Brain size, head size, and intelligence quotient in monozygotic twins

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Article abstract—Many studies of monozygotic (MZ) twins have revealed evidence of genetic influences on intellectual functions and their derangement in certain neurologic and psychiatric diseases afflicting the forebrain. Relatively little is known about genetic influences on the size and shape of the human forebrain and its gross morphologic subdivisions. Using MRI and quantitative image analysis techniques, we examined neuroanatomic similarities in MZ twins and their relationship to head size and intelligence quotient (IQ). ANOVA were carried out using each measure as the dependent variable and genotype, birth order, and sex, separately, as between-subject factors. Pairwise correlations between measures were also computed. We found significant effects of genotype but not birth order for the following neuroanatomic measures: forebrain volume (raw, $p \leq 0.0001$; normalized by body weight, $p = 0.0003$); cortical surface area (raw, $p = 0.002$; normalized, $p = 0.001$); and callosal area (raw, $p \leq 0.0001$; normalized by forebrain volume, $p = 0.02$). We also found significant effects of genotype but not birth order for head circumference (raw, $p = 0.0002$; normalized, $p \leq 0.0001$) and full-scale IQ ($p = 0.001$). There were no significant sex effects except for raw head circumference ($p = 0.03$). Significant correlations were observed among forebrain volume, cortical surface area, and callosal area and between each brain measure and head circumference. There was no significant correlation between IQ and any brain measure or head circumference. These results indicate that: 1) forebrain volume, cortical surface area, and callosal area are similar in MZ twins; and 2) these brain measures are tightly correlated with one another and with head circumference but not with IQ in young, healthy adults.

NEUROLOGY 1998;50:1246–1252

Monozygotic (MZ) twins manifest similarities in cognitive skills and other behavioral characteristics that are attributable, for the most part, to the identity of their genes.[1-5] In light of current knowledge about brain-behavior relationships in humans[6,7] and cellular and physiologic mechanisms underlying brain development in animals,[8,9] one might hypothesize that MZ twins possess similarities in brain anatomy. Until recently, it has been difficult to test this hypothesis quantitatively. With the advent of in vivo brain imaging as a clinical tool over the past quarter century has been the development of computer-based image processing techniques that permit quantitative analyses of neuroanatomic data contemporaneously with behavioral assessment.[10-15] In the present study, we analyzed total forebrain volume, total cerebral cortical surface area, callosal cross-sectional area, head circumference, and full-scale intelligence quotient (IQ) in normal adult MZ twins. In addition to assessing co-twin similarities, we tested for correlations among brain measures, head circumference, and IQ.

Methods. *Study population.* Ten pairs of young, healthy, identical twins were recruited for paid participation. All participants signed written informed consents for phlebotomy, magnetic resonance scanning, and pencil-and-paper tests. A board-certified neurologist or psychiatrist elicited the medical history of each subject; all histories and reviews of systems were negative for symptoms of neurologic or psychiatric disease. All 10 co-twin pairs were reared together and currently live in proximity to one another. All 20 subjects were between the ages of 24 and 43 years (median, 34 years), had at least a high school education, and were right handed (Edinburgh Laterality Quotient[16] range, 74 to 100; median, 88; all wrote and ate with the right hand). Nine RBC surface markers and a standardized questionnaire were used to establish monozygosity.[17,18]

Anthropometric and neuropsychometric data. Head circumference (cm) and body weight (kg) were measured at the time of phlebotomy or at the MRI suite. The Wechsler Adult Intelligence Scale-Revised[19] was administered separately to each subject in a quiet room. The full-scale IQ was scored. Body weight, which is similar in MZ twins[20] and correlates with brain weight in humans,[21-23] was di-

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Supported by NIH awards DC00071 (to M.J.T.) and NS17778 (to M.S.G. and M.J.T.) and Office of Naval Research award N00014-89-J-3035 (to M.S.G. and M.J.T.).

Received August 29, 1996. Accepted in final form December 3, 1997.

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vided into raw forebrain volume, cortical surface area, callosal area, and head circumference to generate normalized data for additional analyses.

Neuroanatomic data. Image acquisition. Details of the brain image acquisition methods used in the present study were published previously.[15,24] T1-weighted MRIs were acquired using a Siemens (Grand Island, NY) 1.0 Magnetum system (in-plane resolution, 1.2 mm) or a General Electric (Milwaukee, WI) 1.5 Signa system (in-plane resolution, 0.9 mm). The head was positioned in the scanner so that a horizontal laser marked the intercanthal line and a vertical laser intersected the midpoint of the nasion and philtrum. For serial coronal sections, the effective thickness was 3.0 mm and the in-plane resolution 0.9 to 1.2 mm. For sagittal sections, the thickness was 5.0 to 8.0 mm, there was an interslice gap of 1.0 to 2.0 mm, and the in-plane resolution was 0.9 to 1.2 mm. In 16 of 20 subjects, coronal sections were obtained using 3D FLASH (TE/TR = 20/400 msec [Siemens] or 9/50 msec [GE]). Before this technique became available at our institution, four subjects (two pairs of female twins) were imaged in serial coronal section by interleaving two sets of 3.0-mm slices that were offset by 3.0-mm gaps. There were no obvious differences in the quality of the latter images, and statistical analyses on a subset of the data taken from the 16 subjects imaged via 3D FLASH showed the same pattern of results as those found for all 20 subjects. Thus, combined data are reported.

Image analysis. MR images were stored on magnetic tape for transfer and display on a Silicon Graphics (Mountain View, CA) computer. The pial surface of each coronal section was traced by hand. Our previous analyses[25] of intra- and interobserver reliability for pial surface tracings showed a coefficient of variation (CV) of 2.7% for hemisphere surface area measurements based on three separate tracings by one technician, CV of 5.4% for hemisphere surface area measurements based on one tracing by four separate technicians, and pairwise correlations ranging from 95.9 to 99.0% for surface area measurements of 27 gross morphologic structures (e.g., gyri) based on one tracing by four technicians. In the present study, three technicians performed pial surface tracings, and tracings for each member of a co-twin pair were never performed by the same individual.

Total forebrain volume was determined from the serial coronal sections by outlining the pial surface of each hemisphere, outlining the ventricles, subtracting the number of voxels within the latter from that within the former, summing the voxel count across sections, and converting voxel count to volume (cm^3; figure 1). This is essentially the same procedure as the "basic volume estimator" discussed by Uylings et al.,[26] except that no correction factor for postmortem shrinkage needed to be included in the expression volume = (slice thickness) $(\Sigma^{N}_{i=1} A_i)$, where A is the cross-sectional area of the *i*th of N sections. Telencephalic and diencephalic gray and white matter were included in this measure.

Our method for measuring the cross-sectional area of the corpus callosum in the midsagittal plane was similar to previously published methods.[27,28] The midsagittal MRI section was displayed on the computer monitor, and the outline of the callosum was traced with a computerized planimeter (figure 2).

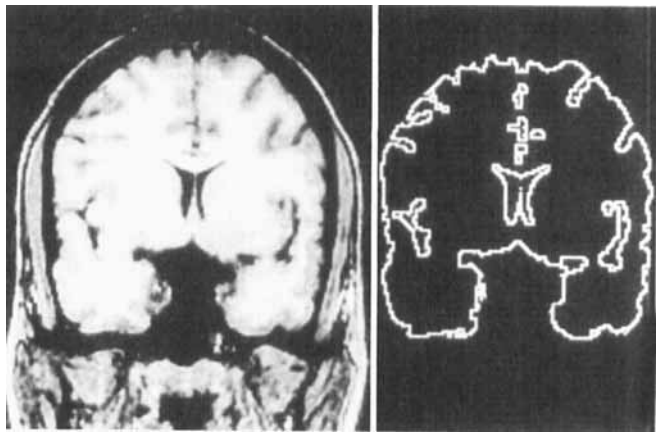

Figure 1. Example of a T1-weighted coronal section through the frontal and temporal lobes (left) and the corresponding pial and ventricular outlines (right) used in total forebrain volume analyses.

Our methods for calculating cortical surface area are detailed elsewhere.[15,24] A three-dimensional computer model of the entire intra- and extrasulcal surface was reconstructed from the pial surface tracings using a triangulation algorithm. The areas of all triangles in the model were then summed. In the context of the original tests for correlations among cortical surface area, forebrain volume, callosal area, head circumference, and IQ presented here and to facilitate comparisons among ANOVAs for all brain measures, previously reported total cortical surface area analyses[15] are presented alongside the original forebrain volume, callosal area, head circumference, and IQ analyses.

Statistical analyses. The working hypothesis was that brain size, head size, and IQ are more similar in individuals with identical genotypes than in individuals with different genotypes. ANOVAs were used to test for differences in each dependent variable across unrelated twin pairs (genotype factor: Twins A versus Twins B versus . . . Twins J) and within co-twins (birth order factor: Twin A_1 versus Twin A_2, Twin B_1 versus Twin B_2 . . . Twin J_1 versus Twin J_2[29,30]). The dependent variables were total forebrain volume (raw and, separately, normalized by body weight), total cortical surface area (raw and normalized by body weight, the midsagittal area of the corpus callosum (raw and normalized by total forebrain volume), head circumference (raw and normalized by body weight), and Full-Scale IQ. In separate series of ANOVAs, we separated the overall effect of genotype into the independent contributions of sex and genotype, removing the sex effect.

Pairwise correlation coefficients and simple regressions were computed for forebrain volume and cortical surface area, forebrain volume and callosal cross-sectional area, cortical surface area and callosal cross-sectional area, forebrain volume and head circumference, cortical surface area and head circumference, forebrain volume and IQ, cortical surface area and IQ, callosal area and IQ, and head circumference and IQ. Both raw and normalized (by body weight) brain measures and head circumference were analyzed. Correlations were tested for the entire study population (n = 20) and a subpopulation comprised of one twin randomly selected from each twin pair (n = 10). The latter were carried out to consider the extent to which correla-

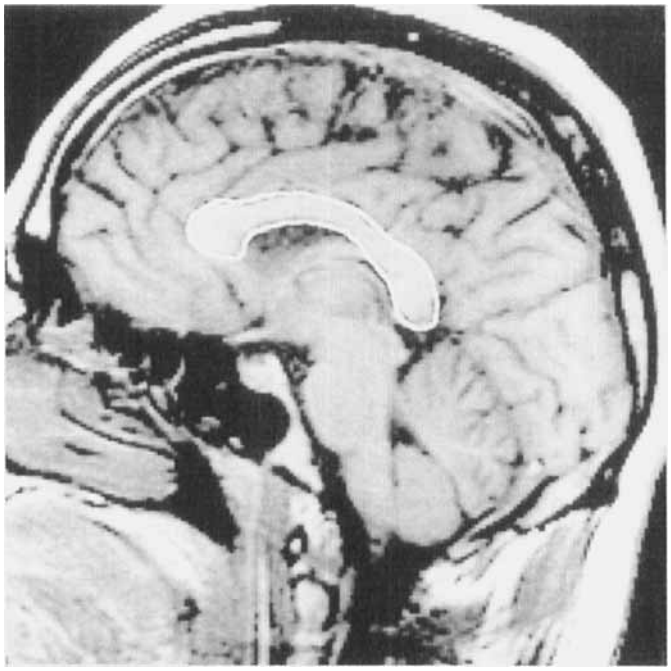

Figure 2. Example of T1-weighted midsagittal MRI showing outline of the corpus callosum used in cross-sectional area analyses.

tions in the population as a whole might arise from redundancies introduced by co-twin similarities.

Results. Table 1 lists the range, mean, and SD of each measure and the results of the ANOVAs.

Total forebrain volume. There were highly significant effects of genotype for both raw forebrain volume ($F(9,9) = 19.49$, $p \leq 0.0001$) and forebrain volume normalized by body weight ($F(9,9) = 14.30$, $p = 0.0003$), indicating great variation across unrelated pairs. No significant effects of birth order were found for either measure (raw, $F(1,9) = 0.22$, $p = 0.65$; normalized, $F(1,9) = 0.04$, $p = 0.84$), indicating little variation within co-twins. No significant effects of sex were found (raw, $F(1,8) = 1.29$, $p = 0.29$; normalized, $F(1,8) < 0.01$, $p = 0.98$), indicating little variation between women and men. The highly significant effects of genotype persisted after the contribution of sex differences across unrelated pairs were removed (raw, $F(8,9) = 18.88$, $p \leq 0.0001$; normalized, $F(8,9) = 16.08$, $p = 0.0002$).

Total cortical surface area. The pattern of results for cortical surface area was similar to that for forebrain volume. There were highly significant genotype effects for both raw cortical surface area ($F(9,9) = 8.66$, $p = 0.002$) and cortical surface area normalized by body weight ($F(9,9) = 9.96$, $p = 0.001$), indicating great variation across unrelated pairs. There was a trend raising the possibility of a weak birth order effect for raw cortical surface area ($F(1,9) = 3.76$, $p = 0.08$) but not for normalized cortical surface area ($F(1,9) = 0.83$, $p = 0.39$), indicating relatively small variation within co-twins, especially when body weight was taken into account. No significant sex effects were found (raw, $F(1,8) = 0.01$, $p = 0.93$; normalized, $F(1,8) = 0.77$, $p = 0.41$). The highly significant genotype effects persisted after adjusting for sex differences across unrelated pairs (raw, $F(8,9) = 9.73$, $p = 0.001$; normalized, $F(8,9) = 10.23$, $p = 0.001$).

Midsagittal callosal area. The pattern of results for callosal area was similar to that for forebrain volume and cortical surface area. There was a significant genotype effect for both raw callosal area ($F(9,9) = 18.90$, $p \leq 0.0001$) and callosal area normalized by forebrain volume ($F(9,9) = 4.65$, $p = 0.02$), indicating that the great variation in raw callosal area across unrelated pairs could not be entirely accounted for by variation in forebrain volume. In contrast, there was no birth order effect for raw ($F(1,9) = 1.06$, $p = 0.33$) or normalized callosal area ($F(1,9) = 1.55$, $p = 0.24$). There was no sex effect (raw, $F(1,8) = 0.72$, $p = 0.42$; normalized, $F(1,8) < 0.01$, $p > 0.99$). The significant genotype effects persisted after adjusting for sex differences (raw, $F(8,9) = 19.50$, $p \leq 0.0001$; normalized $F(8,9) = 5.23$, $p = 0.01$).

Head circumference. There was a highly significant genotype effect for both raw head circumference ($F(9,9) = 14.84$, $p = 0.0002$) and head circumference normalized by body weight ($F(9,9) = 16.80$, $p \leq 0.0001$). No birth order effects were found (raw, $F(1,9) = 0.71$, $p = 0.42$; normalized, $F(1,9) = 0.70$, $p = 0.42$). There was a sex effect for raw head circumference but not for normalized head circumference (raw, $F(1,8) = 7.48$, $p = 0.03$; normalized $F(1,8) = 0.11$, $p = 0.75$). The genotype effects remained highly significant after adjusting for sex difference across unrelated pairs (raw, $F(8,9) = 8.63$, $p = 0.002$; normalized, $F(8,9) = 18.65$, $p \leq 0.0001$).

Table 1 *Measurements of total forebrain volume (FV, cm^3), total cerebral cortical surface area (CSA, cm^2), midsagittal callosal area (CA, cm^2), head circumference (HC, cm), and intelligence quotient (IQ)*

				Genotype		Birth order		Sex	
	Range	Mean	SD	Raw *p*	Nlzd *p*	Raw *p*	Nlzd *p*	Raw *p*	Nlzd *p*
FV	936–1439	1126	125	≤0.0001	0.0003	0.65	0.84	0.29	0.98
CSA	1,685–2264	1906	175	0.002	0.001	0.08	0.39	0.93	0.41
CA	5.7–8.8	7.0	0.9	≤0.0001	0.02	0.33	0.24	0.42	>0.99
HC	54.7–57.2	56.1	1.8	0.0002	≤0.0001	0.42	0.42	0.03	0.75
IQ	85–127	110.8	13.4	0.001	NA	0.66	NA	0.91	NA

p Values for each dependent variable (raw and normalized [Nlzd]) and each between-subjects factor (genotype, birth order, and sex) are also tabulated. See text for corresponding F ratios and degrees of freedom.

NA = not applicable.

Table 2 *Correlation matrix. Coefficients for raw FV, CSA, CA, and HC are in the upper right half of the matrix; coefficients for FV, CSA, CA, and HC normalized by body weight are in the lower left half*

	FV	CSA	CA	HC	IQ
FV	—	0.77†	0.66†	0.51*	−0.06
CSA	0.95†	—	0.53*	0.53*	0.20
CA	0.92†	0.86†	—	0.61*	0.16
HC	0.91†	0.92†	0.87†	—	0.14
IQ	−0.05	0.06	0.05	−0.03	—

* $p \leq 0.0222$.
† $p \leq 0.0015$.

FV = forebrain volume; CSA = cortical surface area; CA = callosal area; HC = head circumference; IQ = intelligence quotient.

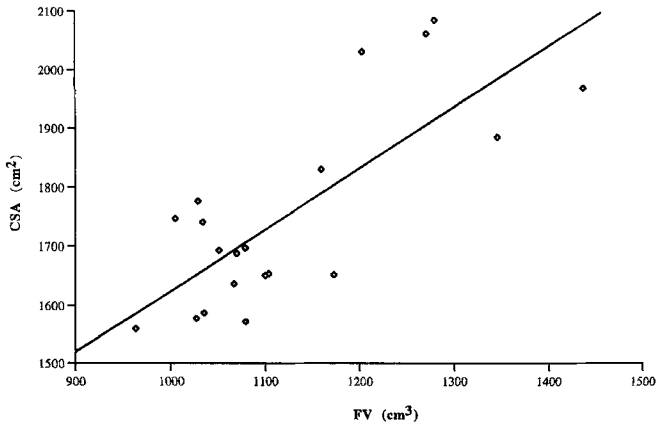

Figure 3. Linear regression of cortical surface area (CSA) on forebrain volume. Cortical surface area = 585 + 1.04 forebrain volume (FV; $R^2 = 0.59$, $p \leq 0.0001$).

Full-scale IQ. There was a significant effect of genotype ($F(9,9) = 9.51$, $p = 0.001$) but not birth order ($F(1,9) = 0.21$, $p = 0.66$) or sex ($F(1,8) = 0.01$, $p = 0.91$). The significant genotype effect persisted after adjusting for sex differences ($F(8,9) = 10.68$; $p = 0.001$).

Correlations between measures. A correlation matrix for all raw and normalized measures is shown in table 2. All pairwise correlations between forebrain volume, cortical surface area, callosal area, and head circumference were positive and significant, with r values ranging from 0.51 ($p = 0.0222$) to 0.95 ($p \leq 0.0001$). The linear regression of raw cortical surface area on raw forebrain volume is illustrated in figure 1 (cortical surface area = 585 + 1.04 forebrain volume; $r = 0.77$, $R^2 = 0.59$, $p \leq 0.0001$). No significant correlations between IQ and either forebrain volume, cortical surface area, callosal area, or head circumference were found (r range = −0.06 to +0.20; all $p \geq 0.40$). For the subpopulation of 10 unrelated individuals, pairwise correlations between brain measures were the same in sign and similar in magnitude, and all remained significant (r range = 0.63 to 0.96, $p = 0.0492$ to $p \leq 0.0001$), with $r = 0.76$ for raw forebrain volume and cortical surface area ($p = 0.0111$) and $r = 0.94$ for normalized forebrain volume and cortical surface area ($p \leq 0.0001$); correlations between head circumference and brain measures were also the same in sign and similar in magnitude, with all normalized measures and raw head circumference and callosal area reaching significance (r range = 0.72 to 0.94; p range = 0.0181 to ≤ 0.0001), raw head circumference and forebrain volume showing a trend ($r = 0.62$, $p = 0.058$), and raw head circumference and cortical surface area falling below significance ($r = 0.48$, $p = 0.164$). Again, no significant correlations between IQ and forebrain volume, cortical surface area, callosal area, or head circumference were found (r range = −0.26 to +0.25, $p \geq 0.47$).

Discussion. For all brain measures, there were highly significant genotype effects but no significant birth order effects, indicating that total forebrain volume, total cortical surface area, and callosal cross-sectional area varied far more across unrelated pairs than within co-twins. Consistent with the results of previous twin studies, co-twins were also more similar than unrelated pairs with respect to head circumference[1] and IQ.[4,5] Genotype effects were not attributable to sex differences across unrelated pairs.

The utility of studying human twins in medical research has been previously reviewed by Hrubec and Robinette.[31] In light of the extensive literature concerning phenotypic similarities between MZ twins reared apart, we interpret the present findings as evidence that prenatal influences on brain development in humans are sufficiently strong to be detectable at the gross morphologic level in vivo using MRI. This interpretation is reinforced by knowledge that the size and shape of the adult brain emerge principally from cellular and physiologic events that take place during prenatal life. In humans, cortical neurogenesis begins around the middle of the first trimester and ends around midgestation.[32] Cortical surface area increases 30-fold and brain volume 60-fold from the beginning of the second trimester to birth.[33] Cortical fissuration begins around the fourth week of life and almost reaches the adult form by birth.[34] The number of callosal axons increases by four orders of magnitude from the first trimester to 5 months after birth.[35]

Our methods do not allow us to differentiate the relative contributions of genetic and maternal factors to prenatal influences on brain size, head size, and IQ. Tighter control of maternal variables in prospective studies would reduce the risk that co-twin similarities arose from similarities in nutritional, mechanical, chemical, or other factors.[36,37] The absence of significant birth order effects among our results argues against the presence of pathologic intrauterine factors that might have otherwise obscured co-twin similarities.

Similarities in postnatal environment may have contributed to the observed co-twin similarities. Brain volume and cortical surface area increase two- to threefold from birth to adulthood,[33] and callosal area increases approximately 40 to 50% from childhood to young adulthood.[28,38] Future comparisons of brain size, head size, and IQ between MZ twins

reared together and MZ twins reared apart would permit estimation of postnatal influences. Although it is generally held that postnatal influences inflate estimates of genetic influences on co-twin similarities, some authors have argued that postnatal influences may lead to underestimations of genetic influences.[39]

Brain size. The present in vivo brain measurements (see the table) correspond well with those previously obtained postmortem[10,33,40-47] and in vivo.[10,11,27,28,48-50] For example, the range of our 20 volume measurements (963 to 1,439 cm^3) overlaps the range found by Zilles et al.[47] (851 to 1,329 cm^3) in 60 cadavers. The range of our cortical surface area measurements (1,685 to 2,264 cm^2) lies within that of previous postmortem measurements (1,469 to 3,031 cm^2).[33,40] Likewise, our midsagittal callosal area measurements (5.7 to 8.8 cm^2) match those found in previous postmortem studies.[41,43,44,46]

The present evidence of co-twin similarity in midsagittal callosal area complements previous evidence of co-twin similarity in callosal shape.[27] The absence of a sex effect on callosal area in our population is consistent with the results of the most extensive in vivo study to date,[28] in which sex differences in the shape of the splenium, but not in the area of the corpus callosum, were found. In general, our and others' observations indicate that both in vivo and postmortem measurements of callosal size and shape are sufficiently sensitive to detect subtle differences between co-twin pairs and unrelated control pairs, men and women,[28,41,50,51] left handers and right handers,[43,52] patients with left-hemisphere and right-hemisphere speech dominance,[48] and musicians and nonmusicians.[49]

Correlations among brain size, head size, and IQ. There was a strong correlation between forebrain volume and cortical surface area. Across mammalian species, cortical surface area increases not as the two-thirds power of volume, as a simple geometric model would predict, but more nearly as the first power.[53] Across different families of the primate order, increases in the proportion of intrasulcal to extrasulcal surface parallel those in telencephalic volume, brain weight, and body weight, with the strongest correlation for telencephalic volume.[54] During development in humans, the ratio of forebrain volume to cortical surface area remains more or less constant.[55] The present finding of a linear relationship between forebrain volume and cortical surface area in the mature brain corroborates that of Elias and Schwartz,[40] who analyzed whole brain volume and cortical surface area in 20 adult cadavers. Thus, a linear relationship between cortical surface area and brain volume exists within the human species and across different mammalian species.

Unified conscious experience relies on callosally mediated interactions between cortical neurons in the left and right cerebral hemispheres.[56] The strong correlation between cortical surface area and callosal cross-sectional area found in the present study suggests constancy in the proportion of cortical neurons that send projections from one hemisphere to the other. Based on our measurements of total cortical surface area (mean, 1,906 cm^2) and previous estimates of 105 neurons per 750 μm^2 of cortical surface[57] and 200 million fibers per adult callosum,[58] we estimate that approximately 1% of cortical neurons project contralaterally in humans.

Head size is routinely measured in pediatrics and obstetrics to assess brain development, and micro- and macrocephaly have long been known as signs of underlying brain pathology.[59] However, the relationship between head size and brain size in healthy adults remains uncertain. We found strong correlations between head circumference and forebrain volume and between head circumference and cortical surface area in our 18- to 43-year-old population.

Measurements of cranial dimensions are the principal means of estimating evolutionary changes in brain size and shape from fossil records.[60-62] To our knowledge, this is the first demonstration of a correlation between head circumference and cortical surface area, the brain measure that has evolved most dramatically in higher mammals.[8,63-67] It does not follow simply that the physical constraints of the skull determine cortical surface area. To the contrary, experimental and theoretical accounts of cortical expansion and folding emphasize the contribution of factors intrinsic to the cortex.[53,55,64,66,67]

Consistent with the results of MZ twin studies previously carried out in much larger populations, we found co-twin similarities in IQ. Studies of MZ twins reared apart suggest that genetic factors may contribute as much as 70% to the variance in IQ scores among the general population.[5] The notion that intelligence correlates with brain size has persisted for over a century in evolutionary biology, although not without controversy.[60-62,68,69] In particular, several authors have remarked on the parallel increases in cortical surface area and behavioral complexity across animal species. In humans, no previous test of a correlation between total cortical surface area and a measure of intelligence has been carried out. We found small, positive, nonsignificant correlations between IQ and cortical surface area. Those for forebrain volume approached zero. In previous in vivo studies, analyses for some brain measures, intelligence measures, and subject subpopulations reached statistical significance,[70-74] whereas others have not.[70-72,75,76] A recent meta-analysis[77] of data from 46 studies carried out over the past 90 years on over 50,000 subjects yielded a highly significant correlation between head size, cranial capacity, or brain size on the one hand and educational achievement, occupational achievement, or psychological test performance on the other. However, most of that analysis was based on head size data in cadavers and retrospective estimates of intelligence, and some negative results from recent in vivo studies were not included. In our view, even if a small, positive correlation existed between measures

of overall brain size and general intelligence that reaches statistical significance for very large populations, one must conclude that brain size is not a sensitive index of intelligence. Certainly, the intelligence of a healthy adult or of an acutely ill patient without a childhood history of neurologic or psychiatric disease cannot be estimated from the size of his or her brain or head.

Our findings of co-twin similarity in both brain size and IQ combined with the absence of a correlation between brain size and IQ suggest that intellectual similarities in MZ twins cannot be accounted for by genetically based neuroanatomic similarities using a straightforward "bigger is better" hypothesis. It remains plausible, and we believe likely, that genetic influences on brain organization (i.e., how the brain is put together, not just how big it is) underlie intellectual similarities in MZ twins. For example, genetic influences on brain organization may be manifested at the gross morphologic level by similarities in the local geometry of folds in the left cerebral cortex,[15] which in the vast majority of humans governs language and abstract reasoning[78,79]—the cognitive skills that distinguish our species in primate evolution and that contribute most to IQ test performance. The notion that genetic influences on intellectual functions might be reflected in regional measures rather than, or in addition to, global measures of brain size resonates with the prevailing view[80-82] that intellect emerges from the concerted action of functionally specialized neural systems distributed within specific regions of the forebrain.

Acknowledgments

We gratefully acknowledge the contributions of Catherine Thomas, Leila Mott, Robert Ferranti, Patrick Brown, and Robert Nordgren.

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