such that HC damage predicts lower levels of cortisol in response to awakening (Buchanan et al., 2004; Wolf et al., 2005). In the sample of young adults, we were interested in examining whether self-esteem and locus of control would moderate the acute cortisol stress response (thereby replicating earlier studies), and to investigate whether these variables would be linked to hippocampal volume in young subjects as well.

Materials and methods

Subjects

Young and old subjects were recruited from the community by ads in the local newspaper. In addition, young subjects were also recruited by posting flyers on university buildings. The data reported here were obtained from two independent studies, which were aimed at investigating several different aspects of cortisol regulation, brain integrity, and personality assessment, but which included identical assessments for structural brain imaging, and self-esteem and locus of control measures. The first study consisted of 23 healthy elderly subjects (16 women and 7 men) between 60 and 84 years of age. The second study included a sample of young adults consisting of 16 healthy men between 20 and 26 years of age. Written informed consent was obtained from each subject prior to entering the study. The Douglas Hospital Research Center Ethics board, and the Montreal Neurological Institute Ethics board approved the study. Each respondent to the ads was first investigated with a physical examination including assessment of medical history to confirm good physical health. Because we wished to focus on a normal range of self-esteem and locus of control, rather than on clinical depression as in some previous research (Davidson et al., 2002), exclusion criteria were current depression assessed with the Geriatric Depression Scale (GDS) in the old subjects, and with the Beck Depression Inventory (BDI) in the young subjects, and a history of depression or other psychiatric illnesses. Occurrences of head trauma in the past served as additional exclusion criteria.

Neuropsychological and psychological assessment

Neuropsychological assessment performed with the elderly subjects included the Mini Mental State Examination (MMSE) in its modified form (3M), and a cognitive assessment especially sensitive for identifying onset of mild cognitive impairment, the cognitive subscale of the Alzheimer disease assessment scale (ADAS-cog) (Molloy and Standish, 1997; Rosen, 1982; Teng et al., 1989). The young subjects were not assessed with these measures.

Psychological assessment, identically performed with all subjects, included measures of self-esteem and locus of control. We administered the Rosenberg Self-esteem Scale (Rosenberg, 1965), the most widely used and well-validated measure of global self-esteem. This measure assesses general feelings of self-worth and self-acceptance, with items such as "On the whole, I am satisfied with myself." We also administered the locus of control measure (Krampen, 1991) that had been strongly predictive of cortisol response in our previous stress research. This measure includes subscales for internal locus of control (e.g., "I can determine many things that are happening in my life") and external locus of control (e.g., "Many events in my life happen by chance"). Based on our previous findings, we were particularly interested in the internal locus of control subscale, since the external subscale was not predictive of the stress response, and the internal scale correlated highly with self-esteem (as has been found in other studies, e.g., Griffore et al., 1990). The validity of these measures for the assessment of self-esteem and locus of control has been established and shown to be generally independent of the emotional status of the subject (Bachman and O'Malley, 1977).

Montreal Imaging Stress Task, saliva sampling, and cortisol analysis in young subjects

Young subjects were exposed to the Montreal Imaging Stress Task (MIST), a combination of social evaluative and mentally challenging tasks. The stress task was performed while being in a Magnetic Resonance Imaging (MRI) Scanner, for the purpose of assessing brain activation during the perception of psychosocial stress. In short, subjects have to complete mental arithmetic under time pressure while being scanned for brain activation, and they receive negative verbal

feedback critical of their task performance between functional runs from the investigator (see Dedovic et al., in press, for a more detailed description of the task). Direct self-reported assessment of stress perception has proved relatively unsuccessful in the past, thus we focused on the standard biomarker of stress, the cortisol stress response, as a better indicator of the perceived stressfulness of the situation (Dickerson and Kemeny, 2004; Kirschbaum et al., 1992). Cortisol was sampled at -30, -20, 0, 20, 40, 50 and 60 min in relation to the onset of the stressful task. The stressful task lasted for 18 min. Cortisol from salivettes was analyzed using a time-resolved fluorescence immunoassay with documented validity and reliability (Dressendorfer et al., 1992). The area under the curve was computed for all values in accordance with two recently described formulas (Pruessner et al., 2003).

Saliva sampling and cortisol analysis in elderly subjects

Elderly subjects were asked to provide saliva samples at prespecified days once a month, over a period of 12 months, at the time of awakening, 30 min after awakening, at 2 and 4 p.m., and before bedtime. Three and one-half by five centimeter filters were cut from Whatman #42 filter paper for the collection of saliva. The top centimeter of 5 cm length was used for recording subject data and was demarcated with a line. The subjects were asked to place the filter paper into their mouth until the saliva front reached just beyond the 4 cm line. The filter was then air dried and stored at $-4°C$. In previous work with this procedure, we have established that protein content, measured in 0.1 n NaOH extracts, in salivary samples collected in this manner, varies by an average of less than 1% across a wide range of samples. Cortisol was extracted from the filter in 2 ml of ethanol for 1 h at room temperature. A 300 μl aliquot of the extract was assayed using [³H]cortisol as radiotracer and a highly specific cortisol antibody (B-63 antibody from Endocrine Sciences, Tarzana, CA). This antibody cross-reacts less than 4% with deoxycorticosterone or deoxycortisol, and less than 0.5% with any other adrenal steroid. Intra- and inter-assay variability is 3.5 and 5%, respectively. The cortisol data were aggregated for each subject in order to reduce the amount of time points for the subsequent statistical analysis, and the cortisol response to awakening was computed using a recently described formula for the computation of the area under the curve (Pruessner et al., 2003). Thus, cortisol assessment in the elderly subjects aimed at describing the basal circadian rhythm of hpa axis regulation, while the endocrine assessment design in the young subjects aimed at monitoring the cortisol dynamics in response to an acute psychosocial stressor.

MR acquisition and analysis

Structural scans for all subjects were acquired using the protocol of the ongoing 'International Consortium of Brain Mapping' (ICBM) initiative to create a statistical atlas of the normal adult brain (Mazziotta et al., 1995). This protocol generates T1, T2, and PD-weighted image volumes with a slice separation of 1 mm for the T1 weighted images. For the purpose of the current analysis, only the T1 weighted images were employed. The T1 volumes were acquired using a three-dimensional spoiled gradient echo acquisition with sagittal volume

excitation (TR = 18, TE = 10, flip angle = 30°, 140 1 mm contiguous sagittal slices). The rectangular field of view (FOV) for the sagittal images was 256 mm (SI) × 204 mm (AP). All images were transferred to a network of Silicon Graphics workstations (Silicon Graphics, Mountain View, CA). Several algorithms were used consecutively to prepare the images for manual segmentation. This included correction for magnetic field nonuniformities (Sled et al., 1998), linear stereotaxic transformation (Collins et al., 1994) into coordinates based on the Talairach atlas (Talairach and Tournoux, 1988), and resampling onto a 1 mm voxel grid before image segmentation using a linear interpolation kernel. It has been shown that the automatic stereotaxic transformation is as accurate as the manual procedure but shows higher stability (Collins et al., 1994). Also, the correction for image intensity has been proven to recover most of the image artifacts present in the International Consortium of Brain Mapping MR database (Sled et al., 1998).

Volumetric analysis was performed with the interactive software package DISPLAY developed at the Brain Imaging Center of the Montreal Neurological Institute. This program allows visualization of MR images in all orientations and rotations. Volumes of Hippocampus and Amygdala were measured using a recently developed protocol (Pruessner et al., 2000, 2002). Total brain volume was measured semi-automatically, by first employing a program developed at the Montreal Neurological Institute to automatically analyze whole brain MR data into clusters of gray and white matter, and CSF (ANIMAL; Collins and Evans, 1997), which was followed by correcting the white/gray, and gray/csf boundaries by a rater trained in neuroanatomy of the central nervous system (JCP). The segmentation protocol for the assessment of hippocampal volume has recently been developed by our group, and we have since been able to validate it in a number of projects (Pruessner et al., 2000, 2001, 2002).

Statistical analysis

For some analyses, we wished to examine extreme groups, comparing those subjects with the highest self-esteem and internal locus of control, versus those with the lowest self-esteem and locus of control. Previous findings from our lab had shown that self-esteem and internal locus of control measures were highly correlated, and that considering these two personality measures in combination yielded the best prediction of the cortisol stress response (Pruessner et al., 1999b). Replicating these earlier findings, it was found that self-esteem correlated strongly positively with internal locus of control ($r = 0.67$, $P < 0.001$ in the young sample, and $r = 0.70$, $P < 0.001$ in the old sample: as in the previous research, the correlations between self-esteem and external locus of control were only weak to moderate: young: $r = -0.17$, $P > 0.20$; old: $r = -0.55$, $P < 0.05$). Following the analytic approach used in previous research, we thus split each sample into two groups, those with either high scores or low scores on self-esteem and internal locus of control (hereinafter referred to as high versus low SEC), in both the young and elderly study populations. In order to obtain a meaningful separation of the total groups, a k-means cluster analysis was performed, employing internal locus of control and self-esteem measures (Wishart, 1998). This type of analysis allows clustering of subjects into different subgroups using more than one variable. After creating two groups with maximum differences in levels of self-esteem and internal locus of

control, we then tested whether age, education, and left and right hippocampal volume were different between these two groups, in both the young and elderly study samples, using t tests or analyses of variance where appropriate. Since the young subjects had been exposed to a psychosocial stress paradigm, we investigated the effect of high and low SEC on the cortisol stress response in this population using a two-factor (group by time) *mixed design* analysis of variance with the seven cortisol stress samples as dependent variables.

In the elderly population, hippocampal volume and cortisol regulation were expected to show some relation to advancing age, based on previous research, so it was critical to take age into account in analyzing relations involving these variables. Exclusively in the elderly population, we therefore investigated age-related changes of brain volumes, cortisol regulation, and neuropsychological performance between subjects with high and low SEC, to find out whether levels of SEC had an impact on age-related decline in these variables. In order to do so, we used Pearson correlations corrected for multiple comparisons, separately in the two groups comprised of high and low SEC subjects. We chose this approach exclusively in the elderly subjects, since the age range was rather small in the younger sample, and age-related changes were virtually absent in this group.

We also computed Pearson product–moment correlations to investigate the association between self-esteem and locus of control, hippocampus and whole brain parameters, and the endocrinological parameters across the entire range of self-esteem and locus of control scores, to assess the global association between these parameters, separately in the young and elderly subjects. Corrections for multiple comparisons were performed according to the Bonferoni method to obtain results significant at a corrected alpha-level of 0.05.

Finally, in order to test whether cortisol regulation mediated the relationship between self-esteem and hippocampal volumes, we performed mediation analyses using a hierarchical regression analysis approach, separately for young and elderly subjects. In a first set of this analysis, we chose hippocampal volumes as the dependent, and self-esteem/locus of control/cortisol regulation subsequently entered as independent variables. Employing the unstandardized regression coefficients and their standard errors between either self-esteem/locus of control, or cortisol regulation, we were then able to compute whether the effect of self-esteem/ locus of control on hippocampal volumes was mediated by cortisol regulation, by employing standardized statistical procedures (Sobel, 1982). In considering an alternative explanation for our findings, we

also tested whether hippocampal volumes mediated the relationship between personality measures and cortisol regulation.

Results

Population demographics and SEC groups

Sixteen young men (age range 20–26 years, mean age 22.45 years), and 23 healthy elderly men and women (16 women and 7 men, mean age 70.3 ± 7.8 years, range 60–84 years) were available for statistical analysis. Neither age, nor hippocampal volume, self-esteem, locus of control, nor cortisol measures was significantly different between men and women in the elderly sample, thus we combined the men and women for our subsequent analyses. The cluster analysis with the self-esteem and internality scores created SEC groups within the young (low $n = 8$; high $n = 8$) and elderly subjects (low $n = 13$; high $n = 10$), which showed significant differences with regard to internal locus of control, and self-esteem. In each case the two groups did not differ with respect to age and education level (Table 1).

Hippocampal volume differences between low and high SEC

In examining the low and high SEC groups, we found that the young subjects with low SEC had a 12% smaller left hippocampus, and a 13% smaller right hippocampus, than those with high SEC ($F_{1,15} = 20.06$, $P < 0.001$, two-factor (SEC × hemisphere) *mixed design* ANOVA). In the elderly people, the low SEC had a 17.4% smaller left hippocampus, and a 15.8% smaller right hippocampal volume than the high SEC group ($F_{1,21} = 7.88$, $P < 0.01$, two-factor (SEC × hemisphere) *mixed design* ANOVA; Table 1). In two samples, then, comprising very different age groups, low self-esteem and low internal locus of control were clearly associated with lower hippocampal volume (see Fig. 1).

Hippocampal volume correlations with measures of self-esteem and internal locus of control

Examining the continuous measures of self-esteem and internal locus of control separately, in both young and old subjects, showed that both were significantly correlated with left and right hippocampal volumes. These correlations ranged from $r = 0.42$ to $r = 0.71$ in the young and old subjects, with only one of them not reaching statistical significance (see Fig. 2). Correlations between

Table 1
Differences between groups of high and low self-esteem and internal locus of control (SEC) as computed by cluster analysis on age, education, and left and right hippocampal volumes (shown in cubic centimeters) in both young ($n = 16$) and old ($n = 23$) study subjects

Young subjects	Low SEC ($n = 8$)	High SEC ($n = 8$)	P	Old subjects	Low SEC ($n = 13$)	High SEC ($n = 10$)	P
Age	22.25 ± 1.95	22.66 ± 2.29	>0.20		69.42 ± 6.98	65.44 ± 6.13	0.19
Self-esteem	21.08 ± 3.57	26.78 ± 3.27	<0.001		20.62 ± 3.92	27.37 ± 2.5	<0.001
Internal locus of control	29.62 ± 3.62	35.22 ± 2.73	<0.001		29.84 ± 5.14	37.62 ± 3.11	=0.001
Education	15.83 ± 1.59	16.17 ± 1.07	>0.20		14.75 ± 3.75	14.55 ± 2.13	>0.20
Left HC	2.96 ± 0.11	3.38 ± 0.19	<0.001		2.46 ± 0.36	2.98 ± 0.43	.008
Right HC	3.05 ± 0.26	3.52 ± 0.26	<0.001		2.5 ± .38	2.97 ± 0.35	0.01

P values based on t tests corrected for multiple comparisons for age, self-esteem, locus of control and education scores, and a two-factor (group by hemisphere) *mixed design* analysis of variance performed separately in the young and elderly subjects for left and right hippocampal volumes.
Characteristics of the two groups of young ($n = 16$) and old ($n = 23$) subjects, and effects of high and low self-esteem on hippocampal volume (shown in cubic centimeters) within the two groups.
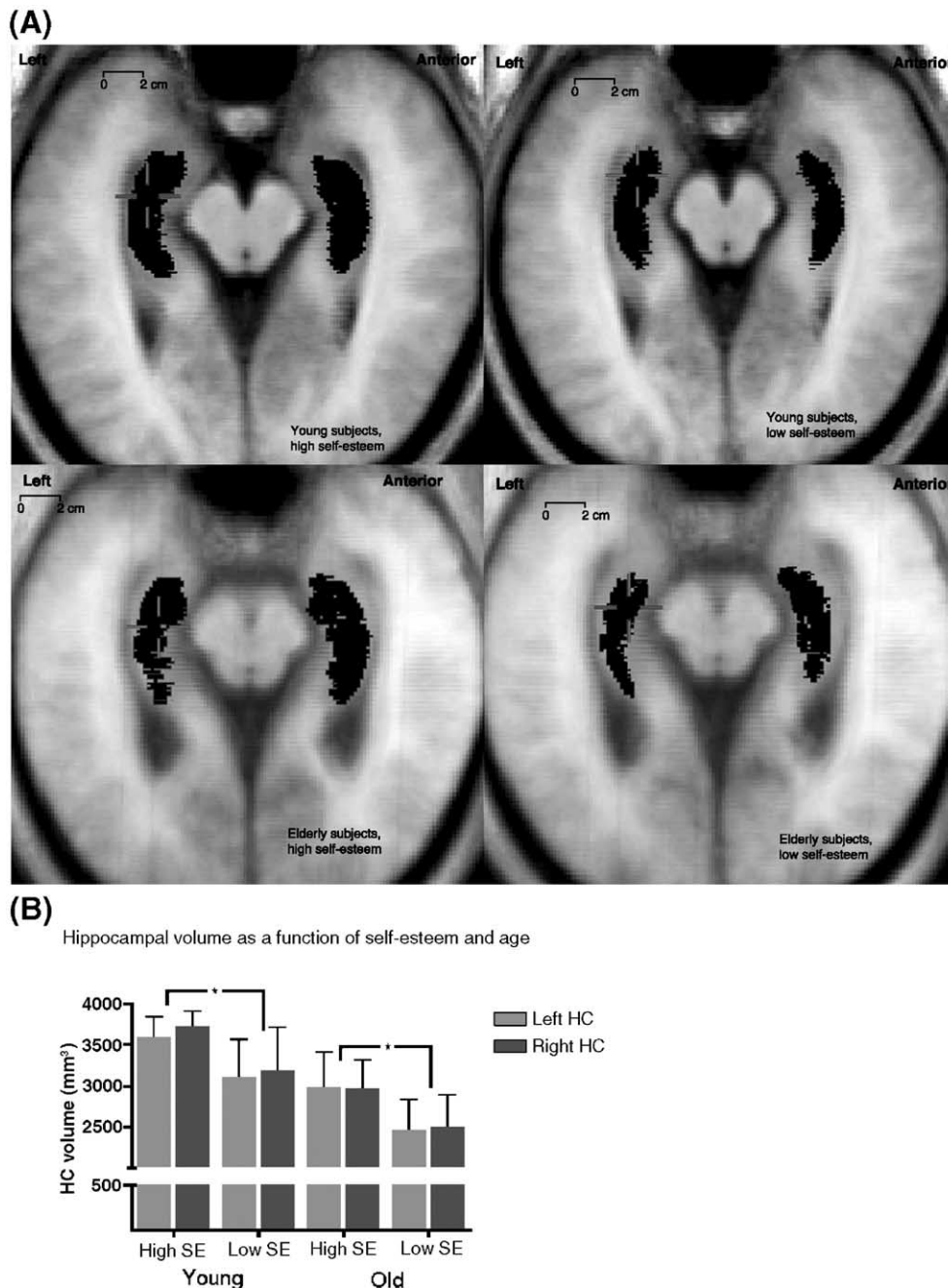
Fig. 1. (A) Probabilistic maps (shown at a 75% probability of any voxel in the medial temporal lobe being hippocampus) displayed in a horizontal section along the long axis of the hippocampus against the average structural image of the four subgroups (young and old, high and low self-esteem). (B) Bar graph for the hippocampal volumes in the four groups.

self-esteem or internal locus of control, with age, years of education, amygdala volume, whole brain gray and white matter, or CSF, were generally nonsignificant and so could not easily account for the association between the personality variables and hippocampal volume (all r with P > 0.20 except two; see Table 2).

Cortisol regulation in response to an acute stressor in young subjects

Since the young subjects were exposed to a psychosocial stress task, cortisol stress levels in response to the task, as well as

performance measures for the mental arithmetic task, were available. Performing a two-factor *mixed design* (group by time) ANOVA with the SEC groups as independent, and the seven cortisol samples as dependent measures, we found a significant main effect of SEC on the cortisol stress response ($F = 6.53$; $P < 0.05$; see Fig. 3).

No differences were observed for mental arithmetic performance between subjects with low and high SEC ($F < 1$, $P > 0.20$). Thus, replicating our previous research, it was observed that low SEC individuals showed a significantly larger cortisol response to a stressful situation (Pruessner et al., 1999b).
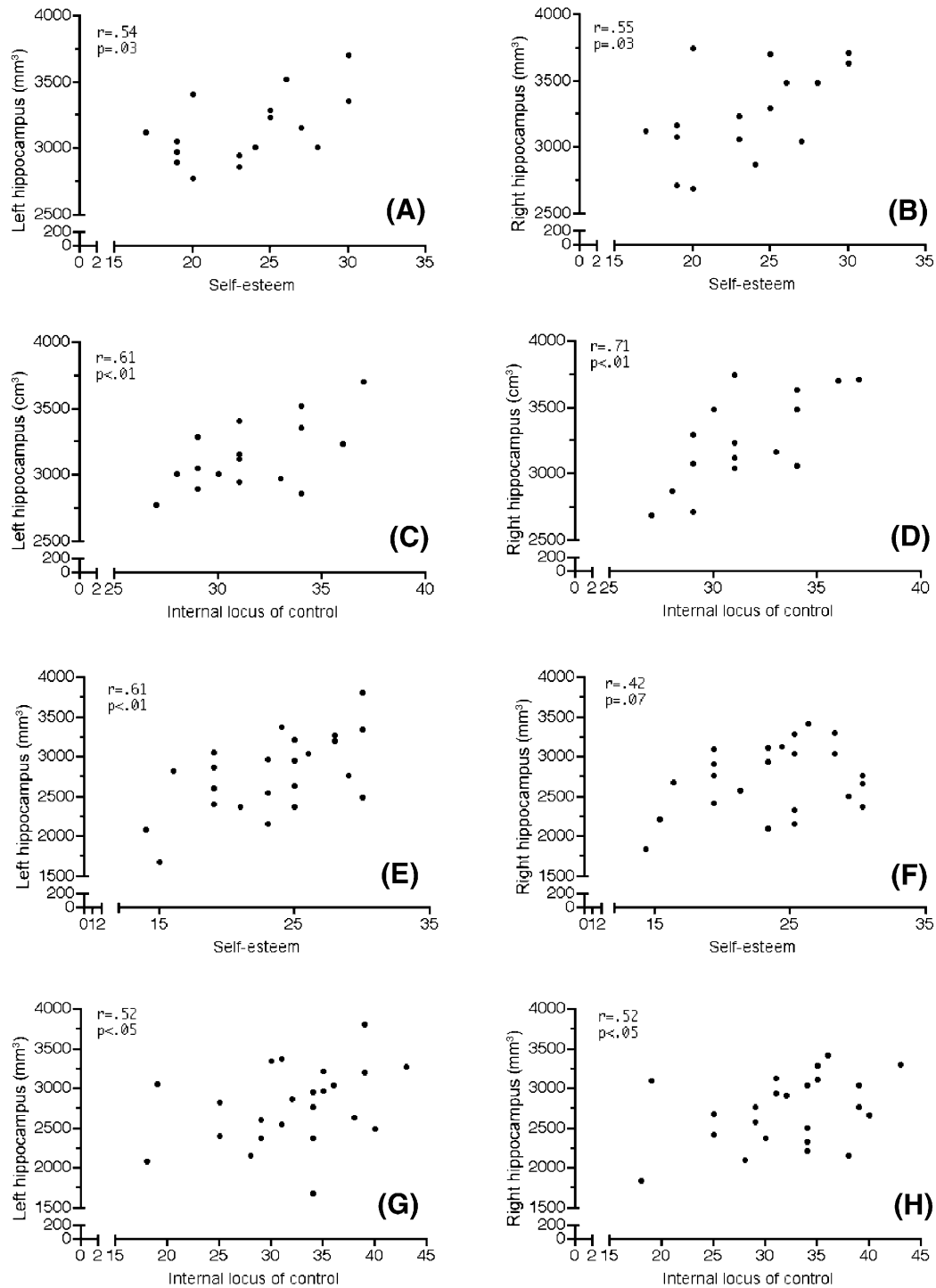
Fig. 2. Correlation between self-esteem and internal locus of control, and hippocampal volume, in young and elderly healthy adults. (A–B) Correlation of self-esteem and HC volume in the left and right hemisphere in young adults. (C–D) Correlation of internal locus of control and HC volume in the left and right hemisphere in young adults. (E–F) Correlation of self-esteem and HC volume in the left and right hemisphere in old adults. (G–H) Correlation of internal locus of control and HC volume in the left and right hemisphere in old adults.

Age-related changes between high and low SEC subjects in the elderly study sample

In the elderly subjects, age range spanned more than two decades, which allowed us to investigate age-related changes of brain imaging, cortisol, and neuropsychological parameters. In order to test effects of age on these parameters, we first conducted Pearson correlations with these variables for the whole group. Here, it could be observed that age was significantly associated with reductions in volumes of left and right hippocampus ($r = -0.41$ and $r = -0.52$, respectively). Similar observations were made for our measures of cognitive performance, the modified

Table 2
Correlations of self-esteem and internal locus of control with age, levels of education, amygdala volume, gray and white matter, and cerebrospinal fluid (CSF) in young ($n = 16$) and old ($n = 23$) subjects

	Young subjects		Old subjects	
	Self-esteem	Internal locus of control	Self-esteem	Internal locus of control
Age	$r = 0.05, P > 0.20$	$r = -0.11, P > 0.20$	$r = -0.29, P > 0.20$	$r = -0.19, P > 0.20$
Education	$r = 0.09, P > 0.20$	$r = 0.17, P > 0.20$	$r = -0.45, P < 0.05$	$r = -0.18, P > 0.20$
Amygdala	$r = 0.15, P > 0.20$	$r = 0.12, P > 0.20$	$r = 0.12, P > 0.20$	$r = 0.07, P > 0.20$
Gray brain matter	$r = 0.02, P > 0.20$	$r = 0.11, P > 0.20$	$r = 0.27, P > 0.20$	$r = 0.38, P > 0.20$
White brain matter	$r = -0.32, P > 0.20$	$r = -0.49, P < 0.05$	$r = 0.24, P > 0.20$	$r = 0.30, P > 0.20$
CSF	$r = 0.25, P > 0.20$	$r = 0.30, P > 0.20$	$r = 0.22, P > 0.20$	$r = 0.39, P > 0.20$

version of the MMSE-3M ($r = -0.65$), and the measure for signs of cognitive impairment (ADAS-cog; $r = -0.54$), for the total sample. We also observed a significant reduction of total brain gray matter with age ($r = -0.66$). Finally, age was found to be weakly negatively correlated with the aggregated cortisol response to awakening over the 12-month period ($r = -0.37, P = 0.09$), giving some evidence that cortisol dysregulation increased with age. Age by itself did not correlate with the self-esteem or locus of control scores ($P > 0.20$).

With age being identified as a significant factor in explaining variability in our brain imaging and neuropsychological variables in the elderly subjects, we then wanted to investigate whether SEC values interacted with age in affecting cognitive, endocrine, and structural parameters. That is, would low and high SEC subjects show different patterns of brain aging? Consequently, we investigated age-related patterns within the two groups of subjects with low and high SEC. We found that age was strongly negatively associated with hippocampal volume in the low SEC group ($r = -0.75, P = 0.008$ and $r = -0.64, P = 0.03$, for left and right hippocampus, respectively), but was not significantly associated in the high SEC group ($r = 0.12$ and 0.21; $P > 0.20$, respectively; Table 3). The magnitude of the correlation with total hippocampal volume was significantly different between the two groups ($z = 2.62, P = 0.001$). Expressed differently, age explained 43% to 55% of variability of left and right hippocampal volumes in the low SEC group, but less than 5% in the high SEC group.
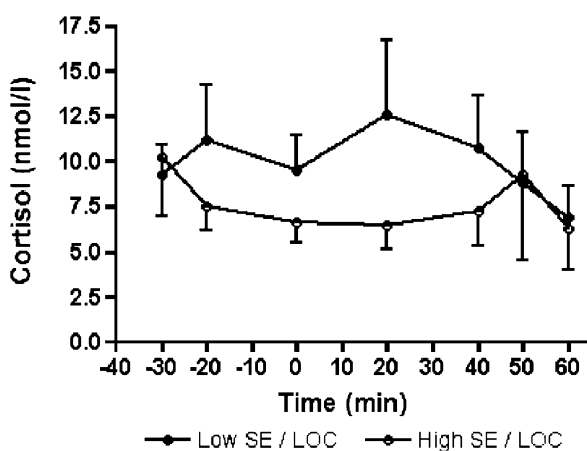

Fig. 3. Cortisol stress response in young subjects as a function of either high or low levels of self-esteem/internal locus of control.

All of the above effects were not modified when scores of the Geriatric Depression Scale were entered as a covariate in the analyses. Moreover, age had a differential effect on cognitive performance as a function of self-esteem and locus of control: the correlation of age with the 3M score was significant for the low SEC group, but not for the high SEC group (Table 3). The same pattern was found for the whole brain gray matter. The correlation of age with brain gray matter was significant with $r = -0.75$ ($P < 0.008$) in the low SEC group, but failed to show a significant impact with $r = -0.35$ ($P > 0.20$) in the high SEC group (Table 3).

As noted above, cortisol response to awakening showed a slight decrease as a function of age in the total group. When separating low and high SEC groups, however, it could be observed that this effect was driven by a highly significant negative correlation between age and the aggregated measure of the cortisol response to awakening over a period of 12 months in the low SEC group ($r = -0.72, P < 0.008$), explaining about 50% of variability in cortisol levels. In contrast, the correlation between age and aggregated awakening cortisol measure was not significant in the high SEC group ($r = -0.07, P > 0.20$; Table 3). Consistent with previous research, then, cortisol dysregulation among elderly subjects took the form of reduced response to awakening, and this effect was associated with increasing age among subjects with low self-esteem and locus of control.

Mediation analyses with personality measures, cortisol regulation, and hippocampal volumes

As part of the statistical evaluation, we conducted several mediation analyses employing hierarchical regression. These analyses were performed separately for the young and elderly study groups. One set of analyses examined the possible role of cortisol regulation as a mediator in the relationship between personality measures and hippocampal volumes. A second set of mediation analyses examined the possible role of hippocampal volume as a mediator in the relationship between self-esteem, locus of control, and cortisol regulation. None of these analyses produced significant results (Sobel ts < 1.4, Ps > 0.15), likely due to the relatively low sample sizes involved.

Discussion

We investigated the association between self-esteem, internal locus of control, hippocampal volumes, and cortisol regulation in healthy young and elderly individuals. A clear association between these personality measures and hippocampal volume

Table 3
Correlations of age with hippocampal volume, aggregated measure of the cortisol response to awakening, MMSE, and total brain gray matter, in the elderly subjects

Correlation of age and	Elderly subjects total ($n = 23$)	Elderly subjects, high self-esteem ($n = 10$)	Elderly subjects, low self-esteem ($n = 13$)
Left hippocampus	$r = -0.41$, $P = 0.03$	$r = 0.12$, $P > 0.20$	$r = -0.75$, $P = 0.008$
Right hippocampus	$r = -0.52$, $P = 0.004$	$r = 0.21$, $P > 0.20$	$r = -0.64$, $P = 0.03$
Cortisol response to awakening	$r = -0.36$, $P = 0.09$	$r = -0.07$, $P > 0.20$	$r = -0.72$, $P = 0.008$
ADAS	$r = 0.54$, $P < 0.008$	$r = 0.41$, $P > 0.20$	$r = 0.52$, $P = 0.07$
MMSE	$r = -0.65$, $P < 0.001$	$r = -0.47$, $P > 0.20$	$r = -0.69$, $P = 0.01$
Total brain gray matter	$r = -0.66$, $P < 0.001$	$r = -0.35$, $P > 0.20$	$r = -0.75$, $P = 0.008$

was evident in both populations. In both young and old populations, people with higher self-esteem and internal locus of control also had larger hippocampi. Contrasting subjects with high versus low self-esteem and internal locus of control, we observed significant hippocampal volume difference ranging from 12.4% (young subjects, left hemisphere) to 17.4% (elderly subjects, left hemisphere). Furthermore, we found an effect of self-esteem and internal locus of control on the cortisol response to an acute stressor, in the young subjects. In the elderly subjects, we found that only individuals low in self-esteem and locus of control showed significant age-related changes in global measures of cognitive functioning, brain volume decline, and decline in the cortisol response to awakening.

The relationship between self-esteem, locus of control, hippocampal volume, and cortisol regulation is likely complex and reciprocal, and the correlational nature of our data does not allow us to make strong causal inferences. However, we would like to at least consider and evaluate some plausible mechanisms that might be at the origin of the observed associations.

Self-esteem, locus of control, hippocampal volumes, and cortisol toxicity

The first interpretation of our findings we consider is that the association between personality traits and hippocampal volume is produced by the effects of the personality traits on cortisol regulation. From previous studies investigating the cortisol stress response in humans, we had reason to believe that self-esteem and locus of control have a significant effect on stress perception, and subsequently the (cortisol) stress response. When investigating the ability of human subjects to habituate to repeated psychological stress, we had found that subjects with low self-esteem and low internal locus of control showed continuous high cortisol stress responses (Kirschbaum et al., 1995). Furthermore, in an induced failure mental challenge group paradigm, where half of the subjects were exposed to a mental arithmetic task that contained a social evaluative component, only the subjects in the failure condition with low levels of self-esteem and internal locus of control showed a significant response (Pruessner et al., 1999b). In the current study with the young sample, low self-esteem and locus of control again predicted a higher cortisol stress response when subjects were exposed to a psychosocial stressor.

When considered over a lifetime, a higher susceptibility for perceiving a situation as stressful, and generating stress hormone release (as in the low SEC subjects), might have an effect on specific brain structures via the neurotoxic effects of cortisol. In line with this argument, personality research has

noted early on that it is not stressful life conditions per se but the perceived inability to manage them which produces detrimental biological effects over time (Bandura, 1992; Maier et al., 1985; Shavit and Martin, 1987). There are a number of models in the literature that suggest long-term negative consequences of increased HPA axis activity on brain function and integrity via the neurotoxic effects of glucocorticoids (Sapolsky et al., 1986; McEwen, 2001).

Supporting this interpretation, we observed a reduction in hippocampal volume among our elderly low SEC subjects that was somewhat more pronounced than among the young subjects. Moreover, among elderly subjects, SEC and age had a joint effect, with the detrimental effects of low SEC subjects becoming increasingly apparent as subjects grew older. It is important to note that the correlation between self-esteem and hippocampal volume remained significant ($r = 0.51$, $P = 0.05$; $n = 17$), even after excluding subjects with the lowest cognitive scores (3M < 28) from the analysis. That is, although subjects with lower cognitive abilities have lower self-esteem as well, the reduction in cognition as seen in some subjects with advanced age (and perhaps indicative of a beginning neurodegeneration) is by itself not sufficient to explain the current association between hippocampal volume and self-esteem scores.

The declining cortisol response to awakening in the elderly sample might seem puzzling at first, since it appears to contradict the proposed increased neurotoxicity from glucocorticoids. However, it has to be kept in mind that the cortisol response to awakening is but one marker of hpa axis regulation, which by itself is complex and multifaceted. Earlier findings using the cortisol response to awakening as a marker of basal HPA regulation support the notion of a decrease of the awakening response in association with burnout, or chronic pain, suggesting the cortisol response to awakening can be a sign of dysregulation of the HPA (Pruessner et al., 1999a; Van Cauter et al., 1996). More recently, two independent studies have reported a lack of a cortisol response to awakening in subjects with hippocampal lesions (Buchanan et al., 2004; Wolf et al., 2005), with one study suggesting that the cortisol response to awakening might serve as a marker of HC integrity (Buchanan et al., 2004). In the current study, we found that, in the whole group, there was a negative correlation between the area under the curve of the awakening response, and aging. When splitting the whole group for subjects with high and low SEC, this correlation between cortisol and age became more pronounced in the low SEC group, while it was no longer present in the high SEC group. This confirms and extends the earlier reports of the cortisol response to awakening as a measure of HC integrity, since the decline in the cortisol

response to awakening was associated with a decline in hippocampal volume in the elderly subjects. Our finding that smaller hippocampal volumes in the elderly subjects were correlated with smaller cortisol responses to awakening, while smaller hippocampal volumes in the younger subjects were associated with a larger cortisol stress response, further raises the question of whether the basal cortisol regulation is generally dissociated from the cortisol responses to stress. Since we did not perform cortisol baseline assessment in the young, or cortisol stress response assessment in the elderly, this question needs to be addressed in a future study.

There are reasons to question the applicability of the neurotoxicity hypothesis of cortisol to our findings, however. First, the relationship between personality measures and hippocampal volume was present in young as well as elderly subjects. Thus, in the young subjects, one would need to assume that the toxic consequences of cortisol had already taken a toll to explain the smaller volumes in association with higher cortisol stress responses (presumably, as a result of higher stress perception due to low self-esteem and low internal locus of control). Since our young subjects were on average at the beginning of the third life decade, it would need to be assumed that the neurotoxic effect of cortisol on especially this part of the brain should then continue to have negative consequences across the life span, with increasing volume differences in middle to late adulthood. Although the elderly subjects did show smaller hippocampal volumes compared to the young, the difference between high and low SEC levels was only slightly more pronounced in the elderly compared to the young (16.6% hippocampal volume difference in the elderly, versus 12.5% volume difference in the young), a difference that seems less than one should expect to result from a lifetime of neurotoxicity.

In addition, the mediational analysis we conducted investigating whether cortisol measures might mediate the association between personality measures and hippocampal volume did not lend support to the idea that the relationship between self-esteem/locus of control and hippocampal volume was mediated by the baseline or cortisol stress assessments in the two populations, thus failing to support the proposed mechanism of causality. Although the number of subjects in both populations was rather small, thus providing only moderate power to uncover a potentially existing mediation in our subjects if existent in the general population, this casts further doubt on the explanation of the observed relationship as a consequence of cortisol neurotoxicity.

Self-esteem, locus of control, and hippocampal volume

We now consider an alternative explanation, that naturally occurring variation of hippocampal volume may be linked causally to self-esteem, locus of control, and cortisol reactivity. Although there are to date very few studies that have investigated the potential relationship between specific brain structures and personality measures, it seems tempting to consider such a relationship for our current set of data. For example, the hippocampus is one of the major limbic system structures involved in the regulation of the stress response (Fuchs and Flugge, 2003), and variations in hippocampal volume might affect the system's ability to regulate cortisol after a stressor has been perceived. Rather than being the result of intoxication by glucocorticoids, therefore, reduced hippo-

campal volume might present a vulnerability factor for higher stress response. A similar idea has recently been proposed in conjunction with risk factors for developing Posttraumatic Stress Disorder (PTSD), in a study investigating hippocampal volume in twin brothers. Here, in subjects who developed PTSD as a consequence of participating in the Vietnam War, the researchers observed lower hippocampal volume compared to subjects who went to war, but did not develop PTSD. Intriguingly, however, lower hippocampal volume could also be observed in the PTSD subjects' twin brothers – who never went to war – suggesting that the hippocampal volume might be a risk factor for, rather than a consequence of, developing PTSD (Gilbertson et al., 2002).

As mentioned, the possibility that hippocampal volume might play a causal role is supported by the fact that we found consistent results even among relatively young adults. Recently, we have reported on variations in hippocampal volume in young populations (Pruessner et al., 2001), suggesting that there is a considerable range of hippocampal volumes already in young subjects. At the same time, self-esteem is known to be a stable trait with considerable intraindividual stability throughout life (Markus and Herzog, 1991). This supports a model in which variations in brain morphology could become a pathway to certain personality characteristics early in life.

To formulate a model of the possible role of the hippocampus in shaping self-esteem and locus of control, we can draw on its known functions. The hippocampus is a primary structure for memory contextualization, and a reduced ability to appropriately contextualize certain life events such as failures or social rejections might be correlated with developing low self-esteem and locus of control. That is, if specific situational and environmental characteristics associated with a negative life event cannot be recalled, this failure of source monitoring could trigger an overgeneralized self-perception of being a failure or being socially rejected in general, which might produce low self-esteem and low locus of control during critical development stages (Davidson et al., 2002; Kernis et al., 1989; Showers, 1992). Of course, the question arises why this should then not be true for positive life events as well, that is a general failure of source monitoring for both positive and negative life events with no net consequences for self-perception. One possible explanation lies in the specific function of the hippocampus within the limbic system, and its role in regulating the hpa system. There is evidence that it is specifically the hippocampus together with the anterior cingulate that are involved in the stress response (Sinha et al., 2004). It is known that the anterior cingulate is involved in error monitoring, when a mismatch between expectations and reality occurs (Wang et al., 2005), and also specifically in the stressful reaction to negative social feedback (Eisenberger and Lieberman, 2004). The coordination between the anterior cingulate and the hippocampus would therefore support a specific role of the hippocampus in reaction to negative life events. In addition, because the hippocampus is critical to autobiographical recall in general, as well as the explicit and reflective overriding of automatic self-judgments (Lieberman et al., 2004), a less optimal level of functioning of this structure may make it difficult for a person under stress to actively call to mind reassuring episodes of success, social support, or acceptance by significant others, all of which are coping strategies employed by high self-esteem and locus of control individuals to maintain a positive mood and positive self-concept (Bartels and Zeki, 2000; Crocker

and Park, 2003; Dodgson and Wood, 1998; Linville, 1987; Setliff and Marmurek, 2002).

The medication analysis failed to yield direct support for the alternative hypothesis that hippocampal volume is a significant mediator in the personality/cortisol regulation relationship, either. Again, this analysis was hampered by the relatively low degrees of freedom, and thus these associations should be investigated in a larger study.

Limitations and future directions

Although our data do not allow us to draw firm causal conclusions, our results clearly demonstrate that self-esteem and locus of control are significantly linked to the volume of the hippocampus in healthy young and elderly subjects. Further, we found evidence that these two factors are also related to the acute and chronic regulation of the major stress hormone in humans, cortisol.

We acknowledge several limitations of the current set of studies, which make a replication in a larger sample set desirable. First, we used a cross-sectional study approach, while aiming to explain changes that are likely to occur as a result of aging. Ideally, longitudinal studies would be required to follow the developing brain and personality and clarify the causal relationship between the variables. In addition, there are likely other factors either related or unrelated to self-esteem and locus of control (e.g., social support, optimism, etc.), which were not assessed in the current study, but certainly warrant investigation in future studies to determine the interaction of other personality traits and environmental factors with the personality traits reported here, and with the assessed brain variables. Relatedly, it should be noted that we did not collect IQ data to complement our personality assessment. Although we included cognitive assessments to control for possible signs of cognitive decline with aging (the 3M scores, for example), this is a less than ideal approach that should be revised in future studies.

Next, there are some methodological issues that render the comparison of the two different study populations difficult. Cortisol was assessed in response to a stress paradigm in the young population, using salivettes and a fluorescence immunoassay for analysis. In contrast, cortisol was only available from baseline measures in the elderly sample, using filter paper and a radioimmunoassay for analysis. This methodological difference is a function of the two different study protocols for the larger projects from which these data were extracted: it will be preferable to employ a common data acquisition and analysis method in future studies, to gain a better understanding of the relationship between hormonal regulation and these personality measures. Another difference between the samples involved gender: in the younger sample, only men were studied, while in the elderly, men and women were investigated, with women comprising the majority of the subjects. Although we observed no gender effects in the elderly sample, additional research is needed to explicitly assess possible interactions of gender with the variables studied here. Finally, self-esteem and locus of control have different theoretical grounds, and the fact that we find very similar effects of both these traits on physiological and anatomical; markers certainly warrants further research by itself. In this context, it is also possible that because both traits were assessed in close temporal proximity to the stress task in the young population, this may have induced a self-affirmation (Steele, 1988) or similar carry-over effect in some

participants, potentially affecting the subsequent stress response (although this would not be a concern for the correlations with hippocampal volume).

Despite these shortcomings, the documentation of brain and endocrine correlates of self-esteem and locus of control is, in itself, an important finding. It will be challenging for future studies to uncover the exact nature and origin of the association we observed.

Acknowledgments

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