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Longitudinal genetic analysis of brain volumes in normal elderly male twins

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Abstract

This study investigated the role of genetic and environmental influences on individual differences in brain volumes measured at two time points in normal elderly males from the National Heart, Lung, and Blood Institute Twin Study. The MRI scans were conducted four years apart on 33 monozygotic and 33 dizygotic male twin pairs, aged 68 to 77 years when first scanned. Volumetric measures of total brain and total cerebrospinal fluid were significantly heritable at baseline (over 70%). For both volumes genetic influences at follow-up were entirely accounted for by genetic influences at baseline, suggesting that the same genetic factors influence variability in brain volume at each time of assessment. Variability in 4-year volume change was due to shared and individual-specific environmental influences. There was little evidence for heritable influences on change measures. These results suggest that variation in longitudinal change of some brain volume measures may have different underlying genetic and environmental architecture from variation in repeat cross-sectional measures, which could have implications for intervention strategies for age-related illness associated with brain morphology. The results of this study are discussed in the context of the small sample size and associated limitations of statistical power.

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Disclosure Statement

The authors have no actual or potential conflicts of interest in relation to any aspect of this manuscript.

Keywords

twins; volumetric MRI; longitudinal; aging

1. Introduction

Genetic statistical modeling based on differences between measurements made in monozygotic and dizygotic twin pairs provides a method for estimating separate contributions of genes and the environment to brain structural size and shape. A cross-sectional study can identify the proportion of genetic relative to environmental factors that account for local morphometric variance measured at a given time. A longitudinal study can identify whether new genetic or environmental factors emerge at a later time point, constituting aging, in morphometric characteristics of the particular brain structures measured.

We have previously shown significant genetic influences on single measurement variability of global and regional brain MRI volumes such as total brain volume, hemispheric volumes, frontal, temporal, parietal and occipital regional volumes (Carmelli, et al., 1998, Carmelli, et al., 2000, Pfefferbaum, et al., 2000); lateral ventricles (Carmelli, et al., 2002, Pfefferbaum, et al., 2004, Pfefferbaum, et al., 2000); total volume of cerebrospinal fluid (CSF) (Carmelli, et al., 1998); and indices of brain aging such as white matter hyperintensities (Carmelli, et al., 1998). Other studies in adult but not elderly twins support significant contribution of genetic factors on total brain volume (Baare, et al., 2001, van der Schot, et al., 2009, Wright, et al., 2002), and on gray and white matter (Baare, et al., 2001, van der Schot, et al., 2009). Unlike results in elderly twins, lateral ventricle volume in twins aged 20 to 30, is influenced by shared environmental factors (39%–59%) as opposed to genetic factors (Baare, et al., 2001, Chou, et al., 2009, Wright, et al., 2002). A greater influence of environmental relative to genetic factors on a given brain region or structure may reflect greater sensitivity of these areas to modification by environmental factors.

This notion is particularly relevant when investigating changes in brain volume as a function of normal aging. Considering that different brain areas show different amounts of shrinkage with age (DeCarli, et al., 2005, Raz, et al., 2005, Resnick, et al., 2003), understanding the role of genetic and environmental factors has implications for intervention strategies for age-related illness associated with changes in brain morphology. In a previous longitudinal genetic analysis of twins from the National Heart, Lung, and Blood Institute (NHLBI) twin study, high genetic influences were found on cross-sectional variation in lateral ventricle volumes measured at each of two assessments (74%–84%), but lower heritability estimates for 4-year volume change (20%–29%) (Pfefferbaum, et al., 2004). Thus, in contrast to consistent high heritability on cross-sectional measurements, heritability of volume change in the same structures was lower, suggesting that the process of change may be under different genetic and environmental influences.

2. Methods

2.1. Subjects

Participants in the National Heart, Lung, and Blood Institute (NHLBI) Twin Study of cardiovascular risk factors were drawn from a population-based registry of twin pairs that was created and maintained by the Medical Follow-Up Agency at the National Academy of Sciences-National Research Council (Jablon, et al., 1967). Originally, 514 twin pairs volunteered to participate in the NHLBI Twin Study which was conducted at five regional

centers in the United States (Feinleib, et al., 1977). All participants were Caucasian male World War II veterans born between 1917 and 1927 and followed for more than 30 years.

Zygosity assessment was initially based on 8 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 (Jablon, et al., 1967). Twins who had identical serotyping at baseline in 1969–70 and who believed themselves to be identical were classified as monozygotic (MZ). Those discordant for one or more of the antigens were classified as dizygotic (DZ). In 1985–86, variable number tandem repeat DNA markers were used to reassess zygosity in the subgroup of self-reported DZ pairs with no difference in serotyping at the entry examination. On the basis of the DNA results, nine pairs were confirmed as DZ, and four pairs were reclassified as MZ.

In 1995–97, NHLBI twins received brain MRI scans (n=409 twin subjects) and again about 4 years later in 1999–2001 (n=234 twin subjects). The institutional review board at each site approved the MRI protocol and each participant gave written informed consent. Analyses in the present study were limited to a non-institutionalized subgroup of 66 twin pairs with Time 1 (T1) and Time 2 (T2) MRI volume data.

2.2 Cerebral MRI scans and image analysis

MRI (1.5T) on GE scanners was performed at four study sites at T1 (Stanford University, Indiana University, UCLA Harbor Medical Center, and West Suburban Imaging Center in Massachusetts) and at three sites at T2 (Stanford, Indiana, and Massachusetts). At T2, the UCLA site did not participate due to personnel changes. Scanner equipment and data acquisition sequences were the same across study sites and times of assessment. A conventional spin-echo, double-echo sequence in the axial orientation with TR = 2000, TE = 20/100, 24 cm field of view, and 5 mm contiguous slices from the vertex to the foramen magnum imaged in a 256×192 matrix and interpolated to 256×256 with one excitation was used. Axial images were angled to be parallel to the anterior-posterior commissure line. Data from the four collection centers were scored by the same individuals at a central location (University of California Davis). Intra- and inter-rater reliabilities of the scoring methods are above 0.9 (DeCarli, et al., 1992). Briefly, using a custom-written semiautomated program (DeCarli, et al., 1992), segmentation of brain parenchyma from CSF was achieved by subtracting second-echo image from the first-echo image. Image intensity nonuniformities were removed from this difference image, and the resulting corrected image was modeled as a mixture of two Gaussian probability functions (DeCarli, et al., 1992, DeCarli, et al., 1996). The segmentation threshold was determined at the minimum probability between the modeled CSF and brain matter intensity distribution (Murphy, et al., 1992).

The average (mean ± SD) interscan interval for the 66 twin pairs was 4.0 ± 0.4 years. CSF volume data were skewed and were log-transformed. Total brain and log CSF volumes were adjusted to account for differences in intracranial volume and data collection site and the residualized values were used in analyses.

2.3. Statistical analysis

Twin analyses were conducted separately for each brain volume measure and consisted of: 1) longitudinal (bivariate) analysis of genetic and environmental variation and covariation across T1 and T2; and 2) univariate genetic analysis of MRI volume change from T1 to T2. Analyses were conducted using the structural equation modeling software program Mx (Neale, et al., 2003).

2.3.1. The twin method—By comparing the degree to which MZ cotwins are similar for a given measure relative to DZ cotwins and using data from twin pairs reared together, phenotypic variance can be decomposed into the additive effects of genes (A), or heritable factors, which contribute to twin pair similarity; to shared environmental effects (C) common to twin siblings such as *in-utero* and family environment, peers, or school factors, which also contribute to twin pair similarity; and to non-shared environmental effects (E), which capture experiences unique to each twin as well as measurement error, and contribute to twin pair dissimilarity.

The pattern of MZ and DZ twin pair correlations provides a description of the relative contribution of genetic and environmental effects on phenotypic variance. The phenotypic correlation between MZ twins is a function of their genetic relatedness and shared environment. Since MZ twin siblings share 100% of their genes and are assumed to also share 100% of their common environment, their phenotypic correlation is expressed as r_{MZ} =A+C. The phenotypic correlation between DZ twins is also a function of their genetic relatedness and shared environment. However, because DZ twin siblings share, on average, 50% of their genes and, like MZ twins, are assumed to share 100% of their common environment, the DZ twin pair phenotypic correlation is expressed as r_{DZ} =0.5A+C. If twin pair similarity is largely due to genetic relatedness, it is expected that the ratio r_{MZ}/r_{DZ} will equal 2 (i.e., C=0). A contribution of both additive genetic and shared environmental factors results in greater similarity of DZ cotwins relative to MZ cotwins and $r_{MZ}/r_{DZ}<2$. The r_{MZ}/r_{DZ} is close to 1 if shared environmental influences are primary contributors to twin pair resemblance and additive genetic effects are not important (i.e., A=0).

2.3.2. Longitudinal analysis—Using a bivariate correlated factors model, we investigated how much of the genetic and environmental contribution to phenotypic variability at T1 accounts for the genetic and environmental contribution to variability at T2. If all of the genetic and environmental variance at T1 accounts for the genetic and environmental variance at T2, a genetic or environmental correlation will equal 1, suggestive of the contribution of the same genetic factors across time. A correlation coefficient of zero would suggest that genetic or environmental variance at T1 does not account for the genetic or environmental variance at T2. A correlation between zero and one would suggest that some of the genetic or environmental variance at T2 is accounted for by genetic or environmental variance at T1 but there is also residual variance specific to T2.

To evaluate the best model fit, we first fit a general correlated factor model allowing for all parameters (A, C, and E at T1, A, C, and E at T2, and each of the genetic (r_a), shared environmental (r_c), and non-shared environmental (r_e) correlations) to be freely estimated. Next, we fit a series of nested models in which parameters were constrained (e.g., setting A or C parameters to zero or equating correlations to zero or one) and compared the fit of the nested models to the fit of the general model using the likelihood ratio chi-square difference test. This test evaluates the significance of the difference between chi-square statistics of the two models at the difference degrees of freedom between the same two models. A significant chi-square difference (p value <0.05) suggests that the nested model fit the data significantly worse compared to the general model. Thus, the constraint placed in the nested model would not be justified and the fit of the general model would be favored. Choice of the best model fit was guided by both the chi-square difference test and by model parsimony evaluated using the Akaike information criterion (AIC). Smaller AIC values including negative values suggest a more parsimonious model; that is, a model that account for the data with the least number of estimated parameters. Bivariate correlated factor models were fit to the observed residual 4 × 4 MZ and DZ variance-covariance matrices of the combined T1 and T2 MRI data, adjusted for intracranial volume and study site.

2.3.3. Univariate analysis of change scores—The relative contribution of genetic and environmental influences on phenotypic variance in MRI change scores (T2–T1) was investigated using univariate "ACE" models. The relative fit of nested genetic ("AE") or environmental ("CE" or "E") models compared to the fit of the general "ACE" model was tested to determine the best model fit by likelihood ratio chi-square difference test and AIC criteria. Univariate models were fit to 2 × 2 MZ and DZ twin pair variance-covariance matrices, generated from T2–T1 change scores adjusted for intracranial volume and study site.

3. Results

Study subjects were on average 71.6 years old at T1 (2.6 SD; range 68–77 years) and 75.2 years old at T2 (2.6 SD, range 72–81 years). Time 1 characteristics of the subgroup of 66 twin pairs (n=132 twins) and the remaining cohort of twins (n=277 twins) are described in Table 1. Study subjects were younger, had more years of education, higher Mini Mental State Exam scores, and lower prevalence of diabetes and probable dementia. In these analyses, MZ twins had lower body mass index, on average, and higher prevalence of hypertension than DZ twins. Overall, the study subjects and the twin cohort in general have similar characteristics to other healthy men of similar age (DeCarli, et al., 2005,Mungas, et al., 2005).

Over the 4 years of follow-up there was a significant decrease in mean score for total brain volume and a significant increase in mean score for CSF volume in the total sample and by zygosity (all $p<0.001$) (Table 2). For clarity, untransformed values are shown in Table 2.

3.1. Longitudinal analysis

The phenotypic correlations across T1 and T2 for intracranial volume and study site-corrected measures were significant for total brain ($r=0.66$, $p<0.01$) and total CSF ($r=0.64$, $p<0.01$). The correlation of intracranial volume between T1 and T2 was 0.91 ($p<0.01$)Twin pair correlations across zygosity for each volume measure at T1 and T2 are shown in Table 3. At T1, the MZ twin pair correlations were about two times larger than the DZ twin pair correlations suggesting the influence of genetic, but not shared environmental factors. At T2, the MZ twin pair correlations were less than two times greater those of the DZ twin pair correlations suggesting a contribution of shared environmental factors. Of note, while all twin pair correlations were elevated at T2 compared to T1 suggesting greater within-pair similarity in brain volumes, the magnitude of the increase in the DZ correlations were larger than the increase in the MZ correlations at T2 compared to T1. The twin pair correlations for intracranial volume were very similar across time: at T1 the correlations were $r_{MZ}=0.88$ and $r_{DZ}=0.64$; and at T2 they were $r_{MZ}=0.89$ and $r_{DZ}=0.72$ (all $p<0.05$).

Model fit statistics for the general and nested bivariate correlated factor models are shown in Table 4. Model fitting proceeded by first testing the significance of each of the A and C parameters at T1 and T2 and after determining the best model fit for genetic and environmental parameters (indicated using italics), the magnitude and significance of the genetic and environmental correlations was tested. The E parameter was always estimated since individual-specific and measurement error factors always contribute to phenotypic variance. The non-shared environmental correlation was never equated to 1 because it is unreasonable to expect that individual-specific factors and error variance would be the same across two times of assessment. The final best fitting models are indicated in bold italics.

Thus, for total brain volume, the model that estimated A and E at T1 and A, C, and E at T2 was deemed best fitting because dropping C at T1 did not significantly worsen model fit relative to the general model (chi-square difference=0.805, p=0.669) and this model had the

lowest AIC (AIC=7.397). Next, equating the genetic correlation to zero significantly worsened model fit (chi-square difference=27.225, $p<0.001$). Equating the genetic correlation to 1 and/or equating the non-shared environmental correlation to 0 did not contribute to deterioration of model fit. The model with lowest AIC (AIC=5.397) was the model where the genetic correlation was set to 1 and the non-shared environmental correlation was freely estimated. Hence, this was the model that was deemed best fitting. The same logic was carried through model fitting procedures for total CSF volume.

Parameter estimates for the best fitting models are shown in the Figure. Volume measures were highly heritable at T1 (74.7% and 73.0% for total brain and CSF, espectively). At T2, a significant influence of shared environment was seen (31.5% for total brain and 33.4% for total CSF) and consequently, a relatively lower heritability (48.0% for total brain and 44.5% for total CSF). Despite the difference in heritability magnitude at T1 and T2, the genetic correlations could be equated to 1 suggesting that all of the genetic variance at T2 was accounted for by the genetic variance at T1 (i.e., there was no genetic variance specific to T2). For both volume measures, the non-shared environmental correlations were significant suggesting that some of the individual-specific and measurement error variance at T2 was accounted for by individual-specific and measurement error variance at T1, but that there was residual non-shared environmental variance specific to T2.

Taken together, these results suggest that the same genetic factors influence variability in total brain and total CSF volume at T1 and T2, but that there are shared and non-shared environmental effects specific to T2.

3.2. Univariate analysis of change scores

Table 5 shows model fit statistics for the general and nested models as well as the A, C, and E parameter estimates for all models. The best fitting models for volume change were the “CE” models based on AIC criteria. For both volume change measures, neither the “AE” nor the “CE” models contributed to deterioration of model fit relative to the general “ACE” model. Thus, the relative contribution of genetic versus shared environmental effects could not be distinguished. However, the “E” models significantly worsened model fit suggesting that both genetic and shared environmental factors were important contributors to phenotypic variance.

4. Discussion

Loss of brain volume is associated with age (DeCarli, et al., 2005, Liu, et al., 2003, Raz, et al., 2005). This study examined the genetic and environmental contribution to variation and cross-variation of total brain and total CSF volumes at two assessments 4 years apart as well as to volume change across the same 4-year period. For both volumetric measures, genetic factors that influenced variability at baseline were the same as those that influenced variability at follow-up. On the other hand, there was evidence for shared environmental effects specific to variation at follow-up. It is possible that the emergence of common environmental factors reflects lifestyle changes shared by twin brothers. Such factors could include retirement, illness or loss (of a spouse) for one brother that has significant psychological stress on both brothers, and shared changes in diet or physical activity. It is difficult to find a plausible biological or environmental reason that could account for such a change that is limited to DZ twins. Therefore, the conclusion that the importance of environmental factors to variability in some brain volume measures increases at older ages must be considered very tentative.

Evidence for the importance of genetic effects on cross-sectional variation in brain volumes in this study is consistent with previous analyses in the NHLBI twins (Carmelli, et al., 1998,

Carmelli, et al., 2002, Pfefferbaum, et al., 2000) and with other twin and family studies in adult but not elderly individuals (Baare, et al., 2001, van der Schot, et al., 2009, Wright, et al., 2002). There is inconsistent evidence for the relative contribution of genetic and environmental influences on CSF volume between the NHLBI twin study and other twin samples where heritability estimates have been much lower ranging from 0% to 32% (Baare, et al., 2001, Chou, et al., 2009, Wallace, et al., 2006, Wright, et al., 2002). The estimation methods employed in those studies and this study were very similar, therefore results for other brain volume measures (e.g., total brain volume) were also very similar. Differences in heritability estimates may result from slight differences in variable definition (total CSF in the present study vs. lateral ventricle volume) or variation in sample age (age range 5–19 (Wallace, et al., 2006); 21–27 (Chou, et al., 2009); 19–54 (Wright, et al., 2002); 19–69 (Baare, et al., 2001)). There is evidence that the amount of genetic variation that accounts for brain morphology changes from childhood to adolescence (Wallace, et al., 2006). It could be that for measures such as CSF volume, genetic influences change in magnitude as a function of normal aging as well.

In contrast to cross-sectional measurements, change in total brain and CSF volumes was largely influenced by shared and non-shared environmental factors. Individual differences in volume changes were highly variable in this study as evidenced by the large standard deviations. Such high variability could be in part due to measurement error, which contributes to the estimate of non-shared environmental parameter in the genetic models. The percent change in brain volume measures and the variability in difference scores that we observed across an average 4 year follow-up are similar to those reported in other studies of older individuals (Liu, et al., 2003, Mungas, et al., 2005, Resnick, et al., 2003). For example, in Mungas et al (Mungas, et al., 2005), across 4 years of follow-up, the annual percent change of gray matter volume in non-demented elderly was −0.6% (SD=1.8) and the annual change in total lacunar volume was −0.002 cm^3 (SD=0.12), thus showing relatively large variability associated with the change scores.

Similar to the results in this study, a previous longitudinal analysis of lateral ventricles volume in the NHLBI twins also showed lower heritability for change relative to a single time measurement (Pfefferbaum, et al., 2004). Longitudinal analyses of repeat cognitive assessment in twins also show that cognitive performance level assessed cross-sectionally is highly heritable but predominantly environmental factors account for rate of change in cognitive performance over time (McGue and Christensen, 2002, Reynolds, et al., 2002, Reynolds, et al., 2005). Taken together, these results suggest that the genetic and environmental mechanisms that contribute to cross-sectional variation at a given point in time are different from those that contribute to change across time.

We also examined several risk factors in our sample (blood pressure, hypertension, body mass index, body weight, waist circumference, sleep apnea, and heart disease) that may help explain the large environmental variance in change volume measures. History of hypertension and weight-related measures were significantly but weakly associated with greater shrinkage of brain volume and larger cerebrospinal fluid volume. While these relationships are no doubt important, considering the low magnitude of the correlations and that the genetic and environmental point estimates for the change volume measures had very large confidence intervals (thereby making the relative contribution of genetic and environmental effects indistinguishable), inclusion of these risk factors in the biometric models would not have further elucidated their importance in terms of accounting for part of the environmental variance on change volume measures.

There are several limitations of this study. First, results may be limited to healthy Caucasian men and may not be generalizable to women, other racial/ethnic groups, or clinical samples.

At least one study has shown no evidence for heterogeneity in genetic and environmental effects across sex for MRI volumes (Baare, et al., 2001). Second, a larger sample size and greater statistical power would allow for delineation between the relative contribution of genetic and shared environmental factors. This limitation could have contributed to inflation of heritability estimates in some of the best fitting bivariate models. In addition, we had also investigated genetic and environmental influences on variation of white matter hyperintensity volume cross-sectionally and longitudinally. However, the sample was underpowered to determine these effects with sufficient confidence to yield interpretable results for that volume measure. Third, genetic and environmental influences on variation and covariation in brain volume measurements may not generalize to longer time intervals between measurements or to different age groups. For example, analyses of change in performance on a cognitive test of executive function showed heritable influences at longer time intervals (Lessov-Schlaggar, et al., 2007). Fourth, the twin models do not account for possible gene–environment interaction or gene-environment correlation, which could bias genetic and environmental parameter estimates. The effects of the former would be included in the estimate of non-shared environment and the effects of the latter would be included in the heritability estimates (Neale, et al., 2003). Fifth, the measures of total brain and total CSF volumes may be too global to interpret in relation to any particular cognitive domain or disease process. Finally, measurement error could have contributed to decreased twin pair resemblance on the brain morphology measures, further impeding our ability to detect significant familial effects. Nonetheless, the volumetric results do motivate further investigation with more detailed examination of the structural anatomy and with functional neuroimaging.

Longitudinal brain volume measurements using structural MRI may serve as biomarkers for cognitive decline (Adak, et al., 2004, Kramer, et al., 2007, Mungas, et al., 2005) and neurodegenerative disease (Bradley, et al., 2002, Kaye, et al., 2005). For example, in a study of MZ twins discordant for dementia, the relationship between lower hippocampal volume and dementia was found to be due to environmental factors. This was evidenced by smaller volumes in the demented twin relative to his non-demented cotwin whose hippocampal volume did not significantly differ from that of control subjects (Jarvenpaa, et al., 2004). Thus, investigation of genetic and environmental influences on brain volume measures can help elucidate the mechanisms responsible for observed associations between brain volume change and age-related conditions.

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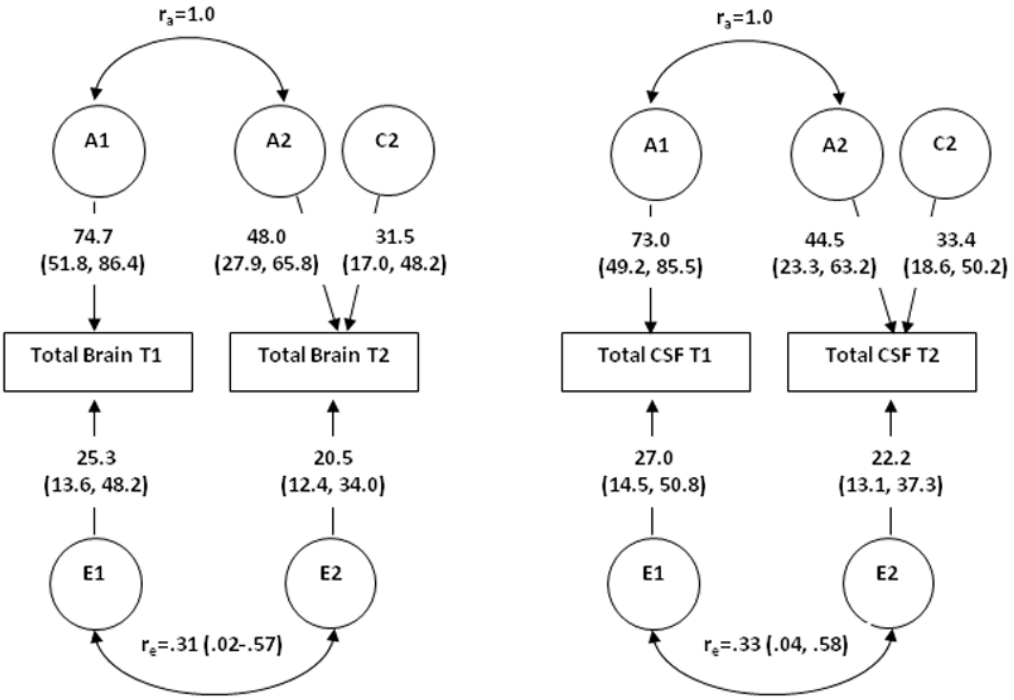

Figure.

Standardized estimates and 95% confidence intervals for genetic, shared environmental, and non-shared environmental parameters for the best fitting bivariate correlated factor models for total brain and cerebrospinal fluid (CSF) volumes measured at T1 (A1 and E1) and T2 (A2, C2, and E2) and adjusted for intracranial brain volume and study site

Table 1

Time 1 (1995–97) characteristics of the participating 66 twin pairs (n=132 twin subjects) and the rest of the NHLBI Twin Study cohort (n=277 twin subjects).

Time 1 Characteristics	This study (n = 132) Mean (SD)	Rest of cohort (n = 277) Mean (SD)	p	MZ (n=33 pairs) Mean (SD)	DZ (n=33 pairs) Mean (SD)	p
Age (yr)	71.6 (2.6)	72.7 (3.0)	<.01	72.0 (3.3)	71.2 (2.8)	.10
Education (yr)	14.1 (2.9)	13.3 (2.9)	.01	14.4 (3.4)	13.8 (3.6)	.27
Body mass index (kg/m^2)	27.2 (3.7)	27.1 (3.5)	.77	25.6 (3.8)	27.9 (4.9)	.04
Mini-Mental State Exam	27.5 (2.2)	26.9 (2.7)	<.01	27.8 (2.1)	27.3 (3.2)	.25
Total Brain (cm^3)	956.5 (78.9)	951.1 (87.4)	.54	961.6 (90)	951.5 (100.6)	.47
Total CSF (cm^3)	313.2 (41.3)	315.8 (45.8)	.59	314.8 (41.5)	311.7 (57.4)	.67
CVD (%)	42.8	32.9	.05	50.0	35.4	.09
Cerebrovascular Dis (%)	7.6	13.7	.07	10.6	4.6	.20
Diabetes (%)	5.3	14.1	<.01	6.1	4.6	.71
Hypertension (%)	47.3	50.9	.50	56.1	38.5	.04
Peripheral Vascular Dis (%)	3.1	3.3	.92	1.5	4.6	.30
Probable Dementia (%)	1.5	6.3	.03	1.5	1.5	.99

CVD = Cardiovascular Disease; CSF = Cerebrospinal Fluid; Dementia was defined on the basis of performance on two components from the Iowa Screening Battery for Mental Decline, including the Benton Visual Retention Test (BVRT; visual perception and memory), and the Controlled Oral Word Association Test (COWA; verbal fluency). A score <0 based on the formula of Iowa = BVRT + 0.765 * (COWA + Education adjustment) − 5.1572 was considered indicative of dementia (Eslinger, et al., 1985).

Table 2

Brain volume at baseline (T1, 1995–97), follow-up (T2, 1999–2001), and volume change of the NHLBI Twin Study.

Volumes	T1 mean (SD)	T2 mean (SD)	p (change)	% Change (SD)
All participating twins (n=66 pairs)				
Total Brain (cm^3)	956.5 (78.9)	932.4 (82.2)	<0.001	−2.53 (3.0)
Total CSF (cm^3)	313.2 (41.3)	353.8 (63.3)	<0.001	13.2 (15.2)
MZ twins (n=33 pairs)				
Total Brain (cm^3)	961.6 (74.6)	937.3 (80.6)	<0.001	−2.6 (3.1)
Total CSF (cm^3)	314.8 (34.4)	355.6 (65.1)	<0.001	12.8 (14.9)
DZ twins (n=33 pairs)				
Total Brain (cm^3)	951.5 (83.2)	927.5 (84.1)	<0.001	−2.5 (2.9)
Total CSF (cm^3)	311.7 (47.5)	351.9 (61.8)	<0.001	13.5 (15.6)

CSF = Cerebrospinal Fluid; % change = ((T2 − T1)/T1)*100

Table 3

Twin pair correlations for brain volume measures adjusted for intracranial volume and study site at baseline (T1, 1995–97) and at follow-up (T2, 1999–2001), and twin pair correlations for volume change across assessments.

	T1		T2		T2–T1 Change	
Volumes	**MZ**	**DZ**	**MZ**	**DZ**	**MZ**	**DZ**
Total Brain	0.65*	0.33#	0.76*	0.60*	0.40*	0.35
Total CSF	0.63*	0.34*	0.73*	0.62*	0.50*	0.56*

*p<0.05,

#p<0.10 relative to zero

Table 4

Goodness of fit statistics for the general and nested bivariate correlated factor models.

Variance Components		Genetic and Environmental Correlations			Model Fit Statistics			Chi-Square Difference Test	
T1	**T2**	**r_a**	**r_c**	**r_e**	**χ^2**	**df**	**AIC**	**χ^2 diff**	**p diff**
Total Brain Volume: testing the significance of variance components									
ACE	ACE	Free	Free	Free	32.592	11	10.592	n/a	n/a
AE	*ACE*	*Free*	*n/a*	*Free*	*33.397*	*13*	*7.397*	*0.805*	*.669*
ACE	AE	Free	n/a	Free	39.065	13	13.065	6.473	.039
CE	ACE	n/a	Free	Free	43.037	13	17.037	10.455	.005
ACE	CE	n/a	Free	Free	42.162	13	16.162	9.570	.008
Total Brain Volume: testing the magnitude of genetic and environmental correlations									
AE	***ACE***	***1***	***n/a***	***Free***	***33.397***	***14***	***5.397***	***0.805***	***.848***
AE	*ACE*	0	n/a	Free	59.817	14	31.817	27.225	.000
AE	*ACE*	Free	n/a	0	37.729	14	9.729	5.137	.162
AE	*ACE*	1	n/a	0	37.729	15	7.729	5.137	.274
Total CSF Volume: testing the significance of variance components									
ACE	ACE	Free	Free	Free	29.626	11	7.626	n/a	n/a
AE	*ACE*	*Free*	*n/a*	*Free*	30.148	13	4.148	0.522	.770
ACE	AE	Free	n/a	Free	34.869	13	8.869	5.243	.073
AE	AE	Free	n/a	Free	34.868	14	6.868	5.242	.155
CE	ACE	n/a	Free	Free	38.621	13	12.721	9.095	.011
ACE	CE	n/a	Free	Free	37.006	13	11.006	7.38	.025
Total CSF Volume: testing the magnitude of genetic and environmental correlations									
AE	***ACE***	***1***	***n/a***	***Free***	***30.148***	***14***	***2.148***	***0.522***	***.914***
AE	*ACE*	0	n/a	Free	53.475	14	25.475	23.849	$.27^{-4}$
AE	*ACE*	Free	n/a	0	35.047	14	7.047	5.421	.143
AE	*ACE*	1	n/a	0	35.046	15	5.046	5.420	.247

T1=baseline; T2=follow-up; r_a, r_c, r_e=additive genetic, shared environmental, and non-shared environmental correlations; χ^2=chi-square; df=degrees of freedom; AIC=Akaike Information Criterion; χ^2 diff=chi-square difference test; p diff=p value associated with χ^2 diff; Free=unconstrained or freely estimated parameter; Best model fit is shown in bold italics
A, additive genetic factors; C, shared environmental factors; E, non-shared environmental factors

Table 5

Goodness of fit statistics and parameter estimates for the general and nested univariate volume change models.

Variance Components	Model Fit Statistics			Chi-Square Difference Test		Variance Components Estimates (95% CI)		
Model	**χ^2**	**df**	**AIC**	**χ^2 diff**	**p diff**	**A**	**C**	**E**
Total Brain Volume Change								
ACE	1.844	3	−4.156	n/a	n/a	7.2 (0, 61.5)	32.1 (0, 56.5)	60.8 (37.9, 85.2)
CE	***1.875***	***4***	***−6.125***	***0.032***	***.859***	***n/a***	***37.5 (14.7, 56.6)***	***62.5 (43.4, 85.3)***
AE	2.674	4	−5.325	1.000	.362	43.1 (16.0, 63.44)	n/a	56.9 (36.6, 84.0)
E	11.583	5	1.583	9.329	.008	n/a	n/a	100
Total CSF Volume Change								
ACE	1.401	3	−4.599	n/a	n/a	6.4 (0, 68.4)	48.6 (0, 68.4)	45.0 (26.3, 66.7)
CE	***1.442***	***4***	***−6.558***	***.040***	***.841***	***n/a***	***53.1 (33.2, 68.5)***	***46.9 (31.5, 66.8)***
AE	4.360	4	−3.640	2.959	.085	60.3 (37.4, 75.3)	n/a	39.7 (24.7, 62.7)
E	22.641	5	12.641	21.239	.000	n/a	n/a	100

χ^2=chi-square; df=degrees of freedom; AIC=Akaike Information Criterion; χ^2 diff=chi-square difference test; p diff=p value associated with χ^2 diff; uncalc=incalculable p value for χ^2 diff=0; 95% CI=95% confidence intervals; Best model fit is shown in bold italics

A, additive genetic factors; C, shared environmental factors; E, non-shared environmental factors