

Genetic variability of human brain size and cortical gyral patterns

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Summary

The development of the primate brain is determined by an interaction of genetic programmes and environmental events. We examined quantitatively the contribution of each of these factors to adult human brain hemisphere volume and global cortical gyral patterns by comparing 3-D MRI renderings of brains of 10 pairs of monozygotic (MZ) and nine pairs of same-sex dizygotic (DZ) twins. Brain volume was highly correlated in MZ pairs [unbiased intraclass correlation coefficient, $ICC(U) = 0.95$, $P < 0.00001$], but not in DZ pairs [$ICC(U) = 0.35$, $P = 0.09$]. Structural equation modelling indicated a 94% heritability of brain volume. Gyral patterns appeared visually more similar in MZ than in DZ pairs. This was confirmed statistically by a cross-correlation analysis of rendered images of lateral and

mesial cortical surfaces. MZ twins exhibited significantly greater similarity than did DZ twins in comparisons of gyral patterns; DZ twins were not more alike than unrelated pairings. Ipsilateral hemispheres were significantly more alike than contralateral hemispheres within MZ pairs, but not within DZ pairs. Contralateral hemispheres within an individual were more alike than contralateral hemispheres between twins in the DZ pairs, but not in the MZ pairs. Heritability for gyral-sulcal patterns, as reflected in the cross-correlation data, was low and ill defined. These results indicate that human cerebral size is determined almost entirely by genetic factors and that overall cortical gyral patterns, though significantly affected by genes, are determined primarily by nongenetic factors.

Keywords: genetics; twins; human brain size; cortical anatomy; gyral patterns

Abbreviations: DZ twins = dizygotic (same sex) twins; $ICC(U)$ = unbiased intraclass correlation coefficients; MANOVA = multiway analysis of variance; MZ twins = monozygotic twins; RMS = root-mean-square; SE = structural equation (model)

Introduction

Neocortical expansion and complex gyrification are among the most obvious differences between the brains of humans and those of other mammals, even of lesser primates (Zilles *et al.*, 1988). As unique as the human brain is, among humans there is still considerable inter-individual variation in its size and the gyral patterns on its surface. The factors that are responsible for the development of the human brain and presumably for such variations across individuals involve both genetic and environmental mechanisms. Anatomical studies in rodents and nonhuman primates have established that genetic programs are major determinants of overall brain size (Roderick *et al.*, 1973; Riska and Atchley, 1985; Leamy, 1988; Cheverud *et al.*, 1990), probably because of genetic control over cell proliferation (Finlay and Darlington, 1995).

In a recent MRI study of cortical surface area of human monozygotic (MZ) twins, Tramo *et al.* (1995) demonstrated that MZ twins were significantly more alike in mean cortical surface area than were pairs of unrelated individuals. While these studies demonstrate that genes play a significant role in determining brain size, they do not address the degree to which genes versus environment contribute to individual differences.

The differential contributions of genes and environment to the development of gyral patterns is also unknown. Earlier in this century the prevailing view was that gyral complexity was largely a result of nongenetic mechanical forces (Ranke, 1910; Bielschowsky, 1915; Schaffer, 1918; Clark, 1945; Turner, 1948; Welker and Campos, 1963).

This view was eventually eclipsed by evidence that gyral formation is under genetic control and is affected by variations in underlying neural connectivity. Evidence of the impact of connectivity is that experimental subcortical lesions in nonhuman primates and developmental cortical anomalies in human and nonhuman primates are associated with alterations in cortical gyri (Caviness *et al.*, 1975; Goldman-Rakic, 1981; Volpe, 1987; Rakic, 1988; Rakic and Singer, 1988; Caviness *et al.*, 1989). The existence of taxon, family, and genus-specific gyral patterns is evidence of the importance of genes (Welker, 1990).

Genes, however, do not appear to account for most of the variance within a primate species. A study of endocranial casts of rhesus macaques found that though brain size is highly heritable, the lengths of most sulci are much less so (Cheverud *et al.*, 1990). In humans, there have been occasional reports of gross inspection of cortical surfaces of brains of monozygotic twins, emphasizing both qualitative similarities and differences in gyral patterns (reviewed by Bailey and Von Bonin, 1951). Recent preliminary studies of cortical surfaces of human brains imaged with MRI have suggested likewise, that in monozygotic twins considerable variation in gyral patterns exist (Weinberger *et al.*, 1992; Steinmetz *et al.*, 1994). In a recent MRI study of asymmetry of the planum temporale in MZ twins, Steinmetz *et al.* (1995) found surprisingly weak correlations between twins of a pair. From these various observations, it seems that genes influence gyral patterning of the primate brain on a basic level, but that other factors contribute a major portion of the variance across individuals.

In this study, we compared brain volumes and gyral patterns on cortical surfaces rendered from 3-D MRI scans of monozygotic and dizygotic twins quantitatively to determine the degree to which genetic and extragenetic factors influence brain volume and gross cortical surface gyral patterns. We demonstrate that variations in brain volume are almost entirely determined by genes but that variations in global cortical gyral patterns are probably not.

Methods

Subjects

Volunteers were recruited from the community by advertisement and word-of-mouth and screened for a history of neurological, psychiatric and other major medical illnesses (one MZ pair had experienced closed head trauma as a result of a car accident). All scans were read by a radiologist and deemed qualitatively normal. The mean age of the MZ pairs (10 pairs, four female pairs) was 31 years (range 19–54), and the average age for the dizygotic twins (nine same-sex pairs, six female pairs) was 23 years (range 18–29). Only twins who matched on 19 red blood cell antigens were considered monozygotic. Population studies indicate that this predicts monozygosity at a conservative minimum 97% confidence level (Vogel and Motulsky, 1986). Information about chorion status was not available.

The study was approved by the NIMH Institutional Review Board and all volunteers gave informed consent to the MRI scans.

MRI scanning and brain rendering

Scans were performed on a General Electric Signa 1.5 Tesla MRI scanner with a T₁-weighted spoiled GRASS sequence (repetition time = 24 ms, echo time = 5 ms). A sagittal series of 124 contiguous 1.5 mm-thick slices with an in-plane field of view of 240 mm across a 256×256 pixel matrix was collected.

Three-dimensional brain renderings were prepared as previously described (Bartley *et al.*, 1993; Kulynych *et al.*, 1993). This procedure involves 3-D alignment of the slice stacks, followed by removal of the skull and extracerebral tissue using a mouse driven cursor. Segmentation was performed in each of the three planes of anatomical section to ensure maximal accuracy. These steps were accomplished using public domain software, 'NIH Image.' The images of the brains were split into hemispheres, the cerebella and lower brainstems removed, and the cerebral surfaces were rendered as 3-D views using 'DIP Station,' (HIPG Inc., Boulder, Col., USA), a commercial program that utilizes a volumetric ray-tracing algorithm (Bomans *et al.*, 1990). Lateral and mesial views were generated. Previous validation studies with this technique in humans and in the rhesus monkey have demonstrated that the renderings are qualitatively and quantitatively high fidelity representations of the cortical surface (Bartley *et al.*, 1993; Kulynych *et al.*, 1993; Noga *et al.*, 1996).

Cerebral volume analysis

The volume of each brain hemisphere was calculated by summing the number of pixels of cerebrum in each slice, converting these values to square centimetre, and multiplying by the slice thickness in centimetres. Whole brain volume was obtained by summing the volumes of the individual hemispheres. One pair of MZ twins and one pair of same-sex dizygotic (DZ) twins were excluded from this analysis because their scans were incomplete.

Gyral pattern analysis

In order to analyse quantitatively gross cortical gyral patterns within individuals (i.e. contralateral hemispheres) and within twin pairs, a cross-correlation algorithm was adapted for comparisons of brain renderings. Cross-correlation is a method of quantifying the similarity of two images at all possible offsets of one image relative to the other (Bartley *et al.*, 1992; Hibbard *et al.*, 1992). For matrices of image grey-scale values, $A_{i,j}$ and $B_{i,j}$, the corresponding cross-correlation matrix, $R_{n,m}$, is

$$R_{n,m}(A,B) = \Sigma_{i,j}(A_{i,j} - A_{ave}) \cdot (B_{i+n,j+m} - B_{ave}) / N_0$$

where the normalization factor N_0 is given by

$$N_0^2 = \Sigma_{i,j}(A_{i,j} - A_{ave})^2 \cdot \Sigma_{i,j}(B_{i,j} - B_{ave})^2.$$

A_{ave} and B_{ave} are averages of brain pixels only in each cerebral rendering; background pixels are excluded throughout the calculation. When these averages are subtracted from the brain pixels, but not from the background pixels which remain zero, the resulting images have an overall mean pixel value of zero. Further, the brain images become positive and negative excursions which themselves average to zero within the perimeter of the brain. This suppresses the ‘pedestal effect’ of a brain image standing out starkly against a background of zeros, and generates a product moment which is independent of pixel-value offset, i.e. the brightness, of either image from the background of zero-pixels. The reasoning is analogous to that employed in computing a Pearson’s product moment correlation coefficient, and, indeed, the cross-correlation matrix employed here is mathematically identical to an array of Pearson’s correlation coefficients computed at every possible offset of two images. The normalization factor, N_0 , removes any effects of pixel-value scaling, i.e. image contrast, and final values can range from +1.0 to –1.0 with +1.0 representing identical image patterns and 0.0 indicating complete dissimilarity of two image patterns. The cross-correlation matrix elements, as calculated by our method, are optimally sensitive to similarities between brain gyral patterns, *per se*, and are relatively insensitive to the shape, size, or positioning of the brain perimeters encompassing those patterns. When two image patterns are optimally aligned, a maximum appears in the cross-correlation matrix reflecting the greatest degree of similarity between the two patterns, and it is this maximal value that we use as our quantitative measure of similarity, R .

Statistical significance of individual cross-correlation values (R) is evaluated from the t distribution with ($n = 2$) degrees of freedom where

$$t = R \cdot \sqrt{n - 2} / \sqrt{1 - R^2}.$$

The number of independent picture elements, n , is estimated by examining the cross-correlation of an image with itself, i.e. its auto-correlation. The auto-correlation always has a maximal value of +1.0, but as the image offset is increased, the values drop towards 0.0 more or less quickly depending upon the complexity of the image pattern. Conservatively, we set a drop to one-quarter maximum, i.e. 0.25, as our criteria for determining a contour of image offsets beyond which the auto-correlation was sufficiently low for one to assume that independent picture elements now overlapped. Thus, we use the cross-sectional area of the autocorrelation peak at one-quarter maximum as the measure of an independent picture element. Dividing this measure into the total cerebral rendering area (excluding background, as noted above) yields an effective number of independent picture elements which is independent of the number of

pixels in the image and solely dependent upon the complexity of the image pattern in question. For the complex gyral structure of our human cortical renderings, the number of independent picture elements, n , averaged 363 ± 7 . This led us to adopt the criteria that a cross-correlation value, R , must exceed 0.135 in order to be considered significant at a conservative $P < 0.01$ level.

A sample of 10 cross-correlation comparisons for hemisphere shapes filled with random patterns at the same density of independent picture elements as our actual brain renderings had maxima ranging from 0.080–0.103 (mean 0.093), all non-significant. In contrast, the interhemispheric cross-correlation value for the lateral surfaces of the brain rendered from 3-D MRI of a rhesus monkey (using the same methods of MRI acquisition and of rendering as described above, *see* Fig. 1) was 0.70, substantially greater than that found for humans (*vide infra*), consistent with the greater symmetry and reduced complexity of cortical gyral patterns in this animal. For the relatively less complex cortical surface of the rhesus monkey, the number of independent picture elements is only ~ 50 , leading to a significance criteria of $R > 0.37$ for $P < 0.01$. Figure 1 provides a schematic illustration of the cross-correlation analysis. For the relatively simple and symmetric rhesus brain, the cross-correlation has a peak which is both broad and high; the peak corresponds to the relative positional-offset of optimal alignment. The more complex and less similar human cortical patterns in the lower portion of the figure lead to cross-correlation matrices with narrower and lower peaks. However, the gyral pattern similarity which may be visually discerned for the pair of twins leads to a higher peak value (R) than that obtained in the comparison with an unrelated individual.

As a test of the potential utility of cross-correlation analysis as a tool for quantifying gyral pattern similarity, a pilot study was performed with a subset of five MZ twins. Black and white photographs of the left hemisphere renderings of these twins were digitally generated. These 10 photographs were distributed to six researchers trained in neuroanatomy, but unfamiliar with the twin MRI scans and blind to pairing. The human raters were asked to pair-up the photographic images into MZ twin pairs based on gyral patterns and any other visual clues they found useful. Only one human rater was able to identify all five MZ twin pairs correctly; three raters matched two pairs of twins incorrectly; one rater selected only a single pair correctly; and one rater did not classify a single pair correctly. Overall, the human raters averaged 50% success in identifying the five MZ twin pairs. Cross-correlation analysis was applied to this same discrimination task. R -values were calculated for the 45 pairwise combinations of images. A maximum likelihood criteria was defined: the subset of five R -values with the greatest sum would be most likely to identify the MZ twins pairs. This simultaneous optimization simulated the human-rater circumstance. A computer program examined the R -value sums for the 945 possible sets of five, and the set of

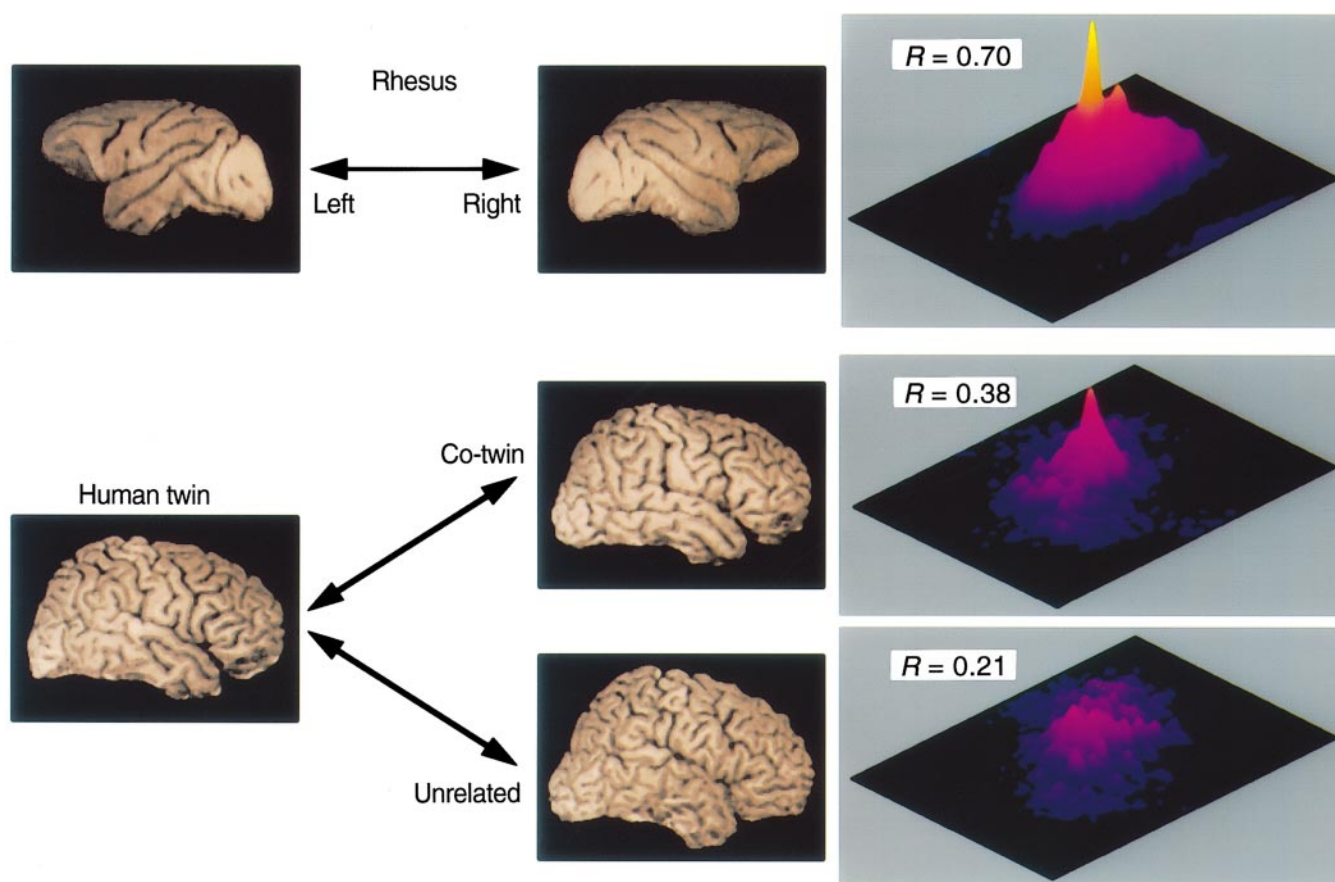


Fig. 1 Schematic illustration of cross-correlation analysis. The left-hand columns show the cortical renderings involved in each comparison; the right-hand column contains perspective views of the 2-D cross-correlation matrices resulting from each comparison. The top row shows the analysis of lateral cortical renderings from 3-D MRI of a rhesus monkey. Prior to cross-correlation, the right hemisphere rendering is 'flipped' to face in the same direction as the left. In the rightmost column a perspective view shows the full cross-correlation matrix whose peak value indicates a high degree of similarity ($R = 0.70$). The lower portion is an example of applying this process to a pair of twins (*middle*) and a pair of unrelated subjects (*lower*). Visual scrutiny reveals more similarities between the gyral patterns of the twins than between the unrelated brains; this difference in the degree of similarity is reflected in the peak values ($R = 0.38$ twins versus $R = 0.21$ unrelated) of the cross-correlation maps.

five with the greatest sum did, indeed, identify the five MZ twin pairs correctly.

R -values were calculated on brain renderings of left and right, lateral and mesial hemispheres paired as follows: each pair of twins, and all possible pairings of the unrelated first born members of each of the MZ twin pairs ($n = 36$ pairings). Nine potential pairings of unrelated people were not included because they involved a twin (in MZ twin pair no. 4) whose MRI scan had inadvertently excluded a small portion of the frontal pole. As a further test of the validity of the cross-correlation analysis, discrimination of MZ twin pairs was attempted on this larger sample by applying the maximum likelihood criteria (*vide supra*) both to left and to right lateral R -values from the unrelated pairings with the corresponding nine MZ twin pairs included ($n = 45$). In this case, the computer program examined the 362 880 possible sets of nine R -values, and, once again, the set with the greatest sum correctly identified all nine twin pairs using either left or right R -value data.

Statistical and heritability analyses

Within twin pair correlations of cerebral hemisphere volumes and whole brain volume were performed using unbiased intraclass correlation coefficients, [ICC(U); Bartko and Carpenter, 1976]. Hemisphere volumes were compared by multiway analysis of variance (MANOVA). Comparisons of cross correlation data across groups of twins were performed by MANOVA following Fisher z -transformation of the R -values (Dawson-Saunders and Trapp, 1990).

To estimate the degree to which genes account for variance in brain volume, several measures of heritability were evaluated. The most rigorous and complex of these followed closely the structural equation (SE) model described by Neale and Cardon (1992). However, computation of model parameters was performed by the 'SEPATH' module of Statistica for Windows (version 5, StatSoft, Inc., Tulsa, Okla., USA) rather than LISREL. In this approach, phenotype variance is viewed as potentially arising from four independent factors, two 'environmental' and two genetic.

Environment in this context is defined quite broadly and encompasses a host of developmental and experiential effects, both pre-natal and post-natal; basically it is all things nongenetic that may shape phenotype. Random environmental variance, E, accounts for 'within-family' variance and allows for individual variation in phenotype measure; random error of measurement is also absorbed by this factor. Siblings raised together are also considered to have shared some degree of common environmental variance, C, leading to 'between-family' variance. Genetic contributions to phenotype variance may be of two types: additive genetic variance, A, and dominance genetic variance, D. In the full SE model (ACED), the observed variance of a phenotypic measure is assumed to be a linear combination of all four sources of variance with correlations between the linear parameters which are determined by zygosity and whether or not the twins have been reared together. Unfortunately, studies, such as ours, which do not include twins who have been reared apart cannot apply the full SE model because shared environmental effects (C) and dominance genetic effects (D) become confounded (Neale and Cardon, 1992). In such instances, partial versions of the SE model may be used to test specific *a priori* hypotheses. Following Neale and Cardon (1992), we tested the following hypotheses for the cerebral volume data: E, no familial similarity; CE, similarity is solely due to shared environmental effects; AE, similarity is solely due to additive genetic effects; ADE, similarity is due to a combination of additive and dominance genetic effects; ACE, similarity is due to a combination of additive genetic and shared environmental effects.

These five hypotheses were also used to assess the heritability of left-right 'symmetry' of gyral patterns by applying the models to covariance matrices derived from within-individual, contralateral *R*-value data (*z*-transformed). For ipsilateral cross-correlation analyses across twin pairs, however, only mean correlation matrices were available. Although SEPATH can handle correlation matrices adeptly, use of correlation-only data reduces the degrees of freedom in the model and only the first three hypotheses (E, CE, AE) may be tested; three-parameter models cannot be tested. In all cases, heritability is estimated as the percent of the total variance accounted for by A ('narrow heritability'), or A and D together ('broad heritability').

In addition to assessing heritability with the SE model, we have also computed measures described by Jinks and Fulker (1970) as 'the so-called heritabilities of the classical approach' for comparison. These measures are:

$$\text{Holzinger (1929)} \quad H = (r_{MZ} - r_{DZ}) / (1 - r_{DZ})$$

$$\text{Nichols (1965)} \quad \text{HR} = 2 \times (r_{MZ} - r_{DZ}) / r_{MZ}$$

$$\text{Vandenberg (1966)} \quad F(V) = (1 - r_{DZ}) / (1 - r_{MZ}) = 1 / (1 - H)$$

where r_{MZ} and r_{DZ} may be either ICC(U)-values or *R*-values depending upon the comparison. Both the usefulness and the genetic interpretation of these 'classical' measures are questionable (Emery, 1976; Jinks and Fulker, 1970). Holzinger's *H* may vary from 0 to 1 corresponding,

supposedly, to a range from no heritability and full heritability; similarly, Nichols' HR may range from 0 to 2. Unlike the other two measures, Vandenberg's *F(V)* may range from 1 to infinity with greater values purportedly indicating ever increasing heritability.

Results

Cerebral volume analyses

Cerebral volume measurements are summarized in Table 1. Left hemisphere, right hemisphere and whole brain volumes were strongly correlated within MZ twin pairs [ICC(U) > 0.94, $P < 0.00001$, for all volumes]. Within the DZ pairs, the correlations were much less robust and none were significant. The differences between the correlations in the MZ twins and those in DZ twins were significant ($P < 0.04$ for all volumes). Repeated measures MANOVA with zygosity as a factor and hemisphere and birth order as repeated measures revealed that the small (1.5%) difference between left and right hemisphere volumes was quite significant ($F = 30.7$, $P < 0.0001$) with no significant main effects of zygosity or birth order. *Post hoc* analyses (Tukey honest significant difference) showed that the leftward volume asymmetry was significant for both MZ ($P < 0.006$) and DZ ($P < 0.008$) twins, and for both first born ($P < 0.02$) and second born ($P < 0.03$) twins.

Heritability analysis of the cerebral volume measures by means of SE modelling established that random environmental effects alone could not account for the observed covariances (hypothesis E rejected, $P < 0.001$, for all volumes). Inclusion of shared environmental effects was similarly inadequate (hypothesis CE rejected, $P < 0.04$, for all volumes). Additive genetic effects, however, provided a reasonable explanation of our volume data for both hemispheres and the cerebrum as a whole (hypothesis AE not rejected, $P > 0.2$ for all volumes). Inclusion of either shared environmental effects (hypothesis ACE) or dominance genetic effects (hypothesis ADE) did not significantly improve the fit to the model ($P > 0.5$ for all volumes); in fact, the inclusion of either degraded the goodness-of-fit, as reflected by increases in the root-mean-squared (RMS) standardized residuals. In short, additive genetic effects alone provided the most reasonable explanation of the observed cerebral volume data, and there was no significant evidence either for dominant gene effects or for shared environmental effects. The fitted parameters indicated that all volumes have a heritability of 94% (Table 2). The 'classical' heritability estimates for hemisphere and whole brain volumes concurred with the SE model findings (Table 2).

SE analysis of volume asymmetry coefficients (left-right difference divided by mean), corresponding to the small but significant leftward asymmetry of hemisphere volume, revealed that random environmental effects alone provided the best explanation of this asymmetry (hypothesis E not rejected, $P > 0.9$). There was no significant evidence either

Table 1 Brain hemisphere volumes in MZ and DZ twin pairs

Pair	Brain hemisphere volume (cm ³)											
	MZ TWINS						DZ TWINS					
	Left		Right		Whole brain		Left		Right		Whole brain	
	A	B	A	B	A	B	A	B	A	B	A	B
1	660	695	655	671	1315	1367	536	506	533	506	1069	1011
2	732	729	743	707	1475	1436	X	X	X	X	X	X
3	617	597	622	588	1239	1185	667	551	660	550	1327	1102
4	X	X	X	X	X	X	703	655	671	643	1374	1298
5	713	774	704	746	1418	1520	497	585	485	595	982	1180
6	628	639	617	632	1245	1271	535	587	519	580	1055	1168
7	523	509	511	501	1034	1010	554	545	534	543	1088	1088
8	585	568	576	563	1161	1131	643	578	637	559	1281	1137
9	503	512	486	510	989	1022	513	512	513	501	1025	1013
10	503	521	499	523	1002	1044						
Mean	607	616	602	605	1209	1221	581	565	569	560	1150	1125
SEM	±29	±33	±30	±30	±59	±63	±28	±17	±26	±17	±54	±33
ICC(U)	0.947		0.948		0.952		0.413		0.271		0.348	
F	47		48		52		3.2		2.3		2.8	
P	<10 ⁻⁵		<10 ⁻⁵		<10 ⁻⁵		0.06		0.13		0.09	

A = 1st born twin; B = 2nd born twin; X = incomplete scan.

Table 2 Summary of heritability estimates by various methods

	Comparison of various heritability measures			
	SE model (%)	Holzinger (%)	Nichols	Vandenberg
Volume measures				
Left	94	91	1.13	11.1
Right	94	93	1.43	13.9
Total	94	93	1.27	13.6
Contralateral <i>r</i> -values	62	54	1.69	2.2
Ipsilateral <i>r</i> -values				
Mesial				
Left	X	17	0.65	1.2
Right	X	13	0.44	1.2
Lateral				
Left	X	8	0.50	1.1
Right	X	7	0.48	1.1

X = inconclusive fit.

for genetic effects or for shared environmental effects contributing to observed variance in asymmetry, and inclusion of either in the SE model degraded the fit, as indicated by a 50% increase in the RMS standardized residuals.

Gyral pattern analysis

Visual examination of the brain renderings (Figs 2 and 3) suggests that the brains of MZ twins appear more alike than those of DZ twins, but that there is considerable variability in how similar the MZ twins look. The overall shapes and sizes of particular brain regions and large fissures (e.g. the temporal lobes, the sylvian fissures) are especially similar

within MZ twin pairs. However, the shapes and courses of individual gyri and sulci tend to be dissimilar.

Overall gyral patterns on lateral and mesial cortical surface renderings were compared using cross-correlation analysis, our approach to measuring the degree of similarity of two images quantitatively. The *R*-values for ipsilateral comparisons within twin pairs are shown in Tables 3 and 4. The *R*-values for the unrelated pairings are not shown in the tables; they were as follows: for the left hemisphere lateral and mesial, 0.188 ± 0.006 and 0.262 ± 0.008 , respectively; for the right hemisphere, 0.194 ± 0.006 and 0.303 ± 0.006 . MANOVA revealed significant overall differences between the three groups

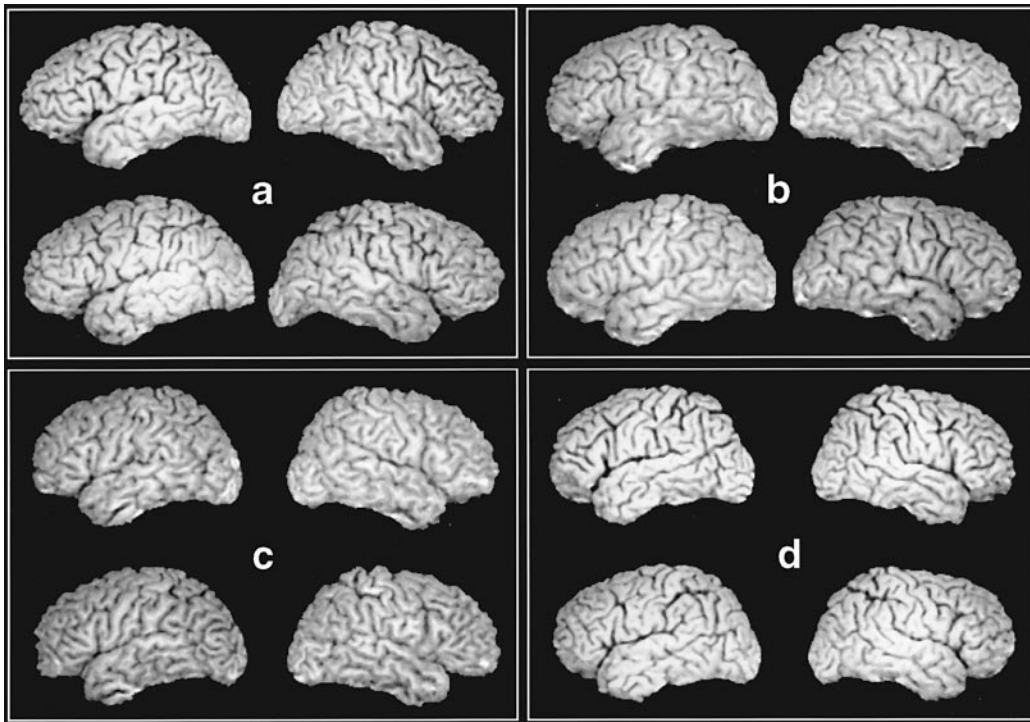


Fig. 2 Examples of MRI renderings of normal MZ twins. Each letter identifies a twin pair. Relative shapes and sizes within pairs appear to be more similar than between unrelated individuals. This is particularly evident, for example, in the temporal lobes. Major sulci which appear relatively early in development (e.g. sylvian fissure) seem to be more similar between twins, than secondary and tertiary sulci (e.g. superior temporal sulcus, various frontal sulci).

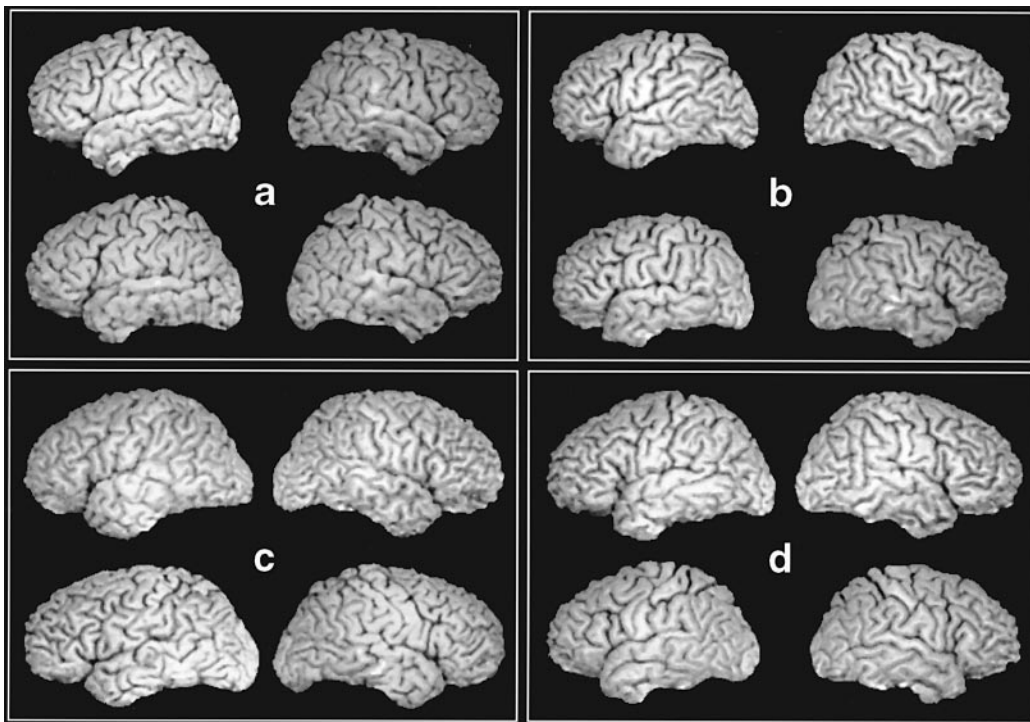


Fig. 3 Examples of MRI renderings of normal dizygotic twins.

(i.e. MZ twins, DZ twins, and unrelated pairings) on the left and right sides, with significant differences between the MZ and DZ twins and between the MZ twins and unrelated

individuals on all ipsilateral cross-correlation measures (Table 5). There were no significant differences between the DZ twin group and the unrelated pairings (Table 5).

SE analysis of the *R*-values for ipsilateral comparisons of gyral pattern similarity determined that random environmental effects acting alone (hypothesis E) could not be rejected as

Table 3 Cross-correlation analysis of ipsilateral cortical surfaces

Pair	MZ twins: ipsilateral cross-correlations (<i>R</i>)*			
	Lateral		Mesial	
	Left	Right	Left	Right
1	0.323	0.378	0.508	0.519
2	0.217	0.252	0.515	0.452
3	0.226	0.165	0.434	0.419
4	0.198	0.240	0.302	0.283
5	0.226	0.235	0.391	0.477
6	0.256	0.219	0.314	0.353
7	0.253	0.199	0.332	0.347
8	0.258	0.319	0.428	0.475
9	0.216	0.222	0.228	0.366
10	0.276	0.264	0.457	0.404
Mean	0.245	0.249	0.391	0.410
SEM	±0.012	±0.019	±0.030	±0.023

**P* < 0.0015 for all values.

Table 4 Cross-correlation analysis of ipsilateral cortical surfaces

Pair	DZ twins: ipsilateral cross-correlations (<i>R</i>)*			
	Lateral		Mesial	
	Left	Right	Left	Right
1	0.198	0.213	0.221	0.437
2	0.187	0.175	0.305	0.331
3	0.171	0.207	0.283	0.290
4	0.220	0.162	0.238	0.308
5	0.170	0.146	0.204	0.226
6	0.179	0.140	0.256	0.341
7	0.148	0.219	0.267	0.296
8	0.153	0.189	0.187	0.263
9	0.225	0.256	0.407	0.381
Mean	0.183	0.190	0.263	0.319
SEM	±0.009	±0.013	±0.022	±0.021

**P* < 0.008 for all values.

a viable hypothesis (*P* > 0.6 for both hemispheres). Acceptance of hypothesis E, however, is prone to Type II error particularly considering the relatively low power of our study which is further diminished by the (necessary) use of correlation here (Neale and Cardon, 1992). Although including either additive genetic effects (AE) or shared environmental effects (CE) in the SE model improved the fit, as indicated by a five-fold decrease in the RMS standardized residuals, this improvement was not significant (*P* > 0.35 for lateral, *P* > 0.12 for mesial). Thus, the SE model approach was inconclusive in assessing the heritability of gyral patterns: additive genetics effects (AE) could not be rejected (*P* > 0.7), but neither was there significant evidence for additive genetic effects. If genetic effects contributed to gyral pattern similarity, as reflected by *R*-values, then these effects were certainly much less robust than those observed for brain volumes. In agreement, the 'classical' heritability estimates for gyral pattern were also low (Table 2).

Cross-correlation analysis was also used to compute *R*-values for contralateral lateral gyral renderings within individuals, a measure of gyral pattern symmetry (Table 6). Repeated measures MANOVA with zygosity as a factor and birth order as the repeated measure found no significant main effects or interactions (*P* > 0.26). However, the concordance in these *R*-values in MZ twin pairs was appreciable and significant [ICC(U) = 0.58, *P* < 0.01], but in DZ twin pairs the concordance was quite low and not significant [ICC(U) = 0.09, *P* > 0.25]. Heritability of the tendency for MZ co-twins to have similar gyral pattern symmetry values was explored with the SE model approach. Although the hypothesis of random environmental effects alone (E) could not be rejected outright (*P* > 0.24), inclusion of shared environmental effects (CE) improved the fit significantly (*P* < 0.033), and inclusion of additive genetic effects (AE) improved the fit even more significantly (*P* < 0.019). Further, the hypothesis of additive genetic effects alone (AE) gave the best fit, i.e. the minimum RMS standardized residual. Inclusion of either shared environmental effects (ACE) or dominance genetic effects (ADE) did not improve the model significantly (*P* > 0.32), so no significant evidence for either existed. In this case, it seemed reasonable to attribute the concordance in lateral gyral pattern symmetry, as reflected by contralateral *R*-values within individuals, to additive genetic effects alone. The heritability of this, as calculated

Table 5 Comparison of ipsilateral cross-correlation values with various sets of pairs

	MANOVA comparison of cross-correlations (<i>R</i>)				
	<i>F</i>	<i>P</i>	Tukey HSD <i>P</i> -values		
			MZ versus SZ twins	MZ versus unrelated pairs	DZ versus unrelated pairs
Left lateral	12.1	< 0.00005	0.001	0.001	0.964
Right lateral	7.1	0.002	0.013	0.015	0.978
Left mesial	19.6	< 0.00001	0.0001	0.0001	0.998
Right mesial	18.1	< 0.00001	0.001	0.0002	0.776

from the parameters of the AE model, was 62% which agreed reasonably well with the 'classical' heritability estimates (Table 2).

Lastly, R -values comparing contralateral hemispheres across twins within a pair were combined with the previously discussed data, i.e. ipsilateral hemispheres across twins within a pair and contralateral hemispheres within individuals (Fig. 4). Repeated measures MANOVA revealed significant main effects of zygosity (MZ versus DZ: $F = 6.95$, $P < 0.018$) and of comparison type (contralateral within

individual versus contralateral across twin pair versus ipsilateral across twin pair: $F = 11.2$, $P < 0.001$) and a significant interaction between these effects ($F = 4.27$, $P < 0.023$). *Post hoc* comparisons (Tukey HSD) showed that between twins of an MZ pair, ipsilateral hemispheres were significantly more alike than were contralateral hemispheres ($P < 0.01$). In contrast, between twins of a DZ pair, there was no difference in likeness between ipsilateral and contralateral hemispheres. MZ twins also exhibited significantly greater similarity in ipsilateral ($P < 0.001$) and in contralateral hemispheres within pairs ($P < 0.01$) than did DZ twins. In the DZ pairs, contralateral hemispheres within an individual were significantly more alike ($P < 0.01$) than were contralateral hemispheres across twins of a pair. In the MZ twins, in contrast, there was no significant difference in the similarity of contralateral hemispheres within an individual and across twins of a pair.

We attempted to determine whether factors other than gyral and sulcal patterns would meaningfully contribute to the cross-correlation results. In particular, if correlations between the brains of MZ twins are higher than in other pairings, this might be due primarily to similarities in brain size or shape. A region of interest of fixed perimeter was applied to the left lateral views of each of the brains, and the R -values were calculated for these regions of interest. These data were compared with the whole view R -values. The common-perimeter R -values (0.183 ± 0.006) actually tended to be slightly smaller as a group when compared with those obtained from the whole lateral view (0.211 ± 0.007), but the two groups of R -values were significantly correlated with each other (Pearson's $r = 0.75$, $P < 0.0001$). The statistical results of cross-correlation analyses using the common perimeter region of interest were of similar magnitude and direction as those derived from the entire brain views detailed above.

The cross-correlation results for the mesial views were affected by the inclusion of midline diencephalic structures which are inherently less complex than are cortical gyri. To address the contribution of these noncortical structures to the cross-correlation data, we constructed a special left hemisphere mesial view by removing with manual segmentation the midline diencephalic structures and corpus callosum, leaving only mesial cortex. The mean cross-correlations were 0.220 ± 0.010 for the MZ twins, 0.169 ± 0.012 for the DZ twins, and 0.143 ± 0.004 for the unrelated pairings. While these cross-correlations are, as expected, less robust than the standard mesial views, the magnitude and pattern of significant differences remained unchanged.

Discussion

This study addresses the contributions of genetics and of environment to variations in human cerebral size and in cortical gyral patterns. The results show that these morphological characteristics of human brain development

Table 6 Cross-correlation analysis of contralateral cortical surfaces

Pair	Contralateral cross-correlations (R)			
	MZ		DZ	
	A	B	A	B
1	0.303	0.286	0.242	0.246
2	0.202	0.168	0.256	0.158
3	0.264	0.240	0.236	0.223
4	0.211	0.146	0.155	0.229
5	0.204	0.200	0.216	0.166
6	0.163	0.199	0.189	0.193
7	0.193	0.219	0.186	0.203
8	0.308	0.224	0.156	0.169
9	0.271	0.281	0.237	0.258
10	0.216	0.219		
Mean	0.234	0.218	0.208	0.205
SEM	± 0.016	± 0.014	± 0.013	± 0.012
ICC(U)	0.585		0.092	
F	4.78		1.55	
P	0.01		0.26	

A = 1st born twin; B = 2nd born twin.

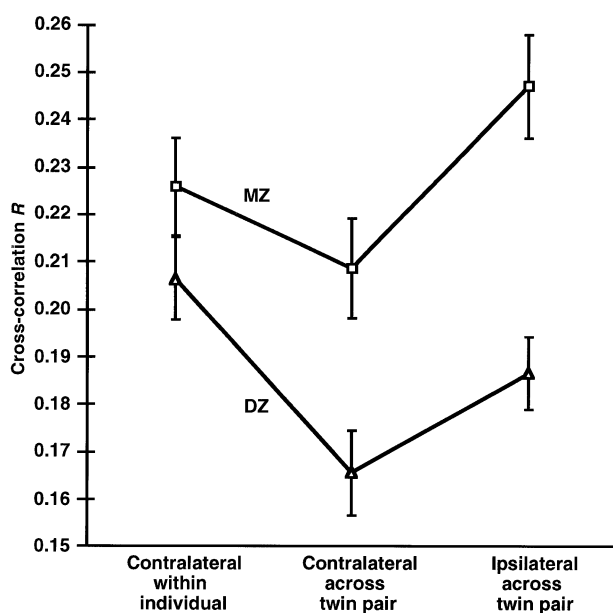


Fig. 4 Comparison of hemisphere cross-correlation values in MZ and DZ twins within individuals and across twins within a pair.

vary dramatically in the degree to which they are under genetic control. Cerebral size is almost entirely explained by genetic factors. Environment appears to play little if any role. These conclusions are based on the findings that the ICC(U)s of brain size in MZ twins are significantly greater than in DZ twins and that the calculated heritability is >0.9 (i.e. $>90\%$). To our knowledge, this is the first demonstration of the degree to which variations in human brain growth are determined by genes. The data are consistent with an earlier study of MZ and DZ twins which found the heritability of cerebral ventricular size studied with CT scans to be 0.96 (Reveley *et al.*, 1982). Comparative anatomical studies indicate that the degree of cellular proliferation early in development accounts for the differences in brain size across species (Finlay and Darlington, 1995), suggesting that the relevant genetic factor(s) involve regulation of cell division.

The variations in overall cortical gyral patterns show less conclusive evidence of significant genetic effects, and in contrast to brain size, most of the variance appears to be determined by random environmental factors. The data suggesting that genes might be significant determinants of variations in gyral patterns include: (i) gyral patterns are significantly more alike within MZ pairs than within DZ pairs; (ii) both ipsilateral and contralateral hemispheres across twins are significantly more alike within MZ pairs than DZ pairs; (iii) the apparent heritability of the degree of interhemispheric gyral pattern symmetry within individuals; (iv) comparisons of contralateral hemispheres within individuals and across individuals do not differ in MZ pairs but do differ in DZ pairs. The data indicating that genes account for only a small degree of variance in gyral patterns include: (i) the qualitative differences in gyral anatomy apparent on the images of even the MZ twins and reflected quantitatively by their relatively small R -values; (ii) the failure of the quantitative SE model approach to find significant evidence for genetics effects; (iii) the low 'classical' heritability values (<0.2); (iv) the lack of differences in comparisons of DZ twins with unrelated pairs.

These conclusions about the effect of genes on cortical gyral development are based on a novel approach to comparing the grey-scale data of MRI images, our cross-correlation analysis. There are several potential limitations of this analysis that should be noted in considering the validity of the results. Although the cross-correlation is insensitive to linear variations in grey-scale (i.e. brightness and contrast), any systematic non-linear variation in signal intensity from one scan to another will adversely bias the R -values. But no such variation is evident on the image data, and we have no reason to believe that this would have occurred systematically with one set of twins and not the other (in fact, both twins of a pair were scanned on the same day in most cases). Edge contrasts are also possible confounding factors that might contribute disproportionately to the cross-correlation results. The perimeter of the brain and variations in perimeter shape are dominant contributions to so-called 'cross-correlation' data computed from raw

images in which the average brain-pixel value has not been subtracted from intracerebral brain pixels or when this value has been subtracted from the entire image, i.e. from both brain pixels and extracerebral (background) pixels. In both these cases, the perimeter of the brain stands out from the background as a 'pedestal' causing shape, size, and perimeter position to dominate the resulting 'cross-correlation' data, which actually constitute a (normalized) product sum rather than the true product moment. These 'pseudo-cross-correlation' data are also dependent upon the extent of the extracerebral background surrounding the brain image, but, nevertheless, have shown substantial utility in aligning the perimeters of two images accurately, even across imaging modalities (Hibbard *et al.*, 1992). In principle, our method will have little if any sensitivity to perimeter effects. Of greater concern, perhaps, is the underlying nature of pattern recognition and pattern comparison. The 'true' cross-correlations which we calculate lead to R -values which are unaffected by translation of one image relative to another, but these R -values will not be invariant under the rotation of one image relative to the other. To control for this, we have re-oriented all our volume MRI data to a common set of axes. Another possible confound is the size or extent of the objects being compared; if one image is spatially scaled relative to another, then the corresponding R -value will be degraded. To control for this, all MRI data were collected with the same field-of-view and slice thickness, but no attempt was made to re-scale the volume MRI data. We also compared the twin groups using a region of interest of fixed size, and the findings were unchanged. Moreover, if size was a major factor in the cross-correlation data, DZ twins should have been more alike than the unrelated pairings and contralateral hemispheres within an individual (especially in the DZ pairs) should have been more alike than ipsilateral hemispheres across twins of a pair. Another, and more difficult issue is that of elastic deformations of a relatively stable basic pattern as might occur during cerebral development. Although the human visual system is adept at recognizing and resolving this situation, as when we recognize an individual in a cartoonist's caricature, the cross-correlation analysis is too 'literal' to cope with this situation; the caricature would have a low R -value relative to an image of the individual it portrays. On the one hand, this might be the single greatest limitation of the cross-correlation analysis for heuristic pattern comparison, e.g. interpretation of cursive handwriting. But, on the other hand, this 'literal' quality of cross-correlation analysis may be of benefit in determining the heritability of gyral patterns. Since the only appreciable elastic deformations of our images would arise as a result of neurodevelopment, these deformations merely become a part of the overall heritability gestalt.

Another important potential confounding factor of the method concerns the process of cortical rendering and image display. In transforming a 3-D, curved surface into a 2-D projection, artifacts involving projection angle, 'lighting,' foreshortening, and parallax invariably occur. In addition, the

anatomical fidelity of the rendering is critically dependent on the accuracy of the removal of extracerebral tissue. We attempted to minimize and standardize rendering artifacts by orienting each volume into a standardized 3-D stereotactic space and insuring that projection and viewing angles and 'lighting' were the same for all renderings. Our approach to the removal of extracerebral tissue, which we have previously validated in qualitative and quantitative comparisons to anatomical standards (Bartley *et al.*, 1993; Kulynych *et al.*, 1993; Noga *et al.*, 1996), also did not vary across twin groups.

In spite of these potential pitfalls, several lines of evidence provide independent validation of the cross-correlation approach to comparing gyral patterns on brain images. Ipsilateral hemispheres across twins of an MZ pair were more alike than were contralateral hemispheres, both within an individual and across twins of a pair. This finding suggests that the method has the capacity to distinguish subtle likeness features. All comparisons within even unrelated pairings were statistically significant (i.e. $R > 0.130$), indicating that the method has the sensitivity to recognize 'brainness,' i.e. certain general features shared by human brains (e.g. a sylvian fissure, superior temporal gyrus, etc.). Also, comparisons of random grey-scale images in the shape of a brain were not significant.

Our conclusions about the quantitative contributions of genes and environment were based on various calculations of heritability. These approaches to quantifying heritability for continuous traits have been used widely in studies of MZ and DZ twins, involving a variety of human biological and psychological characteristics (Osborne and DeGeorge, 1959; Neale and Cardon, 1992; Plomin *et al.*, 1994). In general, the validity of the conclusions that can be drawn from such analyses depends on the accuracy of the trait measurement and on the size of the twin samples. The relatively small number of twins in our study represents another limitation of our data and means that our results should be regarded as preliminary. Nevertheless, it seems unlikely that larger samples would undo the major positive findings of the study or make the gyral patterns of MZ twins qualitatively more alike; but larger sample sizes would be useful in more accurately determining the details of gyral pattern heritability by means of the SE modelling. A full exploration of the SE model would also require groups of MZ and DZ twins reared apart; these groups would eliminate the confound of shared environmental effects with dominance genetics effects in the full SE model of heritability (Neale and Cardon, 1992). Given the difficulties of recruiting sufficient numbers of twins reared apart, this is a shortcoming that is common to the vast majority of twin studies. Also, it may be noted that even the inclusion of twins reared apart will not deal with the issue of shared environment prenatally and at birth.

Our results are consistent with other studies examining the similarity of certain other developmental characteristics in twins. For instance, in an MRI study, Oppenheim *et al.* (1989) showed that the corpus callosum is more similar, but not identical, in twins than in unrelated individuals. Other

MRI studies of twins have found analogous results as noted above (Weinberger *et al.*, 1992; Steinmetz *et al.*, 1994, 1995; Tramo *et al.*, 1995). Similarly, studies of fingerprints have demonstrated that while the general patterns between twins are similar, the prints are not identical (Penrose, 1969). EEG patterns also show similarities as well as differences in MZ twins (Stassen *et al.*, 1987).

MZ twins share virtually identical genomes, but they are not identical people, presumably because of environmental influences. In the majority of cases, MZ twins do not have the same intrauterine environment, and in all cases they do not have the identical postnatal experience (Hrubec and Robinette, 1984; Price, 1950). Whether such environmental differences account for the variations in gyral patterns that we observed is unknown. Whether such variations have functional implications also is unclear. Studies of cognitive and psychological characteristics of MZ twins suggest that, on average, 50% of the variance in such traits is genetically determined (Plomin *et al.*, 1984; Bouchard *et al.*, 1990), a much greater degree of concordance than we observed for gyral patterns. This inconsistency might suggest that gyral pattern variations are trivial in functional terms. Indeed, our data would be consistent with the possibility that genes determine basic gyral configurations and that random mechanical forces account for the rest.

An alternative, and we believe preferred, explanation for our results is that variations in gyral patterns reflect individual differences in brain function and that twins differ to a greater degree than is inferred from ratings of behaviour and tests of cognition. In fact, a recent PET regional cerebral blood flow study of MZ twins found surprisingly few significant correlations in the physiological patterns, despite similar results on cognitive tests (Berman *et al.*, 1995). To the extent that gyral variations are reflections of variations in underlying neural connectivity, the data would suggest that such connectivity varies considerably between MZ twins. Since neural connectivity, especially of intracortical connections, continues to be refined throughout adult life, it is likely that environmental influences have a major impact on this process. Consistent with this assumption and with the possibility that gyral patterns also are affected by primarily environmental factors are data that the degree of overall cortical folding of the human brain approximately doubles from birth to early adult life (Armstrong *et al.*, 1995).

In conclusion, we have shown that interindividual variation in human brain size is almost entirely determined by genes and that variations in overall gyral patterns are determined primarily by environmental factors. Our method has a number of limitations, not the least of which is that it is a general measure of overall similarity performed on 2-D representations. In theory, a more definitive assessment might result from 3-D mensuration techniques (e.g. Tramo *et al.*, 1995), but 3-D approaches to quantifying gyral patterns have not been developed. We also have not made a detailed comparison of exactly which gyri and sulci contribute most to the cross-correlation values. However, since studies of the

development of cortical connections in the primate suggest that the cortex matures as an integrated system and not as a sequential march of functionally independent regions (Zecevic and Rakic, 1991; Lidow and Rakic, 1992), this omnibus approach has relevance. The data show that even genetically identical individuals have considerable variation in the development of their brains.

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