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Quantitative genetic modeling of regional brain volumes and cognitive performance in older male twins

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Abstract

As part of an ongoing longitudinal twin study, data from both MRI brain scanning and from neuropsychological testing were obtained from 139 male–male twin pairs (72 monozygotic [MZ] and 67 dizygotic [DZ]), 69–80 years old at the time of examination. For descriptive purposes, we examined the MZ and DZ intraclass correlations (ICC) of four lobar brain volumes (frontal, temporal, parietal, and occipital), two cerebrospinal fluid (CSF) volumes (lateral ventricle and temporal horn of the lateral ventricles), and two measures of cognitive functioning (verbal memory and executive function). We found that for lobar brain and CSF space volumes, the MZ ICC were significantly greater than zero ($r = 0.37–0.77$) and greater than the corresponding DZ correlations ($r = 0.02–0.49$). Similarly, within-pair correlations for the two neuropsychological factors were statistically significant and significantly larger in MZ twin pairs than in DZ pairs, suggesting the presence of genetic variance. Bivariate genetic analysis revealed that while close to 60% of individual differences in neuropsychological performance were due to genetic influences, less than 50% of genetic effects were in common with those influencing brain volumes. These data may shed light on the genetic liability for brain diseases that affect the elderly. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Quantitative genetic modeling; Regional brain volumes; Male twins

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1. Introduction

Studies in small groups of MZ twins have demonstrated striking similarities among co-twins in brain morphology, but have not distinguished environmental from genetic etiologies (Oppenheim et al., 1989; Tramo et al., 1998). Comparisons between MZ and DZ twins are necessary to separate shared environmental from genetic effects. Such comparisons have been conducted previously in selected samples of twins by examining twin-pair differences and similarities of selected brain structures (Bartley et al., 1997; Pennington et al., 2000).

Our own previous studies in a healthy cohort of elderly male twins found that genetic factors account for more than 70% of the observed variance in intracranial brain volume, white-matter hyperintensity volume, and measures of the corpus callosum and lateral ventricles (Carmelli et al., 1998; Pfefferbaum et al., 2000). More recently, we reported on the heritability (i.e. percent of twin similarity attributable to genetic effects) of bilateral hippocampal volume (40% of variability was due to genetic influences) (Sullivan et al., 2001) and demonstrated genetic regulation of the microstructure of the corpus callosum (Pfefferbaum et al., 2001). The conclusion of genetic etiology for specific brain volumes has been supported recently by several studies of brain morphology in younger twins and their siblings, where genetic factors accounted for more than 80% of the observed variability in gray- and white-matter volume (Baare et al., 2001; Posthuma et al., 2002; Thompson et al., 2001).

A parallel line of work in aging twins provides evidence for substantial (up to 68%) heritability (Finkel and Pedersen, 2000; Finkel et al., 1995; McClearn et al., 1997; Swan et al., 1990; Swan and Carmelli, 2002) for indices of executive control (i.e. the ability to develop action plans; sequence, initiate, and monitor outcomes; and inhibit distracting or competing influences over behavior; Royall and Mahurin, 1995) and on components of verbal memory (up to 56% heritability) (Swan et al., 1999), both critical aspects of cognitive aging (Plomin and DeFries, 1998). Until now, genetic studies of brain and cognitive aging have developed independently of each other. The value, however, of studies in aging twins can be further enhanced through multivariate genetic analyses that examine the extent to which morphometric and functional phenotypes share common or unique genetic influences. Elderly twins are uniquely well suited for the examination of the differential contribution of genes and environment because, in addition to the assumed enduring effects of genes, the twins' longevity has allowed for a lifetime of environmental exposure of the brain regions considered most vulnerable to effects of aging. Multivariate profiles of morphometric and functional phenotypes with demonstrated heritability may be good candidates for use in association and linkage studies of specific gene markers (Lyons and Bar, 2001).

In the present study, we estimated the genetic and environmental contributions to individual differences in specific regional brain volumes (i.e. frontal, temporal, parietal, occipital brain volumes and CSF spaces) and examined their phenotypic and genotypic relationship with cognitive performance in a group of aging twins. Specifically, we used the methods of bivariate genetic analysis to quantify the genetic and environmental contributions to the phenotypic covariation between regional

brain volumes and two measures of cognitive functioning, verbal memory and executive function. On the basis of our previous results in this study population, we hypothesized significant heritabilities for both regional brain volumes and indices of neuropsychological performance. We also tested for the presence of genetic overlap between the various regional brain volumes and cognitive performance.

2. Methods

2.1. Study population

Data for this study were collected in the ongoing investigation of the genetic and environmental influences on brain structure and function in the NHLBI Twin Study (Carmelli et al., 1998). Originally, the NHLBI Twin Study was designed as a longitudinal study of cardiovascular disease (CVD) and associated CVD risk factors in 514 pairs of male twins (254 MZ and 260 DZ). Twins in this study are World War II veterans, born during 1917–1927 and 42–56 years old when first examined in 1969–1972 (Feinleib et al., 1977). Three follow-up examinations, after 10, 16, and 25 years, assessed CVD status and collected repeat measurements of physiological, biochemical, neuropsychological, and psychosocial risk factors. In a more recent follow-up (1995–1997), brain MR imaging was also performed on these subjects. Analyses in the present study are limited to intact twin pairs who participated in the fourth examination cycle and for whom both MRI brain scans and neuropsychological data were available. The MZ and DZ twin groups did not differ significantly in age (mean $\pm$S.D.: MZ = 72.3 $\pm$ 3.0; DZ = 71.8 $\pm$ 2.8; $P = 0.10$), years of education (MZ = 13.5 $\pm$ 3.0; DZ = 13.6 $\pm$ 2.9; $P = 0.40$), or Mini-Mental State Examination (MMSE; Folstein et al., 1975) scores (MZ = 27.4 $\pm$ 2.1; DZ = 27.1 $\pm$ 2.9; $P = 0.38$). Participants in this study are community-dwelling individuals and were not excluded if they achieved MMSE scores in the impaired range (< 24 out of 30). In this sample, 26 (9.3%) individuals had scores < 24, of whom nine were MZ (6.3% of all MZ twins) and 17 were DZ (12.7% of all DZ twins) twins. Among the MZ twins with low scores were seven co-twins whose brothers scored in the normal range and two from a pair of co-twins in which both scored in the low range. Among the impaired DZ twins were 13 co-twins whose brothers scored in the normal range and four from two pairs in which both scored in the low range.

2.2. MRI acquisition and morphometric analysis

MRI (1.5 T) scanning on GE scanners was performed at four study sites using a conventional spin-echo, T1 weighted sequence in the coronal orientation with TR = 500, TE = 17, 24 cm field of view, and 5 mm contiguous slices from the nasium to the occiput imaged in a 256×192 matrix and interpolated to 256×256 with one excitation. After acquisition of the MRI scans, the digital information was transferred to a central location for processing and analysis. Volumetric analysis of the MRI scans was performed with a custom-written program operating on a Sun

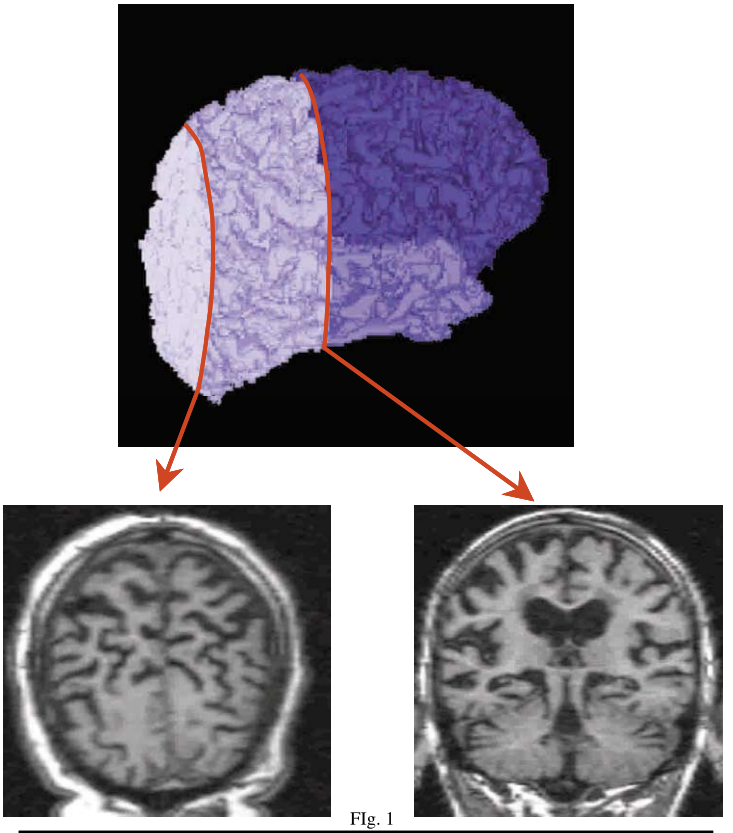

FIg. 1

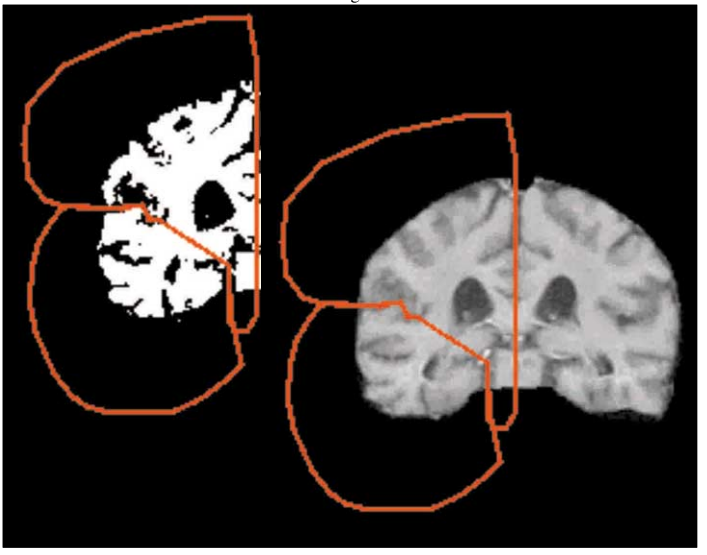

FIg. 2

Microsystems Ultra 1 workstation. Image evaluation was based on a semiautomated segmentation analysis that involves operator-guided removal of nonbrain elements, as previously described (DeCarli et al., 1992). For segmentation of brain parenchyma from CSF, image intensity nonuniformities were removed from the image, and the resulting corrected image was modeled as a mixture of two Gaussian probability functions (DeCarli et al., 1992, 1996). The segmentation threshold was determined as the minimum probability between the modeled CSF and brain matter intensity distribution (DeCarli et al., 1992)

To increase reliability of lobar volumetric analyses, the images were rotated rigidly into anatomic standard space, using common cerebral landmarks. To perform this rotation, the operator viewed the image in three orthogonal planes and then identified the interhemispheric fissure in the axial and coronal planes as well as a line between the anterior and posterior commissures in the sagittal plane. These three markings served as data for the reliable calculation of the transformation into the anatomically standard space. The segmented brain-CSF images were rotated separately from the original image to preserve measurement precision. After transformation of the image into anatomic standard space, the operator returned to the image and identified brain lobar and CSF regions according to previously published methods (DeCarli et al., 1994; Murphy et al., 1996) (see Fig. 1 for an illustration of the lobar regions). In brief, frontal lobar regions were defined as all supratemporal structures anterior to the aqueduct of Sylvius. The temporal lobar region was traced from the anterior pole of the temporal lobe to the aqueduct of Sylvius. The superior-medial temporal lobe boundary was defined as a straight line drawn from the angle of the medial temporal lobe, where it attaches to the temporal stem, to the midpoint of the operculum. The dura of the middle cranial fossa was then traced around each temporal lobar region. An example of these boundaries is displayed in Fig. 2. The parietal lobar region was defined as the brain matter posterior to the aqueduct of Sylvius, extending to the medial transverse fissure of the striate cortex. The remaining caudal portion of the cerebral hemispheres was defined as the occipital lobar region. Regions were traced separately for the left and right hemispheres.

Analysis of central CSF spaces was divided into two volumes. The right and left lateral ventricles and the temporal horns of the lateral ventricles were analyzed separately, the latter as an estimate of hippocampal size (Davis et al., 1995). For convenience in the present study, we use the term ‘temporal horn’ in place of ‘temporal horn region of the lateral ventricle’.

Fig. 1. Three dimensional display of lobar regions. Regions are shaded in decreasing darkness from frontal lobe, to temporal lobe, parietal lobe, and occipital lobe (top). Black and white images indicate anatomic boundaries for separation of the parietal lobe from the occipital lobe (left) and the frontal and temporal lobes from the parietal lobe (right) as described in Section 2.

Fig. 2. Two dimensional display of traced boundaries to distinguish frontal from temporal lobes. The lower right image is an example of the rotated, but unsegmented image for boundary marking. Regional brain volumes are calculated by transposition of these boundary markings onto the rotated segmentation image as seen in the upper left hand corner and as described in Section 2.

Although the regions of interest were drawn on the unsegmented, rotated image, the actual volumes were calculated from the rotated segmentation images (see Fig. 2). The volume of each region was calculated as the sum of the surface areas multiplied by the slice thickness in centimeters. Inter-rater reliabilities for these methods have been published previously (DeCarli et al., 1992, 1994; Murphy et al., 1996). Repeat analysis of intra-rater and inter-rater reliabilities for the purposes of the present study were consistently above 0.90.

2.3. Neuropsychological measures

An extensive battery of neuropsychological tests was given to participants in the fourth examination cycle on the same day of the MRI scan. The following tests were administered: (1) MMSE (Folstein et al., 1975); (2) Digit Symbol Substitution (total correct in 90 s) (Wechsler, 1981); (3) Iowa Screening Battery for Mental Decline (Eslinger et al., 1984); (4) Color–Word Interference Test (total correct in 45 s) (Stroop, 1935); (5) Trail Making A and B (Reitan, 1958); and (6) California Verbal Learning Test (Delis et al., 1987). We employed a principal component factor analysis with varimax rotation to reduce redundancy among these tests. The criterion for significance of a factor was an eigenvalue greater than 1.0, with at least two variables loading on the factor. Two orthogonal factors emerged that accounted jointly for 68% of the total interscale variance. The first factor was marked by high loadings on measures of memory and verbal learning from the California Verbal Learning Test and moderate to low loadings on measures of executive function and recognition memory. The second factor was marked by high loadings on tests of executive function (Digit Symbol Substitution, Color–Word Interference, and Trail Making (Mitrushina et al., 1999)) and low loadings on memory measures from the California Verbal Learning Test. We interpreted the first cognitive factor as reflecting performance in verbal memory and the second as reflecting executive function.

2.4. Statistical analysis

We first calculated the twin intraclass correlations (ICC) on each MRI brain measure in both the right and left hemispheres and cognitive function score, separately for MZ and DZ twins. Comparison of the MZ with the DZ ICC provides initial information on the presence and magnitude of genetic effects. If additive genetic effects are present, the MZ ICC is expected to be twice the DZ ICC. MZ ICCs that are statistically significant and greater than the corresponding DZ ICCs are indicative of significant heritability, the magnitude of which can be roughly estimated by $2(r_{MZ}-r_{DZ})$. An upper bound of the heritability is the MZ ICC, r_{MZ}, (Falconer and Mackay, 1996) and a DZ ICC, r_{DZ}, that is approximately one-half the MZ ICC is suggestive of additive genetic variance (a^2). Nonadditive (e.g. dominance) genetic effects reduce the DZ ICC to less than one-half the MZ ICC. When the DZ ICC is greater than half the MZ ICC, there is evidence of common environmental influences (c^2), the magnitude of which can be roughly estimated by $2r_{DZ}-r_{MZ}$. In

either situation, the remaining unexplained proportion of observed variance ($1-a^2$) or ($1-a^2-c^2$) is a combination of error and nonshared environmental influences (e^2).

To estimate the genetic and environmental components of variance in each volumetric and cognitive function measure, we subjected the variance–covariance matrix of values observed in MZ and DZ twins to structural equation model fitting (Neale and Cardon, 1992). This approach permits simultaneous analyses of all the observed twin data, making assumptions explicit, and testing the goodness-of-fit of different genetic and environmental models. The general twin model assumes four sources of variance: additive genetic effects (A), or nonadditive genetic effects (e.g. dominance) (D), common environmental effects (C), and nonshared environmental effects (E). A recognized limitation of the twin model is that it cannot simultaneously estimate both nonadditive genetic effects (D) and shared environmental effects (C) without available data on other relatives (e.g. parents of twins). Common environment refers to experiences shared by co-twins, including the intrauterine environment, the rearing environment, the frequency of contact between twins, and their joint exposure to the same social and cultural environment. Nonshared environmental influences are all the factors (e.g. accidents, illnesses) that make members of a twin pair different from one another. Shared environmental effects (C) will mask dominance effects (D), and vice versa. However, if dropping the additive genetic parameter (A) from the full model (ACE or ADE) results in a significant

Table 1
Age, education, and mean values of MRI brain volumes and CSF spaces in MZ and DZ twins

Variable	MZ twins ($n = 72$ pairs)	DZ twins ($n = 67$ pairs)
Age, (year)	72.3 (2.9)	71.8 (2.8)
Education, (year)	13.5 (3.0)	13.6 (2.9)
Brain volumes (cm^3)		
Total brain matter	936.8 (91.1)	941.8 (95.0)
R frontal	205.7 (24.3)	206.2 (23.3)
L frontal	203.3 (23.7)	203.4 (22.8)
R temporal	63.5 (8.4)	63.2 (8.5)
L temporal	61.5 (8.0)	60.5 (8.1)
R parietal	152.0 (24.9)	152.7 (25.7)
L parietal	153.1 (26.0)	153.4 (26.7)
R occipital	47.4 (15.8)	49.0 (17.3)
L occipital	51.4 (17.6)	53.3 (16.8)
CSF spaces (cm^3)		
R lateral ventricle	19.2 (9.3)	19.9 (10.8)
L lateral ventricle	20.5 (11.2)	21.7 (11.9)
R temporal horn	0.8 (0.6)	0.8 (0.6)
L temporal horn	0.8 (0.7)	0.8 (0.6)

For both MZ and DZ twins, occipital brain and lateral ventricular volumes in the left (L) hemisphere were significantly greater than those in the right (R) hemisphere, and temporal brain volumes in the R hemisphere were significantly greater than those in the L hemisphere (all $P < 0.01$).

reduction in the maximum-likelihood fit, it serves as a demonstration of the statistical significance of additive genetic variance.

Genetic structural models were fitted by the method of maximum likelihood, using MX software (Neale, 1992). MX calculates the negative log-likelihood ($-$LL) for each model tested, and hierarchical χ^2-values are used to compare the goodness of fit of submodels (AE and CE) with that of the full ACE model. Twice the difference in log-likelihoods between an AE or CE model and the ACE model is distributed as a χ^2 with one degree of freedom. Model fit is evaluated according to the principle of parsimony, in which models with fewer parameters are considered preferable if they show no significant worsening of fit when compared with a full ACE or ADE model. Using this principle, the most restrictive model is selected as the best-fitting one. In the results section, we present parameter estimates for each model, together with goodness-of-fit criteria. Separate univariate models were fit for each brain structure on the right and left hemispheres, as well as for each of the two neuropsychological factor scores.

The final step was to conduct an exploratory bivariate genetic analysis to determine the extent to which observed phenotypic associations between lobar brain volumes and cognitive performance are due to overlapping genetic or environmental influences (Carmelli et al., 2002). Using an exploratory approach, we first compared the cross-twin cross-trait correlations in MZ twins with those in

Table 2
Correlations between MRI volumes and age, education, and cognitive function in twins treated as genetically unrelated individuals ($n = 278$)

Variable	Age	Education	Verbal memory	Executive function
Brain volumes				
Total brain matter	−0.04	0.19**	0.15**	0.17**
R frontal	−0.17**	0.13**	0.11*	0.22**
L frontal	−0.21**	0.12*	0.11*	0.24**
R temporal	−0.20**	0.18**	0.11*	0.20**
L temporal	−0.20**	0.15**	0.10*	0.22**
R parietal	0.04	0.08	−0.02	0.01
L parietal	0.06	0.11*	0.01	0.01
R occipital	−0.02	0.08	0.01	0.11*
L occipital	0.02	0.08	0.01	0.12*
CSF spaces				
R lateral ventricle	0.23**	−0.02	−0.15*	−0.26**
L lateral ventricle	0.24**	−0.03	−0.14*	−0.25**
R temporal horn	0.20**	0.00	−0.10*	−0.20**
L temporal horn	0.21**	0.03	0.07	−0.19**

*$P < 0.05$, **$P < 0.01$. Observations from twin pairs treated as individuals are not independent of each other. Therefore, underestimation of between subject variability may result. The analyses reported in this table were re-run after random selection of one member of each pair ($n = 139$). The overall pattern of results including direction and magnitude of associations remained the same, suggesting that the results of this table are representative of the phenotypic correlation between brain volumes and neuropsychological performance.

Table 3
ICC in MZ and DZ twin pairs

Variable	MZ twins ($n = 72$ pairs)	DZ twins ($n = 67$ pairs)	P value
Brain volumes			
R frontal	0.76 (0.08)[a]	0.43 (0.11)	0.002[c]
L frontal	0.77 (0.08)	0.49 (0.11)	0.004
R temporal	0.69 (0.09)	0.40 (0.11)	0.011
L temporal	0.68 (0.09)	0.47 (0.11)	0.07
R parietal	0.54 (0.10)	0.34 (0.12)	0.09
L parietal	0.57 (0.10)	0.33 (0.12)	0.08
R occipital	0.40 (0.11)	0.24 (0.12)	ns
L occipital	0.37 (0.11)	0.02 (0.12)[b]	0.03
CSF spaces			
R lateral ventricle	0.77 (0.08)	0.32 (0.12)	0.002
L lateral ventricle	0.68 (0.09)	0.29 (0.12)	0.002
R temporal horn	0.62 (0.09)	0.15 (0.12)	0.001
L temporal horn	0.50 (0.10)	0.07 (0.12)[b]	0.007
Cognitive function			
Verbal memory	0.62 (0.09)	0.25 (0.12)	0.000
Executive function	0.63 (0.09)	0.36 (0.12)	0.007

[a] Values in parentheses are the standard errors.
[b] ICC not significantly different from zero.
[c] Indicates the significance of the difference (one-tailed) in ICC between MZ and DZ twin pairs.

DZ twins. Volumetric-function cross-twin correlations between two phenotypically correlated variables (i.e. lateral ventricular volume and executive function) are the average of the correlations between Twin 1's lateral ventricular volume and Twin 2's executive function score, and between Twin 1's executive function score and Twin 2's lateral ventricular volume. When the MZ value is greater than the DZ value, there is evidence for genetic influences in common to volume and function. Twice the difference in the MZ–DZ cross-twin cross-trait correlation can be used as a rough estimate of the bivariate heritability $a^2_{x,y}$ between volumetric and functional measures. When standardized by the square root of the product of the individual heritabilities, it can be viewed as an estimate of the genetic correlation between volume and function, $r_g = a^2_{x,y}/\sqrt{a^2_x a^2_y}$ (Falconer and Mackay, 1996).

Before pursuing formal genetic modeling, we examined the observed distribution of each regional brain and CSF volume. The distributions of all four lobar brain volumes were normal, as reported previously for intracranial brain volume (Carmelli et al., 1998). In contrast, the distributions of CSF volumes were positively skewed toward larger values. To satisfy the requirements of maximum-likelihood estimation, the distributions of the lateral ventricular and temporal horn volumes were subjected to a logarithmic transformation, with transformed values being used in all subsequent analyses.

Table 4
Maximum-likelihood estimates of a^2, c^2, and e^2 with corresponding standard errors and goodness-of-fit statistics for best-fitting genetic model

Variable	a^2	c^2	e^2	χ^2	df	P
Brain volumes						
R frontal	0.75 (0.05)	–	0.25 (0.05)	3.69	4	0.45
L frontal	0.53 (0.18)	0.23 (0.17)	0.24 (0.04)	2.84	3	0.42
R temporal	0.70 (0.05)	–	0.30 (0.05)	2.24	4	0.69
L temporal	0.41 (0.20)	0.26 (0.18)	0.32 (0.06)	1.12	3	0.77
R parietal	0.56 (0.07)	–	0.44 (0.07)	0.59	4	0.96
L parietal	0.57 (0.07)	–	0.43 (0.07)	0.73	4	0.94
R occipital	0.41 (0.09)	–	0.59 (0.09)	3.00	4	0.56
L occipital	0.32 (0.10)	–	0.68 (0.10)	2.77	4	0.60
CSF spaces						
R lateral ventricle	0.78 (0.04)	–	0.22 (0.04)	10.5	4	0.03
L lateral ventricle	0.70 (0.06)	–	0.30 (0.06)	5.2	4	0.27
R temporal horn	0.59 (0.07)	–	0.41 (0.07)	5.3	4	0.26
L temporal horn	0.42 (0.09)	–	0.58 (0.09)	11.1	4	0.03
Cognitive function						
Verbal memory	0.62 (0.05)	–	0.38 (0.05)	3.09	4	0.54
Executive function	0.64 (0.05)	–	0.36 (0.05)	8.22	4	0.08

a^2, c^2, and e^2 are estimates of the proportion of additive genetic, shared environmental and nonshared environmental components of variance, respectively, calculated for the genetic model best fitting the data. The goodness-of-fit statistic is distributed as χ^2. df indicates degrees of freedom. Model fits are summarized by the probability (P). Large P values indicate good fit.

3. Results

Table 1 presents descriptive data on age and education, and lists means and standard deviations for each lobar brain and CSF volume in the left and right hemispheres for MZ and DZ twins. The two zygosity groups were similar in age and education and did not differ in lobar brain or CSF volumes. For both MZ and DZ twins, occipital brain volumes and lateral ventricular volumes were significantly larger in the left than in the right hemisphere, whereas temporal brain volume was significantly larger in the right than in the left hemisphere (all $P < 0.01$). No significant left–right asymmetry of frontal brain volume was observed in this sample of twins.

Table 2 shows correlations of regional brain volumes with age, education, and the two neuropsychological scores. Left and right frontal and temporal brain volumes were significantly and negatively correlated with age, positively correlated with education, and positively correlated with verbal memory and executive function. Correspondingly, CSF volumes (lateral ventricles, temporal horns) were positively correlated with age and negatively correlated with cognitive function.

All MZ ICCs shown in Table 3 were significantly greater than zero (mean ICC = 0.61, range 0.37–0.77), in contrast to the DZ ICCs which were generally lower (mean ICC = 0.29, range 0.02–0.49). In addition, two of the ICCs in the DZ group (left

occipital brain volume, left temporal horn volume) were not significantly different from zero. These values indicate that, for example, while MZ twins shared more than 75% of the variance in right frontal brain volume, they shared much less variance in occipital brain volumes (40 [right] and 37% [left]). In addition, although the proportion of variance shared by DZ twins was lower than that observed in MZ twins for all structures, the MZ–DZ differences in ICC were significantly different from zero for frontal brain volumes and all CSF volumes in both hemispheres and marginally significant for the left temporal brain volume. Similarly, the MZ–DZ differences in ICC for verbal memory and executive function were significantly different from zero, suggesting the presence of genetic variance.

The next step of our analysis was formal estimation of the genetic and environmental components of variance using the combined information in the variance–covariance matrix for each measure. Table 4 presents estimates of a^2, c^2, and e^2 as derived from the best fitting genetic model of the observed data. With the exception of left frontal and left temporal volumes, the AE model provided the best fit to the data for all volumetric and cognitive function measures. The phenotypic variation explained by additive genetic effects was substantial, 75 and 70%, respectively, for right frontal and right temporal brain volumes and 78 and 70%, respectively, for right and left lateral ventricular volumes. We notice a significant influence of common environmental factors on left frontal and left temporal brain volumes, accounting for 23 and 26%, respectively, of the observed phenotypic variance. As Table 4 shows, estimates of heritability are somewhat lower for parietal and occipital brain volumes than for right frontal and temporal brain volumes. In sum, the maximum-likelihood estimates suggest a weaker contribution of genetic effects on the left than on the right hemisphere and a weaker contribution of genetic effects for posterior than anterior regional brain volumes.

Estimates of genetic variance for verbal memory, 62%, and executive function, 64%, are consistent with previous studies of performance on individual tests comprising these factors. Our previous study of the components of verbal learning and memory identified a maximum heritability of 58% (Swan et al., 1999), and for indicators of executive function we found a maximum heritability of 68% (Swan and Carmelli, 2002).

Based on the phenotypic correlations presented in Table 2, we evaluated the cross-twin cross-trait correlations between frontal brain volumes and executive function, between temporal brain volumes and executive function, and between lateral ventricular volumes with both verbal memory and executive function. Except for the difference between lateral ventricles and executive function scores, the MZ–DZ differences in cross-twin cross-trait correlations were not significant. To illustrate, the average MZ cross-twin correlation between the right lateral ventricular volume and executive function was $r_{MZ} = -0.19$, and the DZ cross-twin correlation was $r_{DZ} = -0.10$. The MZ–DZ bivariate heritability difference, $a^2_{x,y} = 2(r_{MZ} - r_{DZ}) = -0.18$, was statistically significant ($P < 0.05$), and when standardized by the square root of the product of the individual heritabilities, the genetic correlation was $r_g = -0.25$. This means that 25% of the observed phenotypic correlation between right lateral ventricular volume and executive function is due to the effect of overlapping

genes. Similar calculations for the left lateral ventricular volume yielded a significant genetic correlation of $r_g = -0.57$, suggesting that almost 60% of the observed relationship between left ventricular volume and executive function is due to the effect of overlapping genes.

4. Discussion

Subjects in this study were World War II male veteran twins, aged 69–80 years when examined. For this sample of elderly twins we found that genetic influences contributed significantly to individual differences in regional brain volumes. For some volumes (e.g. right frontal, right temporal and left and right lateral ventricular volumes), genetic influences accounted for 70% or more of the variance. For other brain volumes (e.g. the occipital regions), estimates of heritability were 60% or less. Since the majority of these twins' lives have been spent apart, the observed high heritabilities suggest that genetic factors durably control certain regional brain volumes in old age. Whether these genetic factors act during development to shape the brain, or later in response to aging, is not known.

In addition, we found that shared environmental factors, most of which may be associated with in utero and early familial factors in an aged twin population (Machin, 1996; Machin et al., 1996), accounted for a significant amount of individual differences in left frontal and temporal brain volumes. Moreover, the effect of early shared environmental influences was predominantly on the left hemisphere, being almost twice as strong on the left in frontal and temporal regions as on the right. One plausible explanation for the increased involvement of environmental factors in left hemisphere regions is likely the more protracted development of the left hemisphere relative to the right hemisphere (Chi and Dooling, 1976), thus making it potentially more susceptible to environmental perturbations, such as the in utero hormonal environment (Geschwind and Galaburda, 1985). The contribution of shared environment further suggests the importance of early developmental events in shaping the brain in these elderly participants (Geschwind and Miller, 2001).

The phenotypic covariation between lobar brain volumes and cognitive function was modest in this study, though statistically significant and stronger with tests of executive function than with tests of verbal memory. From the bivariate genetic analyses, we obtained evidence for a significant genetic correlation between lateral ventricular volumes and performance on executive function tasks. Similar phenotypic associations, however, between fronto-temporal brain volumes and executive function scores were due entirely to common environmental and not to common genetic influences. Univariate estimates of heritability, however, suggest substantial genetic variance for each of the two phenotypes (i.e. brain volumes and components of cognitive function).

Although, a priori, there is a stronger motivation to study the genetic covariation between traits that show a high degree of phenotypic covariation, the link between phenotypic covariation and genetic covariation is not obvious and, in many cases, is

unknown. The magnitude of brain volumetric-function associations in the present study is comparable to those reported in previous studies (Breteler et al., 1994; Longstreth et al., 2000; Swan et al., 2000) and does not suggest attenuation of the phenotypic covariation due to selective attrition. Most likely, strong selection for healthier subjects who have survived to old age has attenuated the genetic covariation between lobar brain volumes and cognitive performance.

Age-related expansion of the lateral ventricles and slowing of mental processing have been posited as the most fundamental factors in brain aging (Pfefferbaum et al., 1994, 1998). Behavioral aging studies reveal negative effects of age on executive functions (Royall and Mahurin, 1995), yet data on the cerebral substrates of these declines are very scarce. It is possible that the genetic dissociation in the present study of frontal lobar brain volumes from executive function lies in the distinction between physiological and pathological aging. While enlargement of ventricular volume may be characteristic of a normal aging process, reduction in frontal brain volume may be affected by pathological features of early dementia of primarily genetic origin that is not characteristic of the present sample of healthy elderly participants.

Our conclusions about the genetic correlation between brain volumes and cognitive function are similar in nature to those from two recently published papers that utilized different approaches to quantification of brain volumes and cognitive function. Thompson et al. (2001) used brain mapping to quantify whole brain and regional gray matter volumes in ten MZ and ten DZ pairs. The Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981) full scale IQ score was used as a summary measure of intelligence. Heritability of gray matter volumes was estimated to be as high as 95%. The phenotypic correlation between frontal gray matter volume and full scale IQ was 0.37–0.45. While the authors suggested the presence of a genetic correlation between brain volumes and IQ, the small sample size limited their ability to estimate the magnitude of this association.

In response to Thompson et al. (2001), Posthuma et al. (2002) examined similar issues in 24 MZ and 31 DZ pairs and 25 additional siblings. Importantly for the present paper, these authors estimated the genetic correlation between brain volumes and general intelligence and working memory. Like Thompson et al. (2001) they found high heritabilities for whole brain gray and white matter (82 and 87%, respectively) and for IQ and working memory (86 and 67%, respectively). The genetic correlations between gray and white matter volumes and full scale IQ were 0.29 and 0.24, respectively, and with working memory, 0.38 and 0.35, respectively.

The estimated heritabilities from Thompson et al. (2001), Posthuma et al. (2002) for regional and whole brain volumes and cognitive function are consistent with those reported in the present paper. Moreover, the magnitude of the genetic correlations between lateral ventricular volumes and executive function observed herein is similar to that reported by Posthuma et al. Although we did not observe a genetic correlation between lobar volumes and cognitive function, we believe the observed negative genetic correlation between lateral ventricular volumes and executive function does have a neuroanatomic basis related to the process of aging.

Age-related enlargement of lateral ventricular boundaries may disrupt several nearby frontal–cortical circuits, one of which is the dorsolateral circuit which is responsible for executive functions (e.g. organizational and memory search strategies, set shifting and maintenance; Cummings, 1993, Mega and Cummings, 1994). We believe our findings, therefore, most likely reflect anatomical brain changes that affect this circuit. Other differences of the present study with those reported earlier that might account for differences in the observed volume–function genetic correlations include: the use of different volumetric measures, the advanced age of the twins, and the use of measures of specific cognitive functions known to be affected by aging as opposed to omnibus measures of general intelligence. Despite the use of different cognitive measures, however, it should be noted that the functions measured in the present study have been shown to be moderately and significantly correlated with full scale IQ (Wright et al., 2001).

Finally, the findings in this report must be considered in light of several limitations. First, the twin sample consists of World War II male veteran twin pairs, in which both co-twins survived to old age and continued their participation in the longitudinal study, thereby representing a highly selected group of individuals. The generalizablility of these results to a broader population of elderly people is, therefore, limited. Second, the quantification of regional brain and CSF volumes may not be precise enough to demonstrate the continuum of genetic influences on specific brain structure as reported in Thompson et al. (2001). Third, while a number of small twin studies have suggested heritability estimates for Alzheimer's disease (AD) as high as 70% (Nee and Lippa, 1999; Gatz et al., 1997), we believe the inclusion of twins with performance in the impaired range on the MMSE in the genetic analyses would result in an underestimation of genetic effects. This is because the age of onset of AD in twins is extremely variable. In a seminal paper, Kumar et al. (1991) showed dramatic discordance in age at onset of AD and striking differences in brain size and function between co-twins in a small group of MZ twins. Due to the variable age at onset, we believe that the presence of dementia within the cohort—even if both twins of a MZ pair should eventually be affected—would, at any one point in time, result in the determination of discordance, thereby substantially reducing heritability estimates of the measures presented in this paper.

Despite these limitations, however, bivariate genetic analysis may provide unique insights into possible biological mechanisms underlying brain-function relationships. The identification of the specific genes involved in brain aging remains a difficult task (Flint and Goodwin, 1999; Petrill et al., 1996) complicated by the myriad interactions of multiple genes of small and large effects, coupled with lifetime environmental experiences. To circumvent this problem, it may be more useful to first locate the genes more closely linked to components of brain aging (Kosslyn and Plomin, 2000). These component phenotypes have been labeled intermediate phenotypes or endophenotypes (Kendler, 1999; Lander, 1988). Ventricular enlargement and/or loss of regional brain volumes, may be useful as intermediate phenotypes in the search for genes involved in brain aging.

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