

A framework to study the cortical folding patterns

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This paper describes a decade-long research program focused on the variability of the cortical folding patterns. The program has developed a framework of using artificial neuroanatomists that are trained to identify sulci from a database. The framework relies on a renormalization of the brain warping problem, which consists in matching the cortices at the scale of the folds. Another component of the program is the search for the alphabet of the folding patterns, namely, a list of indivisible elementary sulci. The search relies on the study of the cortical folding process using antenatal imaging and on backward simulations of morphogenesis aimed at revealing traces of the embryologic dimples in the mature cortical surface. The importance of sulcal-based morphometry is illustrated by a simple study of the correlates of handedness on asymmetry indices. The study shows for instance that the central sulcus is larger in the dominant hemisphere.

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Introduction

The variability of the cortical folding patterns is a continual source of questioning for the brain mapping community. Methods have differed between attempts to use stable sulci as landmarks and those that remove the complicated patterns of the more variable folds. There is no clear consensus, however, on the boundary between these two cortical macroscopic features. Furthermore, the

spatial relationships between the sulcal landmarks and the underlying functional and architectonic maps are questionable (Régis, 1994; Welker, 1988; Zilles et al., 1997). Therefore, the role of the sulcal landmarks in the brain mapping strategies remains unclear. This paper describes a research project that aims at clarifying this role.

Spatial normalization is currently a popular method for comparing brain images (Brett et al., 2002; Collins et al., 1994; Fischl et al., 1999; Fox et al., 1985; Friston et al., 1995). Powerful nonlinear warping methods have been developed for this purpose. Most are driven by the maximization of an intensity-based similarity measure computed between the processed image and a template image (Cachier et al., 2003; Guimond et al., 2001; Hellier et al., 2001; Shen and Davatzikos, 2002). While these methods are very efficient in correcting variations of the global shape of the cortex, their behavior at the level of the folding patterns is highly variable (Hellier et al., 2003). In addition, the lack of clear sulcal-based homologies between individual brains prevents the definition of a gold standard for brain warping. Therefore, these results are difficult to compare. In fact, these methods do not actually attempt a perfect gyral matching across subjects. The similarity measures are plagued by local maxima that affect the optimization algorithm and prevent robustness of sulcal matching. To achieve reliable matching of some landmark sulci, additional constraints have to be added into the similarity measure (Collins and Evans, 1998; Hellier and Barillot, 2003; Johnson and Christensen, 2002; Thompson and Toga, 1996). This approach, however, requires manual definition of these sulci.

We first describe a computer vision system that performs automatic recognition of main sulci (Rivière et al., 2002). These sulci can then be used in a constraint-based warping algorithm (Cachier et al., 2001). Our system relies on a kind of renormalization of the brain warping problem, where renormal-

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ization means a change of the variables used to represent the warping (Houdayer and Martin, 1999). The goal of the renormalization is to efficiently compare the local maxima of the similarity measure, assuming that each maximum of interest corresponds to a different pairing of the cortical folds from the target to the template. Brain warping algorithms look for correspondence between image points, imposing usually a strong regularization on the deformation field. Our renormalization aims at addressing the matching at the scale of the cortical folding patterns. The system first converts each image into an abstract graph-based representation, whose nodes are elementary features corresponding to topologically simple cortical folds (Mangin et al., 1995a) (see Fig. 1). Then, each individual representation is matched with a template graph that embeds all the sulci to be recognized. This template is endowed with a random graph structure whose distribution is estimated from a learning database (Mangin, 1995; Mangin et al., 1995b). Therefore, the matching is

driven by the maximization of a probability that plays the same role as the similarity measures mentioned above. Since the evaluation of a given matching has a low computational burden, the local maxima of the probability can compete during a stochastic optimization. The cost of our renormalization strategy, however, is a strong bias on the interesting ways to match cortical shapes across subjects. Wherever the folds are not relevant features to be matched, our approach will not provide meaningful results.

One general impediment to the design of better spatial normalization methods stems from the frequent interruptions of major sulci. None of the methods mentioned above really addresses this point. In our opinion, however, sulcus interruptions raise some questions that should be considered in brain mapping:

- (1) What kind of spatial normalization should be performed to align a long unbroken furrow with a homologous set of short

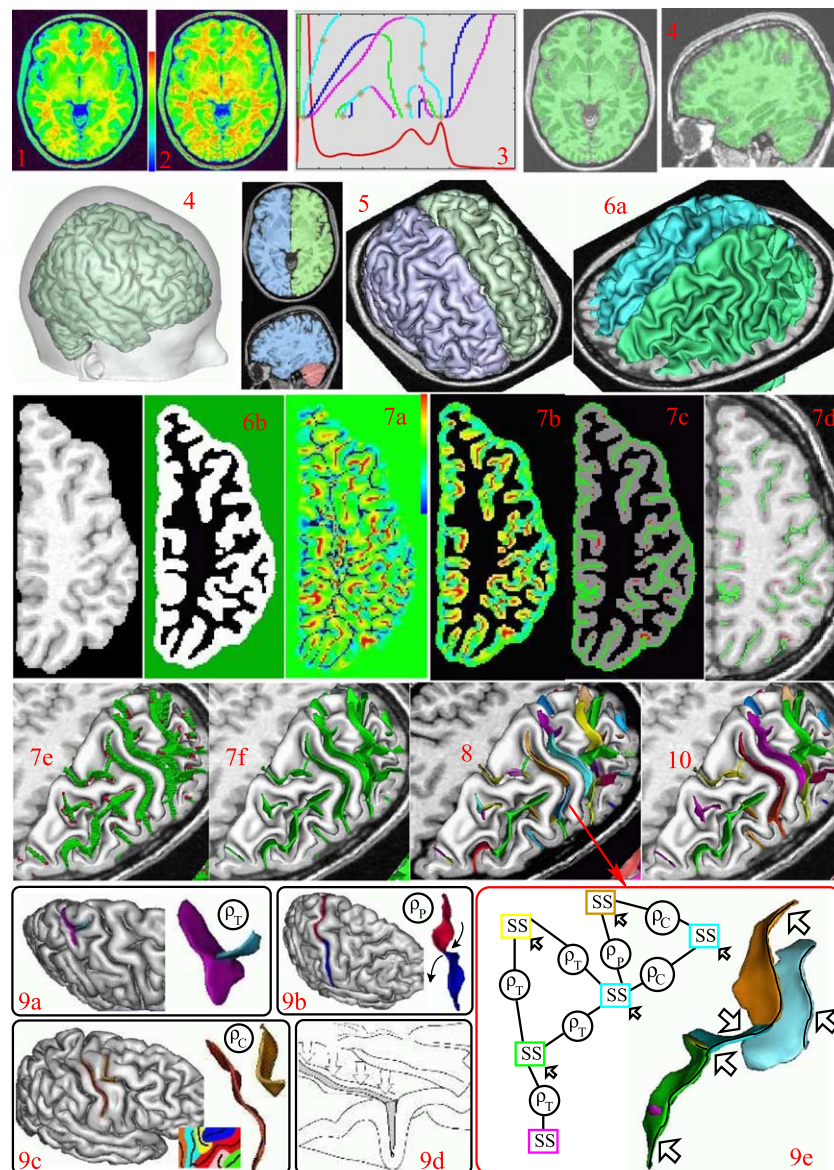


Fig. 1. Computation of a structural representation of the cortical folds from a raw T1-weighted MR image (see text for description).

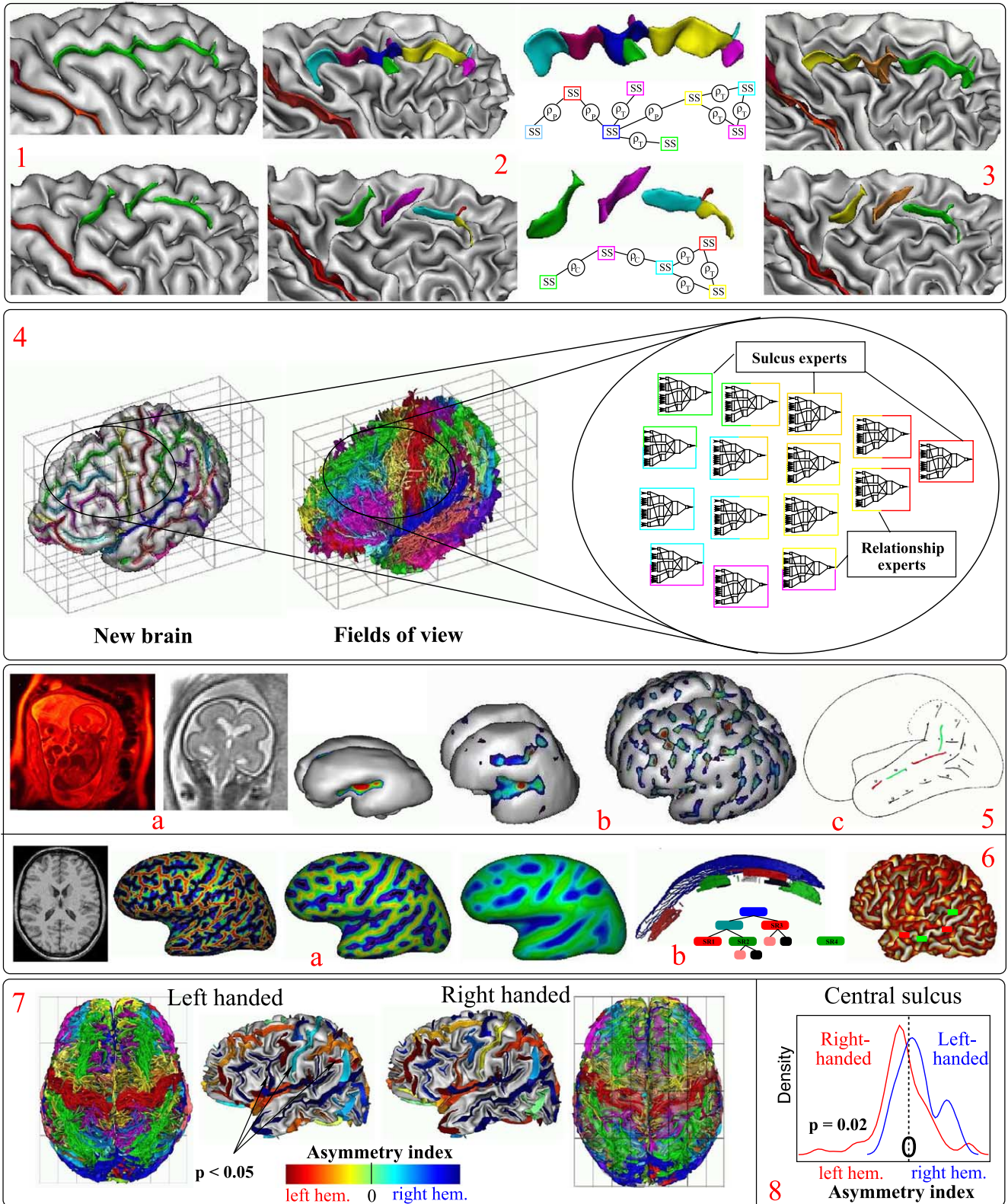


Fig. 2. (1) Two different patterns of the SFS. (2) The elementary folds and their graph-based representation. (3) A sulcal root-based model of the SFS. (4) A view of the congregation of artificial neural nets in charge of the sulcus recognition. (5) Antenatal MR imaging (a) can be used to perform longitudinal studies of the cortical folding process (b). (5c) Sulcal roots of temporal lobe (red and green roots make up STS). (6a) Heat equation applied to curvature of an adult cortical surface. (6b) A sketch of curvature embedded in the STS, whose valleys have been matched manually with the sulcal root model. (7) The sulci of 14 left-handed and 128 right-handed subjects (14 selected for 3D). The median value of sulcus size based asymmetry indices is plotted on a brain chosen randomly, using a lookup table providing the leftward and rightward tendencies. (8) The distributions of the asymmetry index of the central sulcus differ between both populations. The sulcus housing primary motor cortex is larger in the dominant hemisphere.

folds [such as the superior frontal sulcus (SFS) of Fig. 2(1)]? What are the homologous geometric features that should be matched by such a warping? Should the fundus be matched? Should the extremities of the small folds be matched with some points of the fundus of the long furrow?

- (2) What is the ideal template to be used to deal with sulcus interruption? An actual brain with almost no interruption? An actual brain with most of the usual interruptions? A virtual abstract brain without any or with all of the possible interruptions? A collection of brains covering all the possible patterns? The average of a set of brains aligned by some specific process?

Providing answers to these two sets of questions requires a better understanding of the link between the cortical folding patterns and the underlying architectural and functional organizations. For instance, a strong link has been found between the gyrus buried in the middle of the central sulcus, sometimes at the origin of an interruption, and the hand primary motor area (Boling et al., 1999; Régis et al., 1995; Yousry et al., 1997). If this kind of result reveals a general property, there may be a strong mapping between the patterns of sulcus interruptions and the underlying organization to be matched across brains. We then report a model of these interruptions. The principal hypothesis that is investigated considers the usual sulci as aggregates made up of several indivisible atoms that can be found in any brain (see Fig. 2(3)). An additional bolder hypothesis links these atoms with the first dimples appearing on the cortical surface during brain growth, which we call sulcal roots (see Fig. 2(5)).

Initially, spatial normalization aimed at erasing the differences between the brain shapes to provide a simple coordinate-based reference system for comparing functional experiments (Fox et al., 1985). More recently, spatial normalization has become the most versatile tool for morphometric studies (Ashburner et al., 2003; Toga and Thompson, 2002). This evolution has generated some confusion, because of the apparent conflict between normalization and searching for differences. In fact, this difficulty is overcome when the local compression ratios performed by the warping are used in comparison of tissue densities across populations. The confusion with voxel-based morphometry stems also from the poor behavior of most of the normalization algorithms concerning the cortical folds (Ashburner and Friston, 2001; Bookstein, 2001). We thus advocate a complementary kind of morphometry based on the automatic sulcus recognition that alleviates this confusion (Mangin et al., 2003a,b). For this object-based or structural morphometry, the objective is not to erase the variability of the folding patterns but to use it as a probe to discover population-related differences in the underlying organization of the brain.

Recognition of the sulci

This section describes a computer vision system dedicated to the automatic recognition of the cortical sulci. This system relies on a bottom-up strategy. This strategy aims at using a scale of representation dedicated to the shape of the cortex. The transition toward a higher level stems from the conversion of each raw MR image into a structural representation that embeds all the information required for the sulcus recognition. While general purpose computer vision approaches build such representations from generic features

like edges or corners, our approach relies on the cortical shape building blocks, namely the most elementary folds (Mangin et al., 1995a). Other similar methods have been proposed to break up the cortex into component parts related to the folds (Counce and Taylor, 2001; Le Goualher et al., 1997; Lohmann and von Cramon, 2000; Rettmann et al., 2002; Royackkers et al., 1999; Vaillant and Davatzikos, 1997; Zeng et al., 1999). A sketch of our automatic conversion process is shown in Fig. 1. The image processing and visualization tools platform can be downloaded from <http://brainvisa.info>. The framework has been applied successfully on more than 500 brains from various scanners. The main steps of the conversion process are the following:

- (1) The raw T1-weighted MR image usually suffers from inhomogeneities induced by the acquisition process (Fig. 1(1)).

- (2) The first step aims at restoring a meaningful link between image intensity and tissue classes. This is achieved via the estimation of a smooth multiplicative field minimizing the entropy of the intensity distribution (Mangin, 2000) (Fig. 1(2)).

- (3) The next step is the analysis of the intensity distribution to infer the statistics of gray and white matter. A scale-space-based approach provides robustness to the variations observed across MR sequences and subjects (Mangin et al., 1998a) (Fig. 1(3)). The trajectories of the extrema of several histogram derivatives are used first to build a sketch of the various modes embedded in the histogram. Then a simple heuristic selects the modes corresponding to gray and white matter using a priori knowledge about the respective sizes of the underlying classes in a head image.

- (4) Using the results of the previous step, the image is binarized to restrict the following process to the range of intensities of brain tissues. A simple Markovian regularization adds robustness. Mathematical morphology is then used to define a mask of the brain. The binary image is eroded until a stage where the largest connected component does not intersect a layer of 5 mm defined from the scalp. This seed is then reconstructed using a conditional dilation to recover the brain shape (Mangin et al., 1998a) (Fig. 1(4)).

- (5) A second sequence of erosion and conditional reconstruction is used to split the brain mask into hemispheres and cerebellum (Mangin et al., in press). A white matter mask is defined first using a second regularized binarization. A virtual affine normalization to Talairach space is then used to control the extent of the erosion process that leads to the seeds. A template image including another brain already segmented into the three anatomical objects is used for this purpose. As soon as at least one large connected component is found included in each of the three template objects, erosion is stopped and a competitive reconstruction process begins. The seed selection process accepts seeds made up of several connected components, which turned out to be critical for robustness (Fig. 1(5)).

- (6) The next step leads to the segmentation of the hollow object defined between the inner surface of the cortex (Fig. 1(6a)) and the brain hull (Fig. 1(6b)). This hull is defined from a morphological closing, while the gray–white interface is defined from the intensity statistics. A method based on topology preserving deformations imposes the spherical topology of this interface. This method, which is based on a sequence of additions or deletions of topologically simple points, transforms the parallelepipedic bounding box of each hemisphere into the object of interest (Mangin et al., 1995a).

- (7) Then, the hollow object is skeletonized. The erosion applied to compute the skeleton has a nonuniform speed. Indeed, to deal

with variable cortex thicknesses on both sides of the fold, image intensities are used to define the localization of the skeleton. Let us associate intensity with altitude so that white matters are like crests and cerebrospinal fluid (CSF) like crevasses. To impose the skeleton localization in the depth of the crevasses, we use a “crevasse detector”, which is the mean curvature of the MR image isointensity surfaces (Fig. 1(7a)). The mean curvature is computed from partial derivatives after convolution with a 3D Gaussian kernel with 1-mm standard deviation (Thirion and Gourdon, 1995). The crevasse detector amplifies the intensity differences and overcomes situations where the fold includes a very small amount of CSF leading to partial volume effect. This detector, however, is not perfect: some crevasse points are lost. The algorithm used to perform the skeletonization can fill the holes in the crevasse surfaces. This algorithm is a homotopic erosion that preserves the initial spherical topology of the hollow object. The behavior of this erosion is similar to the tide effect on sandcastles. The extent of the castle at the start corresponds to the hollow object (Fig. 1(7b)). The castle altitude at each point corresponds to the crevasse detector value. Each wave removes some sand of the castle outside walls. Little by little, the walls collapse under the water level. The highest parts of the castle are the last to collapse. When two water fronts meet, namely when a point becomes locally a surface point for discrete topology, a skeleton point is created. Fig. 1(7c) illustrates this skeleton, where green points denote surface points and red points denote edge points corresponding to the fold bottom. Skeleton points connected to the outside representing the brain hull are collected and removed (Figs. 1(7d) and (7e)).

(8) The surface points (Fig. 1(7f)) are divided into topologically simple surfaces, namely pieces of surface that do not contain junctions (Mangin et al., 1995a). Each simple surface is split further to represent situations where a gyrus has been buried in the bottom of the fold (cf. Figs. 1(8) and (9e)). The underlying process computes first the Gaussian curvature of the MR volume isosurfaces. Then, each voxel of the hollow object connected to the inside and with a negative Gaussian curvature is deleted. A geodesic distance to the brain hull is computed inside the remaining part of the object. A system of catchment basins is finally computed from this geodesic depth. The buried gyri are supposed to create boundaries in this parcellation. Finally, each simple surface is split according to this parcellation. This step has some similarities with other works (Lohmann and von Cramon, 2000; Rettmann et al., 2002).

(9) The resulting pieces of surface are gathered into a graph structure (Mangin et al., 1995a). Fig. 1(9e) is an example where the central sulcus is split into five pieces. Each node SS is a piece of the surface skeleton. Three kinds of relations are used: topological junction ρ_T (Fig. 1(9a)), split induced by a buried gyrus (a “pli de passage”) ρ_P (Fig. 1(9b)), and neighbor geodesic to the brain hull ρ_C . The last relation is inferred from a Voronoi diagram computed inside the brain hull using the junctions with the folds as seeds (Fig. 1(9c)) These topological junctions with the brain hull are represented by the black lines (in the inset of Fig. 1(9d)) and denoted by white arrows (Fig. 1(9d)).

After the conversion process, the patterns of the cortex are represented by a relational graph, namely a set of elementary folds linked according to their topographical organization relatively to junctions and to proximity on the cortical surface. Various attributes are attached to the nodes and to the links of this graph to keep track of the fold shapes. These attributes are computed after affine spatial normalization relative to Talairach proportional

system. This normalization can either apply to the MR scan, before the conversion process, or remain virtual; namely, it is applied only to coordinates in the native scan. Some of these attributes are (Rivière, 2000)

fold: size; maximal depth; center of mass; average normal; length, extremities and average direction of the intersection with the brain hull, etc.

link: direction between the centers of mass of the linked folds; length and average direction of the junction, etc.

At this stage, the pattern recognition problem amounts to giving a name (or a label) from the sulcus nomenclature to each of the elementary folds (Fig. 1(10)). Because no gold standard definition of main sulci exists, the underlying pattern recognition framework relies on a learning strategy. Hence, different computer vision systems can be derived for competing models of the cortical folding patterns. To train such a system, the elementary folds in a database of brains have to be labeled manually, which is a tedious task. Then the system has to learn from the database the various patterns that can be observed for each of the entities listed in the sulcus nomenclature used for this labeling. Fig. 2(2) provides an example where the frontal sulcus is represented either by one unique label (Fig. 2(1)) or by three labels (Fig. 2(3)), which denote the three putative sulcal roots accounting for the usual interruptions of this sulcus. Whatever the nomenclature, there is a one to many matching between the labels and the elementary folds. Unfortunately, the number of elementary folds associated to a given label is not stable across brains.

The difficulties induced by this variability of the sulcus patterns are similar to those encountered in human vision: the variability of the spatial relationships among elementary parts of a complex object in changes in orientation. An attractive model of human vision addresses this problem by assuming that multiple views of each object are stored in memory (Riesenhuber and Poggio, 2002). We have designed our computer vision system on the multiple-brain-based analogue of the multiple-view-based model: the shape of each sulcus is learned from a set of examples. This choice raises a difficult point: How many brains do we need to cover the variability of each of the entities used in a given nomenclature? In fact, this difficult question is deeply dependent on the nomenclature itself. At the time when the first nomenclatures were coined by early neuroanatomists, the collections of brains were reasonably small. One may think that the emergence of the sulcus notion stemmed from the need to reduce the huge complexity of the global folding patterns to intermediate features, whose variability could be tackled by the human brain. This scale of representation may have been selected to maximize the information delivered by the building blocks corresponding to a few examples of each sulcus (Ullman et al., 2002). Thus, neuroanatomists have the capacity to generalize broadly to new brains. In the current version of our system, the learning database includes 21 brains and 5 additional brains to evaluate the generalization power.

During the training stage, the computer vision system learns to generalize the knowledge embedded in the learning database across large variations of localization, orientation, and shape of the sulci. These variations are large enough to prevent reliable recognition using only localization in Talairach proportional system (Le Goualher et al., 1999). However, the main computational difficulty is the structural variability of the sulci across individuals. A sulcus

corresponding to one elementary fold in one given brain may be made up of several elementary folds in a second brain (Fig. 2(1)). Furthermore, the junctions between sulci are also highly variable leading to difficulties similar to those related to the parsing of handwriting into words.

A small number of sulci, in fact, have a stable enough shape to allow straightforward recognition. Usually, the other sulci are identified using a grouping process allowing the neuroanatomist to recognize the patterns that are made up of a set of neighboring sulci. Furthermore, since the neuroanatomist can only observe a subset of the sulci at a time, we designed a Markovian system (Geman and Geman, 1984) that relies only on local and contextual knowledge: the shapes of the individual sulci and the patterns made up by pairs of neighboring sulci. This choice relies on the assumption that a set of canonical local interactions between pairs of sulci is sufficient to model the patterns made up by more than two neighboring sulci. Each local anatomical knowledge is learned by a multilayer perceptron that is a hyper-specialized anatomical expert. Perceptrons are simple artificial neural nets dedicated to pattern recognition. Two families of such experts are attached, respectively, to the sulcus shapes and to the neighborhood patterns (Fig. 2(4)). Memory-based longer range interactions may also be used by the neuroanatomist during the recognition. This may call for an extension of the set of interacting pairs in the future to take into account for instance the symmetry relationships across the interhemispheric plane.

Each sulcus expert in the first family has a field of view, which is learned from the database, and corresponds to a domain of the standard proportional system (Fig. 2(4)). This field of view is simply the bounding box of all the instances of the corresponding sulcus. During the labeling step corresponding to the recognition of the sulci of any new brain, the label corresponding to a given sulcus can only be given to the elementary folds included in the expert's field of view.

The set of pairs of sulci taken in charge by the second kind of perceptrons is also inferred automatically from the learning database. Each pair of sulci, whose instances in the database are sometimes linked, leads to the creation of a local expert dedicated to the resulting pattern. The contextual information driving the sulcus recognition stems from the sulcus neighborhood built by the second family of experts. The fields of view and this neighborhood endow the congregation of experts with a "corticotopic" organization, which may be related to the retinotopic or somatotopic organizations found in the cortex.

During the recognition step, each expert is in charge of evaluating a small part of the labeling. The evaluation ranges from zero (good) to one (bad). Sulcus experts deal with a subgraph of folds defined by one label, while pair experts deal with a subgraph of folds defined by two labels. The evaluation is a measure of the likelihood of the shape made up by the folds of this subgraph, considering the a priori knowledge embedded into the learning database. To teach this knowledge to the perceptrons, each subgraph is compressed into a simple code made up of a fixed set of synthesized attributes. These attributes can be viewed as descriptors of the subgraph. Some are more syntactic, like the number of connected components; others are semantic, like the total size or the maximal depth of the folds included in the subgraph. These synthesized semantic attributes are computed from the attributes attached to the elementary folds. Each perceptron is trained to give a good evaluation to the examples of the database, and a bad evaluation to random modifications of

these examples. Each expert's reliability is assessed from a second learning base to weight the output of the expert before using it as a potential of the global Markov field (Rivière et al., 2002). Finally, the automatic labeling of the folds of any new brain is driven by stochastic minimization of a global function made up of the weighted sum of the perceptron outputs. It should be noted that the recognition of a given sulcus always requires a consensus among several experts, which contributes to the robustness of the global behavior of the system (Fig. 2(4)).

The system is still at the initial stages of development. It has been trained from 16 manually labeled brains. Ten additional manually labeled brains were used: five as a test set preventing over-learning (overfitting) and five as a generalization set. This last set was not used during training and has allowed us to perform a first evaluation. A nomenclature of 58 sulcus names is used in each hemisphere (Rivière et al., 2002). The training of the 500 multilayer perceptrons on the 21 brains takes about 12 h on a network of 20 Pentium processors. The stochastic minimization leading to the automatic labeling lasts 1 h for one hemisphere with a 2 GHz processor. The performance of recognition decreases from 85% of agreement with the manual labeling on the training set, to 75% on the generalization set, which calls for increasing the size of the training base.

It should be noted, however, that these results do not mean errors of 25%. Because of the large interindividual variability of the folding patterns, indeed, no gold standard exists to evaluate the percentage of correct labeling. This accordance measure, moreover, is highly dependent on the sulcus. For instance, the generalization leads only to 3.8% and 6% of disagreement for central sulcus and lateral fissure, respectively. The disagreement may increase largely for more variable sulci, which leads sometimes to question the manual identification. It would be misleading, however, to overinterpret the respective rates of agreement obtained for each of the sulci (Rivière, 2000), considering the small sizes of the databases. Therefore, it should mainly be understood that the low quality of the identifications obtained for the most variable sulci stems from the weaknesses of the current nomenclature, which calls for a research program aiming at providing a more consistent model of the folding patterns.

The alphabet of the folding patterns

As mentioned in the Introduction, the main impediment for the reliable identification of a stable model of the folding patterns stems from the frequent interruptions of major sulci. In fact, a worse problem is not the interruptions themselves but their aftermath: the pieces of broken sulci merge sometimes according to unusual patterns, creating "monster" sulci not described in the usual nomenclature. Hence, trying to identify the standard sulci in the external aspect of the cortex can sometimes be very confusing. In our opinion, many clues for understanding these kinds of puzzling brains are hidden in the depth of the folding patterns. Indeed, we think that the notion of "pli de passage", namely buried gyri described by early neuroanatomists, may be of great help to understand the variability of the folding patterns (Régis, 1994; Régis et al., 1995; Régis et al., submitted for publication).

A couple of analogies with handwritten text recognition may clarify our point of view. In our opinion, the sulci in the usual nomenclature may be considered as the words of a text. With some writers, the words are split into several connected components,

which may affect recognition. In the worst cases, pieces of different words may join each other leading to one connected component looking like a spurious word. A priori knowledge allows human readers to overcome this difficulty, but it may be sometimes quite challenging (think of the last time you get a handwritten medical prescription). A crucial knowledge to perform well in this split and merge game is the alphabet embedded inside the shapes of the words. Therefore, our research program that has evolved over the last decade aims at inferring the alphabet of the cortical folding patterns.

The research program may look like a hopeless “Holy Graal” quest. However, even partial answers could deeply influence neuroimaging strategies. The aim is to favor the emergence of new anatomical descriptions relying on smaller sulcal entities than the usual ones. Of course, considering the number of points to be addressed, such a program will not be undertaken without large-scale international collaborations.

In the last decade, we initiated two main areas of research. The first is the study of the cortical folding process from antenatal to adult stage, with the idea that the cortical folding alphabet may simply correspond to the first dimples appearing on the cortical surface before birth (Régis, 1994; Régis et al., 1995, submitted for publication). According to several theories—too numerous to describe in this paper—these primal units could be stable across individuals. They may be related to the boundaries of the architectural protomap, which appears before the beginning of the folding process (Rakic, 1988). During ulterior stages of brain growth, some of these dimples, called sulcal roots, merge with each other and form different patterns depending on the subjects. The most usual patterns correspond to the usual sulci. Our project began with the inference of a first map of these sulcal roots from the various observations disseminated in embryologic literature (Fig. 2(5c)). Since then, we have been trying to validate this map.

More recently, we have been developing dedicated antenatal magnetic resonance procedures (Fig. 2(5a)) to perform longitudinal studies of the folding process (Cachia et al., 2001; Scifo et al., 2003). The sulcal roots, indeed, do not appear simultaneously. Therefore, several time steps would be required to observe the whole set of roots in the same brain. This is a challenging endeavor, because of some underlying technical and ethical difficulties, but the first results are promising (Fig. 2(5b)).

The second line of research aims at revealing the traces of the sulcal roots in the geometry of the adult cortex. In our opinion, some clues about these sulcal root fusions can be found in the depth of the adult sulci and detected from the curvature of the cortical surface. Our initial naive attempts, described in the first section of this paper, were based on maxima of geodesic depth and saddle points of the inner cortical surface (points with negative Gaussian curvature). This approach has now been refined using a scale-space-based strategy (Cachia et al., 2003a). The idea is to build a structural representation, called a primal sketch, from the behavior of the curvature extrema and saddle points throughout the scale-space. In our early experiments, this scale-space stems from a geodesic version of the heat equation (Fig. 2(6a)). At each level of scale, the valleys defined by a curvature minimum and a saddle point are supposed to represent an interesting feature of the folding pattern. These entities are tracked throughout the scale-space to infer a sketch of objects called scale-space blobs, which merge together at bifurcation points. This sketch is supposed to include the sulcal roots, which is illustrated in Fig. 2(6b) for the superior temporal

sulcus. In the 3D representation of the primal sketch, the localization of the support of the valleys is moved away according to their scale. The different colors correspond to the different scale-space blobs. In the future, these primal sketches will be compared across subjects to infer structural models of the folding patterns similar to the sulcal root model mentioned above (Coulon et al., 2000; Mangin et al., 2004).

While these two lines of research lead slowly to the emergence of the abovementioned alphabet of cortical folding patterns, our project requires cross validations using other sources of information. For instance, the development of MR diffusion imaging may deeply improve our understanding of the cortical connectivity (Mangin et al., 2002; Poupon et al., 2000). Investigating the link between the patterns of connectivity and the sulcal root model could contribute to the validation of this point of view (Mangin et al., 1998b). Another source of validation should stem from the link with individual functional activations (Coulon et al., 2000). Finally postmortem MRI could also provide the way to perform large-scale studies of the link between the folding patterns and architectonic maps (Krugger et al., 2003).

Sulcal morphometry

In this section, we illustrate the interest of a new complementary morphometry based on the automatic recognition of the cortical sulci (Mangin et al., 2003a,b). We focus on the correlates of handedness on the asymmetries of the sulcal sizes. Other illustrations may be found regarding the patterns of interruptions of the superior temporal sulcus (STS) (Ochiai et al., 2004) or the consequences of a genetic alteration on the development of the intraparietal fissure (Molko et al., 2003).

It is usually assumed that the loss of statistical power induced by the imperfect gyral matching of spatial normalization can be compensated by large population sizes. Two recent large-scale voxel-based morphometry (VBM) studies with hundreds of subjects, however, have reported a surprising absence of results relative to the possible relationship between brain asymmetry and handedness (Good et al., 2001; Watkins et al., 2001), which may reveal some limits of the coordinate-based strategy. Since human handedness can be viewed as a model of proficient or preferred behaviors, several ROI-based morphometric studies have also addressed this issue for a few cortical structures. For instance, the central sulcus, which houses the primary motor cortex, was found to be deeper in the left hemisphere in right-handed people, and vice versa in left-handed people (Amunts et al., 1996, 2000; White et al., 1994). This result remains controversial as other studies did not confirm this interaction (White et al., 1997) or found an inverse pattern (Davatzikos and Bryan, 2002). Methodological differences and age effects may explain these inconsistencies (Toga and Thompson, 2003).

To investigate whether the automatic recognition of the sulci was reliable enough to address this kind of issue, 142 normal volunteers of the ICBM database were processed without any manual correction. These subjects correspond to one of the VBM studies mentioned above (Watkins et al., 2001). On a short handedness questionnaire, 14 subjects were dominant for left-hand use on some tasks; the remaining 128 subjects preferred to use their right hand. The 142 T1-weighted brain volumes were stereotaxically transformed using nine parameters (Collins et al., 1994) to match the Montreal Neurological Institute 305 average template. A set of 58

cortical sulci were recognized in each hemisphere. To lower the risk of large failure of the stochastic minimization leading to the sulcus recognition, the optimization was performed twice for each brain and the lowest minimum was selected for the morphometric study.

For each sulcus, the voxel-based representation stemming from the skeleton was triangulated using a marching cube kind of algorithm. The sum of the areas of the triangles of the resulting smooth mesh was used as an estimation of the sulcus size. This measurement is related to the surface of the medial axis of the cerebrospinal fluid that fills up the sulcus. It should be noted that simply using the number of skeleton voxels as sulcus size estimation would have been biased by the sulcus orientation for sampling reasons. Then, a normalized asymmetry index $[(R - L)/(R + L)/2]$ was computed, where R (respectively, L) denotes the sulcus size in the right hemisphere (left hemisphere). Fig. 2(7) shows the median indices obtained in both groups for the sulci of the external face of the cortex. For this purpose, each sulcus of the left hemisphere of a brain chosen randomly was colored according to the median index to indicate leftward or rightward tendencies. A very interesting observation emerging from the two resulting images, common to both populations, is a leftward increase of the sulcus sizes in the upper part of the frontal lobe versus a rightward increase in the temporo-occipital lobes. This result is flipped relative to the well-known gross asymmetries of these areas called the petalia (Toga and Thompson, 2003). These petalia, which may even lead to impressions on the inner surface of the skull, have been widely observed in various species. The flipped sulcus asymmetry leads to a new understanding of the origin of these petalia: a wider lobe results from a lesser extent of the folding process, which may be related to lesser development of some of the underlying structures (cytoarchitectonic areas, fiber bundles). Further studies taking into account the surfaces of the gyri will clarify this point (Cachia et al., 2003b).

For each sulcus, standard *t* tests were used to compare the distributions of the asymmetry indices of the left-handed and right-handed groups, using “Data-Mind”, a plug-in of brainVISA software (<http://brainvisa.info>) based on R software (<http://www.r-project.org/>). Several significant differences were revealed by our analysis ($P < 0.05$ not corrected for multiple comparison). Primary intermediate branch of intraparietal fissure: $P = 0.01$, RH = -0.49 , LH = 0.11 ; inferior precentral sulcus: $P = 0.01$, RH = -0.06 , LH = 0.30 ; central sulcus: $P = 0.03$, RH = -0.02 , LH = 0.04 , where RH (respectively, LH) denotes the average measurement in the right-handed (respectively, left-handed) group. The three sulci leading to handedness correlates present an asymmetry pattern left–right flipped between both groups: the sulcus is more developed in the dominant hemisphere (Fig. 2(8)). Two of these sulci (central and inferior precentral) define the walls of the motor gyrus. A larger sulcus may simply results from the necessity to increase the local folding process to extend the most active precentral motor gyrus. Interestingly, the handedness correlate is lower for primary motor cortex (central sulcus: $|RH - LH| = 6\%$) than for the structures responsible for planning and coordinating movements (inferior precentral sulcus: $|RH - LH| = 36\%$). Finally, it is also important to note that the pattern of asymmetry obtained for the central sulcus matches the results obtained by most of the manual studies (Amunts et al., 1996, 2000; White et al., 1994).

The third sulcus showing significant handedness correlates is the primary intermediate branch of the intraparietalis fissure. This branch, which is sometimes also called the intermediate sulcus of

Jensen, is a small highly variable fold embedded in the inferior parietal lobule, inside an area usually related to language in the left hemisphere (Wernicke’s area). This result can be easily related to one of the most intriguing results about handedness correlates: the fact that the planum temporale, a region of the posterior superior temporal lobe deeply involved in language understanding, shows marked leftward volume asymmetry that is greater for right-handed people (Habib et al., 1995; Steinmetz, 1996). The planum temporale is defined relatively to the posterior part of the Sylvian fissure. Therefore, the planum is the anterior bank of a gyrus, whose posterior bank corresponds to the primary intermediate branch of the intraparietalis fissure. Hence, the asymmetry pattern observed for this branch, a large leftward asymmetry for right-handed subjects and a slight rightward asymmetry for left-handed subjects, is consistent with current knowledge.

Conclusion

The research program described in this paper is based on the gamble that the cortical folding patterns convey much more information about the cortical organization than usually assumed. This gamble stems from the idea that the cortical folding process follows a trajectory that is sculpted by various architectural constraints competing with each other. Such an idea has been developed recently by Van Essen (1997) relative to the fiber related tension, which could be the main explanation to the patterning of the cortical folds. Considering the complexity of the cortical connectivity and of the cytoarchitectonic parcellations, however, one can guess that several qualitatively different folding patterns could result from the competition process driving morphogenesis. We also hypothesize that slight differences in the sizes of cortical areas can lead to radically different folding solutions during morphogenesis, because of a chaotic behavior of the system, which explains the variability of the adult cortex folding patterns. Hence, simulating the cortex folding process is a very promising research direction, which can improve our understanding of the cortex organization. Such simulations could also be developed backward to reveal the embryological patterns from the adult intricate folding. Our scale-space-based approach, for instance, could be extended toward a more sophisticated evolution scheme, mixing inflating forces with fiber bundle-based tensions stemming from MR diffusion data.

The sulcal root concept and the related notion of “pli de passage” (buried gyri) lead to a different view of the organization of the cortical surface. Trying to figure out if some general principles could underlie the sulcal root map aspect led us to propose the “Meridian-Parallel model”, by analogy with earth (Régis et al., submitted for publication). A similar idea has been proposed recently by Toro and Burnod (2003). Our model considers the cortical surface as a network of orthogonal gyri, which leads to a new definition of sulcal roots as the deep sulcal cortex surrounded by two orthogonal couples of gyri. These two orthogonal axes of gyral organization are especially visible at the fetal stage (Fig. 2(5b)). At the adult stage, however, one axis is usually dominant and the other axis buried, because it seems to be a good folding solution to stabilize the various forces underlying the growing process. For instance, the “meridian” dorsoventral axis is usually dominant in the central region, while the “parallel” rostrocaudal axis is usually dominant in the frontal region. The meridian–parallel model interprets unusual folding patterns as a flip of dominant gyral direction compared to the majority of

individuals. Opening the sulci, however, should always reveal the dual orthogonal gyri. Simulation is again the tool of choice to test these kinds of ideas.

The transition from voxel to image features advocated herein to deal with the cortical folding patterns enhances the ability of neuroscientists to try to understand interindividual variability. Object-based representations, indeed, seem necessary to underpin thought on complex organizations. Furthermore, the objects embedded into the folding patterns may have close links to the brain architectural organization. Therefore, descriptors derived from these objects could be very interesting from a morphometric point of view, as described in this paper. We have shown elsewhere that the sulcal-based morphometry is also a promising approach to develop computer-assisted diagnostic tools (Duchesnay et al., 2004). As an illustration, we have shown that sulcal-based morphometric features were sufficient to guess sex with less than 5% error rate. These promising results have led us to develop similar transitions for the study of the gyri (Cachia et al., 2003b), of the fiber bundles (Mangin et al., 2002), of the basal ganglia (Poupon et al., 1998), and finally of the patterns of activations (Coulon et al., 2000). Addressing the variability of the individual patterns of activations at the cluster level, indeed, could result in a brand new kind of brain mapping strategy (Mangin et al., 2004).

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