Introduction

The diversity of cortical morphology has been well documented from a variety of sources. Recently, efforts to co-register brain images into stereotaxic coordinate space, or an idealized brain template, have revealed tremendous interindividual variability in the size, shape and configuration of cortical gyri and sulci (Keyserlingk et al., 1988; Talairach and Tournoux, 1988; Damasio and Damasio, 1989; Steinmetz et al., 1989a, 1990; Mazzotta et al., 1991; Evans et al., 1992; Thompson et al., 1996). More sophisticated algorithms for matching brain images to a template have only been successful for subcortical structures that are less variable in size and shape than the gyri of the cerebral cortex (Bajcsy et al., 1986; Hochberg and May, 1975; Chu and Damasio, 1980; Habib et al., 1984; Bear et al., 1986; Glicksohn and Myslobodsky, 1993). The resulting three-dimensional surface is a more accurate gauge of tissue area than conventional two-dimensional, or ‘quasi’ three-dimensional measures, of surface area since the delineation of gyri subsumes the sulcal walls as well as the superficially exposed gyral crowns (Zilles et al., 1989; Armstrong et al., 1991; Loftus et al., 1993). The questions addressed are: (i) do individual brains have consistent asymmetries at the level of individual gyri; (ii) can the direction and/or degree of asymmetry be related to theories of asymmetric development; and (iii) what is the range of asymmetry in areas that are not thought to be functionally asymmetric?

Materials and Methods

Anatomical magnetic resonance images were collected from 10 right-handed, male subjects. Subjects were between the age of 21 and 29 and every subject reported being strongly right-handed. Edinburgh laterality indexes confirmed this result for 9 of the 10 subjects (T = 78.51, SD = 13.35, range 61.9–100.0), while an Edinburgh score was not available for the tenth subject. Three millimeter, gapless, T1-weighted images were acquired in the coronal plane for each subject using a General Electric 1.5 T magnet that produced images 256 × 256 pixels in size. Pixel resolution within these matrices was 0.937 mm. Images were obtained with 3-D Flash and a T1/T2 = 20 ms. The head was aligned in the magnet so that a horizontal laser marked the intercanthal line and a vertical laser intersected the midpoint of the nasion and philtrum. Alignment was checked by verifying the presence of midline structures on the same midsagittal locator image. These images were stored on magnetic tape and then transferred to a Silicon Graphics workstation.

Model Construction

Since each image is averaged over 3 mm of thickness, the gapless image set forms a volume that is composed of ‘bricks’. Each brick is 0.94 × 0.94 × 3 mm, or the size of an individual voxel within an image multiplied by

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Variability of Regional Asymmetry • Hutsler et al.

...the distance between images. A white matter model was created by defining a threshold near the gray–white matter border for all of the images simultaneously. These thresholds were then edited by the operator to include only the white matter under the cortical mantle. A triangular mesh was then applied to the resulting volumetric data set using a ‘marching cubes’ algorithm (Lorensen and Cline, 1987). To eliminate errors produced in the automatic creation of the hemispheric cortical surface, preliminary surface models were first calculated between adjacent coronal sections. These preliminary models were edited to remove surfaces that corresponded to non-cortical structures. When editing was complete, a white-matter surface model was created simultaneously for the entire hemisphere. The advantages of creating a white-matter model, rather than a direct surface model, lie mainly in its ability to map accurately the cortical surface that is present within sulci. A white-matter model is not prone to the loss of sulci running parallel to the slice plane, since white-matter sulci are much larger than the slice plane thickness. This allows the acquisition of relatively thick slices (3-4 mm) that increase the definition of the gray–white matter boundary, and plane thickness. This allows the acquisition of relatively thick slices (3-4 mm) that increase the definition of the gray–white matter boundary, and plane thickness. This allows the acquisition of relatively thick slices (3-4 mm) that increase the definition of the gray–white matter boundary, and plane thickness.

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The resulting model was then ‘inflated’ (Dale and Sereno, 1993) to approximate the true cortical surface. The model can be viewed as a triangular mesh that is composed of individual vertices (points) that form the apices of the triangles. The algorithm used for inflation moves an individual vertex within the model toward a gray value in the original volumetric MR data set that lies on the cortical surface (surface vector). In order to create a smooth surface a ‘smoothness’ vector is also applied to the model which constrains vertex movement by taking into account the position of neighboring vertices (Dale and Sereno, 1993). A weight was specified for each vertex to control their relative influence during inflation. These same weights and thresholds were used for both hemispheres of any individual subject.

Regional Identification
To facilitate gyral identification individual cortical locations could be labeled on the whole-hemisphere model with simultaneous reference to the original MR images and small sections of the model that revealed the depths of the cortical sulci. Two cortical locations that could be easily defined were chosen to assess the degree and direction of asymmetry. These were the postcentral gyrus and the cingulate gyrus. The postcentral gyrus was bordered dorsally by the longitudinal fissure, ventrally by the lateral (Sylvian) fissure, anteriorly by the central sulcus and posteriorly by the postcentral sulcus (Fig. 1). In cases where the postcentral gyrus was not continuous, minor surface variation was used to connect the two sulci. Double postcentral sulci (Ono et al., 1991) were not encountered in our sample. The cingulate gyrus (Fig. 2) was bounded dorsally by the cingulate sulcus, ventrally by the corpus callosum, anteriorly by the anterior end of the cingulate sulcus and posteriorly by a combination of the subparietal sulcus and the anterior portion of the calcarine fissure. Due the variation in these posterior sulci, a second set of measures was taken in which the posterior boundary of the cingulate sulcus was redefined in both hemispheres by the coronal slice that corresponded to the rostral edge of the splenium of the corpus callosum just anterior to the marginal branch of the cingulate sulcus (see Fig. 2).

Surface Area/Asymmetry Computation
The surface area of each triangle in the model, and each triangle within a labeled cortical region, was automatically computed by dividing the cross product of its sides by two. These triangles were then summed to obtain the surface area of the region of interest (ROI). An asymmetry coefficient was then computed for each region of each subject based on the surface area of left (L) and right (R) homologues corrected for region size ((L – R)/(L + R)/2) (Galaburda et al., 1987; Leonard et al., 1995). These asymmetry coefficients can range between 2 and –2, with the sign indicating the direction of asymmetry and the value indicating the degree of asymmetry. Perfectly symmetric regions have a value of zero.

Results
Individual subjects often showed marked size asymmetries of either the cingulate or postcentral gyrus. Compared to these regions the whole brain was remarkably symmetric. Figure 3 shows each subject’s asymmetry coefficient for the whole brain (A), the postcentral gyrus (B), and the cingulate gyrus (C). Overall measures of hemispheric surface area were not asymmetric (df = 9, t = 0.533, P = 0.6068), and the mean asymmetry coefficients for the postcentral and cingulate gyri did not differ from symmetry (postcentral: df = 9, t = 1.492, P = 0.1700; cingulate: df = 9, t = -1.986, P = 0.0783). Although the group did not show consistent asymmetries many individual cases were asymmetric. If an asymmetry value of ±0.1 is used to evaluate individual asymmetries, 7 out of 10 subjects had an asymmetric...
cingulate gyrus, while 4 out of 10 had an asymmetric postcentral gyrus. Even if the threshold values are corrected for sample size and variance (see below), 4 out of 10 subjects show asymmetries in the cingulate, and the same proportion show asymmetries in the postcentral gyrus.

Inter-rater Reliabilities
To assess the possibility that error variation in the delineation of cortical regions resulted in significant individual asymmetries, inter-rater reliabilities were conducted for 8 of the 10 subjects. A second set of reliability measurements was not obtained for the two remaining subjects due to the unavailability of the second rater. Each rater was unaware of the other's results. Figure 4 shows the scattergrams of asymmetry coefficients for the two raters. The postcentral gyrus was labeled with a high degree of reliability ($r = 0.855$, $P = 0.0044$). The cingulate gyrus was also labeled reliably ($r = 0.708$, $P = 0.0485$), but only when the posterior boundary was defined by the coronal slice that coincided with the rostral edge of the splenium of the corpus callosum. Surface area measurements that utilized ambiguous cortical landmarks to define the posterior boundary of the cingulate, such as the subparietal and cingulate sulci, were not reliable ($r = 0.543$, $P = 0.1740$). Due to this low reliability all analyses of the cingulate gyrus reported here are based on measurements that truncate the cingulate at the section plane that corresponds to the anterior border of the splenium.

Raters also showed a marked degree of agreement in the direction of asymmetry. In the case of the postcentral gyrus there were six agreements and two disagreements, and for the cingulate the two raters were always in agreement as to the direction of hemispheric asymmetry. Given the degree of agreement between raters, only the first rater's values were used for the remaining statistical analyses.

Individual Asymmetries
It is often desirable to point to individual brains as being either symmetric or asymmetric. Typically a threshold of either ±0.1 or ±0.2 is used to determine if an individual's asymmetry coefficient differs significantly from symmetry (Galaburda et al., 1987). The number of individuals that had marked asymmetries in either the cingulate or postcentral gyrus varied depending on whether a threshold of 0.1 or 0.2 was chosen. As stated above, with an asymmetry threshold of ±0.1 four individuals had an asymmetric postcentral gyrus and seven had an asymmetric cingulate gyrus. If a threshold of ±0.2 is utilized, the number of asymmetric
Ontogeny of Asymmetry

Asymmetric brain regions can develop due to either a unilateral enlargement or reduction of a cortical region while its contralateral homologue is unchanged (Galaburda et al., 1990). If asymmetry is the result of a size reduction in one hemisphere, then as the absolute asymmetry values increase, the combined size of the homotopic regions should decrease. Conversely, if asymmetry results from a size increase in one hemisphere, then as absolute asymmetry values increase, the combined size of the homotopic areas should also increase. If, on the other hand, both regions contribute to the final asymmetry there will be no clear relationship between their combined areas and the degree of asymmetry. Neither the postcentral (r = –0.238, P = 0.5205) nor the cingulate gyrus (r = 0.043, P = 0.9087) showed significant correlations between the absolute value of the asymmetry coefficients and the combined areas. The overall size of the two hemispheres was also not correlated with the absolute value of the asymmetry coefficients (r = –0.022, P = 0.954).

Handedness was related to the size of certain regions in the analysis. Most notably the higher an individual's Edinburgh score (the stronger their right-handedness), the smaller their left hemisphere was also not correlated with the absolute value of the asymmetry coefficients (r = –0.022, P = 0.954).

Discussion

The present results demonstrate that there is substantial individual diversity of left–right gyral asymmetries in the cerebral cortex. Many individuals showed marked asymmetries in the two regions examined; however, neither region was consistently asymmetric across subjects. Information regarding the amount of asymmetry present in structures other than those that are considered to contain a large degree of functional lateralization is critical for a balanced interpretation of data gathered from cortical regions associated with language function — a strongly lateralized ability. The large individual variability indicates that cortical asymmetries may be present even in the absence of clear functional asymmetry.

Mean Asymmetry Scores

Neither area was significantly asymmetric when all of the subjects were combined; however, the present findings agree with previous reports that the right cingulate gyrus may be slightly larger in the general population (Noga et al., 1995). As with this previous study, the trend was non-significant. It is difficult to compare these two studies, since the previous study utilized vastly different methods to our own.

The failure to find any statistically significant mean asymmetries in our study could be accounted for by insufficient statistical power engendered by the relatively small sample size. (10). It has also been suggested that non-significant effects can be due to combining subgroups that show different patterns of asymmetry (Witelson and Kigar, 1992). The possibility that previously reported subgroup effects, such as age, sex and handedness, may have obscured asymmetries must be rejected since the present sample is homogeneous with respect to these potentially confounding factors. This does not, however, eliminate the presence of other undocumented subgroup effects. Finally, the parcellation of gyri employed in the present study may have grouped asymmetric substrutures inside symmetric superstructures and thereby obscured the underlying asymmetries. Recent investigations on morphological asymmetries in the region of the planum temporale (Rubens et al., 1976; Steinmetz et al., 1990; Witelson and Kigar, 1992; Leonard et al., 1993; Loftus et al., 1993) have shown that as the vertically oriented 'parietal' bank of the planum gets larger, the horizontally oriented 'temporal' bank gets smaller. Thus, the combined intrahemispheric surface area of the temporal and parietal banks surface is conserved despite its configuration, and overall left–right symmetry of the total planar surface is maintained even though the temporal and parietal banks are respectively leftward and rightward asymmetric. It is conceivable that other reciprocal asymmetries are hidden in the present data.

Where significant individual asymmetries exist reciprocal asymmetries (asymmetries of opposite valence) may be present in one or more other cortical locations since there is no overall asymmetry in the surface area of each hemisphere. Evidence that such a mechanism could exist comes from experiments in the modification of gyral patterns in the developing monkey cortex (Goldman-Rakic and Rakic, 1984). Prenatal resection of the occipital lobe on one side produces a compensatory enlargement and concomitant asymmetry of the inferior parietal lobule. One proposed mechanism for this effect is that afferent fibers compete for synaptic space within cortical zones of the hemisphere. Successful competition for connections results in an increase in cortical area for one zone at the expense of a decrease in cortical area in a rival zone. Regional anatomic asymmetries could emerge if the outcome of competition within one hemisphere differed from that of the other hemisphere.
ventral end of the postcentral gyrus and spills into the dorsal bank of the Sylvian fissure (Brodmann, 1909). Von Economo’s description of this same region is remarkably similar; however, he explicitly subdivides Brodmann’s area 3 into an area PB and an area PA (area postcentralis giganto-pyramidalis) that covers up to one-third of the surface of the anterior wall of the postcentral gyrus near the bottom of the central sulcus and retains characteristics of the adjoining precentral gyrus (some large Betz cells in layer V). Von Economo’s area PC (area postcentralis intermedius) and area PD (area postcentralis caudalis) are similar to Brodmann’s areas 1 and 2 respectively (von Economo, 1929). Physiologically, each of these cytoarchitectonically defined regions appears to contain a complete representation of the body surface and receives inputs primarily from a single type of sensory receptor. The dorsally located area 42 is a secondary auditory area (SII).

The cingulate gyrus is also composed of several cytoarchitectonic regions. Brodmann defined the anterior cingulate as being composed of two regions: area 33, which borders the corpus callosum at its anterior boundary, and area 24, which covers a larger area on the exposed surface of the cingulate gyrus and continues further posteriorly than area 33. In our study a uniform posterior boundary was utilized to minimize the impact of the highly variable and difficult to define posterior boundary of this region. This boundary through the coronal slice that corresponds to the anterior (rostral) boundary of the splenium of the corpus callosum crosses two other Brodmann’s areas: 31 and 23 (Brodmann, 1909). Von Economo’s description includes several additional subdivisions, but his scheme can be summarized as an agranular cortical type in the anterior portions of the cingulate, a granular type posterior to this (just behind the imaginary extension of the central sulcus) and a region of allocortex lying in a narrow band at the transition between the isocortex of the cingulate gyrus and the corpus callosum (von Economo, 1929).

**Individual Asymmetry Coefficients**

As suggested above, the number of individuals showing asymmetrical cortical regions can be greatly exaggerated (or underestimated) in the absence of data concerning cortical variability. Typically, an arbitrary asymmetry coefficient ranging from 0.1 to 0.2 has been used to assess individual cases. If the variance in the size of cortical regions is high, then this value is an overestimation of the number of individuals in a group demonstrating significantly large asymmetry scores. If, however, the variability is low, these same threshold values may be overly conservative. We instead used the variance in the sample population to determine the minimal threshold necessary to achieve significance. Alternatively, if a particular asymmetry threshold is desired (i.e. ±0.1), then a power analysis can be set to determine the number of subjects required to achieve this threshold.

**Previous Methodology**

Most previously utilized methods for modeling the cortical surface have relied upon the tracing of two-dimensional contours directly from the MR image set. The length of these contours can either be multiplied by the distance between sections, or, using a true three-dimensional approach, can be ‘stitched’ together by triangulation (Loftus et al., 1993). Measurements of the same subjects utilized in the present study reveal that surface areas are consistently smaller with these previous contour-based approaches. Surface areas range from 1399 to 1871 cm² using the old method, while the present results yield a range from 1695 to 2174 cm². In addition, surface area measurements taken from post-mortem brains (Hofman, 1985: 2430 cm²) more closely match the results that we report with the present technique. This correspondence notwithstanding, we would suggest that there are several computational improvements that would make the present method far superior to the contour approach. These include the incorporation of a volumetric thresholding technique that would more accurately model the gray–white matter boundary, and the addition of further mathematical constraints to the inflation algorithm. The present technique (Dale and Sereno, 1993) represents the beginning of a new approach to modeling methods that by incorporating a volumetric white-matter model will more accurately conform to the convoluted walls of the cerebral sulci.

**Function and Implications**

We can only speculate on the functional significance, if any, of regional asymmetry scores. There is evidence that cortical morphology reflects underlying connectivity and architectonic field boundaries (Welker, 1990; Watson et al., 1993; Rademacher et al., 1993) and that these are specified by genetic factors (Weinberger et al., 1992). Surface area techniques, similar to those used in the present study, have also revealed genetic influences on cortical morphology (Tramo et al., 1995). Classically, cortical size asymmetries have been associated with specialized function; however, many of these studies are confounded by measurement artifact (Loftus et al., 1993). Although one might suspect that sensorimotor regions could show a leftward asymmetry due to the prevalence of right-handedness in the general population, our findings, in agreement with those reported previously (White et al., 1997), indicate that this is not the case. The multiple functions that have been proposed for the cingulate gyrus, including its involvement in emotional behavior, memory processing and attention to visual stimuli, do not appear to be highly lateralized in the normal brain.

These findings have important implications for the development of standardized brain templates used for the purposes of intersubject averaging of data gathered with PET or MRI. While it is feasible to develop a so-called ‘average’ template separately for each hemisphere based on the mean size and shape of each homologue, the resulting whole-brain model would be atypically symmetric. The use of such averaged models raises serious concerns for interpreting the results of cortical locations that show marked variance in the distribution of their surface area. Additionally, the large degree of variability in the size of asymmetry coefficients suggests caution in the interpretation of size asymmetries in areas that are presumed to be functionally asymmetric.

**Notes**

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