Acta Genet Med Gemellol 47: 89-100 (1998)

Magnetic Resonance Imaging of Cerebral Central Sulci: a Study of Monozygotic Twins

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Abstract. The cerebral central sulci, seat of the sensorimotor cortex, vary anatomically in form, length and depth among individuals and present a left/right asymmetry. The purpose of this work was to measure central sulcus's lengths, at the surface and in-depth, in each hemisphere of monozygotic twins in order to evaluate the influence of environmental factors on the morphometry and asymmetry of this structure. A measurement technique on MR images of the brains using 3 D software was developed. Two operators applied this technique to measure central sulcus lengths at the surface of the brain and in-depth in each hemisphere. Besides the fact that the technique developed gave high Intraclass Correlation Coefficients (ICC) for the surface lengths (mean value 0.94), and slightly less high for the in-depth length (mean value 0.87), we found a weak (from 0.57 to 0.73 for raw data) but significant ICC between homologous sulci in pairs of twins. In addition, the ICC for asymmetry indices were not significant. Hence, if central sulcus morphometry is in part genetically influenced, these results show that nongenetic factors are nonetheless important in their development.

Key words: Twins, Brain, Asymmetry, Central sulcus, Genetics.

INTRODUCTION

The central sulcus is a fissure separating the frontal and parietal lobes of the brain. It has attracted the attention of anatomists and neurosurgeons since 1870, when Fritsch and Hitzig published the results of their work showing that electric stimulation of the central sulcus of one of the two hemispheres along the frontal lobe led to contralateral muscle contractions in several dogs and cats. Subsequently, Ferrier at the end of the 19th century and Penfield in the first half of the 20th century confirmed that the somalo-motor areas are located on the anterior edge of central sulci (precentral gyri), and the somato-sensory areas on the posterior edge (postcentral gyri). More recently, White et al. [24, 25] studied in depth the morphology and cytoarchitecture of the central sulci in 20 autopsied brains. They concluded that despite their interhemispheric variability in the same subject and variability between individuals, the central sulci represent the macroanatomic feature that reliably locates the sensorimotor cortex and associated regions. Magnetic resonance imaging (MRI) has also led to establishing that the functional zone activated during simple motor tasks most often coincides with the anterior edge of the contralateral central sulcus [26].

To the best of our knowledge, only Vannier et al. [20] compared the reliability of measurements of various cerebral structures made by MRI with those made on one autopsied subject. In the eight other subjects, they made in vivo evaluations of the length of central sulci. More recently, Clarisse [6] extended by illustration the 5 morphologic signs defined by Naidich et al. [11], the presence of which allows identification of the central sulci on MRI. Presently, computerized procedures are being developed to obtain automatic recognition of the many cerebral sulci and a parametric quantification to depict them [10]. However, no study has yet reported on the morphometric characteristics of central sulci in vivo. This is the first aim of this work: to define an in vivo measurement technique of the central sulci, on the surface and in depth, using a 3 D image software.

In the autopsy study cited above, White et al. attempted to correlate handedness with greater development of the contralateral sensorimotor cortex. However, they were not able to show that morphologic asymmetry of the central sulci was related to this functional characteristic (nor asymmetry of the sensorimotor pathways leading from the cortex to the spinal cord), contrary to the results of their preliminary study [23]. Aside from studying possible asymmetry of the right and left sensorimotor areas of which the length of the central sulci is an indication, a second aim of the present study is to determine whether the development of these structures is influenced by environmental factors.

The measurement technique defined was thus used in monozygotic twins (MZT) to assess the degree of similarity and dissimilarity between twins in the morphometry of their central sulci. Dissimilarities observed in a given characteristic between individuals of identical genotype clearly are due to environmental factors in the wide sense, while similarities can be due to genetic and/or environmental factors. Thus, the morphometric differences observed in the central sulci in monozygotic twins demonstrate the influence of non-genetic factors in the formation of this structure involving motor function. Other recent works on twins have attempted to assess the influence of genetic and non-genetic factors on the morphology of brain structures such as the corpus callosum [13], the planum temporale [17], brain size, cortical gyral patterns and head circumference [1, 18, 19, 21], white matter irregularities in the elderly [3], but not on the central sulcus. It should be underlined that in the human (as in mammals), abnormal size or form of a brain structure gives rise to functional deficiencies; however, it is not known to what extent the interindividual morphologic variations observed in normal individuals are correlated to underlying patterns of neuron connections that could result in functional patterns that would lead to more or less effective performance. Recently, a genetic study [19] found no correlations at all between IQ and brain volume, or between IQ and cortical surface area.

In short, the present study has two aims: a) to develop an adapted measurement technique for the central sulcus, at the surface and in depth, and to estimate interobserver reliability, b) to assess the degree of similarity between MZT based on these measurements, and to compare hemispheric asymmetry between the twins for these characteristics.

METHODS

Sample

This study included 20 MZT, 6 pairs of females and 4 pairs of males. They were recruited by announcements at the university, at a twins association, and by personal contact. All gave written informed consent.

The mean age of the subjects was 34.6 ± 9.85 years [range 18-47], mean weight 65.3 ± 12.47 kg [range 48-87] and mean height 1.70 ± 9.18 [range 1.58-1.87].

The studied subjects suffered from no systemic, psychiatric or neurologic disorders; none required a pacemaker or had other metal protheses.

Zygosity was established on the basis of blood antigens for part of the pairs of twins and on the basis of a questionnaire distinguishing zygosity for the whole group [16].

Acquisition of 3 D images

MRI was performed on Sigma equipment, General Electric, 1.5 Tesla. Volumetric acquisition was obtained in a sagittal plane in a T1-weighted spoiled gradient recalled acquisition in the steady state (SPGR) sequence, with parameters TR = 23ms, TE = 5ms, Flip angle = 35, Nex = 1. Field of view was 24 cm. The acquisition matrix was 256 × 192, interpolated to 256 × 256. After transfer to an Advantage Windows station working on Sun, this format allows work on 3 dimension images, reconstructed from 124 sagittal sections at 1.5 mm intervals, using the Voxtool program (G.E.).

Measurement technique

On loading, a pre-thresholding, identical for all MRI images, eliminated most background noise, retaining only voxels with an intensity between 12 and 400. Then a threshold adapted to each MRI image eliminated part of the cutaneous, fat and meningeal envelopes, with the lower and upper thresholds corresponding to a mean of values found in sample voxels chosen randomly but uniformly in the fatty regions and the arachnoid spaces. Lastly, the "open bridge" (N = 3) and "close gaps" (N = 18) functions eliminated the peripheral tissues while filling in the discontinuities in aberrant voxels. Thereafter, the cortical surface of the brain appeared tridimensionally on the screen and the brain volume was given automatically by the Voxtool software [8].

Surface measurement of the central sulcus length was made on the anterior edge so as to be just at the surface of the motor cortex, just opposite to the posterior edge, whose height is sometimes lower. Secondary ramifications were ignored and the anterior edge was followed as closely as possible. In-depth measurement was made by

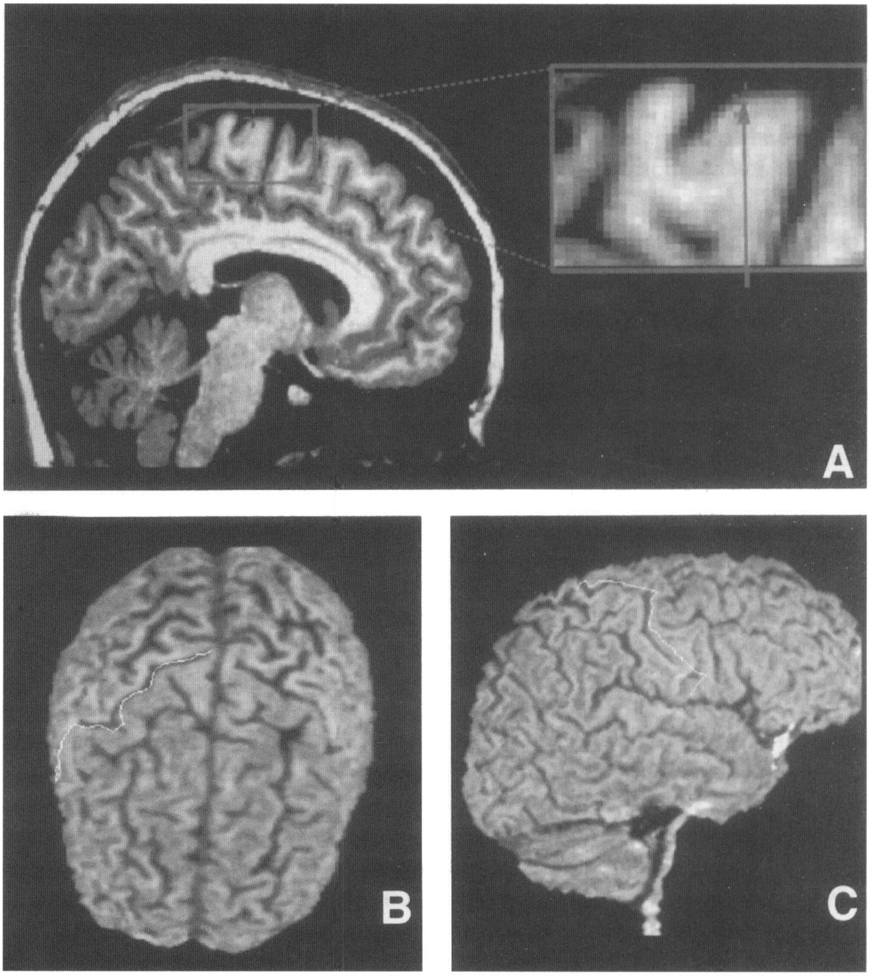

Fig. 1 - A - Sagittal MR images (from a 3D T1 weighted SPGR sequence) of a twin's left hemisphere localized near the longitudinal fissure. The point indicated by the arrow was recorded as the anterior edge of the central sulcus. B - Top view image of the same brain surface rendering model. C - Left view image of the same brain surface rendering model. The trace formed by the recorded points follow the central sulcus on the top view as on the left view.

finding the line between white and grey matter, and not between the cerebrospinal fluid and grey matter.

Measurement precision was obtained by working on 4 visualization windows, simultaneously showing: an acquired sagittal section, the axial section reconstructed according to a plane selected from the sagittal section and 3D images of the brain (integral and surface mode) obtained by thresholding, erosions and dilatations as described above. For the surface measurements, a point was recorded at the anterior edge of the central sulcus in the sagittal (or the axial) section after its location in each window (Figure 1 A).

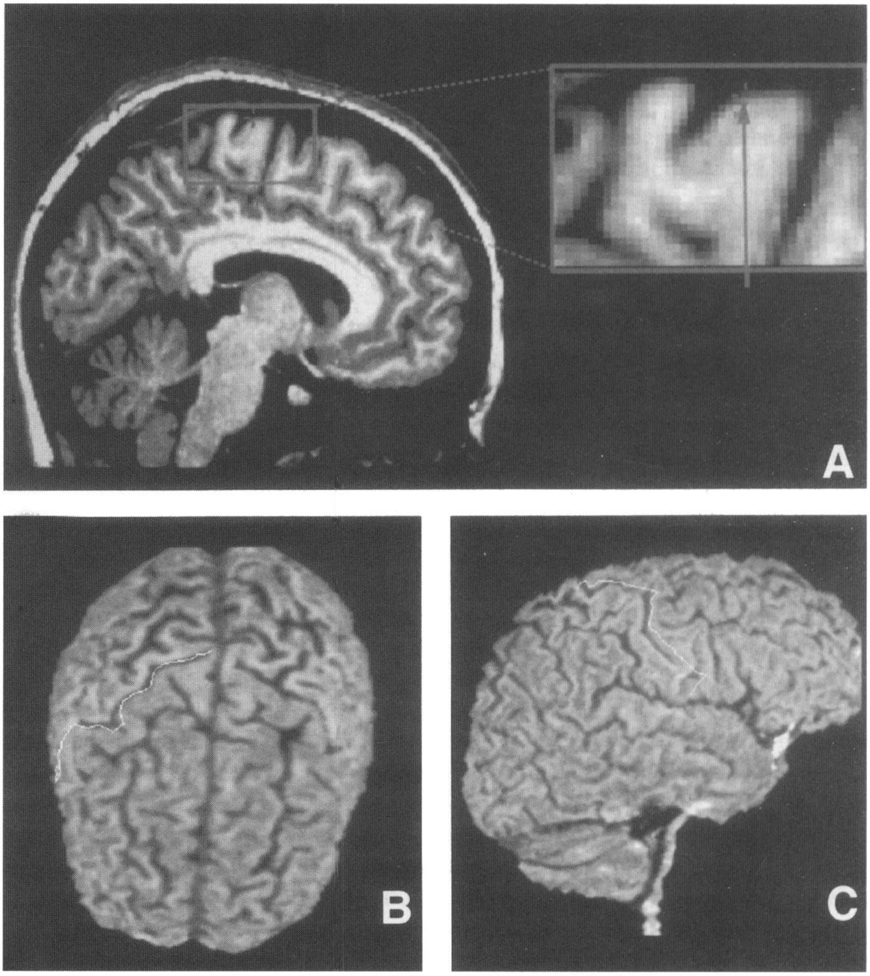

Fig. 2 - A - Axial MR images (from a 3D T1 weighted SPGR sequence) of a twin's left hemisphere localized between the longitudinal fissure and the sylvian sulcus. The point indicated by the arrow was recorded as the bottom of the central sulcus. B - Top view image of the same brain surface rendering model. C - Left view image of the same brain surface rendering model. The trace formed by the recorded points do not follow the central sulcus on these last views.

For the in-depth measurements, the point at the bottom of the sulcus, localized the same way, was recorded (Figure 2 A). From section to section, from the longitudinal fissure to the lateral sulcus, the points formed a tracing that could be compared to the anatomic characteristics on the 3D images for the surface measurements (Figure 1 B, 1 C), but not for the in-depth one (2 B, 2 C). The software automatically indicated the length of the tracing.

Measurement began on a sagittal plane, at the internal side of the hemisphere because of the slight bend in the central sulcus at this point. Then, with the progressive change in plane of the central sulcus in the upper third of its length, due to curvature of the brain, the measurement became more precise in the axial plane; points were then recorded on the axial sections. The measurements were made for each central sulcus of each hemisphere, for each subject and by two different operators. The morphology of the sulcus was examined carefully, in particular its distal extremity near the lateral fissure, since many variations are known at this level [12].

Statistical analysis

To evaluate the interobserver correlation and the co-twin similarity on brain measurements, we calculated the intraclass correlation coefficient (ICC) by the following formula: ICC = between variance - within variance / between variance + within variance.

For analysis of variance of measurements between independent samples (males vs females), we used the "F" of Snedecor. For analyses of dependent samples (surface vs in-depth measurements, or right vs left fissure), we used the Student t test for dependent samples. The significance of differences between two percentages was estimated by the formula in "Statistica" software, where the p-level is computed based on the t-value.[1]

We also calculated the laterality index of the central sulcus in the same subject using the same formula as White et al. [23]: $\{2*(L-R)/(L+R)\}$.

In adjustment for sex or brain volume, these variables were taken as covariates.

RESULTS

The interobserver ICC for length of the central sulcus were highly significant, varying from 0.85 to 0.96 ($p < 0.0001$). More precisely these ICC were 0.85 vs 0.90 for the right vs left in-depth measurements, and 0.91 vs 0.96 for the right vs left surface measurements. Observer errors thus accounted for 3.5% to 15% of the total variation. Thus the means of the two observers' measurements for each length measured were subsequently used for data analysis.

The results are presented in Table 1. In accordance with previous studies [8], the means obtained for brain volume differed significantly according to gender.

For the mean central sulci lengths, the difference according to gender was not significant (Table 2), although the means were always higher for males than for females.

The brain volume was significantly correlated with central sulci lengths. Length measurements were significantly correlated between them (Table 3). The laterality index was not correlated with brain volume or right sulci measurements. There were no significant differences between right and left hemispheres, although mean central sulci lengths were always higher for the left hemisphere. In addition, the surface sulci were significantly longer than in-depth sulci ($t > 11$, $df = 19$, $p < 0.0001$).

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[1] The p-level is computed based on the t-value for the respective comparison:

$|t| = Sqrt[(N1 * N2)/(N1 + N2)] * |p1-p2| / Sqrt(p * q)$

where $p = (p1 * N1 + p2 * N2) / (N1 + N2)$, $q = 1 - p$.

Table 1 - Mean, median, standard deviation and interobserver ICC of brain volumes and lengths of the central sulcus

Variable	Valid N	Mean	Median	Minimum	Maximum	Std. Dev.	Interobserver ICC
LS	20	121.32	117.87	97.40	145.40	12.55	0.96
LD	20	104.89	103.57	90.95	122.50	9.69	0.90
RS	20	120.73	120.30	104.85	142.00	9.77	0.91
RD	20	101.54	103.15	82.15	117.80	8.33	0.85
Brain Volume	20	1211.38	1195.95	1072.60	1489.00	117.21	

ICC = Intraclass coefficient correlation; LS = length of the Left central sulcus at its Surface; LD = length of the Left central sulcus in its Depth; RS = length of the Right central sulcus at its Surface; RD = length of the Right central sulcus in its Depth.

Table 2 - Mean and standard deviation of brain volumes and of left and right central sulci at the surface and in depth, according to gender

Sex	N	Vol. Means	Vol. Std. Dev.	LS Means	LS Std. Dev.	LD Means	LD Std. Dev.	RS Means	RS Std. Dev.	RD Means	RD Std. Dev
M	8	1274.60	129.63	126.20	12.63	108.08	10.81	125.31	10.84	104.44	7.16
F	12	1169.23	90.50	118.06	11.91	102.77	8.68	117.65	8.05	99.61	8.78
All	20	1211.38	117.21	121.32	12.55	104.89	9.69	120.73	9.77	101.54	8.33

Vol. = Volume; LS = length of the Left central sulcus at its Surface; LD = length of the Left central sulcus in its Depth; RS = length of the Right central sulcus at its Surface; RD = length of the Right central sulcus in its Depth.

Table 3 - Correlations observed between lengths of central sulci, left and right, at the surface and in depth, as well as with brain volume and laterality index

Variable	Volume	LS	LD	RS	RD	LAT_S	LAT_D
Volume	1.00						
LS	0.62*	1.00					
LD	0.57	0.87*	1.00				
RS	0.68*	0.69*	0.67*	1.00			
RD	0.49	0.50*	0.57*	0.75*	1.00		
LAT-S	0.11	0.63*	0.46*	−0.13	−0.13	1.00	
LAT-D	0.14	0.47*	0.54*	−0.03	−0.38	0.68*	1.00

* = significant correlation at $p < 0.05$; LS = length of the Left central sulcus at its Surface; LD = length of the Left central sulcus in its Depth; RS = length of the Right central sulcus at its Surface; RD = length of the Right central sulcus in its Depth; LAT_S = hemispheric LATerality for the central sulcus measured at its Surface; LAT_D = hemispheric LATerality for the central sulcus measured in its Depth.

Table 4 - Intraclass coefficient correlation between homologous surface and in-depth sulci, with uncorrected measurements and with brain volume as covariate

Variable	F (10,11)	ICC	p	F (10,10)	ICC	p*
LS	5.20	0.68	0.008	3.22	0.55	0.05
LD	4.16	0.61	0.018	2.64	0.48	0.08
RS	3.67	0.57	0.027	4.09	0.63	0.02
RD	6.3	0.73	0.004	4.29	0.65	0.02

ICC = intraclass coefficient correlation; * = p level for multiple tests; LS = length of the Left central sulcus at its Surface; LD = length of the Left central sulcus in its Depth; RS = length of the Right central sulcus at its Surface; RD = length of the Right central sulcus in its Depth

The twin ICC was highly significant ($r = 0.92$, $p < 0.0001$) for brain volume. It was 0.91 when the sex variable was used as covariate. Twin ICC for weight was 0.91, for height 0.88; but they were 0.83 and 0.82 when the sex variable was taken as covariate. For lengths of homologous central sulci, the ICC were not as high ($r = 0.57$ to $r = 0.73$) but were nevertheless significant (Table 4). Adjusting these lengths for brain volume also gave significant ICC (from 0.55 to 0.65), except for left, in-depth measurements (0.48, $p = 0.08$).

For the laterality index, ICC was not significant for surface ($r = 0.31$, $p = 0.16$) or in-depth ($r = 0.40$, $p = 0.10$) measurements. Eleven of the 20 subjects had predominance of the left hemisphere (55%) for surface measurements, and 13 of 20 for in-depth measurements (65%). Nine subjects had left predominance both on the surface and in depth, while 5 had such predominance on the right. Thus, 9 of 14 subjects (64%) who had the same surface and in-depth predominance had left predominance.

Five of the ten pairs of twins (50%) were discordant for hemispheric predominance on surface measurements, and three of the ten (30%) on in-depth measurements. However, on a purely genetic basis, it would be expected that MZT would present 0% of discordance for hemispheric predominance. The difference between our results and this hypothesis is significant for surface measurements ($p = 0.02$), but not for in-depth measurements ($p = 0.08$). Similarly, only 5 pairs of twins were concordant for both surface and in-depth measurements (50%). The difference between the result expected on the basis of the genetic hypothesis (100%) and the result observed is significant ($p = 0.02$).

DISCUSSION

The first aim of this study was to verify whether good interobserver correlation could be obtained with the measurement technique developed. The results show that the intraclass correlation coefficient is high for surface measurements (0.91 and 0.96), and slightly less for in-depth measurements (0.85 and 0.90). This lack of maximal interobserver correlation may be due to two factors:

1. Control of the surface tracing in a tridimensional model is slightly more reliable than in in-depth measurement. In fact, the general shape of the sulcus, its anterior and posterior edge serve as reference points for the trace recorded and projected on the 3 D images. On the contrary, projection of the in-depth tracing does not correspond to the sulcus visualized on the tridimensional model since there is angulation and thus a discrepancy between the in-depth central sulcus and the surface. Thus, for this measurement, 3D control is less precise and it is sometimes difficult to obtain the same tracings from two observers.
2. White et al. [25], studying the morphology and the histology of the central sulcus on autopsy, consistently found a visible characteristic in the depth of the central sulcus, an interdigitation between the anterior and posterior borders of the sulcus, forming a complex junction at that level. This formation, which had already been described by Cuningham in 1892 and Cambell in 1905, creates a pseudo-discontinuity at the bottom of the fissure that probably biases in-depth measurements.

Whatever the case, the ICC between measurements obtained by the two observers gives a satisfactory interobserver correlation.

The second aim of this work was to examine gemellary similarities with regard to brain volume, the surface and in-depth length of central sulci, and the laterality index.

The similarity between twins was highly significant for brain volume, in agreement with findings in the recent literature. Bartley et al. [1], measuring brain volume on MRI 3D images, found a high intraclass correlation ($r = 0.95$, $p < 0.00001$) that was statistically significant for 10 pairs of MZT, but not for dizygotic twins (9 pairs, $r = 0.35$, $p = 0.09$). In further analysis using the Structural Equation of Neale and Cardon, they found an inherited degree of the brain volume of 94%, mainly explained by the additive effect of the genetic contribution. Tramo et al. [18], in a study measuring 30 cerebral areas of each hemisphere on MRI in 10 pairs of MZT, found that the cortical surface depended on the genotype (both before and after correction for sex). They underscored in a following work [19] that a linear relationship exists between the cortical surface and the forbrain volume. Carmelli and al. [3] calculating the brain parenchyma of more than a hundred elderly twins (74 MZT and 71 DZT) found statistically significant intraclass correlations for all twins, but the ICC was 0.92 for the MZT and only 0.5 for the DZT. Using Neale's "MX software" to analyse their data, they concluded that the additive genetic effects explain 92 % of the brain parenchyma variance without any correction and 0.62 % of it after adjustment for among-pair differences in age and for total cranial volume. In addition, animal studies [4, 14, 15], having established that the size of the brain and of the body are strongly correlated in all mammals, they concluded that genetic factors predominantly determine brain size. Riska et al. [14] determined that in each species the genes controlling embryonic growth and that of its central nervous system are responsible for the correlation between the size of the body and of the brain, since this correlation is the strongest during fetal development. Only Leamy [9] noted the importance of prenatal environment in this correlation. The whole of these works on brain volume supports the conclusion that the similarity between MZT for this characteristic is very high and essentially of genetic origin.

Measurements of the corpus callosum of 5 pairs of MZT made by Oppenheim et al. [13] were also highly significantly correlated ($r = 0.98$, $p < 0.01$), supporting a high similarity of this structure in MZT. Tramo et al. [19] also found a significant genotype effect ($F (9.9) = 18.90$, $p < 0.0001$) for this structure and Biondi et al. [2] reached the same conclusion in testing the capacity of experienced observers to match MRI brain images of 7 pairs of MZT with a morphometric analysis of internal brain structures.

Regarding the length of the central sulcus, significant twin similarity has been found, but to a lesser degree than that of brain volume or corpus callosum. The works of Cheverud et al. [4] had already shown in Rhesus macaques that sulci lengths were inherited to a lesser degree (35%) than brain volume (0.60 to 0.70%). In the study cited above, Bartley et al. [1] in 10 pairs of MZT and 9 dizygotic pairs of the same sex, made a quantitative comparison of the lateral and mesial gyration cortices that delimit several fissures, including the central sulcus, calculating the matrix correlation between MRI images and these surfaces. The ICC obtained on contralateral hemispheres of MZT was similar (0.58, $p<0.01$) to our findings on the central sulci. Overall, Bartley et al. concluded that the morphology of the cerebral gyri and sulci is mainly determined by environmental factors. Tramo et al. [18], analyzing the variance of measured brain surfaces in a work cited above, found a very strong relationship between these surfaces (excepting lobes), their hemispheric location, and the genotype of the subjects. These authors concluded to a predominant influence of genetic factors in the morphogenesis of brain areas of the left hemisphere, excluding lobular surfaces.

Although significant ICC were found for fissure lengths, the results showed no significant similarity for asymmetry of the central sulci. Steinmetz et al. [17] studied 20 pairs of MZT, of which 10 pairs were discordant for handedness. They showed that MZT, whether concordant or discordant, have no significant similarity for the asymmetry of their planum temporale. Given that the implication of the central sulci in handedness is generally accepted, it can be considered that our results are in agreement with those of Steinmetz et al. [17]. Future studies using our technique and measuring handedness should also examine whether these results are in agreement with the work of White et al. [25]. From 67 autopsy cases, they concluded that the preferred use of the right hand in humans occurs without a gross lateral asymmetry of the primary sensorimotor system.

Aside from possible bias due to the small sample size in all these studies, including ours, the overall differences among results no doubt arise from the variable implication of genetic and environmental factors in the various brain structures examined. It is probable that in MZT the similarity in brain structures formed early in embryonic development is greater than for those formed in the last months of pregnancy. Graf et al. [7], comparing brain MRI images, showed that spatial variations of the main sulci are much larger for fissures developed late in embryonic life. The central sulci develop in the fifth month for the single fetus [5], which is late, and the brain maturation of twins is often 2 to 3 weeks later. In addition to these factors, the definitive maturation of primary and secondary cortical sulci is not completed until shortly after birth, the overall cortical surface grows 2 to 3 fold during the first year of life [22], and the birth of twins generally occurs before term. The central sulci morphometric variance, less than 60%, common to monozygotic co-twins would be explained by the same genetic or environmental background. Thus, there may be a prenatal environmental factor differently active for each of the co-twins as soon as the fifth month which could influence this anatomic structure. Other environmental conditions after birth could also play a role. However, the callosal area which presents the within pair similarity we have already mentioned [2, 13, 19], increases from 40 to 50% from childhood to adulthood. Thus, individual environmental factors do not seem to influence greatly this structure for twins reared together. If we follow Tramo et al. [19], who have underscored that co-twin similarity in both brain size and IQ is combined with the absence of correlation of these variables in the same subject, the question remains of the brain neural organisation, its genetic determination and its relationship with functional performance. Knowing that IQ involves a complex contribution of specialized neural systems distributed throughout the brain, it is easier to isolate the sensory-motor subsystem, if possible, to study such a question.

In conclusion, there seem to exist: a) anatomic cerebral data concerning brain volume [3, 1, 18, 19, 21], the corpus callosum surface [2, 13, 19], the cortical surface and the regional and lobar cortical surface area of the left hemisphere [18, 19] for which similarity in MZT is very high; b) data concerning such structures as the central sulci and cortical gyrus [1] for which similarity in MZT is less high and development thus more dependent on environmental factors; c) data concerning asymmetry of the temporal planum [17] and asymmetry of the central sulci for which there is no similarity.

Our results agree with the finding that MZT have a high degree of similarity in brain volume. This characteristic would be essentially influenced by genetic background. With regard to variability of the length of central sulci of the brain, there is a definite influence of environmental factors on the development of these sulci, very probably occurring in utero. To test this hypothesis, it would be interesting to distinguish dichorionic from monochorionic MZ twins and to initiate study into in utero environmental factors capable of influencing the development of the central sulcus.

Acnowledgments: We thank D. Broneer for translation of this paper, JM. Casiez for bibliographic assistance and C. Capron for helpful advice. This work was supported by the Department of Neuroradiology, Pitié-Salpêtrière Hospital and the Department of Genetic Epidemiology, INSERM U155.

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