High-Resolution Intersubject Averaging and a Coordinate System for the Cortical Surface

Bruce Fischl,[1] Martin I. Sereno,[2] Roger B.H. Tootell,[1] and Anders M. Dale[1]*

[1]*Nuclear Magnetic Resonance Center, Massachusetts General Hospital/Harvard Medical School, Charlestown, Massachusetts*
[2]*Department of Cognitive Science, University of California at San Diego, La Jolla, California*

Abstract: The neurons of the human cerebral cortex are arranged in a highly folded sheet, with the majority of the cortical surface area buried in folds. Cortical maps are typically arranged with a topography oriented parallel to the cortical surface. Despite this unambiguous sheetlike geometry, the most commonly used coordinate systems for localizing cortical features are based on 3-D stereotaxic coordinates rather than on position relative to the 2-D cortical sheet. In order to address the need for a more natural surface-based coordinate system for the cortex, we have developed a means for generating an average folding pattern across a large number of individual subjects as a function on the unit sphere and of nonrigidly aligning each individual with the average. This establishes a spherical surface-based coordinate system that is adapted to the folding pattern of each individual subject, allowing for much higher localization accuracy of structural and functional features of the human brain. *Hum. Brain Mapping 8:272–284, 1999.*

Key words: intersubject averaging; coordinate systems; atlas

INTRODUCTION

The cerebral cortex is the largest part of the human brain. Although it is highly folded in many mammalian species, the intrinsic "unfolded" structure of the cortex is that of a 2-D sheet, several millimeters thick. In experimental animals, it is well accepted that: (1) many functional dimensions (e.g., retinotopy, orientation tuning, ocular dominance, somatotopy, tonotopy) are mapped on the cortical surface, (2) these mapped parameters vary much more rapidly in the two dimensions parallel to the surface than they do through the several millimeters of cortical thickness (i.e., they are columnar), and (3) different cortical areas are arranged in a characteristic pattern, or mosaic, across the cortical surface.

In order to relate and compare anatomical features or functional activations across subjects, it is necessary to establish a mapping that specifies a unique correspondence between each location in one brain and the corresponding location in another—that is, to bring the two brains into register. Most comparisons of data across subjects in the human brain have relied on the 3-D normalization approach described by Talairach and Tournoux [1988] and Talairach et al. [1967]. Although this type of approach has certain advantages (ease of use, widespread acceptance, applicability to subcortical structures), it also has significant drawbacks.

Contract grant sponsor: Human Frontiers Science Foundation; Contract grant sponsor: Whitaker Foundation; Contract grant sponsor: National Eye Institute; Contract grant number: EY07980.
*Correspondence to: Anders M. Dale, Nuclear Magnetic Resonance Center, Massachusetts Gen. Hosp. / Harvard Med. School, Bldg. 149, 13th St., Charlestown, MA 02129. E-mail: dale@nmr.mgh.harvard.edu
Received for publication 30 December 1998; accepted 6 July 1999

These drawbacks derive directly from the fact that the intrinsic topology of the cerebral cortex is that of a 2-D sheet, as described above. For instance, estimates of the amount of 'buried' cortex range from 60–70% [Van Essen and Drury, 1997; Zilles et al., 1988]. Thus distances measured in 3-D space between two points on the cortical surface will substantially underestimate the true distance along the cortical sheet, particularly in cases where the points lie on different banks of a sulcus. For example, the lateral tip of the central sulcus frequently lies within a centimeter of the superior temporal gyrus when the distance is measured in the Cartesian embedding space. The distance between the same two points as measured along the actual cortical surface is 10 cm due to the depth of the sylvian fissure.

This problem is compounded by the poor anatomical accuracy afforded by the Talairach normalization approach. As numerous studies have demonstrated, the between-subject variability in the location of cortical anatomical landmarks after Talairach alignment is on the order of several centimeters [Steinmetz et al., 1984; Hunton et al., 1996; Thompson and Toga, 1996; Van Essen and Drury, 1997]. Since many human functional areas (e.g., visual areas V2, V3, VP, V4v, MT+) are <2 cm wide, the Talairach coordinate system does not have sufficient accuracy to differentiate neighboring cortical areas. This type of error makes it impossible to distinguish topographical and fine structural features of the cortical architecture based solely on Talairach coordinates.

In order to achieve a more accurate intersubject alignment, various groups have suggested the use of high-dimensional warpings to register two volumes [Miller et al., 1993; Evans et al., 1994; Christensen et al., 1995; Joshi et al., 1997]. In contrast to Talairach registration procedures, which require only a few parameters to represent the appropriate transformation, these techniques use tens of millions of degrees of freedom to morph one entire 3-D volume into another. This type of nonrigid alignment can, therefore, perform a significantly more dramatic warping of a volume in order to align it accurately with a predefined anatomical "textbook."

Although such high-dimensional warping methods are capable of producing an almost perfect match between the 3-D intensity values of different brains, this does not ensure the alignment of sulcal and gyral patterns of the individual cortical surfaces. This is because the curvature pattern (sulcal and gyral folding) is defined as a property of the 2-D cortical surface and can therefore only be determined from an explicit representation of the surface itself. Since gyral and sulcal landmarks are typically accurate predictors of the location of functional areas, it seems likely that using these features to drive the registration of the cortical surfaces will result in a more accurate alignment of corresponding functional areas than can be achieved using volume-based deformation methods.

Variants of this type of surface-based alignment approach have been proposed in a few recent studies [Drury et al., 1996, 1997; Sereno et al., 1996; Thompson et al., 1996; Dauatzikos et al., 1997; Van Essen et al., 1998]. The approach of Drury et al. [1996, 1997] and Van Essen et al. [1998] has been to apply fluid deformations similar to those of Miller et al. [1993] to flattened representations of the cortical surface, driven by a small number of manually labeled anatomical landmarks. This technique does address some of the issues raised above, but it is important to note that this procedure can be carried out only after several incisions have been made in the cortical surface to allow it to lie flat without major distortion [Drury et al., 1997]. This is problematic, as the resulting surface does not respect the topological structure[1] of the original cortical surface, i.e., neighboring points on the surface that lie on opposite sides of a cut may have very different locations on the flattened surface. Thus the exact position of the incisions can greatly affect the resulting registration. Moreover, the location of the incisions introduces variability in the resulting surface, as it is difficult to make incisions at equivalent points in different subjects. Indeed, the purpose of intersubject registration is to establish precisely this kind of correspondence.

Thompson and colleagues [1996] take a similar approach to that of Drury et al. [1996, 1997] and Van Essen et al. [16] using fluid deformations to warp a manually labeled flattened representation of one individual cortical surface into register with that of another. They avoid the problem of introducing cuts to some degree by using a spherical mapping of the cortical surface, then flattening and registering each octant of the sphere separately. Although no incisions are required in the surface, this approach imposes an arbitrary partitioning into the cortical subregions that are aligned. In addition, it forces the use of manual labeling, as the spherical and flattened representations do not preserve metric properties of the original surface and, therefore, introduce arbitrary distortions

[1]The term "topological structure" is frequently used to refer to the border of a domain as opposed to its global topology [Mortenson, 1997]. For example, once an incision has been made in the cortical surface, it is topologically equivalent to a plane. Further incisions alter its topological structure, but not its topology (unless they result in multiple disconnected components).

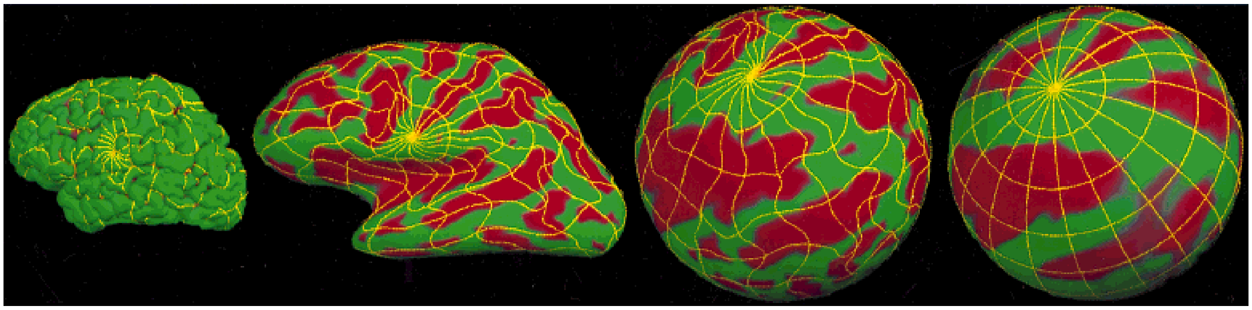

Figure 1.
Different representations of an individual cortical surface as well as the average (40 subjects, right). Red and green regions represent sulci and gyri, respectively.

into the shape of the cortical folding patterns, preventing automated alignment.

The volume- and surface-based normalization or alignment schemes described above can also be used to define a coordinate system for the volume or surface. In the case of the Talairach normalization approach, the coordinate system is based on the 3-D Cartesian embedding space of the standard brain. The main drawbacks of this coordinate system stem from: (1) its poor anatomical precision as noted above and (2) the fact that its metric properties do not reflect the metric properties of the cortical sheet, i.e., Cartesian distances give poor estimates of geodesic distances along the surface. In the case of the postflattening, surface-based alignment approach of Van Essen and Drury, the coordinate system is based on the 2-D Cartesian embedding space of the flattened representation of the cortical surface of the Visible Human. Although the metric properties of this 2-D coordinate system better reflect those of the cortical surface, large distance errors may result from the changes in topological structure caused by cuts needed to allow the surface to be flattened with minimal metric distortion. Furthermore, this coordinate system is not onto, i.e., there are coordinates in the flattened space that do not correspond to any points on the cortical surface. In fact, since the flattened surface boundary is not convex, the average surface-based coordinate of points on opposite sides of a cut may fall outside the surface.

In contrast, the spherical coordinate system proposed here requires no incisions in the surface. This is possible because the cortical surface of each hemisphere is topologically equivalent to a sphere, after closing the surface medially across subcortical structures. The reconstructed surface of each individual subject is first mapped onto a sphere, using a maximally isometric transformation [Fischl et al., 1998]. The surfaces are then morphed into register with an average, canonical surface, guided by a combination of folding-alignment (sulcus/gyrus) and isometry-preserving forces. The canonical cortical surface is generated by combining multiple surfaces that have each been morphed into a parameterizable surface. A unified latitude and longitude system can then be established, allowing surface-based averages across subjects. As with the Talairach atlas, the coordinates of a single point (here latitude and longitude as opposed to x,y,z) are used to index the corresponding point on each individual surface.[2]

This procedure is illustrated in Figure 1. The leftmost image is the reconstruction of the pial surface of an individual subject. This surface is then inflated to determine the large-scale folding patterns of the cortex (second image from left) and subsequently transformed into a sphere in a manner that minimizes metric distortion (third image from left). The folding patterns of the individual are then aligned with an average folding pattern (rightmost image). The natural coordinate system of the average surface, shown at the right, can then be used to index any point on any of the surface representations of the individual. The coordinate lines painted onto the individual surfaces are no longer uniform; rather they occur at the same locations relative to the primary cortical folding pattern across all subjects.

The main advantages of this coordinate system are: (1) it respects the intrinsic topological structure of the cortical surface, (2) the metric distortions introduced in the registration process are explicitly minimized, (3) no manual labeling of anatomical landmarks is needed, as the entire curvature pattern is used in the alignment, (4) the coordinate system is one-to-one and onto, i.e., every point on the surface has a unique coordinate,

[2] Contact http://www.nmr.mgh.harvard.edu for the freely available software used in this study.

and every coordinate refers to a unique point on the surface, and (5) the ''blurring'' of anatomically and functionally defined cortical areas is greatly reduced, as demonstrated below.

One of the main purposes of such coordinate systems is to bring anatomical and functional areas across subjects into register as precisely as possible. Here, we propose a ''blurring'' metric that directly quantifies the degree of blurring introduced by different registration procedures and coordinate systems. This provides an objective criterion for comparing the anatomical and functional precision of such procedures, and also can be used to optimize any free parameters of a given registration procedure.

METHODS

In order to map an individual's cortical surface into a surface-based coordinate system, one first has to obtain an accurate surface reconstruction. We have previously described a largely automated cortical surface reconstruction procedure capable of producing a highly detailed geometric description of the gray-white matter boundary, as well as the pial surface of the human cortex [Dale and Sereno, 1993; Dale et al., 1999]. To establish a coordinate system for this surface, it is necessary to transform or project it into a parameterizable shape, as the parameterization then provides a natural coordinate system for the surface. The coordinate system proposed here uses a sphere for this purpose. This choice is primarily motivated by the fact that the mapping of the cortical hemisphere onto a sphere allows the preservation of the topological structure of the original surface (i.e., the local connectivity). In addition, a coordinate system based on the unit sphere retains much of the computational attractiveness of a flat space, facilitating the calculation of metric properties such as geodesic distances, areas, and angles, properties that are more difficult to compute on less symmetric surfaces such as ellipsoids.

As shown in our previous studies [Fischl et al., 1998, 1999], it is possible to transform the cortical surface into a spherical representation with moderate metric distortions (averaging 15% in cortex). The minimization of metric distortion is important in obtaining a spherical surface that can be used accurately to represent the shape of the folding pattern of the cortex. Once this spherical representation has been established, we can use any of the standard spherical coordinates systems (e.g., longitude and colatitude) to index a point uniquely on the cortical surface. Furthermore, because the energy functional used to generate the spherical transformation ensures that the transformation is invertible, we can use the spherical coordinate system to specify a point on any of the surface representations for a given subject.

Once an individual cortical surface has been transformed into an optimal (from a metric standpoint) sphere, we wish to align the folding patterns of the individual with that of an average. In order to accomplish this, we need to construct a function that accurately and stably represents the folding patterns of the cortex, then treat it as a function on the unit sphere via the mapping established by the spherical transformation. This function can then be used to align the surface using a mean-squared energy functional that measures the difference between the individual folding and that of the average.

Alignment of folding patterns

The alignment of the folding patterns of the cortical surface is carried out by minimizing the mean squared difference between the average convexity across a set of subjects (denoted by $\overline{\mathrm{C}}$) and that of the individual (denoted by C) modulated by the variance of the convexity across subjects. The measure of convexity we use reflects the large-scale geometry of the surface and is less noise-prone than mean curvature [Fischl et al., 1999]. Negative and positive values of C indicate gyral and sulcal regions, respectively. The use of the variance of the convexity allows consistent folding patterns such as the central sulcus, the sylvian fissure, etc., to have a greater effect on the alignment than more variable patterns. The average convexity over N subjects is given by:

$$\overline{C}(\varphi, \theta) = \frac{1}{N} \sum_{i=1}^{N} C_i(\varphi, \theta). \tag{1}$$

An unbiased estimate of the variance is then:

$$\sigma^2(\varphi, \theta) = \frac{1}{N-1} \sum_{i=1}^{N} (C_i(\varphi, \theta) - \overline{C}(\varphi, \theta))^2. \tag{2}$$

Finally, the alignment energy functional is:

$$J_P = \frac{1}{2V} \sum_{v=1}^{V} \left(\frac{\mathrm{G}_\alpha * (C_v - \overline{C}(\phi(v), \theta(v)))}{\sigma(\phi(v), \theta(v))} \right)^2, \tag{3}$$

where $\phi(v)$ and $\theta(v)$ are the spherical (ϕ, θ) coordinates of the v^{th} vertex as established by the spherical transformation detailed in Fischl et al., 1999, V is the total number of vertices in the tessellation, G_α is a Gaussian kernel with standard deviation α and * denotes convolution. The alignment is performed in a multi-scale manner with α initially large and gradually decreasing as the integration asymptotes at each scale.

Note that in practice the alignment is an iterative procedure. First, a single surface is used as an exemplar to generate $\overline{C}$, and all variances are set to unity. Next, a set of surfaces are aligned with this surface, then the aligned surfaces are used as the C_i in equation (3) to generate the canonical surface. This process can then be iterated until the canonical surface converges.

Minimization of metric distortion

Simply maximizing the correlation (or equivalently, minimizing the mean-squared difference) of the folding patterns of a subject with that of the average imposes too few constraints on the types of allowable morphs. For example, transformations that cause folds or distortions in the local topology of the surface are undesirable as the coordinates of points in these regions are not unique. While we wish to afford the surface some flexibility in order to achieve successful alignment, we also require that some of the geometry of the original surface be preserved. In order to fulfill both these criteria, we add two terms to the energy functional that encourage the preservation of local areas and distances. The distance term serves to give the surface some local stiffness, thus discouraging the introduction of excessive shear, whereas the areal term prevents folds and significant compression/expansion. Note that the area is an *oriented* quantity, in which folded regions are assigned a negative value. This is accomplished by using the embedding space to give the spherical surface a consistent outward orientation, as discussed in Fischl et al. [1999]. These two terms are given by:

$$J_A = \frac{1}{2T}\sum_{i=1}^{T}(A_i^t - A_i^0)^2, \quad J_d = \frac{1}{4V}\sum_{i=1}^{V}\sum_{n\in N(i)}(d_{in}^t - d_{in}^0)^2,$$
$$d_{in}^t = \|\mathrm{x}_i^t - \mathrm{x}_n^t\| \quad (4)$$

where superscripts denote time, with 0 being the initial (i.e., on the folded surface) areal and distance values, T refers to the number of triangles in the tessellation, x_i^t is the (x,y,z) position of vertex i at iteration number t, d_{in}^0 is the distance between the i^{th} and n^{th} vertices on the original cortical surface, $N(i)$ is the set of neighbors of the i^{th} vertex, and the functional dependence of the A_is on the position of the vertex and its neighbors has been suppressed to simplify the notation. The full derivation of the gradient of these two terms is given in [Fischl et al., 1999]. Note that in contrast to the spherical transformation or flattening procedures in which the use of long-range distances is desirable, here the distances are to the nearest neighbors of each vertex, as locally correlated errors allow large regions of the surface to undergo modest expansion or contraction in order to account for individual variability in anatomical features.

Complete energy functional

The complete energy functional balances the degree of allowable metric distortion as measured by J_A and J_d, and the amount of alignment of the folding patterns as governed by J_p.

$$J = J_p + \lambda_A J_A + \lambda_d J_d, \quad (5)$$

where the constants λ_A and λ_d determine the degree to which metric distortion is permitted in order to allow alignment of the folding patterns. Increasing λ_d increases the rigidity of the surface, with the morph becoming a rigid alignment in the limit of large λ_d. Conversely, an almost perfect fit can be achieved between the individual and the average if λ_A and λ_d are set to sufficiently small values. It is important to note that this is not necessarily desirable if the goal is optimal alignment of functionally equivalent regions. This is due to the large compression/expansion and shear required to achieve this degree of alignment. Given the imperfect correlation between folding patterns and the location of functional areas, together with the relatively constant size of computational elements of the nervous system across individuals (e.g. columns), it seems unreasonable to allow too much expansion or compression of cortical regions. Nevertheless, the optimal values of λ_A and λ_d remain an empirical question.

Assessment of variability

One of the primary goals of the proposed coordinate system is to reduce the spatial uncertainty associated with the location of a given anatomical or functional area. That is, we would like the coordinates of an anatomical or functional feature to be consistent across subjects. Toward that end we have designed a validation criterion that measures the blurring introduced by the coordinate transformation. This is achieved by computing the spatial spread over which a feature occurs across individuals in a given coordinate system.

Specifically, we define the ‘‘blurring metric’’ V to be:

$$V_l = 100\,\frac{A_{l,pooled} - \overline{A}_l}{\overline{A}_l}, \quad \overline{A}_l = \frac{1}{N}\sum_i^N A_{l,i}, \qquad (6)$$

where $A_{l,pooled}$ is the volume of the l^{th} labeled region across all subjects, $A_{l,i}$ is the area of the same region in the i^{th} subject, and $\overline{A}_l$ is the mean area of the l^{th} region across all subjects. If all labeled regions occur in exactly the same coordinates, the pooled area will be equal to the individual areas, and V will be 0. Conversely, if the coordinates of a labeled region vary widely, then the pooled area will be substantially larger than the individual areas, and V will be correspondingly larger. Note that the absolute value of V is related to the spatial extent of an area—larger areas will be intrinsically more likely to overlap than smaller ones, and thus blurring values should not be compared *across* areas.

RESULTS

In this section we present the results of applying the registration procedure described above to a number of brains. In order to generate an initial template, we begin with an individual surface and align a set of surfaces from other individuals with it, using a transformation with a high degree of rigidity ($\lambda_A = 0.1$, $\lambda_d = 0.5$).[3] This allows the canonical surface to be constructed in a manner that represents the variability of folding patterns across subjects. A truly rigid morph would introduce too much blurring into the average surface. For example, the angle between the calcarine and parieto-occipital sulci is variable enough that averaging a large number of rigidly aligned surfaces causes them to merge. A more aggressive morphing would align all structures exactly and not permit the average surface to quantify the true variability of curvature patterns. Once the initial alignment is completed, we compute the summary statistics of the convexity of the aligned surfaces and generate a canonical surface. Next, we repeat the alignment procedure using the previously computed means and variances, using parameters that allow a less rigid and therefore more accurate morph ($\lambda_A = 0.2$, $\lambda_d = 0.1$).

[3]Note that all alignments are preceded by an optimal rigid alignment that is accomplished by globally searching the space of all rigid alignments in a multiscale manner. The initial rigid alignment is critical to the robustness of the procedure as it ensures that the morphing energy functional begins within the right basin of attraction.

Morphing

Figure 2 illustrates the results of the morphing procedure. The spherical surface in the middle row at the left is the product of semirigidly aligning and averaging 40 individual cortical surfaces, as detailed above (red regions represent convex or sulcal areas; green regions are concave or gyral). The top row contains the spherical surfaces of four typical subjects with the outline of the average sulci overlaid in blue. Initially, as shown, there is a large misalignment in a number of cortical regions. The results of the registration procedure are shown in the bottom row, which contains the same four surfaces after morphing into register with the canonical surface. The blue outlines illustrate the accuracy of the alignment between the average pattern and each of the individuals, indicating the correspondence between sulci and gyri across individuals after the morphing.

Anatomical variability

Since the registration procedure is driven by the gyral and sulcal folding patterns of the cortex, one would expect the major gyri and sulci to be better localized in the spherical coordinate system than in a volume-based system such as that of Talairach. A graphical illustration of this reduction in anatomical variability is given in Figure 3, which depicts the points in the central sulcus of 11 subjects painted onto the surface of a separate subject. The top two surfaces are the folded (left) and inflated (right) representations, with the cross-subject mapping computed in spherical coordinates, whereas the bottom two surfaces are the same mapping computed in Talairach coordinates. The color scale indicates the percentage of the total number of subjects that map to a given point. Note the compact appearance of the spherical union of central sulci as opposed to that of the Talairach representation, which does not even preserve the topology of the sulcus, resulting in noncontiguous labeled regions.

The accuracy of localization is quantified in Figure 4 which plots the degree of blurring of different sulcal features resulting from averaging in Talairach and spherical coordinates across 11 subjects. Note that the anatomical variability, as measured by the blurring metric defined above, is much lower in spherical than in Talairach coordinates.[4] The minimal blurring in the

[4]We use the automated Talairach registration procedure developed and distributed by the Montreal Neurological Institute [Collins et al., 1994]. However, we believe the results to be applicable to any type of low dimensional intensity-based normalization procedure.

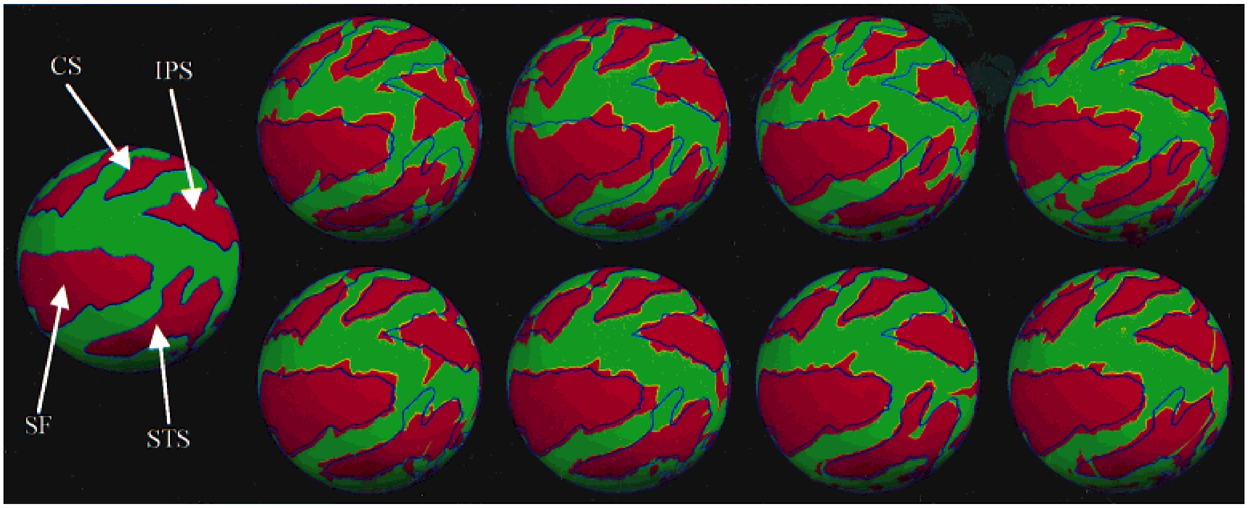

Figure 2.
Four individual hemispheres before (top) and after (bottom) alignment with an average folding pattern (40 subjects, middle left). CS = central sulcus, IPS = intraparietal sulcus, SF = sylvian fissure, STS = superior temporal sulcus.

spherical space demonstrates that the spherical morphing procedure correctly aligns corresponding sulci across subjects, without requiring any manual labeling of anatomical landmarks. This suggests that such a morphing procedure could be used automatically to identify sulcal and gyral features in individual subjects, with a very high degree of accuracy.

Functional variability

One of the main potential applications of volume- and surface-based coordinate systems is for averaging functional data across subjects. Minimizing spatial blurring of the functional data introduced by this averaging process has several benefits: (1) it preserves more information about the detailed relationship between structure and function, (2) it improves the statistical power of statistical parametric maps, by more accurately aligning corresponding functional activations across subjects, and (3) it provides a mechanism for reporting of more accurate coordinates, which facilitates cross-study comparisons.

Given that many functional regions are frequently associated with prominent anatomical features, one would expect a decrease in functional variability to be associated with the increased accuracy of structural localization. Here, we assessed this by using objective functional criteria to label a set of retinotopic and nonretinotopic visual areas and computing the blurring metric for each of the functionally defined areas in spherical and Talairach coordinates.

The retinotopic areas were identified using phase-encoded mapping of the retinotopic coordinates of eccentricity and polar angle [De Yoe et al., 1994, 1996; Engel et al., 1994] combined with the computation of visual field-sign to delineate the borders between neighboring retinotopic areas [Sereno et al., 1995]. The visual field-sign technique provides an objective criterion for specifying the borders of visual areas V1 (upper- and lower visual field), V2 (upper- and lower visual field), V3, VP, and V4v. In addition, the motion sensitive area MT / V5 was identified by comparing the fMRI response to moving vs. stationary rings at low contrast [Tootell et al., 1993, 1995].

The spatial blurring introduced by averaging functional data across subjects in the spherical and Talairach coordinates is illustrated in Figure 5, which shows the union of four adjacent retinotopically defined visual areas across 11 subjects in spherical (top) and Talairach (bottom) coordinates, painted onto the inflated surface of a separate subject. Again, the Talairach normalization generates noncontiguous regions, with greater spread than those resulting from the spherical morphing.

The degree of blurring of these functionally defined areas is quantified in Figure 6. Note that, as was the case for the anatomically defined regions, the blurring is consistently significantly lower in spherical than in Talairach coordinates.

One important benefit of the improved alignment of functional areas in the spherical coordinate system is increased statistical power for cross-subject averaging

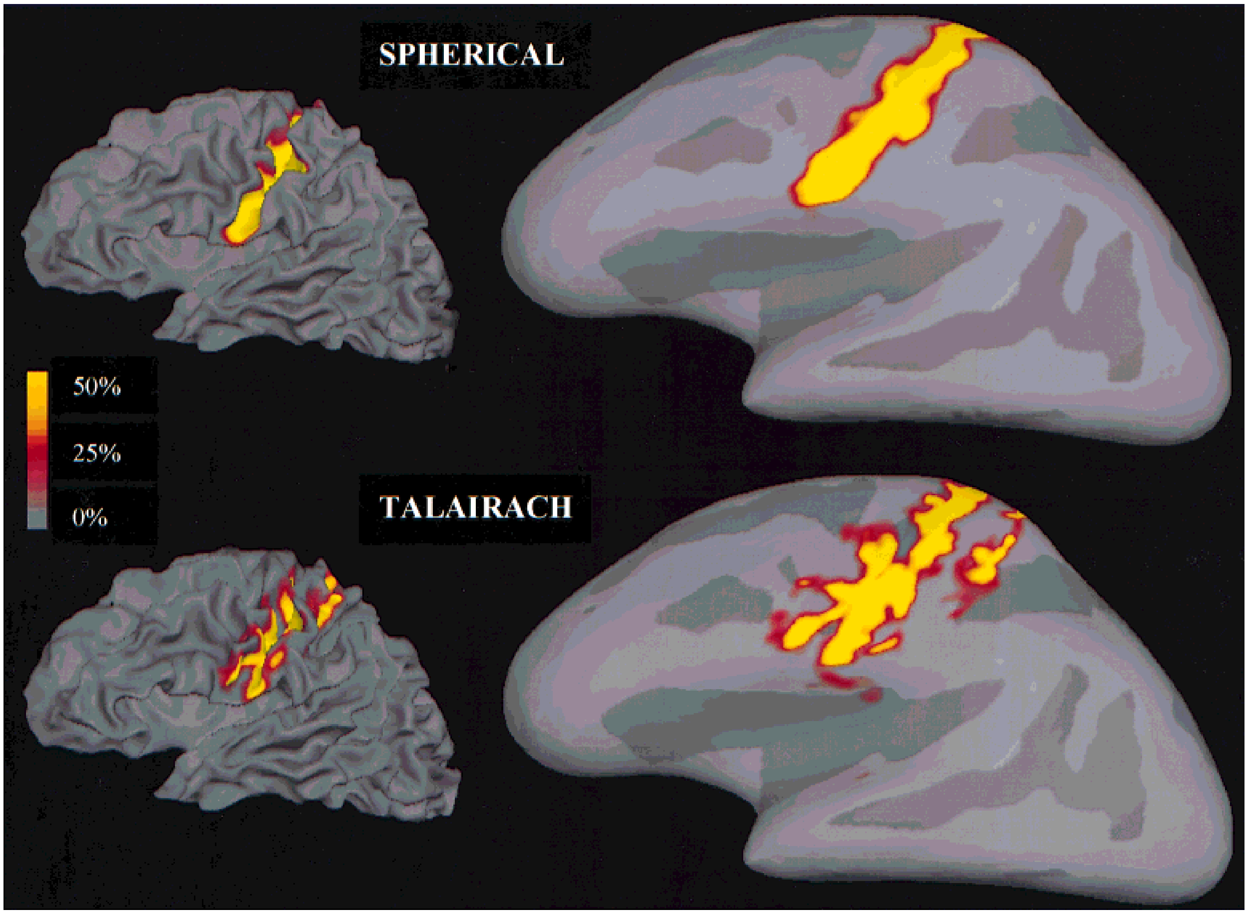

Figure 3.
Mapping of the central sulcus of 11 subjects onto an individual using spherical (top row) and Talairach (bottom row) coordinates. The white matter (left) and inflated (right) surfaces are given for comparison purposes.

of functional data. This is illustrated in Fig. 7, which shows statistical parametric maps of fMRI repetition effects in a visual size-judgment task [Dale et al., 1997] in individual subjects together with the corresponding average maps computed in Talairach and spherical coordinates. Several studies have demonstrated a reduction of activity in a number of cortical regions when a task is performed repeatedly on the same stimulus [Halgren and Smith, 1987; Squire et al., 1992; Raiche et al., 1994; Rugg and Coles, 1995; Ungerleider, 1995; Gabrieli et al., 1996; Buckner et al., 1998; Schacter and Buckner, 1998]. However, such repetition effects are subtle and difficult to detect reliably in individual subjects, as portrayed in the top row of Figure 7. Reducing the statistical threshold reveals an extensive pattern of activation in each subject (second row), although valid statistical inference cannot be drawn at such a low significance level. Typically, Talairach-based cross-subject averaging is used in order to obtain statistically reliable activation patterns (lower left). The improved statistical power afforded by averaging in spherical coordinates results in a more extensive pattern of activation, as illustrated by the map at the lower right.

CONCLUSIONS

The use of a 2-D cortical surface-based coordinate system yields more accurate registration of cortical functional and anatomical areas across individuals than can be attained using the more common 3-D Talairach coordinate system. The reduction in anatomical variability is due to the explicit use of geometric features of the cortical surface to drive the registration procedure. The concomitant improvement in the accuracy of functional localization illustrates the frequent

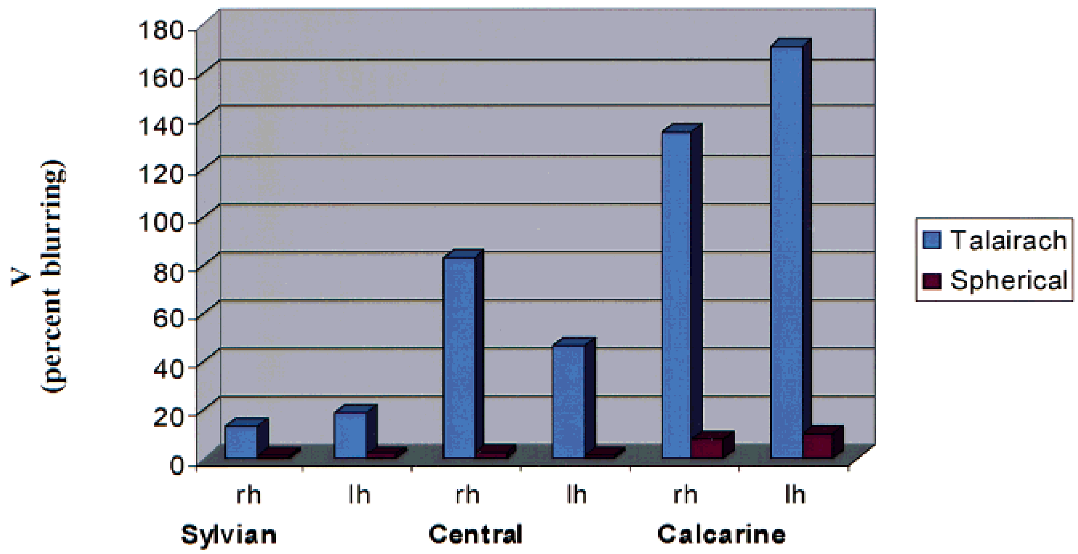

Figure 4.
Percent blurring of three different sulci resulting from averaging in Talairach and spherical coordinates.

association of function with anatomy. The registration procedure employed here makes use of the pattern of folding across the *entire* cortical surface, as opposed to using a small set of manually defined landmarks. This obviates the need for manual intervention as well as eliminating the dependence of the coordinate system on the somewhat arbitrary choice of landmarks. The accuracy of the registration and the associated coordinate system can be assessed using functional data and hand-labeled anatomical data sets. Preliminary results

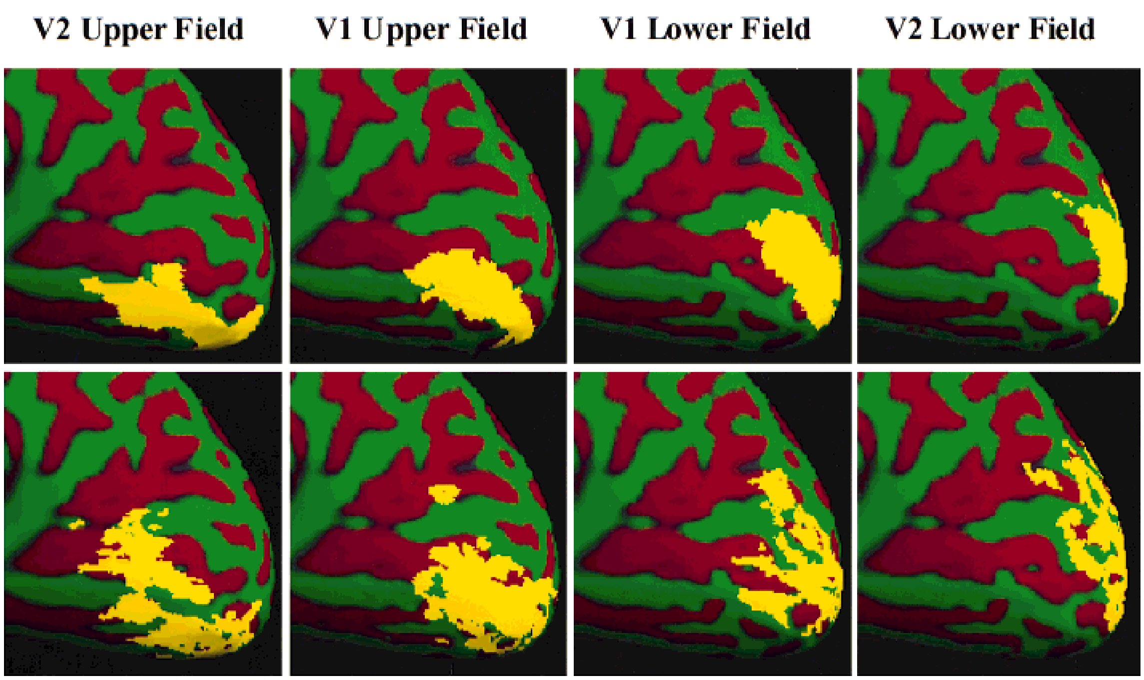

Figure 5.
Pooled visual areas of 11 subjects averaged in spherical (top row) and Talairach (bottom row) coordinates, painted onto a medial view of an individual inflated surface. Anterior is to the left, the occipital pole is at the right.

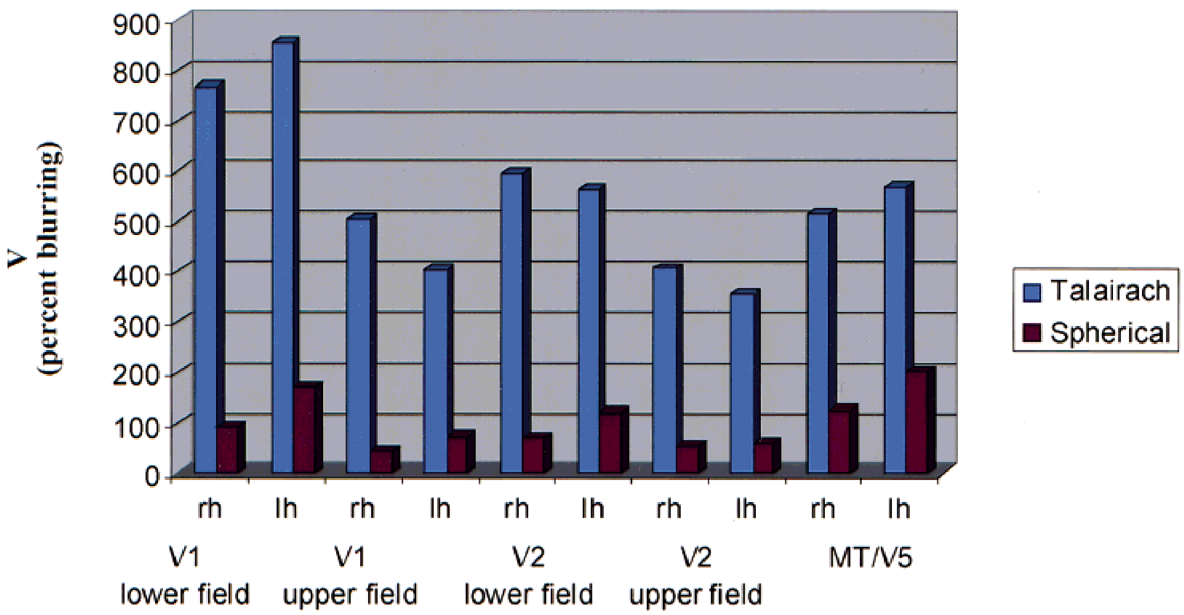

Figure 6.
Percent blurring of visual areas resulting from averaging in Talairach and spherical coordinates.

show that significantly higher localization accuracy can be achieved for both structural and functional regions using such a surface-based approach.

The optimal parameters of the morphing procedure are an empirical issue and depend on the goals of the coordinate system. As discussed previously, optimal *anatomical* alignment does not necessarily result in optimal *functional* alignment. Thus the exact weighting of the preservation of metric properties versus anatomical alignment may change depending on the application, and an optimization procedure can be used to find the optimal parameter values given a set of specific goals. Similarly, the degree to which secondary and tertiary folding patterns are predictive of functional properties is an open question that can be addressed by using curvature to fine-tune the final alignment. Furthermore, if functional alignment is a priority, then functional information such as the automatically delineated retinotopic areas can be used to drive the morphing procedure.

Once the parameter weighting has been fixed, a canonical surface must be chosen as the target of the registration procedure. One alternative is to use an exemplar as the basis for the coordinate system and map individuals into the exemplar. Although this is a straightforward procedure, the use of an average surface has several advantages. Primarily, it prevents the coordinate system from being biased by atypical properties of any individual brain. Furthermore, it allows a direct assessment of the variability of the cortical folding pattern across individuals. Finally, it permits the use of the variability to weight the registration procedure. Thus the alignment of highly variable regions is primarily driven by the more global metric properties of the entire cortical sheet, whereas more stable geometric features are aligned naturally. However, in order to bootstrap the procedure, we propose to use the Visible Human as specified by Van Essen and Drury as the target of the initial alignment, which now exists in spherical form [Drury et al., 1998]. The use of the Visible Human coordinate system as the initial target should facilitate the comparison of data and reported coordinates across coordinate systems. This coordinate system is anchored with its origin at the ventral tip of the central sulcus and oriented such that the zero meridian is approximately parallel to the fundus of the central sulcus (see coordinate lines in Fig. 1). Once the initial alignment of a large number of cortical surfaces has been accomplished, we can average the previously aligned surfaces to generate a probabilistic atlas as the target for the final registration procedure.

The potential applications of the surface-based coordinate system are varied and important and primarily derive from the significant increase in the accuracy of both anatomical and functional localization relative to Talairach coordinates. This increased accuracy makes it possible to distinguish nearby cortical areas based on

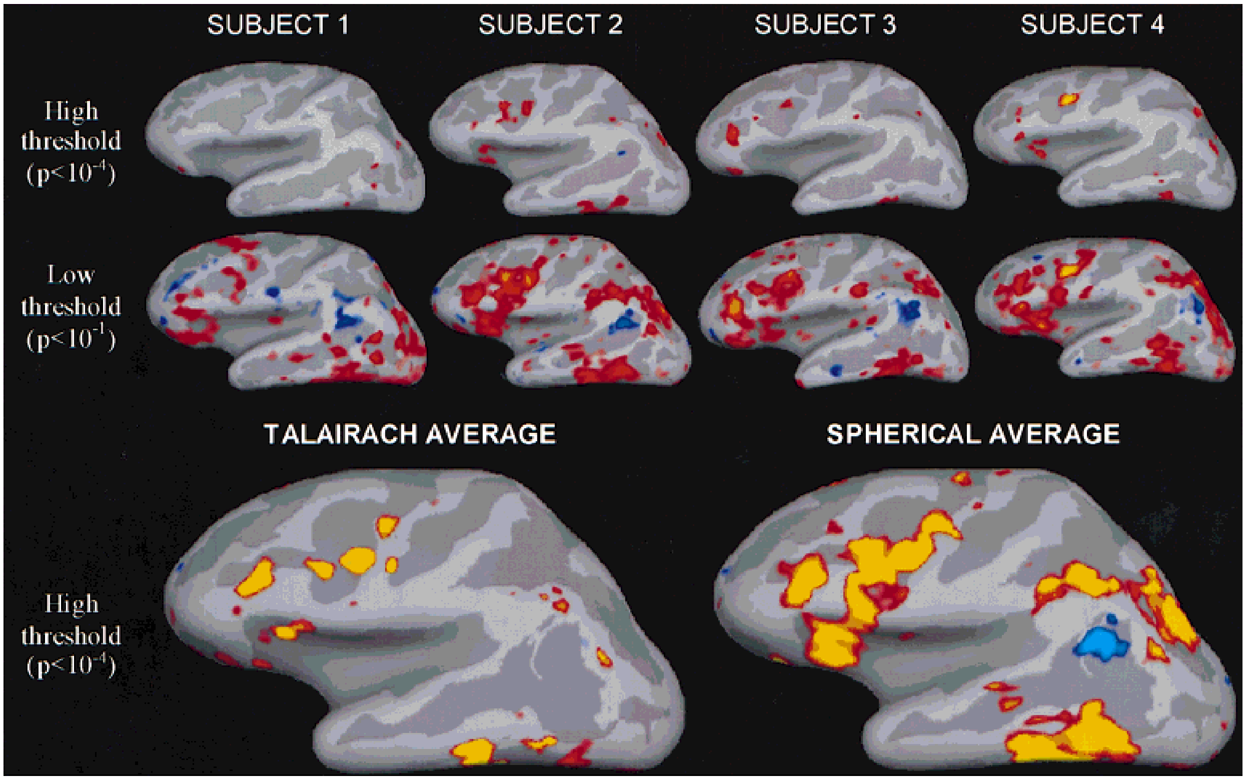

Figure 7.
Increase in statistical power due to averaging in spherical coordinates (bottom right) as opposed to Talairach (bottom left).

their spherical coordinates alone. Furthermore, the reduced spatial blurring associated with the spherical coordinate system directly translates into increased statistical power for cross-subject averaging procedures. This is particularly important for studies of subtle cognitive effects, or for small activation foci.

In addition, the high degree of localization accuracy permits the automatic labeling of functional and structural areas. A generalization of this is the construction of probabilistic atlases of functional, geometric, and histological properties of the cortex, similar to the one proposed in Thompson et al. [1996]. For example, using such an atlas one can generate statistical maps of anatomical properties such as the thickness and volume of cortical gray matter, as well as the degree of expansion / compression and shear required to align an individual with the atlas. These maps can then be used to detect regions with abnormal anatomical or functional measurements within specified areas of cortex. An extension of this idea is to use probabilistic atlases for different subject or patient populations to design optimal discriminant functions for classifying members of each population. Such an approach may have great potential as a clinical tool for detecting and / or assessing subtle functional or anatomical abnormalities.

The combination of automated and accurate methods for surface reconstruction, inflation, flattening, and morphing, together with a cortical surface-based coordinate system, should greatly facilitate the study of both local and global properties of the human cortex. These properties include anatomical features such as cortical thickness and volume, geometric features such as folding patterns, as well as the detailed relationship between structure and function in the human cerebral cortex.

ACKNOWLEDGMENTS

This work was supported by grants from the Human Frontiers Science Foundation to A.M.D. and R.B.H.T.; the Whitaker Foundation to A.M.D., and the National Eye Institute to R.B.H.T. We thank Eric Halgren for useful discussions about validation of the proposed coordinate system, and Sean Marrett and Arthur Liu for suggestions that improved this work. We also thank Janine Mendola and Chris Moore for providing functional data for testing the intersubject averaging procedure, and Heather Drury and David Van Essen for fruitful discussions regarding surface-based coordinate systems.

REFERENCES

Bucker RL, Goodman J, Burock M, Rotte M, Koutstaal W, Schacter D, Rosen BR, Dale AM. 1988. Functional-anatomic correlates of object priming in humans revealed by rapid presentation event-related fMRI. Neuron 20:285–296.

Christensen GE, Miller MI, Marsh JL, Vannier MW. 1995. Automatic analysis of medical images using a deformable textbook. In: Proceedings of Computer Assisted Radiology. Berlin: Springer-Verlag.

Dale AM, Sereno MI. 1993. Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: a liner approach. J Cognitive Neurosci 5:162–176.

Dale AM, Halgren E, Lewine J, Buckner R, Paulson K, Marinkovic K, Rosen B. 1997. Spatiotemporal localization of cortical word repetition effects in a size-judgment task using combined fMRI/MEG. NeuroImage 4:

Dale AM, Fischl B, Sereno MI. 1999. Cortical surface-based analysis I: segmentation and surface reconstruction. NeuroImage 9:179–194.

Davatzikos E. 1997. Spatial transformation and registration of brain images using elastically deformable models. Comput Vision Image Understanding 66:207–222.

DeYoe EA, Bandettini P, Neitz J, Miller D, Winans P. 1994. Functional magnetic resonance imaging (FMRI) of the human brain. J Neurosci Meth 54:171–187.

DeYoe EA, Carman GJ, Bandettini P, Glickman S, Wieser J, Coz R, Miller D, Neitz J. 1996. Mapping striate and extrastriate visual areas in human cerebral cortex. Proc Natl Acad Sci USA 93:2382–2386.

Drury HA, Van Essen DC, Joshi SC, Miller MI. 1996. Analysis and comparison of areal partitioning schemes using two-dimensional fluid deformations. NeuroImage 3:

Drury HA, Van Essen DC, Snyder AZ, Shulman GL, Akbudak E, Ollinger JM, Contruro JM, Raichle M, Collins DL, Neelin P, Peters TM, Evans AC. 1994. Data in standardized Talairach space. J Comput Assist Tomography 18:292–295.

Drury HA, Van Essen DC, Corbetta M, Snyder AZ. 1998. Surface-based analyses of the human cerebral cortex. In: Toga A (ed): Brain Warping. New York: Academic Press.

Corbetta M. 1997. Warping fMRI activation patterns onto the visible man atlas using fluid deformations of cortical flat maps. NeuroImage 5:

Engel SA, Rumelhart DE, Wandell BA, Lee AT, Glover GHL, Chichilnisky EJ, Shadlen MN. 1994. fMRI of human visual cortex. Nature 370:106.

Evans AC, Collins DL, Neelin P, MacDonald D, Kamber M, Marrett TS. 1994. Three-dimensional correlative imaging: applications in human brain mapping. In: Thatcher et al. (eds): Functional Neuroimaging. San Diego: Academic Press, pp 145–162.

Fischl B, Dale AM, Sereno MI, Tootell RBH, Rosen BR. 1998. A coordinate system for the cortical surface. NeuroImage 7:S740.

Fischl B, Sereno MI, Dale AM. 1998. Cortical surface-based analysis II: inflation, flattening, a surface-based coordinate system. NeuroImage 9:195–207.

Gabrieli JDE, Desmond JE, Demb JB, Wagner AD, Stone MV, Vaidya CJ, Glover GH. 1996. Functional magnetic resonance imaging of semantic memory processes in the frontal lobes. Psychol Sci 7:278–283.

Halgren E, Smith ME. 1987. Cognitive evoked potentials as modulatory processes in human memory formation and retrieval. Hum Neurobiol 6:129–139.

Hunton DL, Miezen FJ, Buckner RL, Mier HI, Raichle ME, Petersen SE. 1996. An assessment of functional-anatomical variability in neuroimaging studies. Hum Brain Mapp 4:122–139.

Joshi SC, Miller MI, Grenander U. 1997. On the geometry and shape of brain submanifolds: processing of MR images of the human brain. Inter J Pattern Recognition Artificial Intelligence, special issue.

Miller MI, Christensen GE, Amit Y, Grenander U. 1993. A mathematical textbook of deformable neuroanatomies. Proc Natl Acad Sci USA 90:11944–11948.

Mortenson ME. 1997. Geometric Modeling, 2nd ed. New York: Wiley & Sons.

Raichle ME, Fiez JA, Videen TO, MacLoed A-MK, Pardo JV, Fox PT, Petersen SE. 1994. Practice-related changes in human brain functional anatomy during nonmotor learning. Cerebral Cortex 4:8–26.

Rugg MD, Coles MGH. 1995. ERP studies of memory. In: Electrophysiology of Mind: Event-related Brain Potentials and Cognition. New York: Oxford University Press, pp 132–170.

Schacter D, Buckner R. 1998. Priming and the brain. Neuron 20:185–195.

Sereno MI, Dale AM, Reppas JB, Kwong KK, Belliveau JW, Brady TJ, Rosen BR, Tootell RBH. 1995. Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. Science 268:889–893.

Sereno MI, Dale AM, Liu A, Tootell RBH. 1996. A surface-based coordinate system for a canonical cortex. NeuroImage.

Squire LR, Ojemann JG, Miezin FM, Petersen SE, Videen TO, Raichle ME. 1992. Activation of the hippocampus in normal humans: a functional anatomical study of memory. Proc Natl Acad Sci 89:1837–1841.

Steinmetz HG, Freund HJ. 1989. Cerebral cortical localization: application and validation of the proportional grid system in MR imaging. J Comput Assist Tomography 13:10–19.

Talairach J, Tournoux P. 1998. Co-planar Stereotaxic Atlas of the Human Brain. New York: Thieme.

Talairach J, Szikla G, Tournoux P, Prosalentis A, Bordas-Ferrier M, Covello L, Iacob M, Mempel E. 1967. Atlas d'Anatomie Stereotaxique du Telencephale. Paris: Masson.

Thompson PNM, Toga AW. 1996. A surface-based technique for warping 3-dimensional images of the brain. IEEE Trans Med Imaging 15:1–16.

Thompson PM, MacDonald D, Mega MS, Holmes CJ, Evans AC, Toga AW. 1996. Detection and mapping of abnormal brain structure with a probabilistic atlas of cortical surfaces. J Comput Assist Tomography 21:567–581.

Thompson PM, Woods R, Mega M, Toga A. 1999. Mathematical computational challenges in creating deformable and probabilistic atlases of the human brain. Hum Brain Mapp (in press).

Tootell RBH, Kwong KK, Belliveau JW, Baker JR, Stern CS, Savoy RL, Breiter H, Born R, Benson R, Brady TJ, Rosen BR. 1993. Functional MRI (fMRI) evidence for MY/V5 and associated visual cortical areas in man. Society for Neuroscience 23rd Annual Meeting, Washington, DC.

Tootell RBH, Reppas JB, Kwong KK, Malach R, Born RT, Brady TJ, Rosen BR, Belliveau W. 1995. Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. J Neurosci 15:3215–3230.

Ungerleider LG. 1995. Functional brain imaging studies of cortical mechanisms for memory. Science 270:769–775.

Van Essen DC, Drury HA. 1989. Structural and functional analyses of human cerebral cortex using a surface-based atlas. J Neurosci 17:7079–7102.

Van Essen DC, Drury HA, Joshi S, Miller MI. 1996. Functional and structural mapping of human cerebral cortex: solutions are in the surfaces. Proc Natl Acad Sci.

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