Quantitative Genetic Modeling of Variation in Human Brain Morphology

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The degree to which individual variation in brain structure in humans is genetically or environmentally determined is as yet not well understood. We studied the brains of 54 monozygotic (33 male, 21 female) and 58 dizygotic (17 male, 20 female, 21 opposite sex) pairs of twins and 34 of their full siblings (19 male, 15 female) by means of high resolution magnetic resonance imaging scans. Structural equation modeling was used to quantify the genetic and environmental contributions to phenotypic (co)variance in whole brain, gray and white matter volume of the cerebrum, lateral ventricle volume and associated variables such as intracranial volume and height. Because the cerebral cortex makes up more that two-thirds of the brain mass and almost three-quarters of its synapses, our data predominantly concerns the telencephalon. Genetic factors accounted for most of the individual differences in whole brain (90%), gray (82%) and white (88%) matter volume. Individual differences in lateral ventricle volume were best explained by a model containing common (58%) and unique (42%) environmental factors, indicating genes to be of no or minor influence. In our sample, genetic or environmental influences were not different for males and females. The same genes influenced brain volumes and intracranial volume and almost completely explained their high phenotypic correlation. Genes influencing gray and white matter overlapped to a large extent and completely determined their phenotypic correlation. The high heritability estimates that were found indicate that brain volumes may be useful as intermediate phenotypes in behavioral genetic research.

Introduction

The (human) brain has been the focus of intense research over the centuries. It is well recognized that individuals vary considerable in brain volume, distribution of gray and white matter, gyral patterns and cytoarchitecture (Blinkov and Glezer, 1968; Gould, 1981; Ono *et al.*, 1990; Westbury *et al.*, 1999; Amunts *et al.*, 2000; Geyer *et al.*, 2000). Genetic programs predominate the early stages of brain development (Rubenstein and Rakic, 1999; Ware and Walsh, 1999). Ultimately, however, the development and organization of the brain results from a continuous and complex interaction between genetic factors and environmental influences (Jacobson, 1991; Morgane *et al.*, 1993; McConnell, 1995; Joseph, 1999). Studies in laboratory rodents (Henderson, 1970, 1973; Roderick *et al.*, 1973, 1976; Hahn and Haber, 1978; Atchley *et al.*, 1984; Leamy, 1985, 1988) and primates [rhesus macaques, *Macaca mulatta* (Cheverud *et al.*, 1990)] have provided heritability estimates, usually 50–75%, for brain weight or cranial capacity. The degree to which individual variation in human brain structure is genetically or environmentally determined is less well established.

Most of the information concerning genetic and environmental contributions to individual differences in human brain structure, besides qualitative observations in post-mortem studies (Chi *et al.*, 1977), comes from studies using *in vivo* imaging techniques such as computer tomography (CT) and magnetic resonance imaging (MRI). *In vivo* imaging studies in small samples of monozygotic twins reared together exemplify the influence of familial factors on human brain structure (Oppenheim *et al.*, 1989; Suddath *et al.*, 1990; Tramo *et al.*, 1995, 1998). These studies, however, do not allow differentiation between genetic and common environmental effects, because monozygotic twins share their genes as well as their family environment. Disentanglement of genetic and environmental contributions to variation in human brain structure can be achieved by comparing monozygotic (MZ) and dizygotic (DZ) twins. Both type of twins share their family environment, but in contrast to MZ twins, DZ twins share, on average, only half their segregating genes. Twin studies have been used successfully to investigate the extent to which genetic factors cause human behavioral and physical differences (Plomin *et al.*, 1994; Maes *et al.*, 1997a,b; Martin *et al.*, 1997; Beunen *et al.*, 2000).

To date five studies, four using MRI (Bartley *et al.*, 1997; Carmelli *et al.*, 1998; Pennington *et al.*, 2000; Pfefferbaum *et al.*, 2000) and one using CT (Reveley *et al.*, 1984), have quantitatively investigated brain structure in MZ and DZ twins. Findings suggest that genetic factors account for a large part (>70%) of the individual variance in intracranial (Carmelli *et al.*, 1998; Pfefferbaum *et al.*, 2000), whole brain (Bartley *et al.*, 1997; Carmelli *et al.*, 1998; Pennington *et al.*, 2000), lateral ventricle (Reveley *et al.*, 1984) and white matter hyperintensities volumes (Carmelli *et al.*, 1998) as well as area measures of the corpus callosum and lateral ventricles (Pfefferbaum *et al.*, 2000). The generalizability of some of these findings, however, may be limited because of small (Bartley *et al.*, 1997; Reveley *et al.*, 1984; Pennington *et al.*, 2000) and specific [mainly dyslexic adolescent twins (Pennington *et al.*, 2000)] twin samples.

In the present study, the brains of 112 male and female MZ and DZ twin pairs, and 34 full siblings were studied *in vivo* using high resolution MRI scans. The volumes of intracranial space, whole brain, cerebral gray and white matter, and lateral ventricles were measured using automated segmentation procedures. The present twin study differs from earlier ones in distinctive ways. First, we extended the classical twin design by including full siblings, who share the same proportion of genes as DZ twins but who do not experience the unique (prenatal) environmental conditions shared by twins. This significantly enhances the statistical power (i.e. less twin pairs are needed than in the classical twin design) to detect genetic and especially common environmental influences (Posthuma and Boomsma, 2000). The increased sensitivity to detect common environmental effects reduces a possible bias towards overestimating genetic contributions. Second, we measured gray and white matter volumes, thereby (roughly) separating the functional units of the brain (i.e. the neurons that generate active electrical signals) from the fibers that connect them (i.e. myelinated and unmyelinated axons). Because the cerebral cortex makes up

more that two-thirds of the brain mass and almost three-quarters of its synapses, our data predominantly concerns the telencephalon (Rakic, 1996). To date, heritability estimates for these two classes of brain tissue are not available. The only previous twin study that analyzed the volume of the neocortex had low statistical power to differentiate genetic from shared environmental contributions (Pennington *et al.*, 2000). Third, we used multivariate genetic analysis which allowed us to quantify and explore the genetic and environmental contributions to the phenotypic covariation in brain volumes of interest and associated variables such as intracranial volume and height (Posthuma *et al.*, 2000). The use of multivariate analyses further increases the statistical power of the study (Schmitz *et al.*, 1998). Fourth, we tested explicitly whether the magnitude of genetic and environmental effects differed in males and females (Neale and Cardon, 1992).

Materials and Methods

Subjects

One hundred and twelve pairs of twins, 33 MZ male (MZM), 17 DZ male (DZM), 21 MZ female (MZF), 20 DZ female (DZF) and 21 DZ opposite sex (DOS), and 19 male (SM) and 15 female (SF) full siblings took part in the study. Twins were recruited from the (healthy) twin sample of the department of Psychiatry of the University Medical Center Utrecht, the Netherlands and the Netherlands Twin Registry (Boomsma, 1998). Zygosity was determined by DNA fingerprinting. Siblings of twins were asked to participate. Subjects were required not to have any severe medical diseases. Mental and physical health was assessed by means of the Family Interview for Genetic Studies (Nurnberger *et al.*, 1994) and a medical history inventory, respectively. All subjects gave written informed consent to participate in the study after full explanation of the study aims and procedures. The study was approved by the scientific and ethical committee of the University Medical Center Utrecht.

Image Acquisition and Processing

MR images were obtained on a 1.5 Tesla Philips Gyroscan scanner at the University Medical Center Utrecht. For volumetric analysis a three-dimensional T_1-weighted, coronal, spoiled gradient echo scan (FFE) of the whole head (T_E = 4.6 ms, T_R = 30 ms, flip angle = 30°, 170–180 contiguous slices; 1 × 1 × 1.2 mm^3 voxels), and a coronal dual contrast turbo spin echo (DTSE) of the whole brain (T_{E1} = 14 ms, T_{E2} = 80 ms, T_R = 6350 ms, 120 contiguous slices; 1× 1× 1.6 mm^3 voxels) were acquired.

Images were coded to ensure blindness for subject identification, zygosity and family membership. Image volumes were transformed into Talairach space [no scaling (Talairach and Tournoux, 1988)] and corrected for magnetic field inhomogeneities (Sled *et al.*, 1998). Volumetric measurements were obtained using automated segmentation procedures and included intracranial, whole brain, gray (cortical plus subcortical) and white matter of the cerebrum (excluding cerebellum and medulla), and lateral ventricle volumes (Hulshoff Poll *et al.*, 2000; Staal *et al.*, 2000; Schnack *et al.*, 2001). Automatic segmentation software included histogram analysis algorithms, anatomical knowledge based decision rules and series of mathematical morphological operators to connect all voxels of interest. Intracranial volume was segmented on DTSE scans. Whole brain volume was segmented on the three-dimensional FFE scans using a binary image of the intracranial volume as a mask (Maes *et al.*, 1997a,b). Cerebral gray and white matter volumes were obtained after cerebellar and brain stem tissue was removed [results on cerebellar volumes are reported elsewhere, (Posthuma *et al.*, 2000)]. In lateral ventricle segmentation automatic decision rules bridged connections not detectable and prevented 'leaking' into cisterns. Segmented intracranial, whole brain and lateral ventricle volumes were checked visually and edited if necessary. The segmentation procedures yielded highly reliable volume measurements with inter-rater intraclass correlations all above 0.96.

Statistical Analysis

Because left and right hemispheric measures were highly correlated (0.85 for left and right lateral ventricles, and >0.98 for left and right brain, gray and white matter volumes) analyses were performed on whole structure volumes only. Pearson correlations were calculated to summarize twin and sibling pair similarity and to determine associations between volumes of interest and intracranial volume and height. Structural equation modeling with the Mx software (Neale, 1997) was used to estimate the contribution of additive (*A*) genetic, and common (*C*) and unique (*E*) environmental factors to the phenotypic variation in whole brain, gray and white matter, lateral ventricle, and intracranial volume and height (Neale and Cardon, 1992).

Based on the statistical power tables provided by Posthuma *et al.* (Posthuma *et al.*, 2000), the use of multivariate analyses (Schmitz *et al.*, 1998), and the number of subjects studied, our study approximately has a statistical power of greater than 80% to detect brain structure size heritabilities of 70% (in the full univariate ACE model), a reasonable value to expect given heritability estimates reported in the literature. Moreover, the approximate statistical power of our study to detect common environmental effects of 50% in full univariate ACE models is well above 80%.

ACE, AE and CE models were fitted on raw data because the data consisted of families of different size. The relative contributions of genetic and environmental influences were estimated using maximum likelihood by calculating the negative log-likelihood (–LL) for each pedigree. The goodness of fit of a model was tested using likelihood-ratio chi-square (χ^2) tests. Hierarchic χ^2 tests were used to compare the goodness-of-fit of the AE (familial resemblance explained by additive genetic influences) and the CE (familial resemblance explained by common environment) model to that of the full ACE model. Twice the difference in log-likelihood's (–2LL) between the AE or CE and the ACE model is distributed as a χ^2 with 1 degree of freedom (df). If the $\chi^2_{(df=1)}$ is smaller than 3.84 (not significant; $P > 0.05$) then omitting common environmental influences (in the AE model) or omitting additive genetic influences (in the CE model), does not lead to a deterioration in fit. Utilizing the principle of parsimony, the most restrictive model is accepted as the best-fitting one (Neale and Cardon, 1992).

Univariate AE, CE and ACE models were fitted on all variables with simultaneous correction for the effects of age and sex by means of a linear regression on the observed values of each of the dependent variables. Models were fitted simultaneously on data from males and females to estimate the magnitude of genetic and environmental effects on male and female phenotypes. Next, multivariate models with simultaneous correction for age and sex were fitted to determine the extent to which covariation between volumes of interest, intracranial volume and height were due to genetic and environmental factors (Posthuma *et al.*, 2000). Separate models were fitted on whole brain, and lateral ventricle volumes, whereas gray and white matter volume were analyzed together.

Results

Data on age, height and volumetric measurements for the different subgroups are presented in Table 1. Males were taller and had larger volumes than females. This difference was reflected in significant positive correlations between sex and height (r = 0.71; $P < 0.01$) and all volumetric measurements except lateral ventricle volume (correlation coefficients range from 0.12 to 0.60; $P < 0.01$; Table 2). The subject group as a whole had a mean age of 30.9 years (SD = 9.2; median = 28.7; range 19–69 years). Correlational analysis revealed significant negative correlations between age and height (r = –0.137; $P < 0.05$), and whole brain (r = –0.199; $P < 0.01$) and gray matter (r = –0.433; $P < 0.01$) volumes, indicating that in our sample these variables decrease with age (Table 2). Furthermore, intracranial volume was correlated significantly to all other volumetric measurements (correlation coefficients range from 0.24 to 0.93; $P < 0.01$, after correction for age and sex; Table 2). Significant but small positive correlations also existed between height and intracranial, whole brain, gray and white matter volumes (Table 2). The twin and sibling pair correlations that are presented in Table 3 indicate that for all variables, with the exception of lateral ventricle volume, correlations for MZ twins were higher than for DZ twins and siblings, suggesting the involvement of

Table 1
Descriptive statistics and absolute brain volumes

	MZM	MZF	DZM	DZF	DOS_M	DOS_F	SM	SF
n (individuals)	66	42	34	40	21	21	19	15
Age (years)	31.2 (9.58)	34.1 (11.7)	30.3 (7.0)	30.6 (8.5)	30.3 (12.4)	30.3 (12.4)	28.9 (4.8)	29.5 (4.9)
Height (cm)	182.9 (5.6)	167.2 (5.9)	180.3 (6.6)	169.9 (7.8)	180.9 (7.2)	169.6 (5.4)	183.5 (9.5)	166.8 (5.5)
Intracranial	1523.7 (113.7)	1342.4 (117.8)	1461.7 (83.9)	1333.7 (110.7)	1495.0 (95.9)	1322.3 (107.9)	1528.7 (111.1)	1376.9 (115.7)
Whole brain	1335.2 (108.2)	1176.9 (116.1)	1297.6 (78.5)	1180.5 (110.8)	1307.5 (95.4)	1171.7 (86.2)	1348.1 (92.8)	1211.5 (108.1)
Gray matter	673.3 (66.6)	606.0 (72.7)	646.5 (45.4)	613.5 (55.7)	675.1 (61.5)	614.5 (61.5)	681.6 (51.7)	624.4 (58.8)
White matter	496.8 (53.9)	427.3 (53.6)	492.8 (43.1)	418.9 (56.0)	475.5 (47.4)	412.3 (38.2)	505.3 (49.0)	436.1 (53.4)
Lateral ventricle	15.2 (8.2)	13.9 (6.7)	12.3 (6.0)	10.9 (6.1)	17.2 (9.4)	13.4 (6.2)	13.9 (8.0)	14.2 (7.0)

Brain volumes are expressed in cm^3. Values are means (SDs). MZM/MZF = monozygotic male/female; DZM/DZF/DOS = dizygotic male/female/opposite sex; SM/SF = sib male/female.

Table 2
Pearson correlations between brain volumes, sex, age, intracranial volume and height

	Age	Sex	Height	Intracranial
Sex	–0.059			
Height	–0.137*	0.714**		
Intracranial	–0.074	0.601**	0.551** (0.214**)	
Whole brain	–0.199**	0.568**	0.536** (0.204**)	0.948** (0.932**)
Gray matter	–0.433**	0.413**	0.446** (0.199**)	0.810** (0.840**)
White matter	0.116	0.571**	0.465** (0.127*)	0.859** (0.809**)
Lateral ventricle	0.120	0.120	0.015 (–0.086)	0.256** (0.240**)

Correlations corrected for age and sex are given in parentheses. Two-tailed significance (*$P<0.05$; ** $P<0.01$). $n = 258$.

Table 3
Within twin and sibling pair similarity

	MZM	MZF	DZM	DZF	DOS	TSM	TSF	TSOS
n	33[a]	21[a]	17[a]	20[a]	21[a]	15 + 11[b]	8 + 11[b]	11 + 12[b]
Height	0.81	0.92	0.61	0.64	0.47	0.70	0.31	0.15
Intracranial	0.90	0.92	0.33	0.69	0.40	0.67	0.62	–0.08
Whole brain	0.94	0.91	0.14	0.67	0.37	0.55	0.66	–0.20
Gray matter	0.90	0.89	0.21	0.70	0.55	0.45	0.52	0.17
White matter	0.88	0.92	0.37	0.55	0.20	0.60	0.73	–0.32
Lateral vent.	0.72	0.74	0.52	0.44	0.53	0.72	0.89	0.53

Similarity is expressed as Pearson correlations. MZM/MZF = monozygotic male/female; DZM/DZF/DOS = dizygotic male/female/opposite sex; TSM/TSF/TSOS = twin–sib pair male/female/opposite sex; vent. = ventricles.

[a]Pairs.

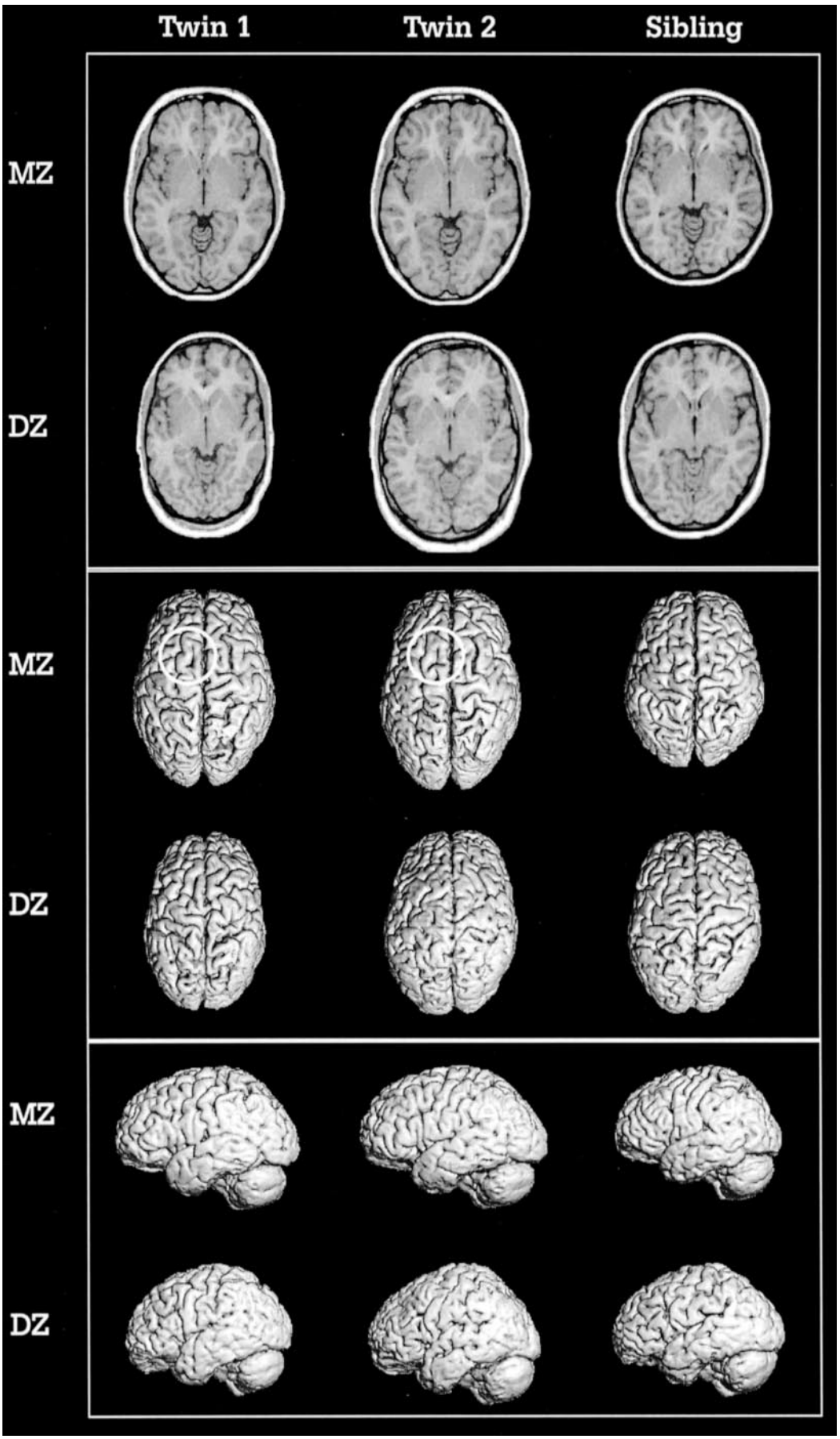
[b]Twin–sibling correlations are calculated as the weighted mean correlation of all 'first' twins with their non-twin sibling and all 'second' twins with their non-twin sibling. The two numbers of pairs denotes the number of first twins with siblings and the number of second twins with siblings, respectively. For TSM and TSF, in all families except DOS families, the non-twin sibling provides two correlations: one with the first twin and another one with the second twin.

genetic factors. The relatively low (r = 0.14) correlation for whole brain in DZ males probably reflects sample error. However, the strength of our approach is that it does not depend on a single group but uses the data from all genetic relationships simultaneously, i.e. the heritability estimates are based on all the available data. For example, the male twin–sibling correlation for whole brain volume, which also is an estimate for half of the additive genetic variance in male full siblings, was 0.55. Finally, a typical illustration of the similarities and differences in brain morphology in MZ and DZ twins and their siblings is presented in Figure 1.

Univariate model fitting determined which models were considered in the multivariate analyses. The phenotypic variance in the variables of interest was decomposed into sources of variance due to additive genetic factors, shared environmental factors and non-shared environmental factors. Simultaneously, the effects of age and sex on the observed scores of height and intracranial, whole brain, gray and white matter, and lateral ventricle volume were corrected for by means of linear regression (Table 4). From the univariate regression analyses the expected value for an individual subject can be calculated. For example, the expected total gray matter volume for a male subject aged 30 is 697.48 – (2.77 × 30) + 56.75 = 671.13 cm^3. There were no differences between parameter estimates for males and females. The AE model best fitted the data in height and intracranial, whole brain, gray and white matter volume (Table 5). The phenotypic variation explained by additive genetic effects with corresponding 95% confidence intervals was 89% (83–92%) for height, 88% (82–92%) for intracranial volume, 90% (85–93%) for whole brain volume, 82% (73–88%) for gray matter volume and 88% (80–91%) for white matter volume. The influence of common environmental factors on these variables was non-significant. The CE model was the most parsimonious model accounting for individual differences in lateral ventricle volume, with common environmental factors accounting for 59% (47–69%) of the phenotypic variance (Table 5).

Next, the multivariate model was fitted to investigate the pattern of covariation between height and intracranial volume and whole brain volume, gray and white matter volumes, and lateral ventricle volume. Multivariate model fitting constrained estimates for genetic and environmental effects to be the same in both sexes. The multivariate results for whole brain, gray and white matter and lateral ventricle volume are represented in path diagrams (Fig. 2*A–C*) with common pathways being expressed as correlations, and 95% confidence intervals for the correlations between genetic components and environmental components are given in Table 6. The multivariate estimates for genetic and environmental effects were nearly identical to those obtained in the univariate analysis. Regression coefficients for age and sex and 95% confidence intervals for heritabilities in the multivariate analysis are not shown as they were similar to those obtained in the univariate analyses. The genetic component of intracranial

Figure 1. The brains of a female MZ (upper row) and DZ (lower row) twin pair and their same-sex siblings. The upper block shows transverse slices in a plane through the anterior and posterior commissures. Slices are in neurological orientation (i.e. left is left). The two lower blocks contain three-dimensional brain renderings showing the top and left side from the brains, respectively. The resemblance in overall shape and size of the head and brain of the MZ twins is clearly larger than the resemblance of either MZ twin to their sibling, of the DZ twins to each other or of either DZ twins to their sibling. Whether this is true for gyral patterns is less obvious. Although MZ twins show some resemblance (white circle) in gyral patterns they are clearly not alike.


Twin 1
Twin 2
Sibling
MZ
DZ
MZ
DZ
MZ
DZ

volume was highly correlated with those of whole brain (r = 0.95), gray (r = 0.90) and white (r = 0.83) matter volumes, indicating that a large proportion of the genes that influence intracranial volumes are also important for whole brain, gray and white matter volumes. Correlations between the environmental components of intracranial and whole brain (r = 0.79), gray (r = 0.49) and white (r = 0.66) matter, and lateral ventricle (r = 0.42) volume were also fairly high. However, because unique environmental factors explain only a small part of the phenotypic variance in the individual variables, most of the phenotypic covariance between intracranial, and whole brain, gray and white matter is due to common genes. For example, using the tracing rules for path analysis (Neale and Cardon, 1992) it can be calculated that common genes account for 85% of the high phenotypic correlation (r = 0.932) between intracranial and whole brain volume. The genes that influenced individual differences in height also accounted to some extent for individual differences in intracranial, whole brain, gray and white matter volume, however, to a much lesser extent than intracranial volume (genetic correlations were 0.23, 0.21, 0.19 and 0.16, respectively). Nevertheless, genes common to height and brain volumes explain almost entirely their (small) phenotypic correlation. Correlations between the environmental components of height and volumetric measurements were low and ranged from –0.21 to 0.05. The phenotypic correlation (r = 0.589) between gray and white matter was completely determined by common genes because their individual environmental factors were not correlated (Fig. 2*C*). Moreover, the genetic correlation of 0.68 indicates that genes influencing gray and white matter overlap to a large extent.

Discussion

The present study is the first to use an extended twin design to quantify the genetic and environmental contributions to the phenotypic (co)variance in height and intracranial, whole brain, gray and white matter, and lateral ventricle volumes in adult males and females. Genetic factors accounted for most of the phenotypic variance in height (89%) and intracranial (88%), whole brain (90%), gray (82%) and white (88%) matter volume. In contrast, lateral ventricle volume was determined by common (58%) and unique (42%) environmental factors. No differences in genetic or environmental influences were found between males and females.

The magnitude of the genetic and environmental contributions to the variation in intracranial and whole brain volume was comparable to those reported in previous human studies (Bartley *et al.*, 1997; Carmelli *et al.*, 1998; Pennington *et al.*, 2000; Pfefferbaum *et al.*, 2000). Additionally, we found high heritabilities for gray and white matter volumes for which to date heritability estimates were lacking. Heritability estimates for brain size in laboratory rodents (Henderson, 1970, 1973; Roderick *et al.*, 1973, 1976; Hahn and Haber, 1978; Atchley *et al.*, 1984; Leamy, 1985, 1988) and a population of primates [rhesus macaques, *Macaca mulatta* (Cheverud *et al.*, 1990)] are generally lower, usually 50–75%, because animal studies generally give narrow sense heritabilities (i.e. proportion of the phenotypic variance solely due to additive genetic factors), whereas human studies report on broad sense heritabilities (i.e. the proportion of the phenotypic variance accounted for by additive plus non-additive genetic factors). The high statistical power of the present study to detect genetic and common environmental influences by virtue of the extended twin design (Posthuma and Boomsma, 2000) buttresses the validity of the pre-existing notion that genetic factors are major determinants of brain structure. The finding of comparative anatomical studies that differences in brain size across mammalian species are probably due to differences in the duration of neurogenesis (Finlay and Darlington, 1995; Darlington *et al.*, 1999) suggests that the main genetic factors determining overall brain size are those controlling cell division in early development. Additionally, genetic factors involved in regressive processes in neurogenesis such as neural cell death may be involved because these phenomena underlie within-species differences in brain structure (Cowan *et al.*, 1984; Breedlove, 1994; Kuan *et al.*, 2000; Sastry and Rao, 2000).

The genetic factors that account for variation in intracranial volume overlapped to a large extent with the genetic factors for whole brain, gray and white matter volumes. Since brain growth is thought to be the main factor determining growth of the neurocranium in early development (O'Rahilly and Müller, 1992; Sgouros *et al.*, 1999), it may be postulated that these common genes are primarily expressed in brain tissue. Indeed, it is well documented that pathological reduction of fetal brain size often leads to a correspondingly smaller skull size (Gamstrop, 1970).

Table 4
Regression estimates of linear regression models on observed scores of height and brain volumes (cm^3)

	β_0 (grand mean)	β_1 (effect of age; age entered in years)	β_2 (deviation of males)
Height	171.94	–0.10	13.28
Intracranial	1344.20	–0.28	170.52
Whole brain	1239.41	–1.96	145.47
Gray matter	697.48	–2.77	56.75
White matter	389.30	1.02	73.15
Lateral ventricle	9.76	0.09	1.97

Table 5
Univariate model fitting results

	Test of presence of common environment, AE versus ACE model		Test of presence of additive genetic influences, CE vs ACE model		Estimates in best fitting model (95% confidence interval)		
	$\chi^2_{(df = 1)}$	P	$\chi^2_{(df = 1)}$	P	A	C	E
Height	1.51	NS	27.55	<0.001	89% (83–92)	–	11% (8–17)
Intracranial	2.56	NS	27.22	<0.001	88% (82–92)	–	12% (8–18)
Whole brain	0.37	NS	39.35	<0.001	90% (85–93)	–	10% (7–15)
Gray matter	0.61	NS	20.67	<0.001	82% (73–88)	–	18% (12–27)
White matter	0.00	NS	31.47	<0.001	87% (80–91)	–	13% (9–30)
Lateral ventricle	5.79	<0.025	2.16	NS	–	59% (47–69)	41% (31–53)

A = additive genetic factors; *C* = common environmental factors; *E* = unique environmental factors. NS = not significant.

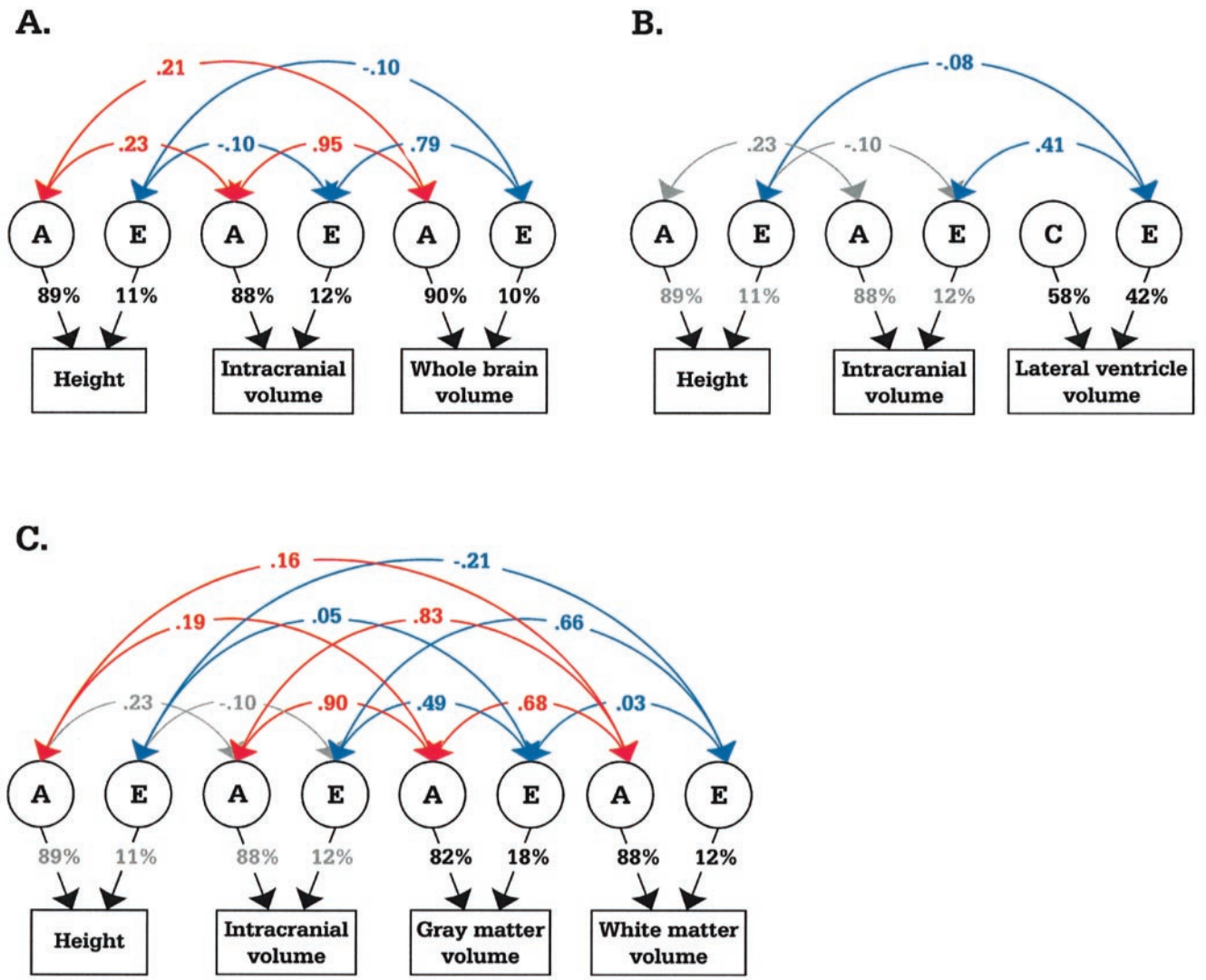


Figure 2. Path diagrams representing the multivariate model fitting results for whole brain (*a*), gray and white matter (*b*), and lateral ventricle (*c*) volume. The effects of age and sex were corrected for by linear regression on the mean of each of the dependent variables in a model. Latent variables are represented by circles with latent variance scaled to unity: *A*: additive genetic variance; *C*: common environmental variance; *E*: unique environmental variance. Boxes represent the measured phenotypes. Covariances were recalculated to represent correlations. Red lines connect A nodes. Blue lines connect E nodes.

Table 6
Genetic and unique environmental correlations with 95% confidence intervals (in parentheses)

Genetic	Unique environmental					
	Height	IC	WB	GM	WM	LV
Height	–	–0.09 (–0.33–0.16)	–0.10 (–0.35–0.16)	0.05 (–0.19–0.29)	–0.21 (–0.44–0.05)	*–0.08 (–0.31–0.16)*
IC	0.23 (0.07–0.37)	–	0.79 (0.68–0.87)	0.49 (0.30–0.65)	0.66 (0.49–0.78)	0.42 (0.20–0.59)
WB	0.21 (0.05–0.35)	0.95 (0.93–0.97)	–	–	–	–
GM	0.19 (0.03–0.34)	0.90 (0.85–0.93)	–	–	0.03 (–0.21–0.28)	–
WM	0.15 (–0.02–0.30)	0.83 (0.77–0.88)	–	0.68 (0.57–0.77)	–	–

Volume measures: IC = intracranial, WB = whole brain, GM = gray matter, WM = white matter, and LV = lateral ventricle. Correlations in italics are not significant as the accompanying 95% confidence intervals include zero.

Reduced brain volumes due to diminished elasticity of the skull are less frequently observed (Sgouros *et al.*, 1999).

The phenotypic covariance between height and intracranial, whole brain, gray and white matter volume was small and primarily due to common genes. Animal studies on brain-size evolution indicate that the correlation between brain and body size results from genetic factors that affect growth in both traits during prenatal and early postnatal growth (Riska and Atchley, 1985). Later postnatal growth primarily affects body growth, thereby reducing an initially high brain–body correlation (Riska and Atchley, 1985).

The volumes of intracranial space, whole brain, gray and

white matter, and lateral ventricles that were obtained in the present study (Table 1) are comparable with those reported in post-mortem (Blinkov and Glezer, 1968; Zilles *et al.*, 1988) and other *in vivo* imaging studies (Peters *et al.*, 1998; Filipek *et al.*, 1994; Schlaepfer *et al.*, 1995). In agreement with earlier post-mortem and *in vivo* findings, males had larger brain volumes and were taller than females (Blinkov and Glezer, 1968; Skullerud, 1985; Witelson, 1991; Breedlove, 1994; de Courten-Myers, 1999). The decrease in height and whole brain and gray matter volume with increasing age are consistent with previous findings (Blinkov and Glezer, 1968; Skullerud, 1985; Jernigan *et al.*, 1991a; Coffey *et al.*, 1992; Pfefferbaum *et al.*, 1994; Sorkin *et al.*, 1999; Courchesne *et al.*, 2000). It should be noted, however, that in our study subjects with ages above 40 were under-represented, and that this decrease thus may reflect a cohort effect in our sample.

The findings of the present study may be of relevance for studies that search for genes underlying normal behavior. For example, although the relationship between human brain volumes and general cognitive performance is controversial (Jerison, 1973; Gould, 1981; Harvey and Krebs, 1990), several recent studies using MRI have reported moderate but significant phenotypic correlations between these two variables (Willerman *et al.*, 1991; Andreasen *et al.*, 1993; Raz *et al.*, 1993; Harvey *et al.*, 1994; Wicket *et al.*, 1994; Reiss *et al.*, 1996; Pennington *et al.*, 2000; Schoenemann *et al.*, 2000). Thus, MRI-derived brain volumes might be used as an intermediate phenotype in the search for genes influencing cognitive ability (Kosslyn and Plomin, 2000). Intermediate phenotypes, in contrast to behavior, are more likely to be influenced by only a few genes, which facilitates detection of these genes (Boomsma *et al.*, 1997). The first requirement for an intermediate phenotype to be of use in genetic linkage or association studies is that it shows substantial heritability. Our results indicate that whole brain, gray and white matter volumes all fulfill this requirement.

Brain structure may also be useful as intermediate phenotypes in genetic research in psychopathology since different indices of brain structure have been associated with disorders such as schizophrenia (Harrison, 1999; Wright *et al.*, 2000), mood disorders (Steffens and Krishnan, 1998; Vawter *et al.*, 2000) and dementia (Kaye *et al.*, 1997; Braak *et al.*, 1999). For example, in schizophrenia, a severe psychiatric disorder in which genetic factors play an important etiological role (Carpenter and Buchanan, 1994; Cardno and Gottesman, 2000), a genetic (or familial) component to brain abnormalities is suggested by such findings as increased sulcal cerebrospinal fluid and reduced brain and gray matter volumes (Cannon *et al.*, 1998; Baaré *et al.*, 2001), smaller thalamic volumes (Staal *et al.*, 1998; Lawrie *et al.*, 1999), and enlarged lateral and third ventricles (Weinberger *et al.*, 1981; Staal *et al.*, 2000) in schizophrenic patients and their non-schizophrenic siblings as compared to healthy controls.

Interestingly, we found that common environmental factors accounted for the largest part of the phenotypic variance in lateral ventricle volume. This was unexpected because earlier twin studies suggested a high degree of genetic control (Reveley *et al.*, 1982, 1984). However, these earlier studies lacked statistical power to detect common environmental influences due to small sample sizes. Our finding suggests that lateral ventricle volume may be a biological marker for shared environmental influences in siblings. Because brain growth is largely completed in the prenatal and early postnatal period (Dekaban and Sadowsky, 1978; Epstein, 1986; Roche *et al.*, 1987), these shared environmental influences might be primarily maternal in origin. However, (familial) environmental factors occurring later in life may also be of influence as lateral ventricle volume has been shown to increase during puberty (Jernigan and Tallal, 1990; Jernigan *et al.*, 1991b) [but see (Pfefferbaum *et al.*, 1994)]. Our finding that lateral ventricle volume was completely environmentally determined disqualifies it as an intermediate phenotype for genetic linkage. Instead it might be a biological marker, at least in healthy subjects, for (familial) environmental influences.

The present study studied gross divisions of human brain anatomy. However, because the genetic information of ~10^5 genes alone cannot account for the enormous amount (±10^{15}) of neuronal interconnections in the human brain and since epigenetic interactions are pivotal in normal brain development, heritability estimates for brain structure indices measured on a smaller scale will most likely be lower and vary regionally. Indeed, heritability estimates for the length of several sulci in primate brains varied and were on average lower (0.44%) than that for cranial capacity (0.75%) (Cheverud *et al.*, 1990). Studies in small samples of MZ (Bonan *et al.*, 1998; Lohmann *et al.*, 1999) and MZ and DZ twins (Bartley *et al.*, 1997; Haidekker *et al.*, 1998; Le Goualher *et al.*, 2000) also suggest regional differences in the genetic and environmental influences on gyral and sulcal shape, size and patterns. Future detailed study of regional features of the brain will allow for quantification of genetic and environmental contributions to the anatomy of the neural networks underlying the different aspects of cognition and behavior (Gazzaniga, 1989, 2000; Mesulam, 1990, 1998; Fuster, 2000).

In conclusion, our results indicate that individual differences in human brain volumes are predominantly determined by genetic factors. The same genes influenced brain volumes and intracranial volume and almost completely explained their high phenotypic correlation. Our findings indicate that brain volumes may be useful as intermediate phenotypes in behavioral genetic research.

Notes

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