NeuroImage **13,** 262–271 (2001)
doi:10.1006/nimg.2000.0688, available online at http://www.idealibrary.com on IDEAL®

Hemispheric Shape of European and Japanese Brains: 3-D MRI Analysis of Intersubject Variability, Ethnical, and Gender Differences

Karl Zilles,*,† Ryuta Kawashima,‡ Andreas Dabringhaus,* Hiroshi Fukuda,‡ and Thorsten Schormann*

**C. & O. Vogt Institute of Brain Research and Institute of Neuroanatomy, University of Düsseldorf, P.O. Box 101007, D-40001 Duesseldorf, Germany; †Institute of Medicine, Research Center Jülich, D-52425 Jülich, Germany; and ‡AOBA Brain Imaging Research Center, TAO, Sendai 980-0872 and IDAC, Tohoku University, Sendai 980-8575, Japan*

Received May 26, 2000; published online December 21, 2000

Hemispheric shape is studied using magnetic resonance imaging and 3-D reconstructions in right-handed, male and female, European and Japanese subjects. Japanese hemispheres are relatively shorter, but wider than European hemispheres. Regions of maximal intersubject variability in hemispheric shape are present in the occipital and temporal lobes in each sample. Deviations from this general pattern are found in the (i) right inferior parietal lobule (European hemispheres are more variable than Japanese), (ii) lower third of the pre- and postcentral gyri (female Japanese hemispheres are less variable than the other samples), (iii) right inferior frontal gyrus (male European hemispheres are more variable than the other samples), and (iv) polar part of the frontal lobe (female European hemispheres are less variable than the other samples). The distribution of intersubject variability between the hemispheres is less asymmetric in female than male brains. Male Japanese hemispheres are shorter but wider than female Japanese hemispheres, whereas European hemispheres show the inverse gender relations. These results demonstrate that hemispheric shape shows a considerable intersubject variability, which is not randomly distributed over the cortical surface but displays distinct regions of higher variability. Despite this intersubject variability significant interethnic- and gender-related differences in hemispheric shape are present, which may be relevant if individual brains have to be warped to a single or mean reference brain or realistic brain models are to be constructed.

Key Words: **hemispheric shape; morphometry; Japanese brains; European brains; intersubject variability; gender differences; lateralization.**

INTRODUCTION

The shape of the hemispheres and the sulcal pattern are not accidental phenomena, but are sculptured by complex interactions between numerous genetically and environmentally influenced processes during life. Neurogenesis, migration, myelination, and development of connectivity are major events influencing gyrification (van Essen, 1996) and hemispheric shape during fetal and early postnatal periods. Processes like differences in sensory input caused by lesions of sensory organs or deprivation can lead to the expression (Rakic *et al.,* 1991) of a new sulcus or architectonic area, which lead to local changes in the 3-D configuration of the cortical surface, i.e., hemispheric shape. Thus, hemispheric shape reflects the sum effect of all these developmental events. Whereas numerous studies of the gyral pattern and its intersubject variability (Evans *et al.,* 1996; Le Goualher *et al.,* 2000; Royackkers *et al.,* 1999; Thompson *et al.,* 1996; Zilles *et al.,* 1997) have been published, observations with adequate three-dimensional measures of the hemispheric shape are lacking. A morphometric analysis of hemispheric shape is also important for functional–anatomical correlations, since functional imaging data are mapped to (i) a spatial reference system containing well defined macroscopical brain structures, e.g., the Talairach atlas (Talairach and Tournoux, 1988), (ii) an individual reference brain selected as the anatomically least deviating (in brain shape) specimen from a larger sample of brains (Roland and Zilles, 1994; Roland *et al.,* 1994), or (iii) a "mean" brain constructed by averaging numerous individual brains (Evans *et al.,* 1996). Mapping to a spatial reference system is also necessary, if anatomical data from different brains with inevitably varying sizes and shapes must be matched. Whereas brain size can be easily normalized by linear transformation, several linear and nonlinear procedures have been proposed for matching brains of different shapes. The different techniques use a wide variety of affine and nonaffine, global, and local transformations (for reviews see Evans *et al.,* 1996; Friston, 1996; Woods, 1996) to reach this goal.

The degree of transformation (deformation) of an individual brain to a spatial reference system depends only on the shapes of the individual and the template brain, if size is normalized. The present observations

1053-8119/01 $35.00

highlight the considerable degree of variability in hemispheric shape between individuals, gender (Zilles *et al.*, 1997) as well as ethnic groups (Thurfjell *et al.*, 1994). This complements recent studies of intersubject variability of sulci and gyri (Evans *et al.*, 1996; Le Goualher *et al.*, 2000; Royackkers *et al.*, 1999; Thompson *et al.*, 1996; Zilles *et al.*, 1997) at the most basic level, i.e., shape of the total hemisphere. Such information is not only valuable for the warping procedures, but also for any anatomic modeling of the human brain, e.g., realistic head and brain models.

The present study answers the following questions: (i) does the intersubject variability in hemispheric shape show the same regional distribution patterns in male or female, European or Japanese brains; (ii) are gender-dependent differences in hemispheric shape detectable within each ethnic group; (iii) are interethnic differences in hemispheric shape detectable in both male and female brains; and (iv) are gender differences in hemispheric shape similar between ethnic groups?

MATERIALS AND METHODS

Samples

Our study comprises 112 human brain. Fifty-six individuals came from Japan (Tohoku University) and 56 individuals came from Germany (University of Düsseldorf). Each of these two samples consisted of 28 female and 28 male brains. All were tested right-handers (Edinburgh Inventory (Oldfield, 1971), Annett-Test (Annett, 1970)). The age of the Japanese individuals varied between 18 to 36 years (20.9 ± 3.0), the age of the European individuals varied between 22 and 49 years (27.0 ± 4.7). There was no significant age difference between male and female Japanese and European individuals.

Imaging

The MRI data were acquired with a GE Yokogawa Medical Systems Vectra scanner for the Japanese sample, and Siemens Magnetom SP for the European sample at magnetic field strengths of 0.5 T or 1.58 T, respectively. T1 weighted images were acquired by a fast, low angle shot (SPGR or FLASH-sequence, respectively). The images ($256 \times 256 \times 128$ voxels) were recorded in horizontal or sagittal planes with an anisotropic resolution of $1.0 \times 1.0 \times 2.0$ mm (Japanese) or $1.0 \times 1.0 \times 1.17$ mm (European) per voxel. The different resolutions were normalized during the 3-D reconstruction.

The original MR images were further processed to segment brain tissue from cranium and cerebro-spinal fluid. As a first step, the outer brain contours were traced interactively on the monitor of an image analyzer (Kontron KS400, Munich, Germany) in all images of the raw data sets. In a second step, the gray-level threshold between brain tissue and cerebrospinal fluid was determined by calculating gray-level histograms of the images after step 1. This was done to remove some remaining parts of the cerebrospinal fluid compartment left after step 1, especially in the opening of the sulci. In a third step, minor segmentation artifacts were filtered out by using morphological and median 3-D filters. Finally, the brain stem with the cerebellum was removed interactively from the images, in order to present a view onto the basal surface of the forebrain.

Two volume representations of each brain were stored. One was a gray-level representation of the forebrain, containing the detailed anatomical information. This volume was used for 3-D reconstructions. The second volume consisted of a binary representation by voxels, which belonged either to brain or "background." The second volume was used for the definition of surface voxels during the procedures as described below.

General Aspects of Spatial Matching

The preservation of brain shape is a prerequisite in the present study. A new noninteractive, i.e., automated technique was used (Dabringhaus *et al.*, 1995) was used for spatial alignment of different brains without altering hemispheric shape. This technique allows the alignment of different brain volumes without using interactively defined anatomical landmarks. In the present study, scaling rotational transformations were used for the spatial normalization of the orientation of all 112 brains. In order to compute the transformation of each brain's volume into an identical spatial reference position and orientation, all possible combinations of any two brains of the samples to be compared were used. Differences in absolute brain size were normalized by applying isotropic scaling between paired brains. Thus, two brains with identical 3-D configurations of their cortical surfaces but different in absolute size would completely match after this transformation. The different steps of this technique are described in the next paragraphs.

Coarse Matching

A coarse spatial matching was the first step (Fig. 1). All brains were separately matched by affine transformation and translation to the standard reference brain of the Human Brain Atlas (Roland *et al.*, 1994). This step leads to a similar position, orientation and size of all brains and reduces the computation time necessary for refining the match (see next paragraph). Matching of brains with a global affine transformation (Schormann *et al.*, 1993) was calculated according to an extension of the principal axis theory by minimizing the absolute volume differences between the actual and the standard reference brain (Schormann *et al.*, 1997). The extension of the principal axis theory with respect to affine transformation is achieved by a parametrization method. The exact solu-

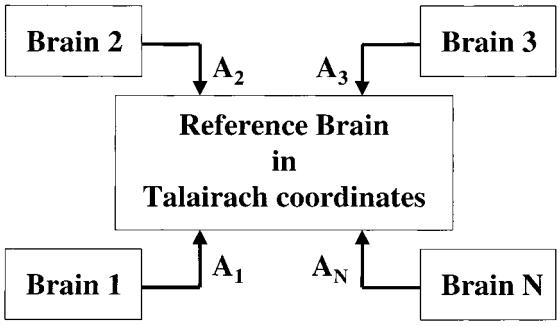


FIG. 1. Scheme of coarse alignment by using the classical principal axis theory, which is generalized to affine transformations (A_1 -A_N; N = number of brains) by a parametrization approach (Schormann *et al.*, 1997). The standard reference brain was adjusted to Talairach coordinates in order to enable comparisons with other studies.

tion is determined by minimizing the difference volume used as a similarity criterion. The minimization is accomplished by an iteration through a 3-dimensional parameter space (three rotations derived from the parametrization) using a simplex minimization algorithm (Press *et al.*, 1994). Although an affine transformation was determined by this first step, the final transformation (including coarse and fine alignments) was calculated as a scaling-rotational transformation whereby the least-square parameters of the original and final positions were derived from automatically defined and correlated reference points (for definition of reference points see below).

Refinement of Matching

A pairwise matching of each brain to all other brains of two samples to be compared was performed after the coarse spatial matching as described above. Thus N^2 transformations (3136 matrices with $N = 56$ for the comparison of two samples) were calculated including the identity transformation. The determination of the least-square 3-D scaling-rotation matrix was estimated from observer-independently defined reference points on the surface of the brain (approximately 3000 points per brain for one comparison yielding one transformation matrix), which were derived from a 3-D extension of an automated procedure for the definition of reference points (for details see Schormann *et al.*, 1993, 1995). Reference points are equally distributed centers of subvolumes, which consist of M^3 voxels covering the surface of the brain and the adjacent background (for determination of the voxels on the surface, see below). M represents the filter size. Then, a least-square 3-D scaling-rotation matrix is determined by the theory according to Umeyama (1991). Coarse and fine transformations were combined by selecting two brains from which the transformations onto the reference brain were known from the first step (coarse matching). Then the coordinates of the reference points, which were defined in one brain (e.g., brain 2 in the coordinate system shown in left upper position in Fig. 2), were transformed onto the other brain (e.g., brain 1 in the coordinate system of brain 2 shown in the left upper position in Fig. 2) by the transformation: $A_{\text{coarse}} = A_2^{-1} * A_1$. The correspondence between reference points in both brains was established by an automated nearest neighbourhood procedure. For this purpose, each reference point of brain 2 is the center of a subvolume of size M^3 (filter size) and was transformed together with its subvolume onto brain 1 (Fig. 2, upper left corner). The voxels of brain 1, which were within the limit of the transformed subvolume, were protocolled in a list of coordinates. From this list, pairs of reference points were selected, which had the shortest geometrical distance between the surfaces of both brains. If multiple combinations of corresponding surface voxels existed, for which the minimum distance could be achieved, the mean position of these voxels belonging to brain 1 was taken as representation of the position of the shortest distance. In this way, systematic errors resulting from the sequential order of reference points in the protocolled list were suppressed. This matching technique (establishing correspondence between reference points, determination of least-square scaling-rotation matrix, and transformation) was repeated until the difference of the least-square residuals in two successive iterations was less than a predefined threshold (in the present study less than 10^{-5}).

Construction of a Mean Brain as a Common Reference System

A mean brain is constructed from all brains (=28) of each of the four samples (for details see next paragraph). The intersubject variability within a sample was calculated as spatial distances between corre-

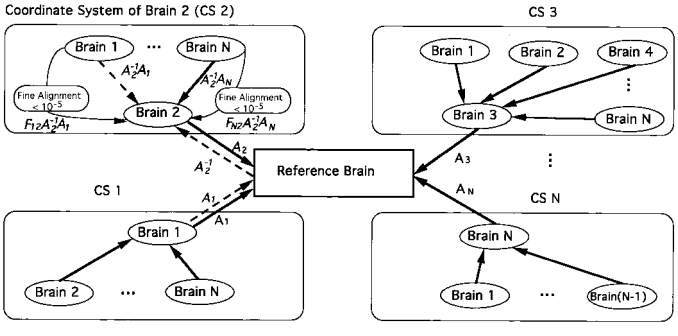
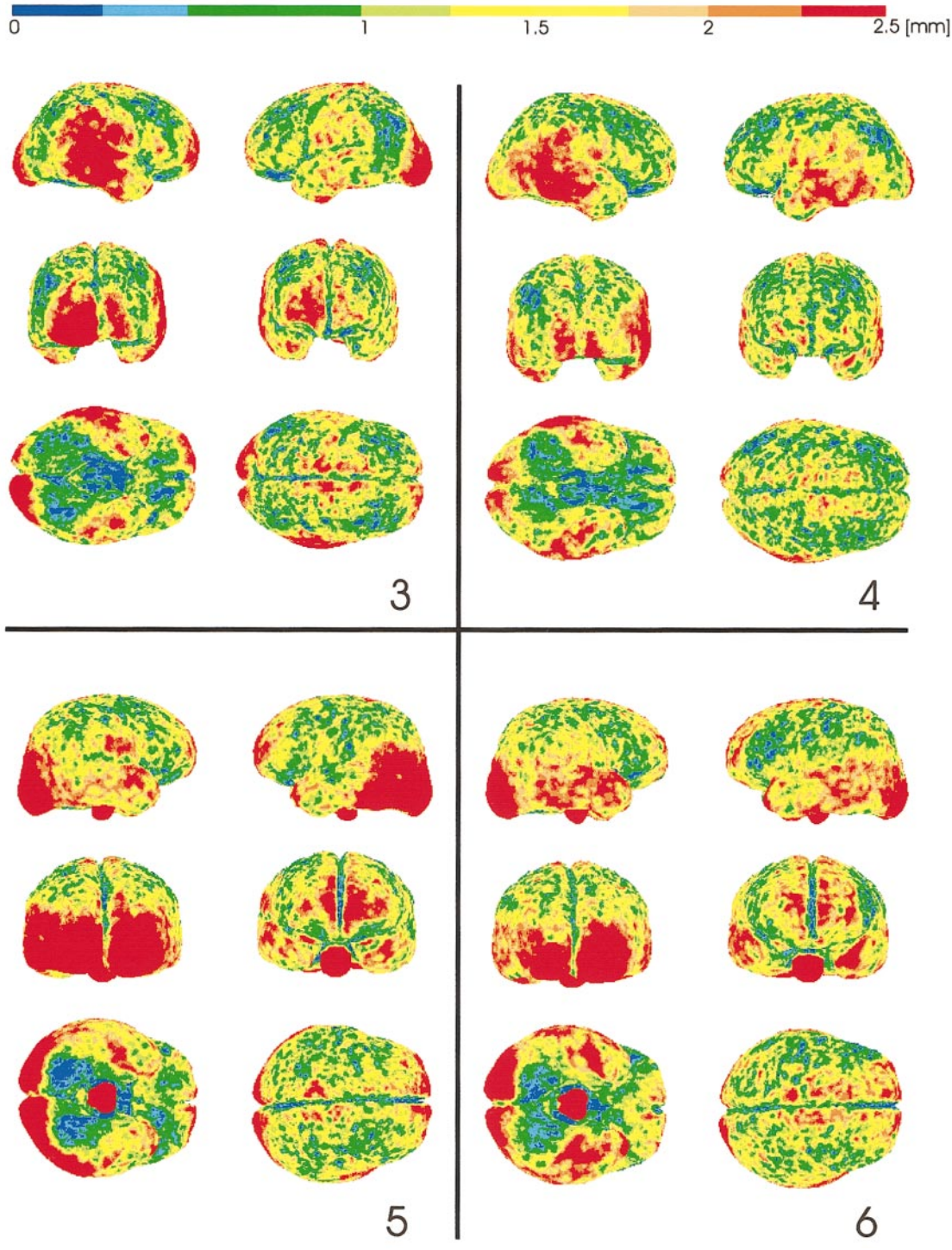


FIG. 2. The fine alignment procedure. Example: The reference points of brain 1 are transformed $A_{\text{coarse}} = A_2^{-1} * A_1$ into the coordinate system of brain 2 (CS2). The nearest neighbor in brain 2 is determined by using the coordinate list (see text for details). The least square, scaling-rotation matrix between all reference points (correspondence achieved by the coarse and the fine matching) in both brains were estimated according to Umeyama (1991). Thus, the common coordinate system could be calculated from N^2 transformation matrices which were determined from $9.4*10^6$ reference points.



FIGS. 3–6. Regional distribution of the degree (see color scale on top) of intersubject variability in hemispheric shape (for details see text). The local degree of intersubject variability is calculated as the standard deviation of the mean distances between each surface voxel of the mean brain of a sample and the respective surface voxels in each individual brain of this sample. The red color indicates the largest standard deviation (±2.25 mm and more), the blue color indicates the minimal standard deviation of the mean distance. The other colors follow the spectral sequence. The intersubject variabilities of male European (Fig. 3), female European (Fig. 4), male Japanese (Fig. 5), and female Japanese (Fig. 6) brains area shown.

sponding surface voxels of each individual and the mean brain. Additionally, all mean brains of the four samples are realigned to the standard space of the reference brain of the Human Brain Atlas (Roland *et al.*, 1994), thereby achieving comparability across the samples and with any future study using the reference

brain of this atlas. Since the Human Brain Atlas provides also Talairach coordinates, a comparison with other atlases is also preserved. For the study of variability within one sample 28*28 = 784 transformation matrices, for the comparison between two samples 56*56 = 3,136 transformation matrices are required, since 56 brains have to be compared for each pair of possible combinations. Thus, the common reference system is determined from approximately $9.4*10^6$ reference points, so that a reference system is constructed by the criterion of the best fit, which has all the brains in an identical position, orientation and size.

Intersubject Variability of Hemispheric Shape in Each Sample

The mean surface of all brains of a sample was defined (Raya and Udupa, 1990) as totality of those voxels at the cortical surface, which belong with at least 50% of their volumes to the individual binary brain volumes (for constructing a binary volume, see above, paragraph Imaging). Once the mean reference brain's surface is determined in each sample, the distance between each voxel at the surface of an individual brain and the corresponding surface voxel of the mean brain was calculated. For each surface voxel of the mean brain, the corresponding surface voxel of each individual brain is determined by a nearest neighborhood approach as described above. Finally, the standard deviations of the mean absolute distances (in mm) between all voxels of the mean brain surface and all corresponding surface voxels of all individual brains are calculated, displayed on the surface of the mean brain and color coded. Highest variability is encoded by red and lowest by blue. These values represent the local degree of intersubject variability in hemispheric shape within a sample (Figs. 3–6).

Confidence Limits of Differences in Brain Shape between Samples

For establishing the confidence limits of differences in brain shape between two samples, the mean surface of all brains of both samples under comparison was determined with the same procedure as already used for the calculation of the mean surface in each sample. Then the distances between the mean surface of both samples and all brains of each sample are calculated accordingly. The significance of the differences in distances between both samples are tested with the Student t test on a voxel basis. Mean standard deviations of distances between the mean surfaces of each sample and the mean surface of both samples are calculated. Assuming a normal distribution of the geometrical differences between the brains, the T value according to T = (mean 1 − mean 2)/sqrt $((N1 - 1)SD_1^2 + (N2 - 1)SD_2^2)$ is calculated from mean (mean 1, mean 2) and standard deviation (SD_1, SD_2) for each voxel with the total number of brains $N1 + N2 = 56$. Assuming a Student t distribution, the P value is determined for $k = 28 + 28 - 2 = 54$ degrees of freedom. The P values are color coded, and their regional distribution is shown in Figs. 11–14. Furthermore, the relative position of the mean surfaces of each sample can be displayed (Figs. 7–10). This allows identification of which part of the mean hemispheric surface of each sample is above ("bump") the corresponding part of the mean surface derived from both samples or which part is below ("dimple"). A Bonferroni-type correction for multiple comparisons is applied following Adler and Hasofer (1976) and Worsley *et al.* (1992). Therefore, the number of voxels representing the anatomical surface variability is reduced by the full width at half-maximum (FWHM) which is set at 4 mm^3 in our study. The map of the P values is median filtered with an effective filter size of 7 voxels, whereby the resulting resels are displayed in Figs. 11–14.

RESULTS

Intersubject Variability of Brain Shape in Each Sample

As a measure of the local degree of intersubject shape variability, the regional distribution of the standard deviations of the mean *absolute* distances between the surface voxels of each individual brain and the respective voxels of the mean brain (calculated for each sample separately) is shown in Figs. 3–6. The distances are measured between each voxel of the mean brain and the respective (nearest neighbourhood) voxel of each individual brain in the 3-D reconstructions of the size normalized and correctly positioned brains. The mean standard deviations of the distances are color-coded according to the scales shown in Figs. 3–6. Thus, the local intersubject variability, not the mean distance is displayed.

The general finding in all samples is the inhomogeneous regional distribution of the intersubject variability. Both in the Japanese and European, male and female brains, the occipital and frontal polar regions show a high standard deviations. Additionally, the surfaces of the posterior part of the temporal lobe and to some extent, the inferior parietal lobule vary also to a high degree, whereas the superior parietal, the basal temporal and the dorsolateral premotor and dorsolateral prefrontal cortices exhibit a relatively lower intersubject variability.

There are also differences in the variability of hemispheric shape between the ethnic groups. The European male and female brains have a large contiguous region of relatively high standard deviations, which covers the inferior parietal lobule and the posterior temporal part of the right hemisphere (Figs. 3 and 4). The same region of the left hemisphere shows a lower

variability when compared with that of the right hemisphere. The Japanese male and female brains show a generally lower variability in the inferior parietal lobule and the posterior temporal region of both hemispheres when compared with the Europeans (Figs. 5 and 6). Furthermore, the occipital region with highest standard deviations is more extended in both the female and male Japanese brains (Figs. 5 and 6) when compared with the Europeans (Figs. 3 and 4). Another focus of interethnic differences can be seen in the occipitotemporal transition region. Here, the European female and male brains show a focus of exceptionally low variability, whereas the respective standard deviations are higher in the Japanese brains. A last finding of differences between the ethnic groups is shown in the right inferior frontal gyrus. There is a spot of intermediate to high standard deviations in the European, but not in the Japanese brains.

Gender differences are focussed on two major aspects: (i) differences in the intensity and extent of variability, and (ii) in the lateralization. The standard deviations of the occipital lobes and poles and of the frontoparietal opercular regions are higher and more extended in the male than female brains of both ethnic groups (Figs. 3–6). A lateralization of a region with highest variability (a larger extent in the left than right hemisphere) is seen in the occipital cortex of the male, but not of the female brains in both ethnic groups. Only in the male Europeans, the frontal polar region shows a larger extent of a region with highest variability on the right than left hemisphere.

Gender Differences and Interethnic Distribution of Gender Differences in Brain Shape

Figures 7 and 8 show the regional distribution of outbending and depressed parts of the hemispheric surfaces in a gender comparison. The female Japanese brains are outbended over the male brains in the frontal and occipital pole regions, whereas the male Japanese brains are outbended over the female brains in the parieto-occipito-temporal and the dorsolateral premotor regions (Fig. 8). Areas encoded by white color represent regions of identical cortical surface positions in male and female brains. The *P* value image (Fig. 12) shows that these gender differences reach significant levels in the occipital, frontal and temporobasal pole regions.

A completely different situation is found in the European brains (Fig. 7), because here the pole regions show an outbending in the males (Fig. 7), but not the females (as found in the Japanese brains), whereas the parieto-occipito-temporal, the dorsolateral premotor and the basotemporal regions are outbended in the female European brains. The statistical image (Fig. 11) shows that on the right side the polar frontally, on the left side the parieto-occipito-temporally and on both sides the basal temporally located differences are significant. Thus, gender differences in the localization of hemispheric petalia are different and even inverse between the ethnic groups.

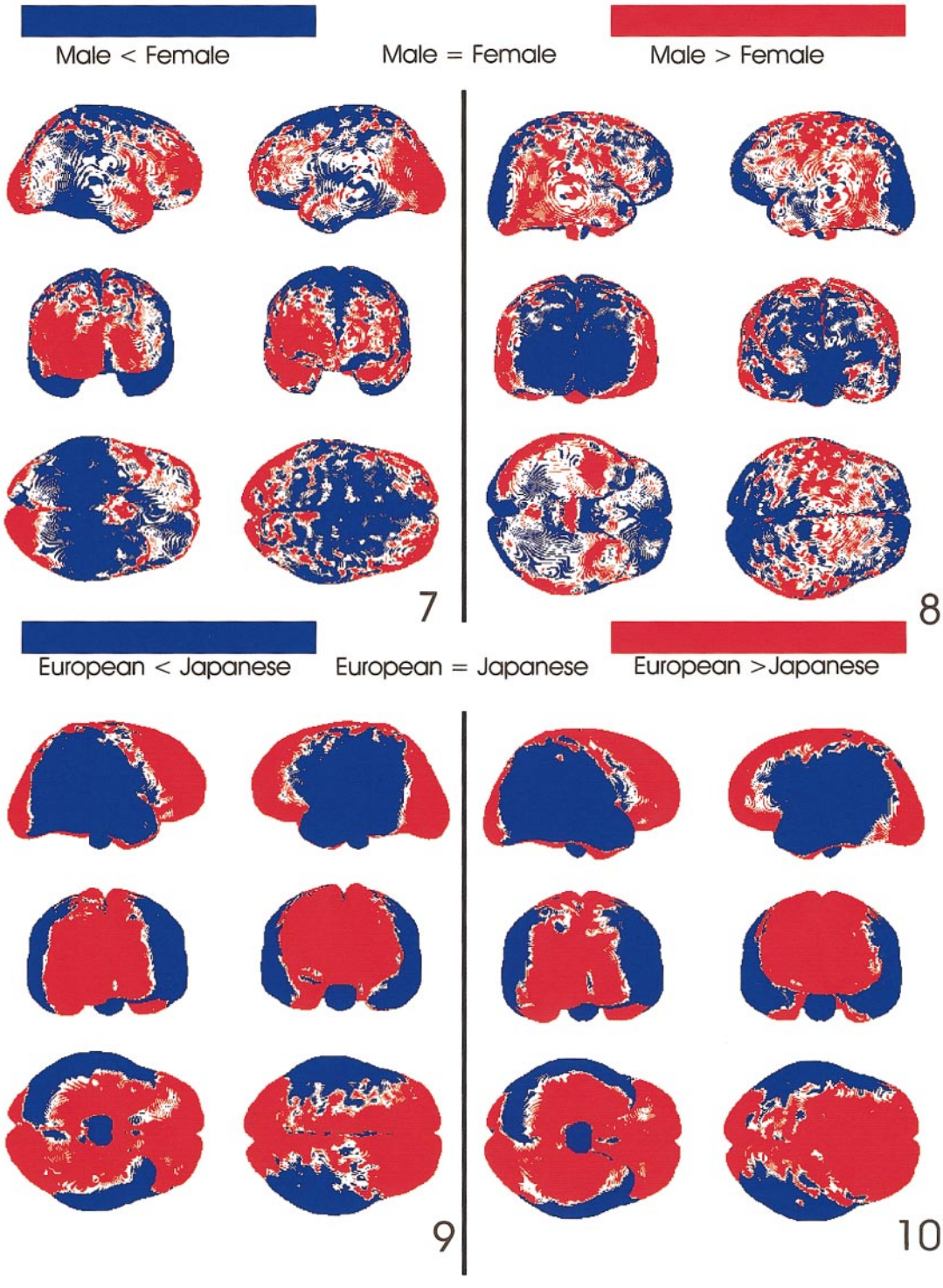
Interethnic Differences in Brain Shape

The previously described variability of the standard deviations of the mean absolute differences between the hemispheric surfaces do not show the direction of the differences, i.e., high standard deviations can be caused by a localized outbending (petalia) or depression of the hemispheric surface. Figures 9 and 10 provide this lacking information. In both sexes, the European brains show an outbending of the hemispheric surface in the occipital and frontal poles and of the whole dorsal aspect of the hemispheres, whereas the Japanese brains show an outbending in the interposed regions. That means that the Japanese brains are shorter, but wider than the European brains. These findings are statistically significant as shown by the *P* value images in Figs. 13 and 14.

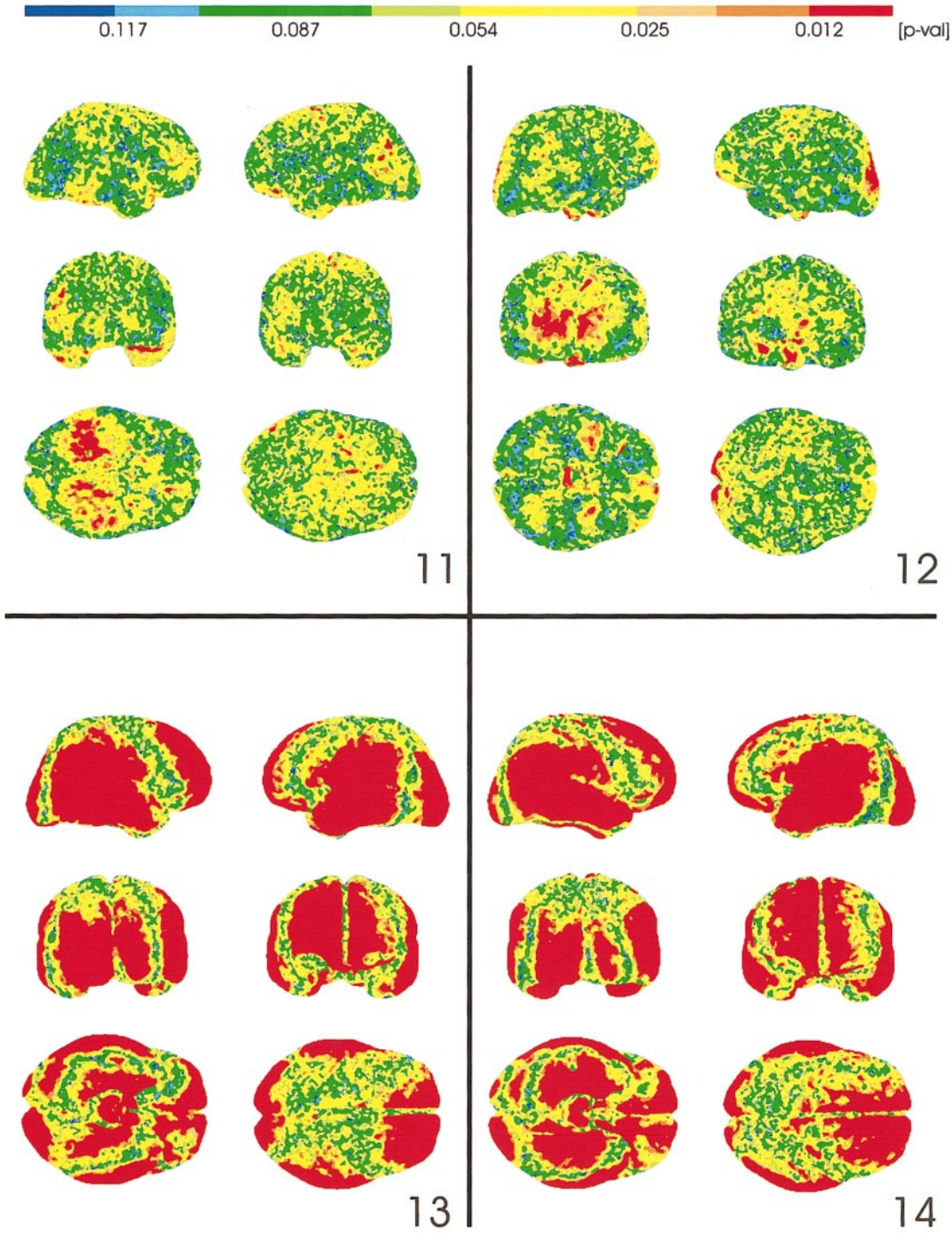
DISCUSSION

The aim of the present study was to analyze the intersubject variability of hemispheric shape and to define gender and interethnic differences between the hemispheric shape of male and female European and Japanese brains. Such an analysis can provide useful criteria for the evaluation of spatial standard reference systems and brain maps projected onto single or "averaged" reference brains. A single reference brain may be selected as the brain most similar in shape to all the other brains of a sample and can be used as reference structure for spatial normalization of individual brains (Roland and Zilles, 1994, 1996; Roland *et al.*, 1997).

The present observations show that the shape of European and Japanese hemispheres differ in a brain size-independent manner by the 3-D configuration of the hemispheric surface. A major condition for an analysis of the variation in hemispheric shape is an optimal spatial alignment of all individual brains to a common spatial reference system *without* altering the original 3-D configuration of the hemispheric surface. Most alignment procedures described in the literature are based on a stereotaxic reference system, which requires the definition of anatomical landmarks (e.g., Talairach and Tournoux, 1988). Minor errors in defining CA–CP can considerably impair the matching of other anatomic landmarks with a relatively far distance from the CA–CP like the cerebral cortex with its sulci and gyri (Steinmetz *et al.*, 1989, 1990; Zilles *et al.*, 1997). Moreover, the local degree of misalignment differs between different surface voxels, since misalignment increases with increasing distance from the anterior and posterior commissures. Since the present study is focussed on hemispheric shape, which is de-



FIGS. 7–10. Gender and ethnic differences in hemispheric shape between male and female European (Fig. 7), male and female Japanese (Fig. 8), European and Japanese male (Fig. 9), and European and Japanese female (Fig. 10) brains. Regions which are labeled by blue color indicate those parts of the male (Figs. 7 and 8) or European (Figs. 9 and 10) hemispheres which are below the hemispheric surface level of the corresponding female or Japanese brains (local "dimples"). Those parts of the male or European hemispheric surface which are bulging out over the hemispheric surface of the female or Japanese brains are labeled in red. The white color indicate regions of the hemisphere where male and female (Figs. 7 and 8) and European and Japanese (Figs. 9 and 10) cortical surface voxels are located at the same spatial level. Figures 7–10 do not show variability in terms of absolute distances or standard deviations, but only in which *direction* (below, same level, or above) the position of the mean cortical surface of one group differs locally from that of the other group.



FIGS. 11–14. Regional distribution of *P* values of the spatial differences described in the legend of Figs. 7–10. Figure 11 represents the map for the differences between European, male and female hemispheres; Fig. 12, the differences between Japanese, male and female hemispheres; Fig. 13, the differences between male, European and Japanese hemispheres; and Fig. 14, the differences between female, European and Japanese hemispheres.

fined by the 3-D configuration of the surface voxels, any minor error in positioning the CA-CP plane, and any error varying systematically with the distance of each cortical surface voxel from this reference plane would influence the outcome of our study. In the present study, therefore, spatial alignment of brains is not based on interactively defined landmarks, but on a new alignment procedure based on minimization of the dis-

tances between the respective surface voxels of different brains. Furthermore, the transformation of an individual brain to the Talairach proportional grid is an empirical decomposition of an individual brain into 12 subvolumes, and thus, does not preserve the original shape of the brain.

Our studies have also shown that the degree of intersubject variability of the shape of the hemispheric surface is not homogeneously distributed over the whole forebrain. There are regions which vary to a higher degree than other regions, indicating that even in a "homogeneous" sample of e.g., righthanders of the same gender and ethnic group the shape of some regions of the cortical surface differ to a higher degree than other regions between subjects.

Interestingly, the hemispheric regions with the highest intersubject variability are those regions with the highest gyrification, i.e., the polar frontal, parietotemporal, and extrastriate visual cortex. At these three rostrocaudal levels local maxima of gyrification have been demonstrated in European brains (Zilles *et al.*, 1988). Since gyrification has been explained as a result of mechanical processes during hemispheric growth (Richman *et al.*, 1975) and since the local expression of gyri and sulci is influenced by cortical connectivity (Rakic *et al.*, 1991; van Essen, 1996), hemispheric shape may reflect gender and ethnically specific, normal, or pathologically impaired neuronal organization in the brain hemispheres.

In conclusion, the shape of the human hemispheres shows regionally varying intensities of intersubject variability and differs significantly between male and female as well as European and Japanese brains. The neurobiological meaning of this finding is not clear, but studies of the occipital and frontal petalia in nonhuman primates and humans have been used to monitor localized maxima of brain evolution (Galaburda *et al.*, 1978). Furthermore, our ongoing studies in schizophrenic patients (Falkai *et al.*, in preparation), psychopathic subjects (Schneider *et al.*, in preparation) and hyperkinetic children and adults (Peterson *et al.*, in preparation) show regionally distinct alterations of the hemispheric shape indicating localized over- or underdevelopment of cortical or white matter tissue volumes and the potential value of 3-D hemispheric shape analysis.

ACKNOWLEDGMENTS

This work was supported by grants of the Deutsche Forschungsgemeinschaft (Zi 194/A6 and Zi 192/12-1) to K.Z. and by the JSPS-RFTF (97L00202) to R.K.

REFERENCES

Adler, R. J., and Hasofer, A. M. 1976. Level crossings for random fields. *Ann. Probabil.* **4:** 1–12.

Annett, M. 1970. A classification of hand preference by association analysis. *Brit. J. Psychol.* **61:** 303–321.

Dabringhaus, A., Schormann, T., Steinmetz, H., Schlaug, G., Zilles, K., and Roland, P. E. 1995. What is a standard brain? Intersubject variability of the shape of the human forebrain. *Hum. Brain Mapp.* **1**(Suppl.): 64.

Evans, A. C., Collins, D. L., and Holmes, C. J. 1996. Computational approaches to quantifying Human neuroanatomical variability. In *Brain Mapping: The Methods* (A. W. Toga and J. C. Mazziotta, Eds.), pp. 343–361. Academic Press, San Diego.

Friston, K. J. 1996. Statistical parametric mapping and other analyses of functional imaging data. In *Brain Mapping: The Methods* (A. W. Toga and J. C. Mazziotta, Eds.), pp. 363–386. Academic Press, San Diego.

Galaburda, A. M., LeMay, M., Kemper, T. L., and Geschwind, N. 1978. Right-left asymmetries in the brain. *Science* **199:** 852–856.

Le Goualher, G., Argenti, A. M., Duyme, M., Baaré, W. F., Hulshoff Pol, H. E., Boomsma, D. I., Zouaoui, A., Barillot, C., and Evans, A. C. 2000. Statistical sulcal shape comparisons: Application to the detection of genetic encoding of the central sulcus. *NeuroImage* **11:** 564–574.

Oldfield, R. C. 1971. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* **9:** 97–113.

Press, W. H., Teukolsky, S. A., Vetterling, W. T., and Flannery, B. P. 1994. *Numerical Recipes*, Cambridge Univ. Press, Cambridge.

Rakic, P., Suner, I., and Williams, R. W. 1991. A novel cytoarchitectonic area induced experimentally within the primate visual cortex. *Proc. Natl. Acad. Sci. USA* **88:** 2083–2087.

Raya, S. P., and Udupa, J. K. 1990. Shape-based interpolation of multidimensional objects. *IEEE Trans. Med. Imaging* **9:** 32–42.

Richman, D. P., Stewart, R. M., Hutchison, J. W., and Caviness, S. V. 1975. Mechanical model of brain convolutional development. *Science* **189:** 18–21.

Roland, P. E., and Zilles, K. 1994. Brain atlases—A new research tool. *Trends Neurosci.* **17:** 458–467.

Roland, P. E., and Zilles, K. 1996. The developing European Computerized Human Brain Database for all imaging modalities. *NeuroImage* **4:** 39–47.

Roland, P. E., Graufelds, C. J., W(Ehlin, J., Ingelman, L., Andersson, M., Ledberg, A., Pedersen, J., Åkerman, S., Dabringhaus, A., and Zilles, K. 1994. Human brain atlas: For high-resolution functional and anatomical mapping. *Hum. Brain Mapp.* **1:** 173–184.

Roland, P. E., Geyer, S., Amunts, K., Schormann, T., Schleicher, A., Malikovic, A., and Zilles, K. 1997. Cytoarchitectural maps of the human brain in standard anatomical space. *Hum. Brain Mapp.* **5:** 222–227.

Royackkers, N., Desvignes, M., Fawal, H., and Revenu, M. 1999. Detection and statistical analysis of human cortical sulci. *NeuroImage* **10:** 625–641.

Schormann, T., v. Matthey, M., Dabringhaus, A., and Zilles, K. 1993. Alignment of 3-D brain data sets originating from MR and histology. *Bioimaging* **1:** 119–128.

Schormann, T., Dabringhaus, A., and Zilles, K. 1995. Statistics of deformations in histology and application to improved alignment with MRI. *IEEE Trans. Med. Imag.* **14:** 25–35.

Schormann, T., Dabringhaus, A., and Zilles, K. 1997. Extension of the principal axes theory for the determination of affine transformations. In *Mustererkennung 1997* (E. Paulus and F. M. Wahl, Eds.), pp. 384–399. Springer, Berlin.

Steinmetz, H., Fürst, G., and Freund, H.-J. 1989. Cerebral cortical localization: Application and validation of the proportional grid system in MR imaging. *J. Comput. Assist. Tomogr.* **13:** 10–19.

Steinmetz, H., Fürst, G., and Freund, H.-J. 1990. Variation of perisylvian and calcarine anatomic landmarks within stereotaxic proportional coordinates. *AJNR* **11:** 1123–1130.

Talairach, J., and Tournoux, P. 1988. *Co-Planar Stereotaxic Atlas of the Human Brain*, Thieme Verlag, Stuttgart.

Thompson, P., Schwartz, C., Lin, R. T., Kahn, A. A., and Toga, A. W. 1996. Three-dimensional statistical analysis of sulcal variability in the human brain. *J. Neurosci.* **16:** 4261–4274.

Thurfjell, L., Bohm, C., Greitz, T., Eriksson, L., and Ingvar, M. 1994. Accuracy and precision in image standardization in intra- and intersubject comparisons. In *Functional Neuroimaging: Technical Foundations* (R. W. Thatcher, M. Hallett, T. Zeffiro, E. R. John, and M. Huerta, Eds.), pp. 121–130. Academic Press, San Diego.

Umeyama, S. 1991. Least-squares estimation of transformation parameters between two point patterns. *IEEE Trans. Pattern Anal. Machine Intell.* **13:** 376–380.

Van Essen, D. C. 1996. Pulling strings to build a better brain: a hypothesis for why, where and how the cerebral cortex is folded. *NeuroImage* **3/3/2:** S299.

Woods, R. P. 1996. Correlation of brain structure and function. In *Brain Mapping: The Methods* (A. W. Toga and J. C. Mazziotta, Eds.), pp. 313–341. Academic Press, San Diego.

Worsley, K. J., Evans, A. C., Marrett, S., and Neelin, P. 1992. Determining the number of statistically significant areas of activation in subtracted studies from PET. *J. Cereb. Blood Flow Metab.* **12:** 900–918.

Zilles, K., Armstrong, E., Schleicher, A., and Kretschmann, H.-J. 1988. The human pattern of gyrification in the cerebral cortex. *Anat. Embryol.* **179:** 173–179.

Zilles, K., Schleicher, A., Langemann, C., Amunts, K., Morosan, P., Palomero-Gallagher, N., Schormann, T., Mohlberg, H., Bürgel, U., Steinmetz, H., Schlaug, G., and Roland, P. E. 1997. Quantitative analysis of sulci in the human cerebral cortex: Development, regional heterogeneity, gender difference, asymmetry, intersubject variability and cortical architecture. *Hum. Brain Mapp.* **5:** 218–221.