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A multivariate twin study of hippocampal volume, self-esteem and well-being in middle-aged men

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Self-esteem and well-being are important for successful aging, and some evidence suggests that self-esteem and well-being are associated with hippocampal volume, cognition and stress responsivity. Whereas most of this evidence is based on studies on older adults, we investigated self-esteem, well-being and hippocampal volume in 474 male middle-aged twins. Self-esteem was significantly positively correlated with hippocampal volume (0.09, $P = 0.03$ for left hippocampus, 0.10, $P = 0.04$ for right). Correlations for well-being were not significant ($Ps > 0.05$). There were strong phenotypic correlations between self-esteem and well-being (0.72, $P < 0.001$) and between left and right hippocampal volume (0.72, $P < 0.001$). In multivariate genetic analyses, a two-factor additive genetic and unique environmental (AE) model with well-being and self-esteem on one factor and left and right hippocampal volumes on the other factor fits the data better than Cholesky, independent pathway or common pathway models. The correlation between the two genetic factors was 0.12 ($P = 0.03$); the correlation between the environmental factors was 0.09 ($P > 0.05$). Our results indicate that largely different genetic and environmental factors underlie self-esteem and well-being on one hand and hippocampal volume on the other.

Keywords: Aging, heritability, hippocampus, self-esteem, twins, well-being

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Reduced hippocampal volume has been associated with mild cognitive impairment, Alzheimer's disease and other disorders (Gilbertson *et al*. 2002; Nelson *et al*. 1998; Seab *et al*. 1988; Sheline *et al*. 1999; Shen *et al*. 2010). The hippocampus is a major target of cortisol released in the hypothalamic-pituitary-adrenal (HPA) axis, a major stress–response system (Hauger *et al*. 2006). HPA axis dysregulation is inversely correlated with hippocampal volume in some, but not all, studies (Kremen *et al*. 2010a; Lupien *et al*. 1998; MacLullich *et al*. 2005; Pruessner *et al*. 2007; Wolf *et al*. 2002). HPA axis responsivity to stress is also associated with self-esteem (Bushman *et al*. 2009; Ford & Collins 2010; Pruessner *et al*. 1997). Chronic stress might result in reduced self-esteem or high self-esteem might buffer responses to stress. Thus, self-esteem could be associated with hippocampal volume.

Pruessner *et al*. (2005) found that self-esteem was significantly correlated with left and right hippocampal volume, averaging $r = 0.55$ in young and $r = 0.52$ in older adults. A significant correlation was replicated in men, but not women (Pruessner *et al*. 2007). In elderly adults, the same group found no significant correlation between self-esteem and hippocampal volume (Engert *et al*. 2010).

Given the sometimes strong but inconsistent relationship between self-esteem and hippocampal volume, we sought to extend the findings of Pruessner and colleagues in our large twin sample ($n = 474$). With our focus on twins, we were also interested in the genetic underpinnings of this relationship. The heritability of hippocampal volume in our sample was 0.63 in the left and 0.64 in the right hemisphere (Kremen *et al*. 2010b). The median heritability estimate for self-esteem in adolescents and adults using the Rosenberg Self-Esteem Scale (Rosenberg 1965) is 0.40 (range: 0.29–0.62; Kamakura *et al*. 2001, 2007; Kendler 1990; Raevuori *et al*. 2007; Roy *et al*. 1995). Keyes *et al*. (2010) estimated the heritability of well-being at 0.52. In the present sample, the correlation between self-esteem and well-being is 0.72. Other studies have shown that self-esteem is stable across age except in

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terminal decline (Gerstorf *et al*. 2008). We therefore expect that well-being would correlate similarly with hippocampal volume as did self-esteem.

Here we address two issues: (1) whether hippocampal volume is associated with self-esteem and well-being and (2) the extent to which associations between self-esteem, well-being and hippocampal volume are accounted for by common genetic influences. The sample of late middle-aged twins we use here is nearly 15 years younger on average than the older groups in previous studies.

Materials and methods

Participants

Details of the sample can be found in the study by Kremen *et al*. (2006, 2010a). Participants were 474 individuals with analyzable magnetic resonance imaging (MRI) data who are part of a sample of 1237 twins who participated in wave 1 of the Vietnam Era Twin Study of Aging (VETSA); there were 404 paired twins [110 monozygotic (MZ) and 92 dizygotic (DZ) pairs] and 70 unpaired twins. All participants are male–male twins who both served in the US military sometime between 1965 and 1975. Sixty-three percent of the twins with MRI data were not exposed to combat. All participants gave informed consent as approved by the Institutional Review Boards of participating institutions.

Mean age of the participants was 55.8 (2.6) years (range: 51–59). Mean years of education was 13.9 (SD = 2.1), and 85.2% were right-handed. Most participants were employed full-time (74.9%), 4.2% were employed part-time and 11.2% were retired. There were 88.3% non-Hispanic white, 5.3% African American, 3.4% Hispanic and 3.0% 'other' participants. Self-reported overall health status was as follows: excellent (14.8%), very good (36.5%), good (37.4%), fair (10.4%) and poor (0.9%). These demographic characteristics did not differ from the entire VETSA sample, nor were there significant differences between MZ and DZ twins. Basic demographic and health characteristics of the VETSA sample are comparable to the US census data for similarly aged men (National Health and Nutrition Examination Survey 1999–2004; Kremen *et al*. 2006).

Measures and procedures

MRI images were acquired on Siemens 1.5 Tesla scanners [241 at University of California, San Diego; 233 at Massachusetts General Hospital (MGH)]. Sagittal T1-weighted magnetization prepared rapid-gradient echo (MPRAGE) sequences were employed with a transverse relaxation time (TI) = 1000 milliseconds, echo time (TE) = 3.31 milliseconds, repetition time (TR) = 2730 milliseconds, flip angle = 7°, slice thickness = 1.33 mm, voxel size 1.3 × 1.0 × 1.3 mm. Raw Digital Imaging and Communications in Medicine (DICOM) MRI scans (including two T1-weighted volumes per case) were downloaded to the MGH site. Images were automatically corrected for spatial distortion caused by gradient nonlinearity and B_1 field inhomogeneity. The two T1-weighted images were registered and averaged to improve signal-to-noise ratio.

Volumetric segmentation (Fischl *et al*. 2002, 2004a) and cortical surface reconstruction (Dale *et al*. 1999; Dale & Sereno 1993; Fischl *et al*. 1999, 2002, 2004a,b) methods were based on the publicly available FreeSurfer software version 3.0.1b package. The semiautomated, fully three-dimensional whole-brain segmentation procedure uses a probabilistic atlas and applies a Bayesian classification rule to assign a neuroanatomical label to each voxel (Fischl *et al*. 2002, 2004a). A widely used training atlas has been shown to be comparable to that of expert manual labeling (Fischl *et al*. 2002, 2004a), but we created a VETSA-specific atlas that further increased accuracy compared with expert manual labeling (Kremen *et al*. 2010b).

Self-esteem was assessed using the 10-item Rosenberg Self-Esteem Scale. The Rosenberg is a reliable and valid measure of self-esteem (Schimmack & Diener 2003). Global well-being was assessed using 18 items developed by Ryff to measure psychological well-being (Ryff 1989; Ryff & Keyes 1995).

As a check on other factors that could affect the results, we also included the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff 1977), Combat Exposure Index (Janes *et al*. 1991) and report of doctor diagnosis of psychiatric and medical conditions.

Table 1: Descriptive statistics for self-esteem, well-being and left and right hippocampal volume

	Mean	SD	Minimum	Maximum
Self-esteem	3.43	0.47	1	4
Well-being	4.74	0.63	2	6
Left hippocampus (mm^3)	3991.75	390.98	2794.00	5359.00
Right hippocampus	4225.29	431.40	2846.00	5771.00

Statistical analysis

Models were fitted to the raw data using full information maximum likelihood using OpenMx (Boker *et al*. 2011). Descriptive statistics for self-esteem, well-being and left and right hippocampal volumes are presented in Table 1. We tested four multivariate models of self-esteem, well-being and left and right hippocampal volume: Cholesky, independent pathway, common pathway and two-factor models.

The Cholesky model is illustrated in Fig. 1. The first latent variable causes variation in all four observed variables. The second factor is uncorrelated with the first and causes variation in all except the first variable. The remaining factors are similarly configured, such that factor *i* influences only variables *i* to 4. This model is a simple way to estimate all variances and covariances subject to the constraint that the covariance matrix is positive definite. This patterning of factor loadings is specified for the additive genetic (A), common environmental (C) and unique environmental (E) sources of variance. The Cholesky model thus estimates all A, C and E variance covariances and therefore yields the best fit to the data using these variance components. The estimates from the Cholesky model can be standardized to yield genetic correlations, a

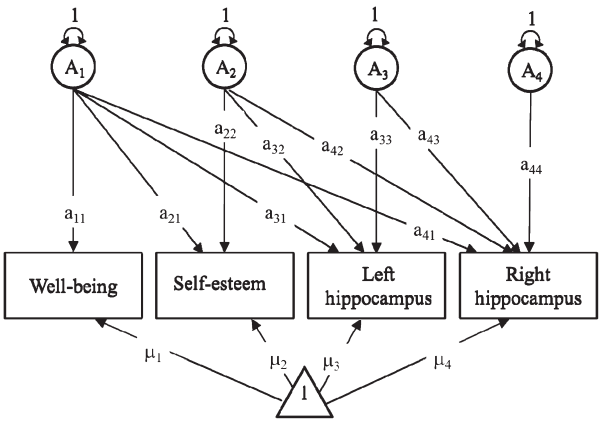

Figure 1: Path diagram of Cholesky model. Variables in circles represent latent variables or factors (shown only for genetic factor). Variables in boxes represent observed variables. Triangles represent means. Diagram is shown only for twin 1. Paths between variables represent estimated genetic contributions to phenotypic variance of observed variables.

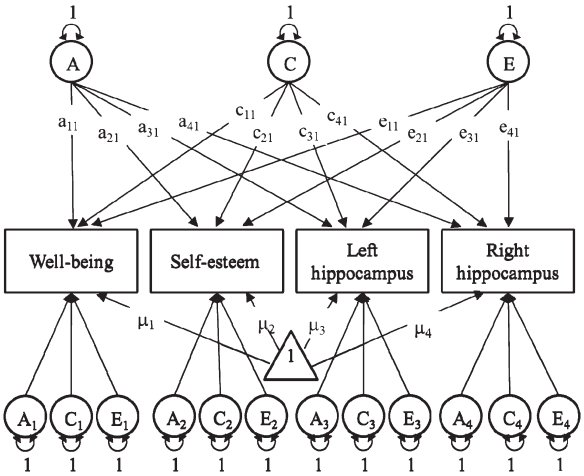

Figure 2: Path diagram of independent pathway model. Variables in circles represent latent variables or factors. Variables in boxes represent observed variables. Diagram is shown only for twin 1. Paths between variables represent estimated additive genetic, common environmental and unique environmental contributions to phenotypic variance of observed variables.

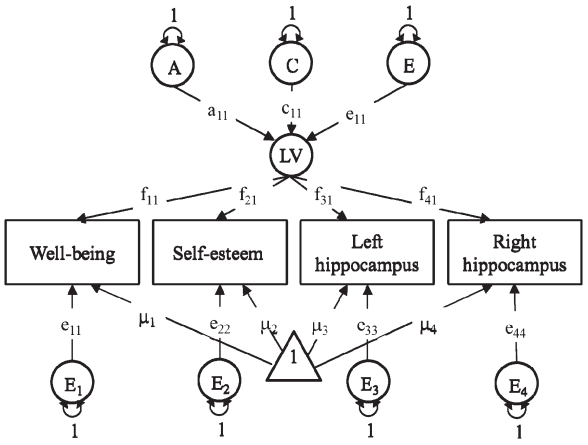

Figure 3: Path diagram of common pathway model. Variables in circles represent latent variables or factors (shown only for genetic factor). Variables in boxes represent observed variables. Paths between variables represent estimated additive genetic, common environmental and unique environmental contributions to phenotypic variance of observed variables.

measure of the extent to which genetic influences of one variable overlap with another variable. Although convenient for keeping estimation matrices positive definite, the parameter estimates from the Cholesky model are not always easy to interpret. However, its fit to the data is very useful as a baseline model against which other models may be compared.

The independent pathway model, sometimes called the biometric model (McArdle & Goldsmith 1990; Neale & Cardon 1992), is depicted in Fig. 2. In this model, the A, C and E components are made from a common factor component, which influences all the four variables and unique components specific to each variable. Thus, the common factors generate variance within and covariance between the variables, while the unique factors generate only variance within each variable. Note that the A and C common factors generate both cross-twin within variable and cross-twin cross-variable covariances, while the A and C unique factors contribute only to cross-twin within-variable covariances.

The common pathway model, sometimes called the psychometric model, is depicted in Fig. 3. This model is more restrictive than the Cholesky or independent pathway models. The common pathway model specifies that the covariation between variables is caused by a single underlying phenotypic variable, which in turn is caused by genetic and environmental factors. In other words, this model tests the hypothesis that covariance between well-being, self-esteem and hippocampal volume all come from a single latent variable. Like the independent pathway model, this model has variable-specific genetic and environmental source of variance. This model can be extended to include multiple intermediate latent variables, although in this article we use only a single factor.

Finally, we also fitted a two-factor model, depicted in Fig. 4. Well-being and self-esteem were constrained to load on one genetic factor and left and right hippocampus on the second factor. These two factors were allowed to correlate. This same two-factor structure was used for the C and E common factors.

Predictive fit indexes assess model fit in a hypothetical replication of the same population and of the same size as a researcher's sample. The best known predictive fit index under maximum likelihood estimation is Akaike's Information Criterion (AIC). AIC is a parsimony-adjusted statistic used to select among competing models. The model with the smallest AIC is chosen as most likely to replicate. More complex models are less likely to replicate (Kline 2005).

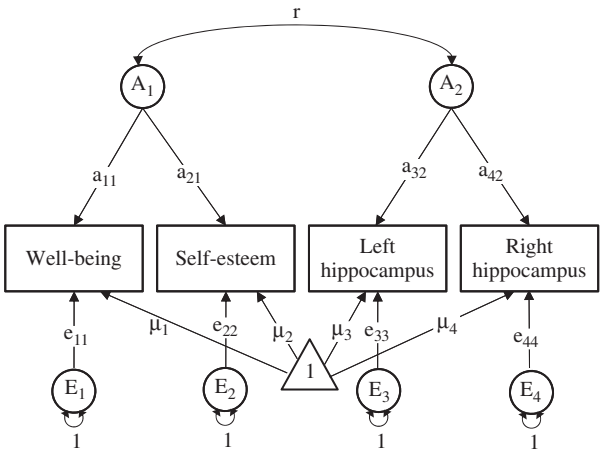

Figure 4: Path diagram of two-factor model. Variables in circles represent latent variables or factors (shown only for genetic factor). Variables in boxes represent observed variables. Triangles represent means. Diagram is shown only for twin 1. Paths between variables represent estimated genetic contributions to phenotypic variance of observed variables.

Results

Phenotypic analyses

Phenotypic correlations of self-esteem and well-being with age and hippocampal volumes are displayed in Table 2. Self-esteem was significantly positively correlated with left (0.09, $P = 0.03$) and right (0.10, $P = 0.04$) hippocampal volume. The phenotypic correlation between self-esteem and well-being was 0.72 ($P < 0.0001$). Correlations between

Table 2: Phenotypic correlations of self-esteem and well-being with hippocampal volumes

	Self-esteem	*P*	Well-being	*P*
Age	0.05	0.21	0.08	0.08
Left hippocampus*	0.09	0.03	0.05	0.23
Right hippocampus*	0.10	0.04	0.01	0.77

*$N = 474$. After restricting sample to subjects in good health ($N = 168$), these correlations were no longer significant. If intracranial volume is not controlled for, these correlations become 0.13 for both left and right hippocampus.

well-being and hippocampal volumes did not reach significance but showed the same general pattern. Age was not significantly correlated with either self-esteem or well-being. To be more comparable to the sample of Pruessner *et al*. (2005), we reran the analyses excluding participants with depression (based on scores above 16 on the CES-D), history of any psychiatric illness, history of head trauma and other medical conditions. The corresponding correlations in this subsample ($N = 168$) were −0.08 between self-esteem and left hippocampal volume ($P > 0.30$) and −0.04 between self-esteem and right hippocampal volume ($P > 0.58$). Adjusting for the possible stress of prior combat exposure had little impact on the results; correlations with self-esteem were 0.11 ($P = 0.03$) for left hippocampal volume and 0.15 ($P = 0.001$) for right hippocampal volume.

Twin analyses

The model fitting results are summarized in Table 3. Comparison of ACE and additive genetic and unique environmental (AE) models showed no deterioration of fit after dropping C from the model, so results are listed only for AE models. Neither the independent nor the common pathway models provided a good fit to the data. Only the two-factor model had acceptable fit based on its nonsignificant χ^2 value. We, therefore, selected the two-factor model as the best-fitting model. The heritabilities for well-being, self-esteem and left and right hippocampal volumes based on the AE two-factor model were estimated at 0.47, 0.44, 0.74 and 0.77 (Table 4). The remainder of the variance was attributable to environmental influences not shared by the twins. The correlation between the two genetic factors was 0.12 ($P = 0.03$). The correlation between the two environmental factors was 0.09 ($P > 0.05$).

Table 4: Estimates of additive genetic (A) and unique environmental (E) variance for well-being, self-esteem and left and right hippocampal volume computed from two-factor model

	Two-factor model	
	A (95% CI)	E (95% CI)
Well-being	0.47 (0.32, 0.59)	0.53 (0.41, 0.68)
Self-esteem	0.44 (0.29, 0.57)	0.56 (0.43, 0.71)
Left hippocampus	0.74 (0.66, 0.80)	0.26 (0.20, 0.34)
Right hippocampus	0.74 (0.66, 0.80)	0.26 (0.20, 0.34)

Correlation between genetic factors = 0.12. Correlation between environmental factors = 0.09.

Discussion

Although the phenotypic correlations between self-esteem and left and right hippocampal volumes in this study were significant, these correlations were small and substantially lower than those reported by Pruessner *et al*. (2005) for 16 healthy individuals aged 20–24 and 23 individuals aged 60–84, including both males and females. Multivariate analyses in our large, genetically informative study showed that both the genetic and environmental factors underlying self-esteem/well-being and hippocampal volume are mostly distinct, the correlations being 0.12 for the genetic factors and 0.09 for the environmental factors.

Studies by Pruessner and colleagues have found a significant relationship between self-esteem and hippocampal volume (Pruessner *et al*. 2005), a significant relationship for men only (Pruessner *et al*. 2007) and a nonsignificant relationship (Engert *et al*. 2010). Although we found a small, but significant relationship, our results are probably most consistent with the previous negative findings in much smaller samples. Sampling differences (e.g. susceptibility of small samples to stochastic processes, age or sex differences) could be one factor underlying inconsistent results. Differences in imaging methods might also be a factor, but high correlations (≈0.85) for hippocampal volumes between FreeSurfer and manual tracing make it unlikely that the size of the observed inconsistencies would be accounted for by these methodological differences (Tae *et al*. 2008). The results of Engert *et al*. suggest another possibility, namely, that main effects may be obscured by mediating or moderating effects of self-esteem or well-being.

Not surprisingly, self-esteem and well-being were highly phenotypically correlated ($r = 0.72$), indicating that these

Table 3: Model fitting results for multivariate analysis of self-esteem, well-being and left and right hippocampal volume

Model	−2LL	parameters	df	χ^2	Δdf	*P*-value	AIC
Cholesky	14 566.86	24	1868	–	–	–	10 830.86
Independent pathway	14 611.91	20	1872	45.05	4	<0.001	10 867.91
Common pathway	15 018.64	22	1871	451.78	2	<0.001	11 276.64
Two-factor	**14 568.65**	**22**	**1870**	**1.79**	**2**	**0.41**	**10 828.65**

Best fitting model has been provided in bold.
−2LL, minus twice the log likelihood; Δdf, change in degrees of freedom; AIC, Akaike's Information Criterion.

constructs are very similar. We found moderate heritabilities of 0.47 for scores on the Ryff Psychological Well-Being Scale and 0.44 for scores on the Rosenberg Self-Esteem Scale. The remaining variance in each was accounted for entirely by unique environmental influences. These results are very similar to previous heritability estimates for psychological well-being in adults (Keyes *et al*. 2010).

There is a need for mediational studies that could be tested longitudinally as further waves of the VETSA data become available. Such models are consistent with the notion that self-esteem and well-being are important in successful aging and that well-being is both a predictor and a consequence of successful aging (Lyubomirsky *et al*. 2005). Cognitive ability, socioeconomic status, family environments, stressful life events, personality variables other than self-esteem, such as resilience, and other brain regions might modulate the relationship between self-esteem, cortisol response and hippocampal volume. It may be that as the hippocampus atrophies with age, the stress–response system becomes less efficient, but there are characteristics (e.g. higher cognitive ability and greater self-esteem) and conditions (good health and not smoking) that make this decline in efficiency less acute.

In conclusion, we found a small but significant association between self-esteem and hippocampal volumes in a large sample of middle-aged men. One earlier study found a fairly strong association between hippocampal volume and self-esteem (Pruessner *et al*. 2005) but another did not (Engert *et al*. 2010). As suggested by the study of Engert *et al*., inconsistencies may be due to the fact that self-esteem is a mediator rather than a characteristic with a direct relationship to hippocampal volume. We do not know if our results would generalize to women; however, Pruessner *et al*. (2007) replicated the association in men but not in women. It is also possible that the results may not generalize to individuals who did not serve in the military. On the other hand, we have noted that our sample is in many ways representative of similarly aged American men. Moreover, there are many published studies based on twins from this registry, and these have been largely consistent with those from other samples. In addition, adjusting for prior combat exposure had little impact on the results. Given the importance of these psychological (self-esteem) and biological (hippocampus and HPA axis function) processes, it will be important for future studies to continue to examine influences on brain structure and function in healthy and pathological aging.

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