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Journal

Human Brain Mapping, 32(4)

ISSN

1065-9471

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Publication Date

2011-04-01

DOI

10.1002/hbm.21054

Peer reviewed

Published in final edited form as:
Hum Brain Mapp. 2011 April ; 32(4): 641–653. doi:10.1002/hbm.21054.

Genetic Patterns of Correlation Among Subcortical Volumes in Humans: Results From a Magnetic Resonance Imaging Twin Study

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Abstract

Little is known about genetic influences on the volume of subcortical brain structures in adult humans, particularly whether there is regional specificity of genetic effects. Understanding patterns of genetic covariation among volumes of subcortical structures may provide insight into the development of individual differences that have consequences for cognitive and emotional behavior and neuropsychiatric disease liability. We measured the volume of 19 subcortical structures (including brain and ventricular regions) in 404 twins (110 monozygotic and 92 dizygotic pairs) from the Vietnam Era Twin Study of Aging and calculated the degree of genetic

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correlation among these volumes. We then examined the patterns of genetic correlation through hierarchical cluster analysis and by principal components analysis. We found that a model with four genetic factors best fit the data: a Basal Ganglia/Thalamus factor; a Ventricular factor; a Limbic factor; and a Nucleus Accumbens factor. Homologous regions from each hemisphere loaded on the same factors. The observed patterns of genetic correlation suggest the influence of multiple genetic influences. There is a genetic organization among structures which distinguishes between brain and cerebrospinal fluid spaces and between different subcortical regions. Further study is needed to understand this genetic patterning and whether it reflects influences on early development, functionally dependent patterns of growth or pruning, or regionally specific losses due to genes involved in aging, stress response, or disease.

Keywords

behavioral genetics; hippocampus; amygdala; striatum; pallidum; caudate; putamen; thalamus; ventricles

INTRODUCTION

Subcortical structures in the human brain, all of which play an important functional role in both basic and higher-order cognitive and emotional behaviors, vary considerably in size between individuals, even when overall differences in head size are taken into account [Lupien et al., 2007]. These individual differences in volumes appear to be moderately correlated with individual differences in cognitive and emotional performance within healthy samples, although findings have been mixed [Amat et al., 2008].

In an effort to understand the etiology of brain organization and its functional consequences, examination of the volumetric covariance between brain structures is expected to help to identify subsystems that may be functionally or developmentally linked. Little is known, however, about the genetic and environmental factors that influence that covariance. Studies that have examined the inter-relationship between the size of different structures within the healthy human brain have examined both cortical and subcortical structures and generally found distinct patterns of inter-regional correlation [Colibazzi et al., 2007; Kennedy et al., 1998; Lerch et al., 2006; Mechelli et al., 2005; Pennington et al., 2000; Tien et al., 1996; Wright et al., 1999]. Some of the correlations have mirrored patterns of functional association, and others have been interpreted as consistent with developmental similarities. The exact patterns have varied across studies, perhaps due to differences in the number and selection of brain regions, the measure of brain structure used (e.g., volume, thickness, or gray matter density), the sample composition (e.g., pediatric vs. adult and pathological vs. healthy), the method used to explore patterning (e.g., qualitative examination of correlations vs. factor analysis vs. structural equation modeling), or a low variable-to-subject ratio in many studies. None of these studies directly addressed the contribution of genetic or environmental factors to the observed covariation patterns.

Brain volume of individual cortical and subcortical structures is under substantial genetic control [Schmitt et al., 2007a; Wallace et al., 2006]. In adult samples, this high heritability does not appear to be reduced when differences in head size are taken into account. Thus, individual differences in the volume of most brain structures within equivalently sized heads are largely determined by genes. What is not yet clear is whether the same genes play a role in determining size for all structures or whether there are multiple underlying genetic factors at work. Furthermore, it is not known to what degree the covariance patterns observed at the phenotypic level are paralleled by similar patterns of genetic influences. Studies of gene expression patterns in animals and humans have observed distinct regional differences in the

genes that are active, suggesting that there may be genes that influence the development, size, and function of some brain regions but not others [Abrahams et al., 2007; Hovatta et al., 2007; Sun et al., 2006]. Twin studies are ideally suited to examine the genetic patterning of brain structure size because they allow one to calculate the genetic correlation (i.e., the degree of genetic overlap) between multiple in vivo measures. The genetic correlation is the *genetic* covariance between two variables divided by the square root of the product of their *genetic* variances [Neale and Cardon, 1992]. Patterns of genetic correlation do not necessarily mirror the patterns seen at the phenotypic level (see Kremen et al. [2010] for an example of a dissociation between phenotypic and genetic factors in a behavioral measure).

Inter-regional brain structure patterns have been examined in four genetically informative samples, and two of these were entirely pediatric. Pennington et al. [2000] performed a phenotypic factor analysis of 13 measures (seven cortical regions, three subcortical regions, cerebellum, brain stem, and total white matter) across their entire sample ($N = 132$, heavily weighted with reading-disabled individuals) and identified a primarily cortical factor and a primarily subcortical one. They found that scores on these two factors were more highly correlated among monozygotic (MZ) than dizygotic (DZ) twins, suggesting high heritability. Patterns of genetic correlation were not examined because phenotypic factor analysis cannot separate genetic and environmental influences underlying correlations between measures. Schmitt et al. [2007b, 2008] based their analyses on a large pediatric twin sample ($N = 326$, 308, respectively). In Schmitt et al. [2007b], six regions (cerebrum, cerebellum, lateral ventricles, corpus callosum, thalamus, and basal ganglia) were selected, and genetic correlations among the volumes of these regions were examined. They found that a single genetic factor explained most of the covariance in volume among these regions. After accounting for total brain volume, however, a genetic factor that included thalamus and basal ganglia was found, as well as a factor influencing the size of the cerebrum and corpus callosum. Schmitt et al. [2008] applied principal components analysis (PCA) to the genetic correlations between thickness in 54 different cortical regions. These correlations were estimated using data from 600 pediatric twins and singletons. A single cortical factor explained most of the genetic variance between cortical regions, but when mean cortical thickness was accounted for, a six factor solution was observed, with thickness in multiple regions of the frontal and parietal cortex loading on the first factor. Baare et al. [2001] examined the genetic and environmental correlation among several global brain measures, including intracranial volume, total brain volume, gray and white matter volume, and lateral ventricle size in a sample of 54 adult MZ twins, 58 DZ twins, and 34 full siblings of the twins. They found high genetic correlations between whole brain, gray and white matter volumes, and intracranial volume, but not between intracranial volume and lateral ventricle size. Posthuma et al. [2000] also reported a moderate genetic correlation between cerebellar volume and intracranial space in the same sample. Genetic correlations between gray and white matter volumes and between these and cerebellar volume were also fairly high [Baare et al., 2001; Posthuma et al., 2003]. The one adult twin study to examine patterns of genetic correlation between regionally parcellated brain structures [Wright et al., 2002] found a frontal–parietal factor similar to that seen in the Schmitt et al. [2008] pediatric study, but these preliminary results may not be reliable given that genetic correlations of 92 brain regions were examined in a sample of only 10 MZ and 10 DZ pairs. Thus, very little is known about the pattern of genetic correlations between specific brain regions in healthy adults.

We have collected high-resolution magnetic resonance images on a large sample of middle-aged male twins from the Vietnam Era Twin Study of Aging (VETSA). Using automated segmentation and probabilistic atlas-based parcellation procedures, we measured the volume of 19 subcortical regions (seven bilateral brain structures, two bilateral ventricular measures and third ventricle volume). We examined the degree to which the same or different genetic

factors influence the volume of these structures by conducting a factor analysis of the genetic correlations between subcortical volumes. Prior studies either selected brain regions of convenience (i.e., regions included in the analysis were simply those that had already been measured), utilized very small samples, or had small subject-to-variable ratios. We elected to begin with an analysis of genetic correlations among subcortical measures because the number of variables in the analysis is appropriate compared to the number of twins in our sample, yet represents the size of nearly all the structures beneath the cortical mantle. In addition, based on preliminary results, measures of cortical size appeared relatively genetically independent from subcortical measures and thus will be examined in a separate analysis.

We aimed to test whether one or more factors would best characterize the pattern of genetic correlations. Although previous analyses of the pattern of phenotypic correlations in brain size generally suggested the existence of more than a single factor, such results are uninformative about whether more than one *genetic* factor might underlie such patterns. Our hypothesis, however, was that more than a single genetic factor was likely to emerge, indicating the actions of multiple genetic influences. As shown in Table I, there are many potential patterns of genetic correlation among subcortical structures that may be observed and each has different implications for the nature of genetic patterning in the human brain. Given the lack of well-powered, genetically informative studies of regional volumes in adults, the present study aimed to use the twin method to explore the nature and pattern of genetic correlations among subcortical volumes as measured by magnetic resonance imaging.

METHODS

Participants

The overall goals and design of the VETSA project have been described previously [Kremen et al., 2006]. VETSA participants were selected from a group of individuals that had participated in a previous study [Tsuang et al., 2001] drawn from the Vietnam Era Twin (VET) Registry [Goldberg et al., 2002], a sample of male–male twin pairs born between 1939 and 1957 who had both served in the United States military between 1965 and 1975. The VET Registry and the VETSA sample are not VA or patient samples, and the large majority of individuals were not exposed to combat. At the time of data analysis, there were 474 individual VETSA participants with analyzable MRI data. Of those, 404 were paired (i.e., 202 twin pairs): 110 MZ and 92 DZ pairs. Twin zygosity was initially classified according to questionnaire and blood group information. These classifications are being updated on the basis of 25 microsatellite markers. To date, 56% of the MRI study participants have DNA-determined zygosity. Consistent with the overall VETSA project, 95% of the questionnaire-based classifications were in agreement with the DNA-based classifications; when differences occurred, we used the DNA-based classifications. To examine whether this minor proportion of misclassification would be likely to influence the observed genetic associations, we compared estimates of heritability made using DNA-based versus questionnaire-based zygosity determinations for three representative variables from the overall VETSA sample and the MRI subsample. In the overall sample, 374 sets of twins had been classified by both methods; in the MRI subsample, 114 twins had both determinations. Heritability estimates were nearly identical using the two methods (digits forward: DNA-based = 0.49 vs. questionnaire-based = 0.46; negative emotionality: 0.50 vs. 0.47; total brain volume: 0.89 vs. 0.90).

Potential participants in the VETSA MRI study were screened for standard MR exclusions. Only 6% of VETSA participants who were invited to undergo MRI declined to participate; 59% of those who agreed were included. The remaining participants were not included for

reasons such as possible metal in the body (7%), claustrophobia (3%), testing being conducted in the twins' hometown (5%), scanner problems (8%), cotwin being excluded (9%), and other reasons (3%).

Mean age of the MRI 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 and are comparable to U.S. census data for similarly aged men [Centers for Disease Control and Prevention, 2003; National Center for Disease Statistics, 2003]. There were no significant demographic differences between MZ and DZ twins.

All participants gave informed consent to participate in the research, and the study was approved by the Institutional Review Boards of the University of California, San Diego, Boston University, and the Massachusetts General Hospital.

Image Acquisition

Images were acquired on Siemens 1.5 Tesla scanners (241 at University of California, San Diego; 233 at Massachusetts General Hospital). Sagittal T1-weighted MPRAGE sequences were employed with a TI = 1,000 ms, TE = 3.31 ms, TR = 2,730 ms, flip angle = 7°, slice thickness = 1.33 mm, voxel size 1.3 ×1.0 × 1.3 mm^3. Raw DICOM MRI scans (including two T1-weighted volumes per case) were downloaded to the MGH site. These data were reviewed for quality, registered, and averaged to improve signal-to-noise ratio. Of the 493 scans available at the time of these analyses, quality control measures excluded 0.6% (three cases) due to scanner artifact and 3% (16 cases) due to inadequate image-processing results (e.g., poor contrast caused removal of nonbrain to fail). The resultant 474 available cases included 202 twin pairs (404 individuals) that were used in the present study.

Image Processing

Using volumetric segmentation methods based on the publicly available FreeSurfer software package [Fischl et al., 2002, 2004a,b], volumetric measures were created for hippocampus, amygdala, caudate, putamen, nucleus accumbens, thalamus, and ventricles (see Fig. 1). The automated, fully 3D whole-brain segmentation procedure [Fischl et al., 2002, 2004a,b] uses a probabilistic atlas and applies a Bayesian classification rule to assign a neuroanatomical label to each voxel. The atlas consists of a manually derived training set created by the Center for Morphometric Analysis (http://www.cma.mgh.harvard.edu/) from 20 unrelated, randomly selected VETSA participants. Automated volumetric measurements based on this atlas were within the 99% confidence interval with respect to the "gold standard" manual measurements made at the Center for Morphometric Analysis. This process required only qualitative review to ensure no technical failure of the application.

Data Analysis

Descriptive statistics for each region of interest (ROI) were calculated in SAS (Version 9.1.2). Pearson correlations were used to assess the phenotypic association between a single ROI and all other ROIs and to calculate crosstwin, crosstrait correlations for MZ and DZ pairs separately (results of these analyses are available upon request).

Genetic Modeling

Data were passed from the statistical programming environment R [Ihaka and Gentleman, 1996; R Development Core Team, 2005] to Mx [Neale et al., 2003], a matrix-based structural equation modeling package to estimate the genetic, shared environmental and unique environmental influences shared between subcortical ROIs.

The degree of relatedness between members of MZ and DZ twin pairs is used to estimate the contribution of genetic and environmental effects to the phenotypic variation of subcortical volume for each ROI. Phenotypic similarities between MZ twins arise from the sharing of all their additive genetic information and all shared environmental influences. Similarities between DZ twins result from sharing on average 50% of their additive genetic information in addition to shared environmental influences. Influences from unique environmental effects diminish the similarity between members of a twin pair, regardless of their zygosity. Models using twin data thus utilize MZ and DZ twin pair variances and covariance to estimate the proportion of total phenotypic variance due to additive genetic, shared environmental and unique environmental influences. Additive genetic variance (A) refers to the additive genetic effects of alleles at every contributing locus. Shared environmental variance (C) is the variance that is due to effects shared by a twin pair. Unique environmental variance (E) is the variance due to effects not shared by a twin pair and also includes measurement error.

Univariate variance components analysis—Univariate ACE, AE, and CE models were fitted for each ROI to test the significance of additive genetic and shared environmental effects. Optimization of these data used maximum likelihood (ML) [Edwards, 1984] by calculating twice the negative log-likelihood of the raw data for each twin pair and summing across all pairs. The use of ML in measuring model fit allows for hypothesis testing between an original model (ACE) and its nested models (AE, CE, and E only). The difference between an original model and its respective submodels follows a χ^2 distribution with degrees of freedom equal to the difference in model parameters ($df = 1$).

Multivariate analysis—Data on two or more variables collected from the same pairs of twins provide additional statistics with which it is possible to estimate the amount of genetic and environmental influences that are shared in common *between* ROIs. The three primary sources of information are the within-twin crossvariable covariance (the phenotypic covariance), and the MZ and DZ crosstwin, crossvariable covariances. For example, an increased crosstwin, cross-ROI correlation in MZ pairs compared to DZ pairs suggests that the covariance between two ROIs may be due to genetic factors. A standard approach for estimating shared genetic and environmental effects utilizes a Cholesky decomposition, which is a triangular decomposition of the expected variance–covariance matrix between ROIs. The first variable in a Cholesky decomposition is the result of a latent factor that explains the variance in the initial variable and all subsequent variables. A second latent factor explains the variance in the second variable and all subsequent variables. The common genetic effects between ROIs utilized an expected variance/covariance matrix parameterized to have 19 ROIs loading on the first genetic factor (A1), 18 ROIs on the second factor (A2), 17 on the third (A3), and so forth, until only one ROI was loaded on the 19th factor (A19) (see Fig. 2). This parameterization was also specified for the latent C and E factors. An advantage of the Cholesky decomposition is that it places few expectations on the structure of the latent factors. Further, it produces separate genetic and environmental variance/covariance matrices that are positive semidefinite, consistent with the idea that variation is caused by factors that operate in a linear additive fashion.

The genetic covariances between the ROIs were used to calculate genetic correlations to indicate the degree to which genetic effects are shared between the two ROIs. The genetic correlation between two ROIs is defined as

$$r_{x,y} = \frac{A_{xy}}{\sqrt{A_x \times A_y}}$$

where A_{xy} is the genetic covariance between structures x and y and A_x and A_y represent the heritability of x and y. The multivariate model produced a 19 × 19 genetic correlation matrix. The Cholesky decomposition uses many factors as there are variables entered to estimate the genetic covariance matrix. It is saturated in that, subject to the matrix as a whole being non-negative definite, there is one free parameter for each genetic variance and covariance. However, a model with fewer factors may explain the data as well as the Cholesky. As is usual with factor analysis, we specified genetic factor models with one or more latent common genetic factors, plus a residual genetic component specific to each observed variable. The same factor approach may be applied to the additive genetic, shared environment and specific environment components. Factor submodels with a constrained number of genetic and environmental factors were tested against the Cholesky to determine the minimum number of factors which adequately explained the genetic relationships between ROIs in the presence of shared and unique environmental effects. Genetic and environmental factors were identified as the number of factors with eigenvalues greater than 1 when estimated from their specific correlation matrices. One hundred and seventy models of testing the number of genetic and environmental factors were assessed. Model complexity ranged from zero genetic, zero shared environmental, and one unique environmental factor to four genetic, five shared environmental, and seven unique environmental factors. Reduced models were assessed if they produced no significant differences in fit compared to the Cholesky. Cluster analysis and PCA were then separately applied to the genetic correlation matrix to determine the strength of genetic relationships and to identify the genetic relatedness between the subcortical regions.

Cluster analysis—The correlation matrix was visualized as a heatmap using the heatmap.2 function within the gplots package in R [Ihaka and Gentleman, 1996; R Development Core Team, 2005]. This program also performs a hierarchical cluster analysis by treating the correlations as Euclidean distances in an agglomerative fashion and displays the genetic relationships between regions as a dendrogram in which the distance from one structure to another along the path of the dendrogram is related to the similarity of their patterns of genetic correlation. The ordering and proximity of the regions in the dendrogram and heatmap is thus not specified by the user, but is a reflection of the strength of their genetic relationship.

Principal components analysis—PCA was conducted on the genetic correlation matrix to reduce the dimensionality of the matrix and identify factors that account for a large amount of the total genetic variance within the measured ROIs. The genetic correlation is a standardization of the genetic covariance, which is easier for the interpretation of factor structure. Additionally, the factors resulting from an analysis of a correlation matrix allows for comparison of factor structures between studies [Jolliffe, 2002]. Factors identified in PCA describe the predominant genetic relationships between the subcortical regions, and factor loadings quantify the correlations between a latent genetic factor and an ROI. PCA was conducted in SAS using a promax (oblique) rotation to efficiently account for the high intercorrelation between ROIs. Performing PCA in SAS provides additional efficiency in the

identification of the ROIs that constitute a given factor and provides estimates of the amount of the genetic variance accounted for by each factor. The genetic variance attributable by a given factor is calculated as the sum of the squared factor loadings divided by the number of variables. PCA was also conducted on the phenotypic correlation matrix.

RESULTS

The means (SDs) for the volume of the 19 subcortical regions are presented in Table II. After correcting for multiple comparisons, there were no significant differences between zygosity group for either the means or variances in any region (data available upon request). Heritability estimates for these subcortical regions have been previously published [Kremen et al., 2009]. All structures were significantly and highly heritable (ranging from 0.37 for the right inferior lateral ventricle to 0.85 for the left putamen). The focus of this article is to examine whether these strong genetic influences reflect common genetic factors across the subcortical regions.

The genetic correlations are presented in Table III and range from −0.004 to 0.996. A visual heatmap representation of the genetic correlations and results of a hierarchical clustering analysis (represented as a dendrogram) are shown in Figure 3. The figure illustrates the high degree of genetic correlation between left and right homologous regions and the segregation between brain tissue and ventricular measures. Among the brain tissue measures, the cluster analysis reveals a division between basal ganglia/ diencephalic and limbic structures.

Models with four genetic factors did not significantly differ in fit from the Cholesky (Table IV) and had the lowest values of Akaike Information Criterion suggesting a superior balance between goodness-of-fit and parsimony [Akaike, 1987]. Further, there was a significant improvement in fit between the model with three genetic factors and the model with four genetic factors (change in −2 log likelihood [Δ−2LL] = 87.81, change in degrees of freedom [Δ*df*] = 19, $P < 0.001$). Thus, we concluded that the four-factor structure provided the best representation of the data.

Consistent with the model-fitting results, the rotated factors of the PCA of the full genetic correlation matrix identified a model with four genetic factors that each had eigenvalues greater than one. These four factors together explained 81% of the total genetic variance. Table V presents the results of this four-factor solution. Bilateral volumes of the putamen, pallidum, caudate, and thalamus loaded heavily on the first genetic factor, which we therefore labeled as the Basal Ganglia/Thalamic factor. This factor explained 43% of the variance. The second factor consisted of all the ventricular measures and explained 23% of the variance. The third factor, which we termed the Limbic factor, explained 9% of the variance and had the highest loadings for bilateral hippocampus and amygdala. The fourth factor consisted only of bilateral accumbens volume and explained 6% of the variance. The Basal Ganglia/Thalamic factor and the Limbic factor were correlated with each other ($r = 0.54$), but there were no other large correlations between factors (rs < 0.17).

Because the fourth factor contained only left and right measures for a single structure, we conducted a second PCA that constrained the number of factors to three. In this solution, the accumbens loaded on the Limbic factor and the three factors together accounted for 75% of the total genetic variance. As mentioned earlier, however, the four-factor model was preferred based on genetic modeling. There was no discernible structure to the pattern of shared and unique environmental correlations between the volumes of the subcortical structures (data available upon request).

A four-factor model also fits the phenotypic correlation matrix. The factor loadings for the phenotypic data are presented in Table VI, and the patterns are similar to those observed for

the genetic analysis. A distinct separation between brain and ventricles is similarly observed for the phenotypic measures, and loadings for the four factors are similar to those seen in the genetic analysis.

DISCUSSION

This study was the first large-scale investigation of the degree and pattern of genetic relationships among multiple subcortical brain volumes in adults. We found strong genetic correlations among volumes of subcortical brain tissue and among volumes of subcortical cerebral spinal fluid-filled spaces, but weaker genetic relationships between these two categories. Volumes of homologous regions of brain and ventricles in each hemisphere were highly genetically correlated. PCA further suggested that genetic variance in subcortical brain volumes could be partitioned into a Basal Ganglia/Thalamic factor, a Limbic factor, and a Nucleus Accumbens factor. The pattern of phenotypic covariance was very similar to the pattern of genetic covariance and there was little structure to the environmental covariance patterns, suggesting that the observed phenotypic covariance structure is largely genetically determined.

The results suggest that multiple genetic influences determine subcortical volumes for different structures. Our findings therefore argue against a model of brain development or deterioration in which a single set of genes determines the size of all subcortical structures (see Table I, Patterns 1 and 4). The fact that neighboring brain volumes loaded positively on the factors (consistent with Table I, Pattern 5a) also suggests that genetic influences on volume growth or shrinkage do not result in a zero-sum process in which the size of one structure is limited by the size of another nearby (see Table I, Pattern 5b). Within the measures of subcortical brain tissue, we found some evidence for different genetic influences on basal ganglia and thalamic volumes compared to limbic structures such as hippocampus and amygdala and compared to the nucleus accumbens. This finding is largely consistent with those of previous large-scale studies of pediatric twins [Schmitt et al., 2007b, 2008], in which evidence for multiple factors was observed in one analysis that included both cortical and subcortical volumes and another that included only cortical thickness measures. However, that study did not measure the different basal ganglia structures separately. An interesting difference between the findings is that Schmitt et al. only observed multiple factors after covarying for intracranial volume or mean cortical thickness, whereas our finding of multiple factors was observed without correction for intracranial volume. Possibly, genetic correlations in children are more influenced by factors affecting global brain size because their gray matter structures are still growing. In general, it is difficult to compare directly the findings from these studies to the present one because the samples differ dramatically in age and the brain measures included are different.

Despite the physical distance separating left and right hemisphere subcortical structures, we observed high genetic correlations between the volumes of homologous regions. These high genetic correlations are consistent with both prior investigations in a pediatric twin sample [Schmitt et al., 2007b, 2008] and with results of phenotypic covariation analyses [Mechelli et al., 2005; Salvador et al., 2005; Tien et al., 1996], including our own based on the present data. The strong interhemispheric genetic correlations we observed suggest that the shared genes could be active early in development when the hemispheric fate of neurons is determined. The findings are also consistent with the idea that shared genetic influences serve to grow or shrink subcortical structures over the lifespan in a manner that is not lateralized.

We also found evidence for different genetic influences on subcortical brain tissue compared to subcortical CSF spaces (consistent with Table I, Pattern 3). This argues against the notion

that ventricular volume is directly yoked, via shared genetic mechanisms, to the volume of surrounding gray matter structures (which would have led to opposite loadings on a common factor, i.e., negative genetic correlations; see Table I, Pattern 2). Because we did not measure subcortical white matter volume by region, however, we are unable to say whether the genes influencing ventricular volume may be the same as those influencing the integrity or volume of white matter surrounding the ventricles.

Among the gray matter structures, we found some evidence for distinct genetic influences on nucleus accumbens versus basal ganglia/thalamic regions versus limbic structures, although the latter two factors did show some genetic overlap. The patterns of genetic correlation among volumes of subcortical brain tissue that we observed parallel the results of two previous studies of phenotypic correlations among the volume of brain regions that both found basal ganglia and limbic/medial temporal lobe factors [Colibazzi et al., 2007; Tien et al., 1996], and we found similar results in our own phenotypic analysis. Furthermore, both limbic and basal ganglia/thalamic clusters were observed in a multivariate investigation of functional activity during rest in 90 brain regions as measured by functional magnetic resonance imaging [Salvador et al., 2005]. This genetic covariation bears some consistency with the strong anatomic connections between the structures that comprise each factor, and the regions seem to have somewhat dissociable roles to play in cognitive and emotional behavior. Thus, at least some of the genes that are differentially involved in determining volumes within each cluster may be those whose expression is related to the unique functional specialization of the neurons in these regions, especially ones that have to do with activity-dependent growth or survival of neurons (see Table I, Pattern 5a). Still, the functional division between the factors is not at all complete, and indeed, there are many ways in which regions in our Limbic factor communicate and functionally interact with those in our Basal Ganglia/Thalamic factor and with the nucleus accumbens. Consistent with this, we found a correlation of 0.54 between these two factors, suggesting a certain amount of commonality in genetic influences. The thalamus in particular is functionally important in motor, cognitive, and emotional behavior and is directly or indirectly interconnected with all the other subcortical structures. Perhaps consistent with this, thalamus volume loaded moderately on both the Basal Ganglia/Thalamic factor and the Limbic factor. It should also be noted that the borders of the nucleus accumbens are difficult to validly identify on T1-weighted MRI images, and this measure is thus referred to as the “accumbens area” in the output of Freesurfer. Still, the heritability of this measurement ($L = 0.63$, $R = 0.51$) was similar to that of most other subcortical structures, suggesting that it was reliably measured in our sample (since measurement error contributes to unique environmental variance and thus decreases the apparent heritability of measures).

In addition to functional explanations, the observed pattern of genetic factors could also be due to genetic distinctions between the regions in neurotransmitter receptor densities, how and when the structures develop within individuals, how and when the structures evolved in humans, or regionally specific sensitivity to trophic or regressive agents or pathologies. The present study was not designed to disentangle these possibilities, but future studies of candidate genes that might influence the size of subcortical brain structures should focus on genes whose effects might be regionally specific in the patterns found here.

To date, some specific genes have been examined in relationship to the volume of subcortical structures. Polymorphisms of the gene coding for brain-derived neurotrophic factor (BDNF) seem to be related to size of the hippocampus [Bueller et al., 2006; Frodl et al., 2007; Pezawas et al., 2004] and to the magnitude of age-related change in amygdala volumes [Sublette et al., 2008], but the relationship of this gene to basal ganglia, thalamic, and nucleus acumbens volumes has been less studied [Agartz et al., 2006], although BDNF is found in these regions [Murer et al., 2001]. Apolipoprotein E (APO-E) polymorphisms

have also been examined in relation to size of hippocampus and amygdala, and the evidence is mixed [Jak et al., 2007], suggesting that if APO-E influences subcortical gray matter volumes, it may not do so in a way that parallels the genetic factors we observed. More research is needed to help determine which specific genes or sets thereof underlie the patterns of genetic covariation that we observed.

Because the present sample included only men, further studies will be needed to examine whether the pattern of genetic correlations is similar in women. We also elected to focus our analysis on subcortical structures, and so we were not able to examine possible genetic correlations between cortical and subcortical volumes. Although cortical–subcortical anatomic connectivity and functional dependence is well established, a thorough examination of the genetic relationships between cortical and subcortical size is made difficult due to several factors such as the large number of regions involved in such an analysis (leading to a low subject-to-variable ratio even in our large-scale study).

In the largest twin MRI sample to date, we have shown that different genetic influences determine the size of distinct subcortical networks. Observed patterns of covariance at the phenotypic level appear to be primarily due to similar patterns of genetic covariance. This argues against idea that observed correlations between the size of structures have to do primarily with shared environmental factors, such as insults or toxins that might differentially influence growth or shrinkage of particular subcortical regions. Shared genes influence the volume of homologous brain regions in each hemisphere, and distinct genetic influences determine brain volume compared to cerebrospinal fluid spaces. Genetic influences do not appear to act in an ex vacuo manner for ventricular volumes nor is there evidence for a zero-sum or push–pull effect on neighboring gray matter structures. The rotated genetic and phenotypic factor structure was consistent with recognized subcortical functional systems. Of course, factor loadings can be rotated in an infinite number of ways, without changing how much of the variation and covariation in the data that they explain. Still, the rotated pattern we observed makes sense given what we know about the anatomical and functional connectivity between these regions. Thus, the precision of genetic association studies aimed at finding genes related to the development and function of subcortical structures may be enhanced through the utilization of brain structure phenotypes based on the genetic factors observed in the present study.

Acknowledgments

Contract grant sponsor: National Institute on Aging, National Institutes of Health (NIH); Contract grant numbers: U24 RR021382, R01 AG18386, R01 AG18384, R01 AG22381, R01 AG 22982; Contract grant sponsor: National Institute for Mental Health, NIH; Contract grant number: R01 MH20030; Contract grant sponsor: National Institute for Drug Abuse, NIH; Contract grant number: R01 DA18673; Contract grant sponsor: VA Desert Pacific Mental Illness Research Education and Clinical Center.

The U.S. Department of Veterans Affairs has provided support for the development and maintenance of the Vietnam Era Twin Registry. Numerous organizations have provided invaluable assistance, including VA Cooperative Studies Program; Department of Defense; National Personnel Records Center, National Archives and Records Administration; the Internal Revenue Service; National Institutes of Health; National Opinion Research Center; National Research Council, National Academy of Sciences; the Institute for Survey Research, Temple University; Schulman, Ronca, and Bucuvalas, Inc. Most importantly, we gratefully acknowledge the cooperation and participation of the members of the Vietnam Era Twin Registry and their families. Without their contribution this research would not have been possible.

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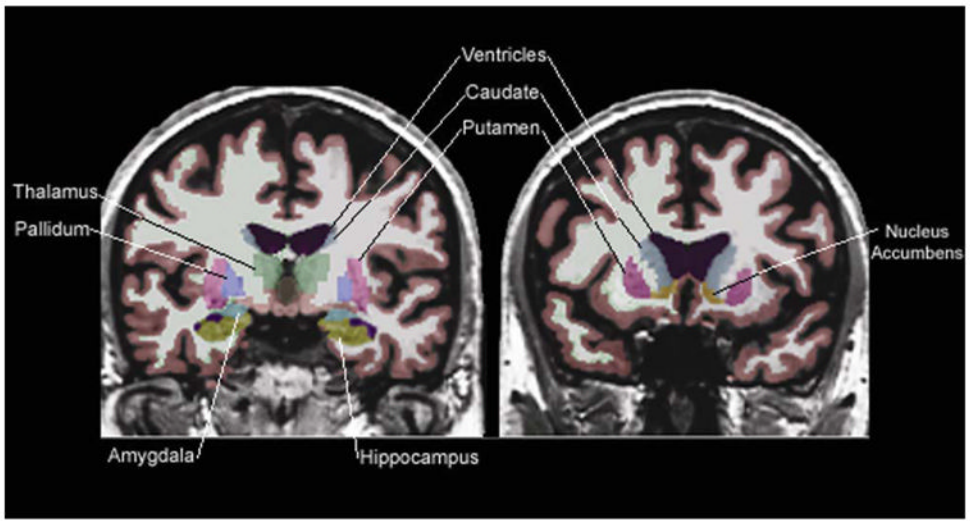

Figure 1.
Representative parcellation of subcortical regions using Freesurfer software.

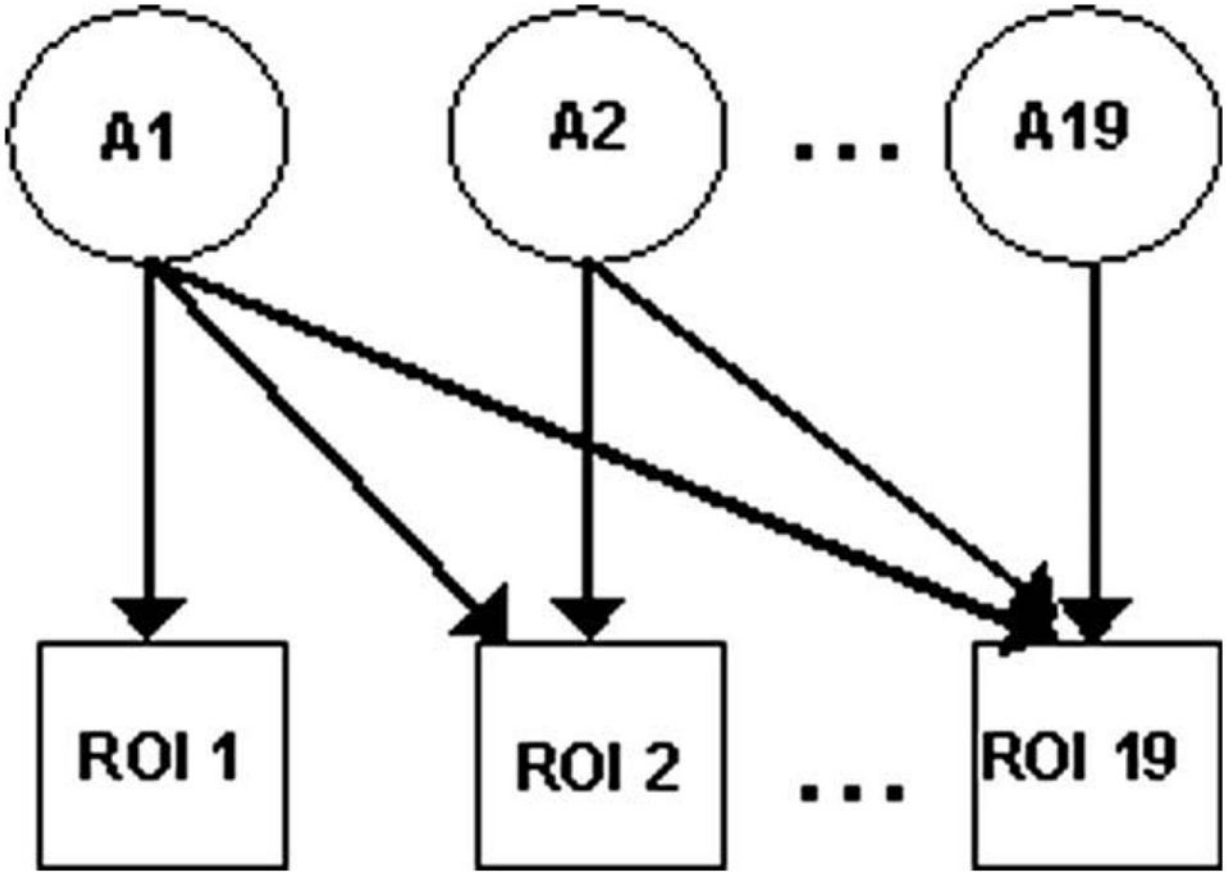

Figure 2.
An example of the Cholesky parameterization used to determine genetic covariance of the 19 subcortical regions of interest.

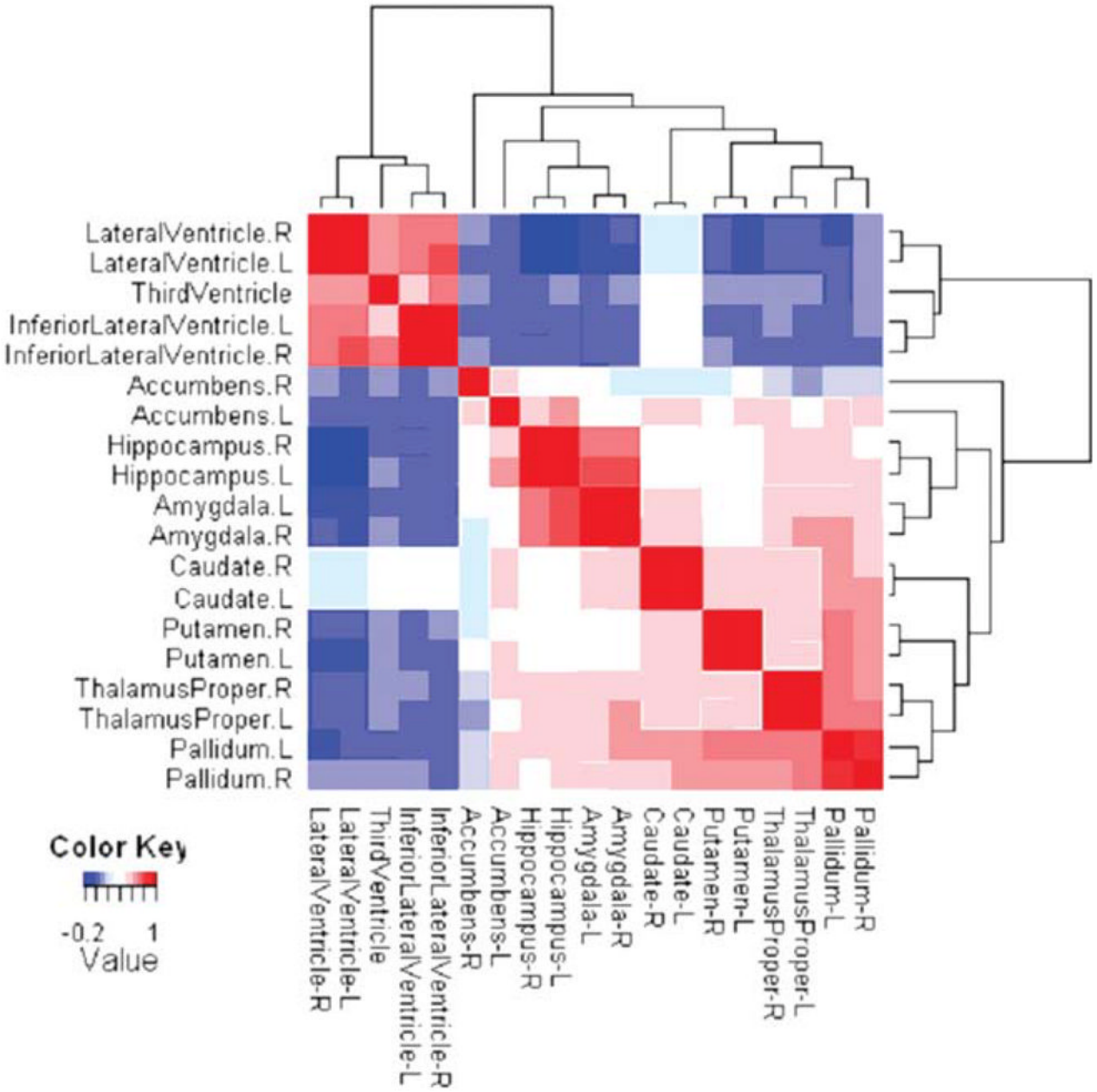

Figure 3.
Heatmap representing magnitude of genetic correlations between subcortical regions of interest and dendrogram representing results of a hierarchical cluster analysis. Warmer colors represent more positive genetic correlations.

TABLE I

Interpretation of possible genetic factor structure patterns

Factor structure	Consistent explanatory models
1. Ventricles load positively on same factor(s) as brain structures	Genes determine size of cranium and hence all subcortical structures and spaces
2. Ventricles load negatively on same factor(s) as brain structures	Genes determine size of gray matter structures; ventricular volumes determined through ex vacuo effects of these genes
3. Ventricles load on different factor(s) from brain structures	Different genetic influences determine gray matter versus ventricular volume
4. Single brain factor *	One set of genes determines the size of all subcortical structures, perhaps genes involved in global growth promotion
5. Multiple brain factors *	
5a. All structures load positively on the factors	Different genetic influences act on different subcortical structures due to distinct: • phylogenic patterns • early developmental trajectories • functional connectivity (including anatomical connectivity and/or neurotransmitter systems) • ongoing cell repair or cell death mechanisms (e.g., nerve growth factor) • sensitivity to effects of stress, age, or pathology
5b. Some structures load negatively on factors	As above, but with additional evidence that genes act in a zero-sum manner for neighboring structures (e.g., greater growth of the hippocampus means less growth of the amygdala)

* Each of these possibilities could occur with any of the ventricular patterns above.

TABLE II

Descriptive statistics for the subcortical regions of interest

ROI	Mean	SD	Minimum	Maximum
Accumbens – L	599.38	87.27	370	901
Accumbens – R	541.59	110.9	273	963
Amygdala – L	1,915.28	206.92	1,248	2,555
Amygdala – R	2,054.86	216.74	1,458	2,894
Caudate – L	3,498.72	435.28	2,483	5,032
Caudate – R	3,731.34	474.3	2,518	5,232
Hippocampus – L	3,991.75	390.98	2,794	5,359
Hippocampus – R	4,225.29	431.4	2,846	5,771
Inferior lateral ventricle – L	636.34	244.68	139	1,967
Inferior lateral ventricle – R	686.32	240.84	217	2,085
Lateral ventricle – L	12,371.9	5,983.27	3,253	38,722
Lateral ventricle – R	11,822.8	5,828.1	3,847	37,339
Third ventricle	1,341.96	418.72	677	3,957
Pallidum – L	1,658.83	210.67	1,115	2,372
Pallidum – R	1,568.63	198.87	1,078	2,507
Putamen – L	4,927.1	560.93	3,171	6,735
Putamen – R	5,003.05	540.02	3,409	6,708
Thalamus – L	6,275.08	680.63	4,506	8,535
Thalamus – R	6,492.97	669.9	4,431	9,006

TABLE III

Genetic correlations between subcortical regions of interest

	Lat. ventricle		Inf. lat. ventricle			Thalamus		Caudate		Putamen		Pallidum		Hippocampus		Amygdala		Accumbens	
	L	R	L	R	Third ventricle	L	R	L	R	L	R	L	R	L	R	L	R	L	R
Lat. ventricle – L	1.000																		
Lat ventricle – R	0.971	1.000																	
Inf. lat. ventricle – L	0.739	0.710	1.000																
Inf. lat. ventricle – R	0.810	0.748	0.927	1.000															
Third ventricle	0.692	0.676	0.555	0.712	1.000														
Thalamus – L	−0.004	−0.012	0.048	0.045	0.145	1.000													
Thalamus – R	−0.017	−0.011	0.093	0.084	0.104	0.975	1.000												
Caudate – L	0.289	0.292	0.394	0.360	0.354	0.521	0.498	1.000											
Caudate – R	0.286	0.290	0.395	0.377	0.367	0.492	0.474	0.996	1.000										
Putamen – L	−0.091	−0.091	0.075	0.060	0.101	0.520	0.476	0.611	0.603	1.000									
Putamen – R	−0.045	−0.062	0.084	0.094	0.089	0.577	0.527	0.558	0.549	0.981	1.000								
Pallidum – L	−0.063	−0.090	0.044	0.022	−0.052	0.770	0.738	0.691	0.661	0.721	0.733	1.000							
Pallidum – R	0.129	0.108	0.124	0.074	0.164	0.712	0.665	0.625	0.580	0.670	0.646	0.863	1.000						
Hippocampus – L	−0.164	−0.196	0.027	0.061	0.096	0.529	0.540	0.376	0.373	0.449	0.406	0.493	0.497	1.000					
Hippocampus – R	−0.157	−0.216	−0.002	0.060	0.087	0.506	0.512	0.364	0.361	0.374	0.338	0.479	0.464	0.984	1.000				
Amygdala – L	−0.139	−0.080	0.011	−0.053	0.029	0.582	0.547	0.511	0.499	0.425	0.379	0.572	0.504	0.795	0.765	1.000			
Amygdala – R	−0.088	−0.040	0.055	0.014	0.118	0.621	0.575	0.584	0.577	0.455	0.411	0.623	0.549	0.780	0.753	0.987	1.000		
Accumbens – L	0.040	0.061	0.013	0.054	0.065	0.419	0.470	0.522	0.521	0.482	0.435	0.543	0.560	0.629	0.564	0.430	0.446	1.000	
Accumbens – R	0.042	0.156	0.086	0.101	0.117	0.124	0.233	0.300	0.287	0.367	0.303	0.191	0.210	0.382	0.321	0.325	0.259	0.492	1.000

Note: Inf. = inferior; Lat. = lateral; L = left; R = right.

TABLE IV

Model fitting summary of four-factor models

Number of factors							
A	**C**	**E**	**−2LL**	**AIC**	**BIC**	**Δ−2LL**	***P***
Cholesky			16,527.5	−306.5	−15,312.8		
4	4	6	16,802.5	−525.5	−15,867.1	275.0	0.11
4	4	7	16,767.6	−522.5	−15,831.4	240.1	0.28
4	5	6	16,777.2	−512.8	−15,826.6	249.7	0.15
4	5	7	16,741.8	−510.2	−15,791.0	214.3	0.39

Note: A = additive genetic; C = common environmental; E = unique environmental; −2LL = model fit as measured by −2 log likelihood; AIC = Aikake's Information Criterion, BIC = Bayesian information criterion; Δ−2LL = Change in the –2 log likelihood compared to the full Cholesky.

TABLE V

Four-factor solution with promax rotation from PCA of *genetic* correlations among subcortical volumes

Subcortical region	Basal Ganglia/Thalamic factor	Ventricular factor	Limbic factor	Accumbens factor
Putamen – R	**0.952**	−0.134	−0.211	0.225
Putamen – L	**0.911**	−0.154	−0.168	0.327
Pallidum – L	**0.911**	−0.123	0.096	−0.084
Pallidum – R	**0.806**	0.040	0.115	−0.061
Thalamus – L	**0.686**	0.006	0.347	−0.364
Caudate – L	**0.681**	0.332	0.079	0.152
Caudate – R	**0.652**	0.341	0.082	0.169
Thalamus – R	**0.621**	0.015	0.367	−0.282
Inferior lateral ventricle – L	−0.008	**0.941**	−0.123	−0.048
Inferior lateral ventricle – R	−0.024	**0.927**	0.031	0.030
Lateral ventricle – R	−0.029	**0.918**	−0.118	0.023
Lateral ventricle – L	0.034	**0.873**	0.001	−0.010
Third ventricle	−0.032	**0.806**	0.116	0.013
Hippocampus – R	−0.099	−0.040	**0.958**	0.177
Hippocampus – L	−0.051	−0.047	**0.933**	0.237
Amygdala – L	0.075	−0.031	**0.871**	0.050
Amygdala – R	0.154	0.031	**0.832**	−0.007
Accumbens – R	0.013	0.039	0.205	**0.786**
Accumbens – L	0.316	−0.016	0.329	**0.478**

Note: Factor loadings greater than ± 0.40 are indicated in bold.

TABLE VI

Four-factor solution with promax rotation from PCA of *phenotypic* correlations among subcortical volumes

Subcortical region	Basal Ganglia/Thalamic factor	Ventricular factor	Limbic factor	Accumbens factor
Putamen – R	**0.840**	−0.118	−0.108	0.150
Putamen – L	**0.869**	−0.100	−0.111	0.102
Pallidum – L	**0.909**	−0.042	−0.030	−0.153
Pallidum – R	**0.758**	0.039	0.040	−0.016
Thalamus – L	**0.721**	−0.041	0.284	−0.244
Caudate – L	**0.566**	0.344	0.067	0.251
Caudate – R	**0.559**	0.311	0.035	0.301
Thalamus – R	**0.699**	−0.045	0.274	−0.215
Inferior lateral ventricle – L	−0.042	**0.804**	0.023	−0.052
Inferior lateral ventricle – R	−0.070	**0.806**	0.061	−0.145
Lateral ventricle – R	0.047	**0.857**	−0.104	0.006
Lateral ventricle – L	0.053	**0.875**	−0.135	0.013
Third ventricle	−0.078	**0.769**	0.155	0.009
Hippocampus – R	−0.046	0.065	**0.914**	−0.007
Hippocampus – L	0.050	0.058	**0.841**	−0.013
Amygdala – L	0.095	−0.106	**0.648**	0.174
Amygdala – R	0.067	−0.046	**0.679**	0.210
Accumbens – R	−0.167	0.006	0.080	**0.807**
Accumbens – L	0.114	−0.190	0.093	**0.676**

Note: Factor loadings greater than ± 0.40 are indicated in bold.