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Morphological changes in aging brain structures are differentially affected by time-linked environmental influences despite strong genetic stability

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Abstract

This longitudinal study used the full twin model to estimate change and stability of genetic contributions to morphology of two brain structures, the corpus callosum and lateral ventricles. The 142 subjects were 34 monozygotic (MZ) and 37 dizygotic (DZ) elderly male twin pairs from the National Heart, Lung, and Blood Institute (NHLBI) Twin Study who underwent brain magnetic resonance imaging twice, separated by a 4-year interval. Genetic factors accounted for a substantial portion of individual differences in the size of the corpus callosum and its substructures and of lateral ventricular size. Longitudinal genetic analyses revealed no significant change in the heritability of these structures and no evidence for new genetic variance at Time 2 not present at Time 1. However, both the callosal and ventricular measures showed evidence for new environmental variance at Time 2 not present at Time 1. Confirming a previously posed hypothesis, the phenotypic correlation between absolute change in height of the corpus callosum and absolute change in ventricular volume was significant. Bivariate genetic analysis estimated a significant genetic correlation between the changes in these two structures and the genetic variance in the change of callosal height was entirely due to genes involved in the expansion of ventricles. Genetic stability was present even in old age when brain and other morphological changes can be rapid and highly variable across individuals, inconsistent with an hypothesis that random DNA damage is the cause of aging.
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1. Introduction

The role of genes in determining the ultimate dimension of somatic structure has traditionally been relegated to early development [9]. However, the concept of temporally-linked genetic influences on development and aging has also been introduced, with evidence for turn-on/turn-off genes operating at different times in life [16]. These potential breaches in genetic continuity may be discerned in human phenotypes when the twin model is applied to longitudinal data. Age-related somatic changes may be associated with differential genetic influences, the identification of which could provide critical phenotypical leads for focusing genetic linkage and gene mapping studies.

Genetic statistical modeling based on differences between measurements made in monozygotic (MZ) and dizygotic (DZ) twin pairs provides a method for estimating separate contributions of genes and the environment to brain structural size and shape. Cross-sectional study can identify the proportion of genetic relative to environmental factors that account for local morphometric variance measured at a given time. Longitudinal study can identify whether new genetic or environmental factors emerge that contribute to stability or change, constituting aging, in morphometric characteristics of the particular brain structures measured. A recent study based on a mutant mouse model used to identify genetic mechanisms responsible for premature aging suggested that DNA damage underlies transcription and repair failure and vigorous apoptosis [5]. This result would predict discontinuity and instability of genome variance with age, i.e. diminished heritability, if DNA damage is random.

The current investigation is, to our knowledge, the first quantitative analysis to use the twin model in a longitudinal study to test stability of genomic variance with age and to quantify differential contributions from genes and environment to human brain morphometry in old age. The brain structures considered were the corpus callosum and the lateral ventricles. Twin studies of the corpus callosum have revealed nearly 80% heritability of callosal size even in old age, with little contribution from environmental influences, whereas lateral ventricular size is significantly influenced

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by both genetic and environmental factors [14,15]. Dysmorphology of the corpus callosum is associated with developmental disorders, themselves with substantial heritability, including schizophrenia [1,20,24], and with later onset conditions, including cardiovascular disease [3]. Expansion of the lateral ventricles is a nonspecific yet consistent marker of normal aging studied longitudinally [19,21] or cross-sectionally [6,13,17] and diseases of the central nervous system [8]. Thus, both of these brain structures have known sensitivity to aging and disease, both phenotypes are readily visualized with neuroimaging techniques, and both carry a substantial genetic component, measurable even in old age, but with differential influence from environmental factors. An additional feature of these structures is their mutual influence on morphology, in that age-related change in the contour of the corpus callosum is substantially determined by the size of the lateral ventricles [12,15,21]. Thus, examination of this morphometric dynamic can contribute to parsing of the genetic versus environmental influences on the size versus shape of the corpus callosum with reference to concurrent expansion of the lateral ventricles. Further, this comparison can provide data on an interaction between factors contributing to reduction in callosal size and ventricular expansion arising from changes in time-linked differences in genetic and environmental factors affecting these structures.

2. Methods

2.1. Subjects

Participants comprised 34 intact MZ and 37 intact DZ pairs drawn from the National Heart, Lung, and Blood Institute (NHLBI) Twin Study (e.g. [2,15]). The sample was drawn from a population-based registry of twin pairs of Caucasian men and was created and maintained by the Medical Follow-up Agency at the National Academy of Sciences, National Research Council. Originally, 514 twin pairs volunteered to participate in the NHLBI Twin Study, a study of cardiovascular risk factors conducted at five regional centers in the United States. All participants were World War II veterans born between 1917 and 1927 and followed for 27–32 years. Twins first received brain MRIs in 1995–1997 (Time 1) and then again 4 years later in 1999–2001 (Time 2). Analyses in the present study were limited to the subgroup of 71 intact twin pairs with Time 1 (T_1) and Time 2 (T_2) brain scan data. The protocol was approved by all location institutional review boards, the research was conducted according to the principles of the Declaration of Helsinki, and all participants gave written informed consent.

Zygosity assessment of twins was initially based on eight red cell blood groups (ABO, MNS, Rh, Kell, Lewis, Duffy, Gm, and Kidd), comprising 22 antigens, as well as on the twins' own opinion of their zygosity [7]. Twins who had identical serotyping at baseline in 1969–1970 and who believed themselves to be identical were classified as MZ. Those discordant for one or more of the antigens were classified as DZ. In 1985–1986, variable number tandem repeat DNA markers were used to reassess zygosity in a subgroup of DZ pairs with no difference and revealed no change in serotyping from the entry classification. On the basis of these DNA results, nine pairs were confirmed as DZ, and four sets were reclassified as MZ [18].

2.2. MRI measurements

MRI data were collected at three locations: Stanford University, Indiana University, and West Suburban Imaging Center in Massachusetts. All data from both scanning sessions were collected on 1.5 T GE Signa systems and were analyzed as a single data set at SRI International, using in-house software written by A.P. for image alignment and region of interest quantification. The average (mean ± standard deviation) interscan interval was 4.0 ± 0.4 years. A nongenetic, aging analysis of these twin-pair plus additional twin singleton data has been previously published [21]. Procedures for this project were approved at each participating institution by its review board for use of human subjects in research.

2.3. MRI acquisition and quantification

2.3.1. Corpus callosum

The corpus callosum was measured on a sagittal midline slice extracted from the native data (spin-echo series; TR = 300–500 ms; TE = 8–14 ms; thickness = 4 mm, skip = 1 mm; encompassing the midline) after interpolation, alignment, and reslicing. A full description appears in Sullivan et al. [21]. The midsagittal image was extracted for semi-automated edge identification of the corpus callosum (Fig. 1). Interrater reliability was determined with intraclass correlations (ICC) ($n = 50$, total area $r = 0.99$). In addition to the total cross-sectional area of the corpus callosum, regional areas and a shape-related variable (height) were quantified with our previous method [15].

2.3.2. Lateral ventricles

The lateral ventricles were measured on three slices taken from a multislice, coronal, single-echo proton density-weighted or a dual-echo, spin-echo scan, manipulated to give proton density contrast; thickness = 5 mm, skip = 0 mm, encompassing the entire brain. The images were aligned to standard coordinates based on the anterior commissure (AC) and posterior commissure (PC). Three coronal slices (at the level of the AC, AC + 10 mm, AC − 10 mm) perpendicular to the AC–PC plane were extracted for semi-automated edge identification; the sum of the resultant three areas was the volume estimate for the left and right ventricles separately (Fig. 2). Interrater ICC for ventricular measurements was high ($n = 30$, left $r = 0.99$, right $r = 0.99$).

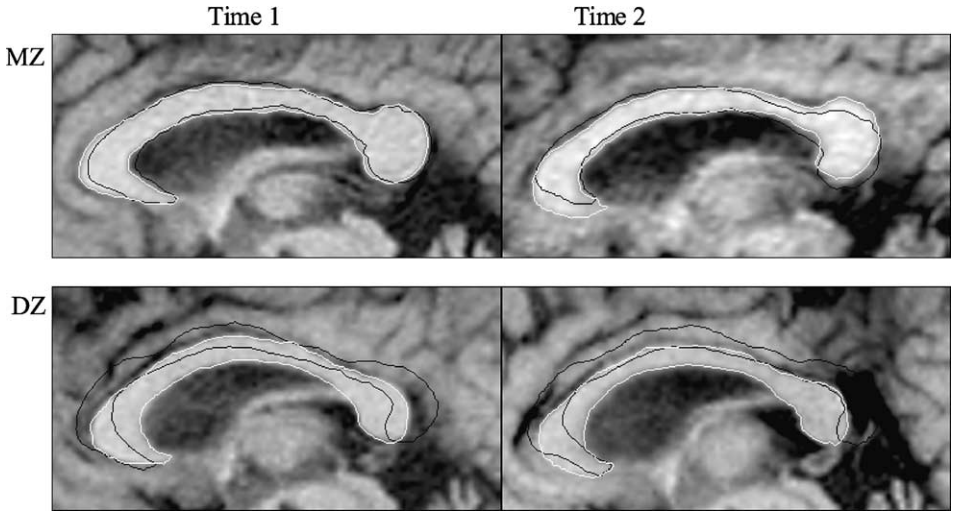

Fig. 1. Midsagittal MR brain images of the corpus callosum from two individuals (one MZ twin and one DZ twin) at Time 1 and Time 2. The corpus callosum profile of each twin is outlined in white and the profile from his brother is superimposed in black. Note the similarity in the shape of the corpus callosum in the MZ twin and his brother at both times vs. that of the DZ pair.

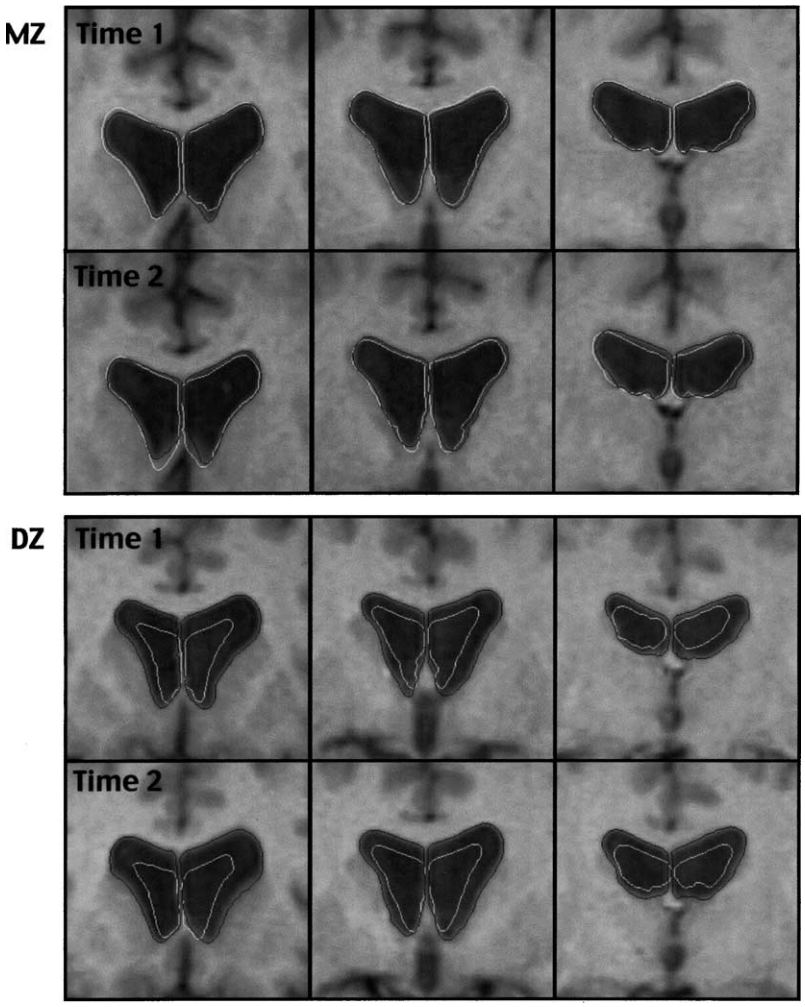

Fig. 2. Three coronal MR brain images through the lateral ventricles from two individuals (one MZ twin and one DZ twin) at Time 1 and Time 2. The ventricle profile of each twin is outlined in black and the profile from his brother is superimposed in white. Note the similarity in the size and shape of the ventricles in the MZ twin and his brother at both times vs. that of the DZ pair.

2.4. Statistical analysis

Statistical analyses are in four parts: (1) cross-sectional, univariate genetic analysis at each time; (2) univariate genetic analysis of change scores; (3) longitudinal analysis to determine change over time of genetic and environmental influences; and (4) longitudinal analysis to determine stability over time of genetic and environmental influences. All the biometric genetic analyses conducted used the program Mx [10].

2.4.1. Cross-sectional univariate genetic analysis

First, cross-sectional, univariate genetic analyses were performed separately on T_1 and T_2 data to characterize the genetic and environmental variances associated with each brain measure at each time point. Accordingly, twin-pair ICCs were calculated for each brain structural measure separately for each zygosity group. An initial comparison of the MZ to the DZ correlation provides information regarding the magnitude and type of genetic and environmental effects. If additive genetic effects are influencing the observed individual differences, then the MZ correlation is expected to be twice the DZ correlation. Nonshared environmental effects, unique to an individual twin, are suggested by a MZ twin correlation that is less than unity. Nonadditive (i.e. dominance) genetic effects reduce the DZ correlation to be less than one-half the MZ correlation, whereas a DZ correlation greater than one-half the MZ correlation suggests the presence of shared environmental influences.

We used structural equation models to test the significance of the suggested pattern of twin correlations observed for each brain structure. A series of univariate models was then fit to the observed MZ and DZ variance–covariance matrices. The general genetic twin path model partitions the observed total variance into four latent variables: $G =$ additive genetic effects, with the expected correlation between MZ twins being 1.0 and between DZ twins being 0.5; $C =$ common environmental effects, with the expected correlation being 1.0 for both zygosities; $E =$ unique nonshared environmental effects, with the expected correlation being 0.0 for both zygosities; and $D =$ dominance, which was tested with the current data set. The causal relationships of these latent variables on the observed phenotype (i.e. brain measure) are expressed by partial regression coefficients parameterized as h (for G, the genetic factor), c (for C, the common environmental factor), and e (for E, the nonshared environment and error factors), and are obtained by maximizing the likelihood of the data under a specific structural model. The model incorporating the GCE factors was always tested first. The fit of the full model was compared to the fit of submodels created by removing one or more variables at a time to determine the best fit with the fewest variables.

A χ^2 test, which compared the observed covariance matrices with the expected covariance matrices, was used to evaluate the goodness of fit of a structural model. Submodels or nested models were compared to the full models by the likelihood-ratio χ^2 test (the χ^2 difference between a full and reduced model). The principle of parsimony holds that models with fewer parameters are considered preferable if they show no significant worsening of fit when compared with a full GCE model. Comparison of models were also made using the Akaike's information criterion (AIC), computed as $\chi^2 - 2$ d.f., as a measure indicative of both goodness of fit and model parsimony. Components of variance were calculated by dividing the squared value of a given parameter by the total variance or the summed squared values of the parameters.

2.4.2. Univariate genetic analysis of change scores

In an initial longitudinal univariate analysis, we determined the contribution of genetic and environmental influences to change scores, which were $T_2 - T_1$ raw difference scores calculated for each MRI measure.

2.4.3. Longitudinal genetic analysis of change and stability

Longitudinal genetic models were fit to the two-wave data to estimate stability and change in the contribution of genetic and environmental influences to twin-pair similarity at each time point. Specifically, a bivariate Cholesky model was fit to the 4×4 variance–covariance matrices of the combined T_1 and T_2 brain image data. This model assumes that common genetic (G_1) and common environmental (E_1) effects observed at Time 1 are influencing the T_1 and T_2 data, whereas new genetic and environmental effects emerging after the initial observation only influence the T_2 data. Fig. 3 depicts the longitudinal structural model for one member of a twin-pair. G_1 and E_1 are genetic and

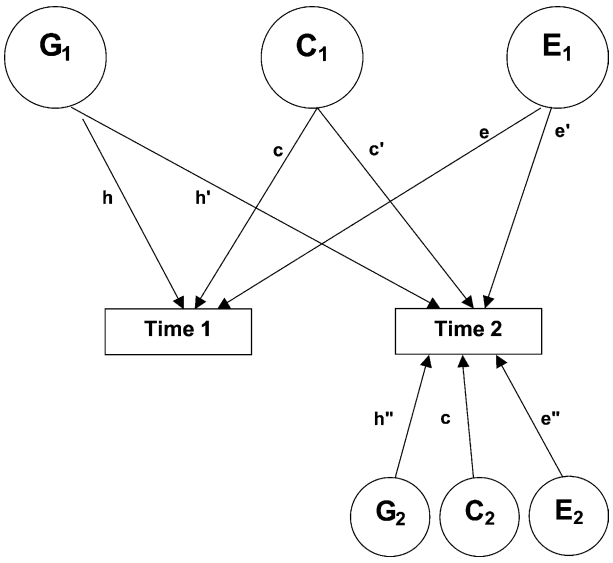

Fig. 3. The longitudinal structural model for one member of a twin-pair. G_1, C_1, and E_1 are genetic, common environmental, and unique environmental influences common to T_1 and T_2, and G_2, C_2, and E_2 are the genetic, common environmental, and unique environmental influences specific to T_2. The magnitude of the effects of G_1, C_1, and E_1 are represented by the path coefficients h, h', c, c', and e, e', whereas magnitude of the specific G_2, C_2, and E_2 effects are represented by path coefficients h'', c'', and e''.

environmental influences common to T_1 and T_2, and G_2 and E_2 are the genetic and environmental influences specific to T_2. The magnitude of the effects of G_1 and E_1 are represented by the path coefficients h, h' and e, e', whereas magnitude of the specific G_2 and E_2 effects are represented by path coefficients h'' and e''. A parallel structure exists for the common environmental effects (C_1 and C_2). The likelihood-ratio χ^2 test and AIC statistic were used to compare submodels, in which one or more parameters were dropped, according to the principle of parsimony, from the full bivariate model. Phenotypic stability analyses involved calculation of (1) path coefficients between time points as the square root of the heritability estimate at each time; (2) genetic chain of paths ($h_1\ r_G\ h_2$, where h_1 = heritability at T_1, r_G = genetic correlation between T_1 and T_2, and h_2 = heritability at T_2) which are standardized covariances; and (3) the stability measure, which equaled the genetic chain standardized by the correlation at T_1 and T_2 [11].

3. Results

3.1. Cross-sectional univariate genetic analysis

The first analysis step was to partition the variance of each brain measure at each time point into genetic and environmental components. Table 1 summarizes the MZ and DZ ICCs for the midsagittal corpus callosum, the comparison of which yields a rough measure of heritability, for each brain measure at each time, and variance estimates from the best genetic model fitting the data (GE). The goodness of fit statistics, with C removed, was not significant in any case (χ^2 range for T_1 and T_2 = 7.2–0.57, P = 0.12–0.96). All callosal measures were highly heritable at each measurement time. Heritability of the total callosal area increased from 80% at T_1 to 85% at T_2. The largest increase in heritability was for the genu, which increased from 68% at baseline to 81% at follow-up. To test the significance of this increase, we constrained the genetic parameters to be equal at T_1 and T_2. Comparing the constrained model ($\chi^2 = 8.18$, d.f. = 10) to a model in which the parameters were allowed to differ across occasions ($\chi^2 = 5.02$, d.f. = 8) resulted in a nonsignificant χ^2 difference ($\chi^2 = 3.16$, d.f. = 2, $P = 0.25$).

Table 2 summarizes univariate results for lateral ventricles. Over time the ICC of both zygosity groups declined in all ventricular measures. The estimated heritability of bilateral ventricular volume declined from 84 to 78%. The change in goodness of fit statistics, with C removed, was not significant for any measure at either time point (χ^2 range for T_1 and T_2 = 4.77–0.80, P = 0.31–0.94).

3.2. Univariate genetic analysis of change scores

The MZ and DZ ICCs for calculated raw $T_2 - T_1$ change scores were significant only for changes in height and length of the corpus callosum. Subjecting these data to genetic modeling revealed that 48% of the variability in height change scores could be attributed to genetic influences and 52% could be attributed to environmental influences. Corresponding variance components for changes in length

Table 1
Intraclass correlations and estimates of genetic and environmental variance of the corpus callosum and its substructures at T_1 and T_2 and $T_2 - T_1$

Structure	Intraclass correlation		Variance estimates	
	MZ	DZ	G	E
Total callosal area				
T_1	0.84	0.30	0.80	0.20
T_2	0.89	0.36	0.85	0.15
$T_2 - T_1$ change	−0.10	0.22	–[a]	–[a]
Genu				
T_1	0.66	0.48	0.68	0.32
T_2	0.81	0.34	0.81	0.19
$T_2 - T_1$ change	0.02	−0.02	–[a]	–[a]
Body				
T_1	0.86	0.25	0.83	0.17
T_2	0.85	0.37	0.81	0.19
$T_2 - T_1$ change	0.12	0.16	–[a]	–[a]
Splenium				
T_1	0.79	0.34	0.75	0.25
T_2	0.85	0.30	0.83	0.17
$T_2 - T_1$ change	0.06	0.10	–[a]	–[a]
Height				
T_1	0.84	0.40	0.85	0.15
T_2	0.81	0.43	0.83	0.17
$T_2 - T_1$ change	0.55	0.09	0.48	0.52
Length				
T_1	0.78	0.51	0.75	0.25
T_2	0.77	0.46	0.73	0.27
$T_2 - T_1$ change[b]	0.69	0.55	0.76	0.24

[a] Intraclass correlations that are nonsignificant or those that are greater for DZ than MZ pairs violate the assumption of genetic variance, i.e. heritability.

[b] For callosal length, the ACE model is the best fit, where $G = 0.48$, $C = 0.27$, and $E = 0.25$.

Table 2
Intraclass correlations and estimates of genetic and environmental variance for left, right and total ventricular size at T_1, T_2 and $T_2 - T_1$

Structure	Intraclass correlation		Variance estimates	
	MZ	DZ	G	E
Total ventricles				
T_1	0.81	0.40	0.84	0.16
T_2	0.77	0.36	0.78	0.22
$T_2 - T_1$ change	0.33	0.01	0.27	0.73
Right ventricle				
T_1	0.73	0.32	0.77	0.23
T_2	0.70	0.26	0.74	0.26
$T_2 - T_1$ change	0.26	−0.03	0.20	0.80
Left ventricle				
T_1	0.82	0.46	0.83	0.17
T_2	0.76	0.34	0.76	0.24
$T_2 - T_1$ change	0.36	0.02	0.29	0.71

of the corpus callosum were 48% genetic, 27% shared environment and 25% nonshared environmental influences.

The majority of observed individual differences in ventricular $T_2 - T_1$ change scores were attributable to nonshared environmental factors, ranging from 71 to 80%. Univariate genetic modeling of change scores suggested significant genetic variance for change computed for the combined ventricle measures (left+right). However, the estimates of genetic variance for the $T_2 - T_1$ change scores do not meet model assumptions because, even though the ICC for MZ twins was significant, the ICC for DZ twins was essentially 0.

Given that the greatest aging effects were observed in the lateral ventricles and height of corpus callosum [21], we performed a heritability analysis on raw changes from T_1 to T_2 on these two brain measures to estimate the contribution of genetic influences to intraindividual variation in changes of brain measurements. The MZ ICC for changes in ventricular size was 0.33 and for changes in height of the corpus callosum it was 0.55 (both significant at $P < 0.01$). However, the maximum likelihood estimates of additive genetic variance based on the GE model were not significant [27% for changes in ventricles ($\chi^2 = 6.74$, d.f. $= 4$, $P = 0.15$) and 48% for changes in height of the corpus callosum ($\chi^2 = 7.22$, d.f. $= 4$, $P = 0.12$)]. Thus, there was not statistically significant evidence for genetic control of these age-related changes.

3.3. Longitudinal genetic analysis of change

We estimated the separate genetic (r_G) and environmental (r_E) correlations between brain measures at the two time points. When a correlation is 1.00, all the variance is considered to be in common. When the correlation is less than 1.00, new variance not operating at T_1 is assumed to be operating at T_2. This analysis indicated that for the corpus callosum and its substructures (genu, body, splenium), r_G ranged between 0.98 and 1.00, revealing close to complete overlap in genetic influences across the two time points (Table 3). The environmental correlations, r_E, for the corpus callosum and substructures were less than 1.00 and ranged from 0.37 to 0.56, indicating that half or less of the environmental influence at T_2 was in common with that at T_1. For the height of the corpus callosum and ventricular volumes, both the genetic and the environmental correlations approached 1.00, suggesting near complete continuity of both genetic and environmental influences for these measures.

Genetic and environmental components at follow-up were then decomposed into those that were specific to T_2 and those in common with baseline (i.e. T_1). No new genetic effects were identified at follow-up for any callosal or ventricular measure. In contrast to the absence of new genetic effects, distinctions between effects specific to T_2 and those common with T_1 were detected for the nongenetic (environmental) component of variance, especially notable in the ventricles. Even though environmental effects for the corpus callosum area accounted for 15% of the total variation at T_2, only 4% of this nongenetic variation resulted from the direct path between T_1 and T_2 (i.e. in common with T_1). A similar pattern (3% common, 13% specific or new) was present for ventricular volume.

We also investigated the sources of covariation between changes in ventricles and changes in the callosal height. Using a bivariate Choleski decomposition, we determined that 42% of the 48% additive genetic variance in changes of the height of the corpus callosum was common with genes responsible for changes in ventricles. In addition, the significant phenotypic correlation ($r = 0.36$, $P = 0.0001$) between changes over time in these two structures was entirely due to common genetic effects and not common environmental effects (i.e. $hr_G h' = 100\%$, $er_E e' = 0\%$). The results of this analysis suggest a common genetic mechanism underlying the phenotypic relationship between changes in ventricles and changes in the height of the corpus callosum.

3.4. Longitudinal genetic analysis of stability

Here we applied the bivariate longitudinal model to the combined MZ and DZ MRI data for each brain measure from the two time points. We first tested the fit of a full model, which allowed for common (present in T_1 and T_2) and specific (present in T_2 only) additive genetic (G_1 and G_2) and nonshared environmental effects (E_1 and E_2). For the total area of the corpus callosum, sequential elimination of the genetic and environmental correlations from the full

Table 3
Estimates of genetic and environmental correlations and the genetic and environmental contributions stability

Structure	r_{ph}	r_G	r_E	$h_1 r_G h_2 / r_{ph}$ (%)	$e_1 r_E e_2 / r_{ph}$ (%)
Total callosal area	0.92	1.00	0.49	90	10
Genu	0.85	1.00	0.37	87	13
Body	0.92	0.99	0.56	88	12
Splenium	0.88	0.98	0.53	88	12
Height	0.97	0.99	0.92	85	15
Length	0.97	0.97	0.97	74	26
Total ventricle	0.98	1.00	0.91	83	17
Right ventricle	0.98	1.00	0.92	77	23
Left ventricle	0.98	1.00	0.91	81	19

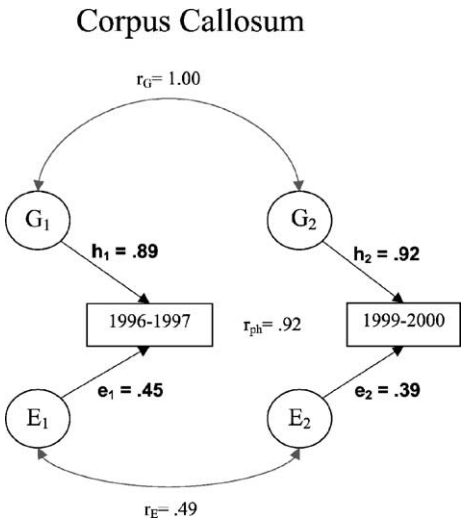

Fig. 4. Path model for estimating the separate genetic (r_G) and environmental (r_E) correlations between total corpus callosum area at the two time points. When a correlation is 1.00, all the variance is considered to be in common.

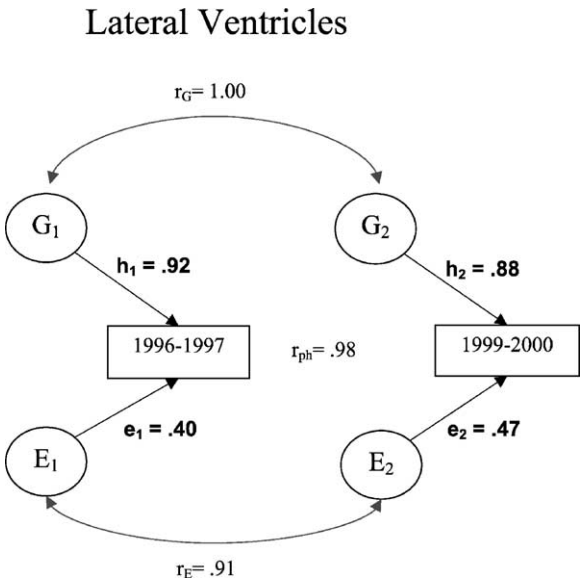

Fig. 5. Path model for estimating the separate genetic (r_G) and environmental (r_E) correlations between ventricle size at the two time points. When a correlation is 1.00, all the variance is considered to be in common.

model resulted in a worsening in fit (χ^2 statistics with 1 d.f. = 9.8 for genetic, 19.77 for environmental, both $P < 0.01$). Thus, both additive genetic (G_1) and environmental influences (E_1) on callosal size expressed at T_1 contributed significantly to individual differences at T_2.

We next tested whether new genetic or environmental influences specific to T_2 contributed significantly to observed variation in corpus callosum area at T_2. Elimination of the T_2 genetic parameter did not worsen the fit, but elimination of the T_2 environmental parameter did. This pattern of results supports the conclusion that the best longitudinal genetic model fitting these data is a model where all the genetic variance from T_1 was transmitted to T_2 with the addition of new environmental variance at T_2 not present at T_1. Parameter estimates for this model are shown in Figs. 4 and 5. Similar results were observed for size measurements of the lateral ventricles volumes and the substructures of the corpus callosum (Table 3).

Finally, we examined the genetic and environmental contributions to phenotypic stability. This analysis partitioned the proportion of the phenotypic correlation (r_{ph}) due to genetic chain of paths from the proportion due to the environmental chain of paths [11]. The path coefficients h_1, h_2, e_1, and e_2 represent the square roots of the genetic and environmental proportions of variance at T_1 and T_2. For example, for the total area of the corpus callosum (Table 1), the heritability at T_1 was 0.80 and at T_2 was 0.85, resulting in path coefficients of $h_1 = 0.89$ and $h_2 = 0.92$. The genetic chain of paths, therefore, was $0.89 \times 1.00 \times 0.92 = 0.82$. The genetic contribution to stability was computed by dividing the genetic chain by the phenotypic correlation, i.e. $0.82/0.92 = 0.90$. Similar calculations were done for each brain structure (Table 3). In general, for all measures phenotypic stability was determined primarily by genes with a far smaller contribution from environment.

4. Discussion

This longitudinal analysis provided the opportunity to test genetic stability and change as determinants of brain morphometric alteration with aging. It also permitted estimation of additional influences from new environmental forces during the interval examined. Within the limitations of the assumptions of statistical genetic modeling, the results revealed no significant change in the heritability of the two structures examined over time and no evidence for new genetic variance at Time 2 not present at Time 1. In spite of the genetic stability, the callosal and ventricular measures showed evidence for new environmental variance at Time 2 not present at Time 1. This new variance was greater for ventricular than callosal measures.

The determination of the separate contributions of genes and the environment to the variance associated with a measure, in our case, ventricular and callosal size, is estimated by using a statistical twin model. The variance is parsed into three major components: genes (G), shared environment (C), and nonshared environment (E). The full twin model based on pairs of MZ and DZ twins, with twin pairs reared together for at least early postnatal development, allows estimation of only additive components of G, C, and E. This twin model is also defined by the fact that the standardization of the total variance is equal to one. In the present analysis, where C did

not make a significant contribution, the total variance was described by two factors with one degree of freedom. By definition, as one factor changes in a sum of two proportions, the other factor changes proportionately in the opposite direction. Thus, the stability of genetic influences over time can appear smaller if the environmental influences increase over time. In order to address the composition of the genetic and the environmental factors, we need to be able to test for $G \times E$ interactions, which could be positive or negative. In order for a twin model to estimate $G \times E$ interactions, a design is needed where the genes are constant and the environment is different, as occurs when MZ twins are reared apart. The converse, where evidence for new genetic variance is sought, requires an experimental manipulation impossible in humans.

The results support cross-sectional conclusions regarding the heritability of the size of the corpus callosum and lateral ventricles and confirm that different brain structures are differentially susceptible to genetic influences and common environmental factors even within the same brain [4,14,15,22,23]. The differential genetic effect is further evidence that brain structure is not a homogeneous gene product, but rather that different structures may be susceptible to influence from different genes and at different times by different environmental factors.

Genetic analysis of change scores indicated that the mainstay of variance (71–80%) associated with change in ventricular size was attributable to nonshared environmental factors. Thus, although genetic factors may exert an influence on change in ventricular size in late life (∼25%), other environmental factors, possibly from disease or trauma, play an even greater role in determining ventricular size. In contrast to ventricular size, which enlarges at a rate of about 3% annually, callosal size is very stable, with less than 1% shrinkage per year, usually detectable only with longitudinal design [21]. Although the MZ and DZ ICC for callosal area measures of change were too low to permit genetic model fitting, heritability of callosal morphometric measures of change in height and length could be tested and yielded a different pattern of genetic–environmental influences from that observed for the ventricles. Whereas the genetic:environmental ratio was on average 25:75 for ventricular change, this ratio was about 50:50 for callosal height change and 75:25 for callosal length change. These proportional patterns provide evidence that common genes or experiences do not necessarily exert a uniform influence on age-associated change in brain structure.

With aging, although brain structures change in shape and size, the MZ versus DZ twin data indicate that the between-twin/within-twin ratio remains constant with aging, and thus, the genetic contribution to structural morphology remains stable. The pattern of strong genomic stability, evidenced in consistent twin–twin variation over time, does not support aging hypotheses that invoke random DNA damage as the mechanism of aging, at least for the two brain structures examined over the interval in which there was small but detectable thinning of the corpus callosum but substantial expansion of the ventricles. Support of this hypothesis would require evidence for genetic instability of a phenotype, which we did not observe. It may still be the case that DNA damage contributes to aging, but if that occurred in these twins, then both men within an MZ pair would exhibit susceptibility to the same damage. Indeed, the DNA damage concept may apply to instances of premature aging, but it may not necessarily apply to normal aging of the brain's ventricles and corpus callosum.

In conclusion, the complete carry-forward of genetic contribution to phenotypical stability observed in the corpus callosum and lateral ventricles was accompanied by significant environmental contribution that was nearly twice as great on ventricular variance as it was on callosal variance. Genetic stability was present even in old age when brain and other morphological changes can be rapid and highly variable across individuals.

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