Negative Association of Neuroticism with Brain Volume Ratio in Healthy Humans

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Background: *Brain volume decreases with normal aging. We sought to determine whether, in addition to age, individual differences in stress reactivity (i.e., neuroticism) would also predict reductions in brain volume.*

Methods: *Brain volume ratios were calculated for a sample of 86 healthy volunteers, based on segmented brain volumes taken from T_1-weighted magnetic resonance imaging and corrected for intracranial volume. Standardized self-reported measures of dispositional neuroticism were concurrently obtained by administering the Revised NEO Personality Inventory.*

Results: *After statistically controlling for age and sex, neuroticism showed a significant negative association with the ratio of brain to the remainder of the intracranial volume, but was not related to intracranial volume itself. In particular, subfactors of neuroticism related to the chronic experience of arousing negative emotions were associated with reduced brain ratio.*

Conclusions: *These results suggest that individual differences in stress reactivity contribute to reductions in brain volume observed during adulthood.* Biol Psychiatry 2001;50:685–690 © *2001 Society of Biological Psychiatry*

Key Words: Stress, neuroticism, personality, brain volume, intracranial volume, magnetic resonance imaging

Introduction

Individual humans vary widely in brain size (Appel and Appel 1942). To date, scientists have documented several factors that contribute to this variation. Factors related to brain growth, such as sex and body size, are thought to influence the maximal size that an individual's brain attains by 16 years of age (Carmichael 1990; Raz et al 1998; Sgouros et al 1999). Since the growth of the brain, meninges, and cerebrospinal fluid spaces drive skull growth during childhood, investigators can estimate maximal lifetime brain volume by measuring the intracranial volume (ICV) of the skull (Blatter et al 1995; Courchesne et al 2000; Pfefferbaum et al 1994).

Other factors influence reductions in brain volume that occur with aging subsequent to puberty. By combining measures of brain volume with measures of ICV, investigators can infer how much reduction in volume has occurred since brain volume was at its peak (Jenkins et al 2000). In adults, age robustly predicts reductions in brain volume. Following its peak at approximately 16 years of age, brain volume declines roughly 1.64% each decade (Dekaban 1978). Recent evidence suggests that a history of stressful life events (in the form of physical or sexual abuse during childhood) also may influence both brain growth (indexed by ICV) and brain shrinkage (De Bellis et al 1999). In addition, researchers have reported reductions in brain volume in a variety of psychiatric disorders, including Post Traumatic Stress Disorder (PTSD), mood disorders, and schizophrenia (Bremner 1999; Friedman et al 1998; Goldstein et al 1999; Soares and Mann 1997). One factor common to all of these disorders is an increased subjective experience of distress. If chronic stress can produce reductions in brain volume, this relationship might partially account for observed reductions in brain volume associated with various psychiatric disorders.

In addition to variations in ICV, individuals also differ in terms of their propensity to experience stress. Based on the seminal observations of Pavlov, who documented individual differences in the stress reactions of dogs during difficult discriminative learning tasks (Pavlov 1935), Eysenck postulated that stress reactivity characterized a primary feature of a personality trait that he labeled "neuroticism" (Eysenck 1998). The centrality of stress reactivity to neuroticism is reflected in the content of many current standardized personality measures (Cloninger 1987; Costa and McCrae 1995; Tellegen et al 1988). Since neuroticism shows high stability within individuals after they reach puberty (Costa and McCrae 1994), its measurement at any time during adulthood should provide a reliable estimate of stress reactivity over the life span. In

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Table 1. Demographics and Personality Variables

	Male (n = 38)		Female (n = 48)			
	Mean	SD	Mean	SD	T(84)	p
Age at scan (years)	29.4	6.7	31.4	7.5	1.26	NS
Education (years)	16.5	2.7	16.3	2.1	.43	NS
Height (cm)	175.6	6.9	165.2	6.2	6.00	<.001
Weight (kg)	79.2	10.2	65.8	13.5	4.15	<.001
Neuroticism	48.3	9.2	44.3	8.7	—	—
Extraversion	55.6	8.7	53.0	9.5	—	—
Openness	54.2	10.1	54.4	11.7	—	—
Agreeableness	53.3	8.3	50.7	8.8	—	—
Conscientiousness	51.5	10.0	48.1	10.3	—	—

addition, because stress consists of an individual's reaction to an event rather than the event itself, individuals may vary widely in their stress response to the same event. Thus, neuroticism may provide a more accurate index of the biological effects of stress than estimates of the severity of stressors.

While a few investigators have examined potential relationships between a history of traumatic events and brain structure (Bremner 1999; De Bellis et al 1999; Stein et al 1997), none have addressed whether individual differences in stress reactivity might be associated with reductions in brain volume that occur during adulthood. We set out to examine this relationship by correlating neuroticism with the ratio of brain volume to ICV in a sample of healthy adults who had no history of psychiatric disorder or trauma.

Methods and Materials

Participants

Eighty-six physically and psychiatrically healthy volunteers (38 males, 48 females) participated in the study (see Table 1). Volunteers were recruited through the Normal Volunteer Office of the Clinical Center of the National Institutes of Health between the years 1994 and 2000. The sample was between 19 and 45 years of age and was representative of the population of suburban Maryland (65% White, 16% Black, 9% Asian, and 7% Hispanic). On the basis of history, physical examination, blood chemistry, and a negative urinary drug screen, all participants were judged to be medically healthy. Based on structured clinical interviews (Structured Clinical Interview for DSM III-R) administered by trained social workers, no participant had current or past psychiatric disorders meeting DSM-III-R Axis I or Axis II criteria, including PTSD (APA 1998). Participants also had no first-degree relatives with a history of alcoholism or drinking problems, and no history of head trauma leading to unconsciousness. None of the participants reported drinking more than three alcoholic beverages per day on a regular basis. All participants provided written informed consent to participate in the study, which was approved by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Institutional Review Board.

Magnetic Resonance Imaging Scan Acquisition and Processing

Participants were scanned with a 1.5 Tesla Magnetic Resonance Imaging Scanner (GE Medical Systems, Milwaukee, WI) using a fast spoiled-grass (FSPGR) sequence. We acquired a contiguous series of high-contrast, 2 mm thick T_1-weighted coronal images (TR = 25 msec, TI = 5 msec, TE = 16 msec, Flip = 60°, NEX = 1). Images had a 256 × 256 pixel acquisition matrix with a 240 × 240 mm field of view. Thus, each brain volume consisted of 124 contiguous coronal slices with a voxel size of .9375 × .9375 (in-plane) × 2.0 mm (through-plane). The parameters of this magnetic resonance imaging (MRI) protocol remained constant across the 6 years of data acquisition.

We manually separated intracranial tissue from the skull on coronal sections with a hand-driven cursor. The ICV included the cerebrum and cerebrospinal fluid (CSF) spaces covering the cortex, but excluded the cerebellum and CSF of the posterior fossa. Interrater reliability for manual identification of the ICV of 10 randomly selected MRI volumes was high (intraclass correlation = .97). Next, ICV was automatically segmented into gray matter, white matter, sulcal CSF, and ventricular CSF, using previously described and validated computerized methods (Momenan et al 1997) (see Figure 1). The ratio that indexed brain volume reduction was computed with the following compositional formula: (gray matter volume + white matter volume) / ((gray matter volume +

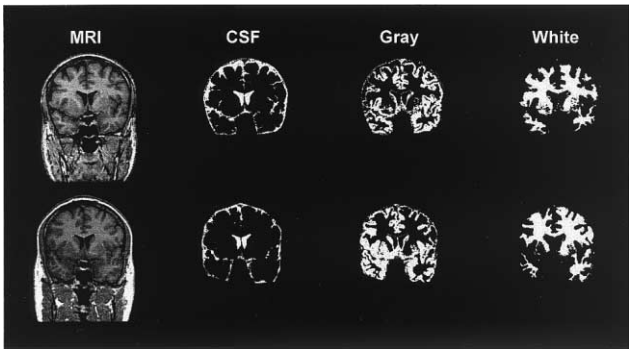

Figure 1. Brain measures of two representative healthy males scoring high (top: Neu T = 59; ICV = 1458.92 mL; brain ratio = 3.73; age = 29) versus low (bottom: Neu T = 27; ICV = 1393.33; brain ratio = 6.71; age = 29) in neuroticism.

Table 2. Brain Volume Measures

	Male		Female			
	Mean	SD	Mean	SD	T(84)	*p*
Sulcal CSF (ml)	231.1	35.5	214.8	40.7	1.95	NS
Ventricular CSF (ml)	17.7	7.8	13.5	5.5	2.93	.004
White Matter (ml)	548.9	55.6	486.8	48.2	5.54	<.001
Gray Matter (ml)	589.2	63.9	524.1	55.8	5.04	<.001
Brain Volume (ml)	1141.0	94.3	1010.8	88.7	6.57	<.001
Intracranial Volume (ml)	1372.1	99.4	1225.5	113.6	6.27	<.001
Sulcal CSF Ratio	.20	.04	.21	.04	−1.08	NS
Ventricular CSF Ratio	.01	.01	.01	.00	1.84	NS
White Matter Ratio	.68	.08	.66	.08	.72	NS
Gray Matter Ratio	.75	.08	.75	.07	.26	NS
Brain Ratio	5.04	.85	4.84	.81	1.14	NS

white matter volume + ventricular CSF volume + sulcal CSF volume) − (gray matter volume + white matter volume)). This formula yields the ratio of brain to the remainder of intracranial contents and thus provides a measure of brain shrinkage from its maximal volume (Agartz et al 1999; Aitchison 1983). Investigators can calculate compositional ratios of gray matter, white matter, sulcal CSF, and ventricular CSF by substituting any of these compositional volumes for the "(gray matter volume + white matter volume)" term in the above formula.

Personality Assessment

Five factors of personality (neuroticism, extraversion, agreeableness, conscientiousness, and openness) and their subfactors were assessed with a computer-administered, 240-item version of the Neuroticism-Extraversion-Openness Personality Inventory-Revised. Sex-normed broad personality domain factor scores were calculated by combining 48 items for each of the five factors. Similarly, sex-normed facet scores for neuroticism were calculated by combining eight items for each of the five subfactors comprising neuroticism (anxiety, angry hostility, depression, self consciousness, impulsiveness, and vulnerability) (Costa and McCrae 1992).

Statistical Analysis

Demographic and brain volume variables across males and females were compared with *t* tests (NEO PI-R factors were not compared because they were derived from sex-normed scores). An analysis of covariance (ANCOVA) model enabled us to investigate the relationship between neuroticism (the covariate of interest) and brain volume reduction while statistically controlling for potential influences of sex (female vs. male) and age at scan. Auxiliary analyses verifying the specificity of the findings were conducted using the same model and substituting alternative brain volume or personality variables. Tests of parallelism of regression slopes were performed to ensure that the relationship between brain volume measures and personality variables was similar for males and females. Alpha was set at .05 (two-tailed) for both the primary hypothesis that neuroticism would show an association with brain volume ratio, as well as for exploratory analyses examining whether this association would be most pronounced for neuroticism subscales related to stress reactivity. With the current sample of 86 participants, power (=81) was adequate to detect a medium effect size of 0.30 using a bivariate product moment correlation (two-tailed) (Cohen 1988).

Results

In the present sample, men were taller ($t(84) = 6.00$; $p < .001$), and heavier ($t(84) = 4.15$, $p < .001$) than women, but did not differ in age (combined mean = 30.5, SD = 7.2) or years of education (combined mean = 16.4, SD = 2.4; see Table 1). Although men had larger brain and ICVs than women ($t(84) = 6.27$, $p < .001$), sex was not significantly associated with any of the brain ratio measures (see Table 2).

In support of the primary hypothesis, neuroticism was negatively associated with brain ratio (beta = −.23; $t(82) = -2.31$, $p < .05$; see Figure 2), as was age at scan (beta = −.31; $t(72) = -3.12$, $p < .005$; see Figure 3). Tests of parallelism indicated that the slopes of these associations did not differ significantly for women versus men. When different components of brain volume were substituted in the model for brain ratio, only sulcal CSF ratio remained negatively associated with neuroticism (beta = .24; $t(82) = 2.38$, $p < .05$), indicating that the reductions in brain volume associated with neuroticism were not selective for gray or white matter. Sulcal CSF ratio (beta = .35; $t(82) = 3.53$, $p < .001$) was also associated with age.

Substitution of other broad personality domain scales for neuroticism in the model (i.e., extraversion, openness, agreeableness, conscientiousness) revealed no other significant associations with brain ratio measures; however, substitution of the neuroticism facet scales for the broad domain scale revealed more selective associations. Specifically, N1 (anxiety; beta = −.25, $t(82) = -2.51$, $p < .05$) and N4 (self consciousness; beta = −.22, $t(82) = -2.21$, $p < .05$) retained negative associations with brain ratio, while N2 (angry hostility), N3 (depression), N5 (impulsiveness), and N6 (vulnerability) did not (see Table 3). Inclusion of ICV as a covariate in the all of the above models yielded essentially identical results, indicating that the brain ratio measures were not dependent upon ICV.

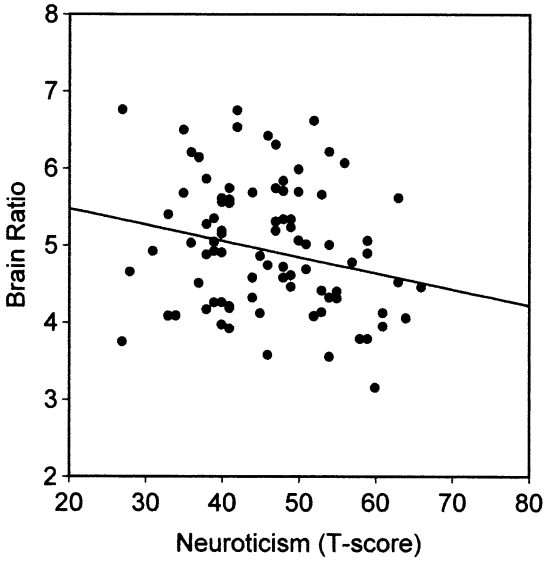

Figure 2. Plot of neuroticism (*t* score) versus brain volume corrected for intracranial volume ($n = 86$).

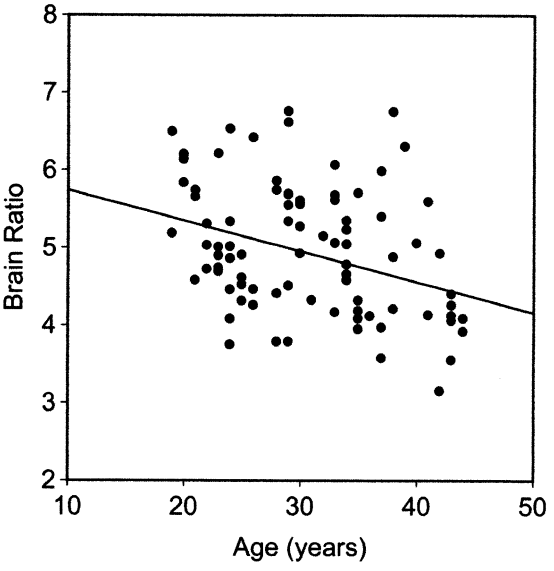

Figure 3. Plot of age at scan (years) versus brain volume corrected for intracranial volume ($n = 86$).

Discussion

These findings demonstrate a significant negative association between brain volume ratio and personality variables related to stress reactivity. Beyond age and sex, neuroticism was negatively associated with the ratio of brain volume to ICV. Auxiliary analyses suggested that this effect manifested most prominently as an increase in sulcal CSF, and that subfactors of neuroticism related to chronic experience of arousing negative emotions showed the most robust negative associations with brain ratio measures.

One other study has documented an association between personality variables and brain structure (Matsui et al 2000). Matsui et al reported significant associations between several scales of the Minnesota Multiphasic Personality Inventory (MMPI) and reductions in prefrontal volume relative to the rest of the brain, particularly in males. We did not observe a significant difference between neuroticism and reduced brain ratio for males versus females in this sample. While the MMPI was developed to discriminate psychiatric from nonpsychiatric patients, the NEO PI-R was derived from trait theories of normal personality. Thus, while the MMPI clinical scales are designed to predict a general tendency toward psychopathology, only some of the NEO PI-R factors have been shown to predict specific psychopathological outcomes. For instance, longitudinal research indicates that only neuroticism robustly predicts future incidence of affective and anxiety disorders (Krueger et al 1996). These differences in scale derivation might explain why Matsui et al observed correlations between many MMPI subscales and brain volume reductions, while we detected a more selective relationship between neuroticism and brain ratio.

Exploratory analyses of neuroticism subscales further confirmed the selectivity of the association between neuroticism and brain ratio. As mentioned earlier, a central component of stress reactivity involves the chronic experience of arousing negative emotions, such as anxiety (Watson and Pennebaker 1989). Thus, one might expect anxiety-related facets of neuroticism to show the most robust negative associations with brain ratio measures. Indeed, we found that the neurot-

Table 3. Partial Correlations between Brain Measures and Neuroticism Facet Scales ($n = 86$)

	N1	N2	N3	N4	N5	N6[a]
Intracranial Volume	−.09	.16	.06	.05	.07	.09
Gray Matter Ratio	−.12	.03	.03	−.05	.03	−.01
White Matter Ratio	−.11	−.12	−.15	−.15	−.10	−.09
Ventricular CSF Ratio	−.01	−.07	.00	−.05	−.03	−.04
Sulcal CSF Ratio	.24[b]	.10	.15	.22[b]	.07	.10
Brain Ratio	−.25[b]	−.10	−.13	−.22[b]	−.06	−.10

[a]N1, Anxiety; N2, Angry Hostility; N3, Depression; N4, Self-consciousness (Social Anxiety); N5, Impulsivity; N6, Vulnerability (Lack of Coping).
[b]$p < .05$ when substituted for neuroticism in an otherwise equivalent ANCOVA including sex and age.

icism anxiety subscale (N1) was negatively associated with brain ratio, while the angry hostility (N2), depression (N3), and impulsiveness (N5) subscales were not (see Table 3). Surprisingly, the vulnerability (N6) subscale was not associated with brain ratio, whereas the self consciousness (N4) subscale was; however, subsequent qualitative item analysis of these subscales revealed that the facet labels did not fully represent item content. Specifically, items in the self consciousness subscale appeared to index the experience of highly arousing negative emotions in social contexts (e.g., "At times I have been so ashamed, I just wanted to hide."), whereas items in the vulnerability scale appeared to reflect an inability to cope with the experience of stress (e.g., "When I'm under a great deal of stress, sometimes I feel like I'm going to pieces.") (Costa and McCrae 1992). Taken together, these exploratory findings suggest that the experience of stress per se, rather than participants' ability to cope with it, shows the most consistent negative association with brain ratio.

The negative association between neuroticism and brain ratio is consistent with the idea that brain ratios index degree of brain shrinkage, while ICV indexes processes related to growth (Jenkins et al 2000). In the present study, variables relevant to brain growth during childhood development were associated with ICV. For instance, sex was strongly associated with ICV, which fits with the observation that as a group, males ultimately attain larger brain size than females. The fact that neuroticism was not associated with ICV, but was instead associated with brain ratio suggests that this association developed during adulthood, after the brain had reached its maximal volume, at least among physically and mentally healthy volunteers.

The specificity of this association between neuroticism and brain ratio raises the question of why neuroticism is not also associated with reduced ICV. A number of possibilities exist. First, while neuroticism typically shows high stability over the postadolescent adult life span (Costa and McCrae 1994) and carries a substantial heritable component (i.e., approximately 50%)(Bouchard 1994), instruments have not been developed to measure this construct in children. It is possible that neuroticism may show less cross-temporal stability during childhood. Second, the healthy volunteers in our sample both scored low in neuroticism (t score range = 27–66) and lacked a history of psychological trauma. It is possible that people with higher levels of neuroticism or a history of psychological trauma or both might show reductions in ICV in addition to brain ratio (De Bellis et al 1999). The cross-sectional design of the current study limits our ability to assess the likelihood of either of these possibilities, which can only be adequately addressed in the context of longitudinal research that tracks stress reactivity and stressors from childhood to adulthood.

Nonetheless, at least one causal mechanism could plausibly account for the observed relationship between neuroticism and brain volume reduction. As mentioned previously, people who score high in neuroticism report experiencing more stress in a variety of situations (Watson and Pennebaker 1989). Theorists have persuasively argued that chronic stress can lead to dysregulation of the hypothalamic-pituitary-adrenal axis, which can induce hypercortisolemia (Chrousos and Gold 1992). Accordingly, investigators have observed increased plasma and salivary cortisol in people who score high in neuroticism (Miller et al 1999; van Eck et al 1996). Hypercortisolemia can speed naturally occurring excitotoxic processes in neurons (Sapolsky 1994), and investigators have documented damage to both hippocampal and cortical neurons in the brains of monkeys who lived under severely stressful social conditions (Uno et al 1989). The effects of hypercortisolemia can have a global impact on cerebral volume in humans as well. For instance, patients with Cushing's Disease, which is characterized by hypercortisolemia, show premature brain atrophy (Simmons et al 2000). Thus, in addition to a history of psychological trauma, a predisposition toward stress reactivity may also promote brain volume reductions. The present study cannot directly address this proposed mechanism due to the absence of diurnal cortisol measures, but future studies may.

It is not clear whether reductions in brain volume associated with neuroticism have any functional significance—they may simply provide an additional marker of stress reactivity. Even so, the findings suggest an underlying mechanism that might account for the reductions in brain volume observed across many different psychiatric disorders. Thus, these results highlight the importance of considering individual differences in stress reactivity when modeling the effects of psychological trauma on biological systems, and also suggest that chronic stress may have deleterious effects on brain regions that extend beyond the hippocampus (Sanchez et al 2000). Future research will have to determine whether specific brain areas show preferential reductions, whether the rate of shrinkage can be slowed, and whether glucocorticoids mediate the shrinkage, as we have suggested.

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