AUTOMATED ANALYSIS OF

STRUCTURAL MRI DATA

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Chapter 5 for *Brain Imaging in Schizophrenia*

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Introduction

Recent advances in medical imaging have revolutionized our ability to investigate disease. Current brain mapping initiatives are charting brain structure and function in thousands of subjects (e.g. Mazziotta et al., 2001; *N*=7000, including 5800 genotyped subjects and 342 mono- and dizygotic twins; Rapoport et al., 1999; *N*=1000+ children and adolescents). An urgent goal of these projects is to analyze patterns of altered brain structure and function in disorders such as schizophrenia, Alzheimer's disease, and abnormal childhood development.

The near-exponential pace of data collection (Fox, 1997) has stimulated the development of image analysis algorithms that compare, pool and average brain data across whole populations. Even so, brain structure is complex and varies dramatically across normal subjects, so systematic patterns of altered structure are hard to detect. This statistical challenge has ignited the rapidly growing field of *computational anatomy* (Miller et al., 2002; Thompson and Toga, 2001; Fischl et al., 2000; Ashburner et al., 2003). This field combines new approaches in computer vision (Fitzpatrick and Sonka, 2000), anatomical surface modeling (Thompson et al., 2000; Fischl et al., 2000; Gerig et al., 2001), differential geometry (Miller et al., 2002), and statistical field theory (Friston et al., 1995; Worsley et al., 1999; Taylor and Adler, 2000) to capture anatomic variation, encode it, and detect group-specific patterns. Many computational anatomy techniques are highly automated, making studies of brain structure feasible on a scale not previously imaginable, with extraordinary power to explore disease effects.

Increased Automation. As brain mapping analyses begin to draw upon hundreds or even thousands of images (Evans et al., 1994, *N*=305; Good et al., 2001, *N*=465; Mazziotta et al., 2001; *N*=851), computational approaches must distil information from these images in a highly automated way. Extracting scientifically useful data requires a sequence of image processing steps, and these are becoming increasingly easy to apply. Automated scalp editing, image

registration, warping, and tissue classification methods are making it faster to pre-process brain images (Woods et al., 1998; Toga, 1998; Ashburner et al., 1999; Shattuck and Leahy, 2001; Smith et al., 2002). Brain parcellation and labeling algorithms are also approaching human accuracy in delineating anatomy (Collins et al., 1995; Fischl et al., 2000; Zhou et al., 2001; Pitiot et al., 2002). Last but not least, signal detection methods are being rapidly optimized, drawing on groundbreaking research in image statistics (Gaussian field theory, statistical flattening, and non parametric methods), as well as novel data transformations (tensor maps, scale space, adaptive filters, etc.). These mathematical developments benefit large-scale clinical and basic science studies, as well as smaller ones where sample sizes or detection power are limited (Thompson et al., 2000, 2001).

Statistical Atlases. Statistics that describe how brain structure and function vary in a population can also empower the automated analysis of new images (Ashburner et al., 1998; Gee et al., 1998; Dinov et al., 2000). *Computational brain atlases*, for example, warehouse this statistical information in standard 3D coordinate system (Mazziotta et al., 2001; Thompson et al., 2002). Computational algorithms can then use normative criteria find structures in new images, and also to map patterns of abnormalities in disease. They can also uncover surprising relationships between genotype and phenotype (Thompson et al., 2001; Styner and Gerig, 2001; Cannon et al., 2002), and dynamic brain changes in response to therapy (Haney et al., 2001; Toga and Thompson, 2003). Due to hardware and network advances, large image analyses can now be run on remote, or distributed, servers. Supercomputing resources can then be harnessed to mine brain data for population trends (Toga et al., 2001; cf. Collins et al., 2002; Warfield et al., 1998).

Organization of this Chapter. In this chapter, we review computational methods to detect structural differences in the brain. We describe the mathematical concepts underlying several common approaches, including voxel-based morphometry, deformation morphometry, and tensor-based morphometry, as well as shape modeling, and traditional volumetrics (see Fig. 1; Table 1 summarizes these concepts). We also cover hybrid approaches (e.g., cortical pattern matching) which analyze shape and tissue distribution in the same analysis. Each technique is optimized to detect specific features, and has its own strengths and limitations. We highlight illustrative clinical findings from studies of development, dementia and schizophrenia. We also describe newer techniques that map patterns of brain change over time (e.g., to study disease progression or medication effects). Finally we describe how imaging statistics can be expanded to assess genetic effects on brain structure, in family, twin or allele-based designs.

Goals. Morphometric methods are powerful in a variety of settings. Identifying structures with altered volume or

shape can help understand the biological basis of a disease, pin-pointing when and where deficits occur. Gross structural changes may indicate cellular processes such as neuronal loss or atrophy, delayed myelination, or aberrant migration and connectivity (Goldman-Rakic and Selemon, 1999; Bogerts, 1999; Falkai et al., 1999; Weinberger et al., 2001; Weinberger and McClure, 2002). Structural changes can also be correlated with functional, metabolic, spectroscopic, or architectonic data (McCarley et al., 1999; Buchsbaum et al., 2002). If structural measures link with behavioral or cognitive measures, or with clinical outcomes, they may provide a biological marker, or 'endophenotype', for a disease. MRI studies reveal early brain changes in subjects at genetic risk for Alzheimer's disease (ApoE4 carriers; Laakso et al., 2000), and can expedite early diagnosis and treatment. They can uncover drug effects in clinical trials (Fox et al., 1999, 2000, 2001). *Dynamic brain maps*, in particular, capture how the brain changes over time. They reveal growth spurts in childhood (Thompson et al., 2000), gray matter loss in adolescence (Giedd et al., 1999; Sowell et al., 1999), and dynamic waves of brain changes in dementia and schizophrenia (Thompson et al., 2001, 2002). These maps can also clarify how disease processes spread dynamically in the brain (Thompson et al., 2001, 2002). Statistics of these brain changes can also be stored in digital brain atlases. These can be used in medication studies to map where therapy is slowing down a disease process (Haney et al., 2001). Deficits can also be compared across cohorts, including chronic, first-episode and early-onset patients, or subgroups with different symptom profiles (Giedd et al., 1999; Narr et al., 2002; Job et al., 2002). Screening relatives is also vital for early diagnosis and understanding disease transmission. Structural image analyses can now produce g*enetic brain maps* (Thompson et al., 2001, 2002). These pinpoint deficit regions in genetically at-risk relatives (Cannon et al., 2002; Narr et al., 2002; Baare et al., 2001). Genetic designs reveal regions where brain structure is under strongest genetic control, linking structural variation with heritable differences in cognitive function (Thompson et al., 2001; Posthuma et al., 2002). The computational format of these large-scale brain atlases makes it easy to stratify them to search for differences in subpopulations with known environmental risk, or with allelic variations at candidate loci, to identify possible pathogenic factors and explore their effects.

Automated and Manual Approaches. Brain image analysis is considerably faster when some or all of the image processing steps are automated. Traditionally, manually intensive approaches (such as tracing 3D regions of interest on brain images) have been the mainstay of structural image analysis. They reveal a consistent pattern of deficits in the dementias (Mega et al., 2000) and schizophrenia (Lawrie and Abukmeil, 1998) and provide fundamental data on brain growth in childhood and adolescence (Jernigan et al., 1991; Kennedy et al., 1998). Manually-derived measures also continue to provide extremely valuable information (Lawrie et al., 2002), and serve as a gold standard to validate newer, more automated techniques (Tisserand et al., 2002; Job et al., 2002).

In this chapter, we focus on more automated techniques for analyzing MRI data. We compare these with standard volumetric measures in terms of the results they have found, their statistical power and biases, and the range of features they assess. Despite the overarching goal of automating image analyses, often significant information is gained by combining manual approaches with more automated ones. For example, sulci may be traced manually on a cortical model extracted automatically, to increase the power of a gray matter analysis (Fig. 2; Thompson et al., 2001; Davatzikos et al., 2001). Automated labelings of the brain may also be manually corrected for greater accuracy (Collins et al., 2002).

2 Image Pre-Processing

MRI Scanning. Magnetic resonance imaging (MRI) is now the modality of choice for clinical and basic science studies of brain structure (Toga and Mazziotta, 2002). 3-dimensional MR images provide high-resolution maps of anatomy (even permitting the measurement of cortical thickness; MacDonald, 1998; Fischl et al., 2000). They also provide excellent tissue contrast to differentiate tissue types, such as gray matter, white matter and CSF. They are sensitive to disease-specific changes in anatomy, including progressive gray matter loss and ventricular enlargement in dementia and schizophrenia, as well as white matter and vascular lesions. A variety of tools have been developed to analyze these images, linking patterns of altered brain structure with diagnosis, symptoms, or demographic factors (Fig. 2). We describe some of these key processing steps next.

Image Preprocessing. The first step in most structural image analyses involves placing MRI data from different subjects into a common 3D coordinate system, or stereotaxic space (Collins et al., 2002). The success of brain mapping has been promoted by the international adoption of a coordinate-based 3D reference system for brain data. This helps to pool data across subjects and studies. Images and brain maps are aligned with a standard brain template, typically one based on the Talairach stereotaxic atlas (Talairach and Tournoux, 1988). Anatomical maps and locations can then be referenced in standard coordinates; mathematical techniques can average images across subjects, detect disease-specific patterns, hemispheric asymmetries, and subtle group differences in cortical function, in whole populations.

Stereotaxic Coordinates. The first brain atlas used widely in brain mapping was that defined by the neurosurgeon Jean Talairach (Talairach and Tournoux, 1988). Using a stereotaxic device anchored to a patient's skull, neurosurgeons

can accurately position surgical apparatus within a patient's brain to target biopsy locations, epileptic foci, and vascular lesions identified in 3D reference coordinates. The Talairach atlas was developed before intraoperative imaging, to make it easier to identify deep nuclei in stereotaxic coordinates. At the time, these structures were imaged with very limited resolution using pneumoencephalography.

Talairach Space. In addition to a series of labeled anatomical plates, reconstructed from histologic material, Talairach defined a mechanism to transfer new images onto the atlas. In the Talairach stereotaxic system, piecewise affine transformations are applied to 12 rectangular regions of brain, defined by vectors from the anterior and posterior commissures to the extrema of the cortex. These transformations re-position the anterior commissure of the subject's scan at the origin of the 3D coordinate space, vertically align the interhemispheric plane, and horizontally orient the line connecting the two commissures. Each point in the incoming brain image, after it is 'warped' into the atlas space, is labeled by an (x,y,z) address referable to the atlas brain. Originally developed for surgery, the Talairach stereotaxic system rapidly became an international standard for reporting functional activation sites in PET studies, allowing researchers to compare and contrast results from different laboratories (Fox et al., 1985, 1988; Friston et al., 1989, 1991).

MRI Brain Templates. The Talairach templates were based on *post mortem* sections of the brain of a single 60 year-old female subject, and the atlas plates had a variable slice separation (3 to 4 mm), and inconsistent data from orthogonal planes. To address these limitations, a composite T1-weighted MRI dataset was constructed from 305 young normal subjects (239 males, 66 females; age: 23.4±4.1 years) whose scans were individually mapped into the Talairach system by a 9-parameter linear transformation, intensity normalized, and averaged on a voxel-by-voxel basis (Evans et al., 1994). The resulting average brain made it easier to develop automated image alignment methods to map new MRI and PET data into a common space (Fig. 2, *top left*). The *International Consortium for Brain Mapping* (ICBM; Mazziotta et al., 1995; 2001) subsequently applied the same image averaging procedure to a subset of 152 brains. This produced a template that is widely used as part of the *Statistical Parametric Mapping* image analysis package (SPM2; Friston et al., 1995).

Automatically Aligning New Data to an Atlas. New MR data are typically aligned with an atlas template by defining a measure of intensity similarity between the overlapping dataset and atlas. This measure of fit is optimized by tuning the parameters of the alignment transformation until the similarity is maximized (Woods et al., 1998; Ashburner,

2001). Intensity-based registration measures include 3D cross-correlation (Collins et al., 1994, 1995), ratio image uniformity (Woods et al., 1992, 1993), or mutual information (Viola et al., 1995; Wells et al., 1997), or the summed squared differences in intensity between the scans (Christensen et al., 1993, 1996; Ashburner et al., 1998; Woods et al., 1998). Both linear (global) transforms, and nonlinear transforms may be used (nonlinear techniques are reviewed in detail in Toga, 1998; Thompson et al., 2001). Registration algorithms therefore make it feasible to automatically map new subjects' MRI data to an atlas coordinate space based directly on the Talairach reference system.

Analysis of brain data in a stereotaxic space makes it easier to (1) compare data across groups, experiments, and data modalities, or over time; (2) define spatial masks to restrict the analysis to a particular anatomical region; (3) employ powerful statistical methods based on random-field theory; (4) gather spatial statistics (sometimes called 'priors') to guide the behavior of an image analysis algorithm (e.g. a tissue classifier); and (5) rapidly re-analyze data using different processing streams (Collins et al., 2002). In addition to the ICBM template described previously, some groups have aligned data to special templates that reflect the anatomy of Alzheimer's patients (Thompson et al., 2000), or children (Wilke et al., 2002). Holmes et al. (1998) averaged together 27 scans of a single subject, to create a high-resolution MRI atlas template. Kochunov et al. (2002) adjusted the shape of this template to the population mean. High-dimensional warping algorithms (Thompson et al., 2000) may also be employed to create customized anatomic templates with the mean shape and intensity for the specific group being studied, with well-resolved cortical features in their mean locations. All these templates can be used in the image analyses described next.

3 Voxel Based Morphometry

Voxel based morphometry (VBM; Wright et al., 1995; Ashburner and Friston, 2000) is perhaps the simplest and fastest approach to detect group differences in brain structure. VBM has been used to study aging and gender effects in normal subjects (Sowell et al., 1999; Maguire et al., 2000; Good et al., 2001) as well as Alzheimer's disease (Baron et al., 2001; Mummery et al., 2000), frontotemporal and Lewy body dementia (Rosen et al., 2002; O'Brien et al., 2002; cf. Studholme et al., 2001), Parkinson's disease, and even *herpes simplex* encephalitis (Gitelman et al., 2001). One of its earliest applications was to map gray matter deficits in chronic schizophrenia (Wright et al., 1995, 1999), and these deficits have subsequently been subsequently replicated in first-episode (Job et al., 2002) and childhood-onset patients (Thompson et al., 2001). The following steps are typically used.

Tissue Classification. MR images are first segmented using a tissue classifier, producing images showing the spatial distribution of gray matter, white matter, and CSF (Fig. 1). Tissue classifiers may be supervised (where a user selects some points representing each tissue class to guide classification) or unsupervised (no user intervention). Bayesian segmentation methods (Warfield et al., 1998; Ashburner and Friston, 2000; Shattuck and Leahy, 2001) assign each image voxel to a specific class based on its intensity value as well as prior information on the likely spatial distribution of each tissue in the image. The classification step may be preceded by digital filtering to reduce intensity inhomogeneities due to fluctuations and susceptibility artifacts in the scanner magnetic field. This step is often called RF (radio-frequency) correction or bias correction. Well validated RF-correction methods include N3 (non-parametric non-uniform intensity normalization) which is based on histogram entropy maximization (Sled, 1997), and BFC (bias field corrector; Shattuck and Leahy, 2001; Arnold et al. (2001) compares these and other approaches). In so-called 'expectation-maximization' techniques, RF correction and tissue classification steps are combined, using one to help estimate the other in an iterative sequence (Warfield et al., 1998).

Jacobian Modulation. In VBM, segmented gray matter images are warped to the standard ICBM brain template, or to an average gray matter image representative of the group being studied. Linear (uniform scale and shears) or full nonlinear (warping) transforms may be applied. Since this warping transformation changes the shape of the brain being measured, the intensity in the gray matter image (usually ones, as the image is binary) is divided by the local volumetric expansion factor, to preserve the total amount of tissue in the original images (Goldszal et al., 1998; Davatzikos et al., 1998; Good et al., 2001). This step is known as the 'Jacobian modulation' or 'volume preservation' step, and it sensitizes the analysis to true volumetric differences between groups, rather than just differences in the proportion of gray matter after spatial normalization. Regions compressed by the warping transform have their gray matter measure (known as gray matter 'density' or 'concentration') increased. The local expansion factor, or Jacobian, is computed from the deformation gradient, or Jacobian matrix, of the 3D warping field. After spatial normalization, the same voxel location in each image corresponds roughly to the same brain structure (see later for caveats). Normalized gray matter images are then smoothed with a filter (typically a Gaussian or box filter with 8-15 mm FWHM; see Salmond et al., 2002, for different choices). By the 'matched filter theorem', larger filters optimize detection of diffuse or widespread effects, at the expense of blurring observations from different anatomic regions. This smoothing (1) partly accounts for registration errors and reduces inter-individual variance, increasing detection sensitivity; and (2) makes the data better a better approximation to a Gaussian random field. There is some inherent data averaging when applying a filter, and the

Central Limit Theorem states that the average of many observations drawn from non normal distributions still tends to be normally distributed. This normality of the residuals is a requirement if parametric statistics are used in later processing.

Statistical Parametric Maps. Statistical analysis in VBM typically proceeds by fitting the general linear model (GLM) to the data (gray matter density) from all subjects at each voxel. This identifies voxels where tissue density relates to diagnosis, cognitive scores, etc., after discounting confounding effects (e.g., age, IQ, etc.). As in volumetric studies, a measure of total gray matter or whole brain volume may also be used as a covariate of interest, and to detrend brain size effects from the data (see *Footnote 1*).

Footnote 1. *Brain Size Confounds.* Note that if the groups being compared have differences in average brain size, it may be surprisingly difficult to detrend brain size effects from local measures. Artifactual regional effects may then appear that are in fact attributable to variations in overall brain size (this is not just an issue with VBM but with all stereotaxic comparison methods; see Thompson et al., 2003 for a review of its impact on reports of sex differences in the corpus callosum). Because brain substructures do not scale linearly with brain volume (Jäncke et al., 1997), the mean location of a given structure linearly mapped into stereotaxic space may differ in small and large brains. To avoid these effects masquerading as local differences, the dependency of warping fields on brain scale can be modeled using multiple regression (Stuart et al., 2001), and used to adjust the voxel level effects.

Including the overall amount of gray matter as a covariate in the model enables the detection of regionally specific differences in gray matter density, over and above any global differences. Multiple regression and ANOVA, used widely in volumetric analysis, are special cases of the GLM, and are widely used. A statistical parametric map (SPM; Friston et al., 1995) is generated in which each voxel contains a statistic quantifying the group difference at that stereotaxic position. At each voxel, the actual statistic is compared with a reference (or *null*) distribution for the statistic (e.g., the values it takes when groups are sampled from the same population, and no effect is present). This gives a *p*-value for how likely it is that such a difference could occur by accident, if only that voxel were assessed. Although VBM is designed to evaluate group differences, it is also possible to compare a single subject with a group, so long as the data are first smoothed with a filter of at least 12 mm FWHM. This smoothing is necessary to guard against non normality of the residuals, which occurs when one of the groups examined consists of only a single subject (Salmond et al., 2002).

Caveats. Some caveats are required in interpreting the findings of VBM, because it can infer local anatomical differences (1) from systematic registration errors in one group relative to the other; and (2) from systematic shifts in unaffected regions that result from differences in truly affected structures (Bookstein, 2001; Ashburner and Friston, 2002). VBM findings can, however, be confirmed using shape based or volumetric methods (see below for an effect characterized with both techniques).

Example in Childhood Onset Schizophrenia. Fig. 3(a) shows an example from a VBM study of childhood onset schizophrenia (COS; Sowell et al., 2000). In COS, as in adult onset schizophrenia, the third and lateral ventricles are enlarged. In Fig. 3, voxel level differences between groups are detected in vicinity of the occipital horns. These voxels contain white matter in controls and CSF in patients. In the average patient image, an arching of the corpus callosum, in the midsagittal plane, places CSF into voxels that are classified as gray matter in controls. These voxels appear in the map of gray matter differences. In this study, volumetric analyses of the lateral ventricles in native image data space confirmed significantly higher volume in posterior, but not anterior, regions (Sowell et al., 2000), suggesting that VBM may be a rapid way to identify these volumetric differences.

Several other groups have applied VBM in cohort studies of schizophrenia, finding stereotaxic differences in tissue distribution (Wright et al., 1995; Ananth et al., 2002; Suzuki et al., 2002). In a recent longitudinal study of childhood onset schizophrenia, we used a variant of VBM (called *cortical pattern matching*; see Section 5) to detect a wave of progressive cortical gray matter loss, spreading from parietal to frontal and temporal brain regions. This wave of loss spread and intensified over a five-year period and correlated with global assessments of function (CGAS scores; Thompson et al., 2001). Wilke et al. (2001) noted a similar link between gray matter loss and global assessment of function (GAF) scores in 48 adult-onset schizophrenia patients and 48 controls analyzed with VBM. The more severely ill patients had greater gray matter deficits in the left inferior frontal and inferior parietal lobes. A similar VBM study of first-episode patients (Job et al., 2002) identified significant gray matter deficits in the right anterior cingulate, right medial frontal lobe, left middle temporal gyrus, and left limbic and postcentral regions of the left hemisphere. In a recent very large study (159 patients and 158 controls), Hulshoff Pol et al. (2001) detected decreased gray matter density in the left hippocampus and amygdala, consistent with the reduced hippocampal volumes found consistently in volumetric studies of schizophrenia (Lawrie and Abukmeil, 1998).

Multiple Comparisons Correction. In VBM or any statistical mapping approach, a vast number of voxels are assessed (typically millions). *P*-values must therefore be corrected for multiple comparisons before the significance of the overall map is assessed, unless there was an *a priori* hypothesis of an effect at a specific stereotaxic voxel. Bonferroni corrections, which adjust *p*-values based on the total number of independent tests, are not used because data at neighboring voxels are highly correlated. Approaches to obtain corrected *p*-values include the theory of stationary Gaussian random fields (Friston et al., 1995; Frackowiak et al., 1997), and non-parametric methods such as permutation (Bullmore et al., 1999; Thompson et al., 2000; Nichols and Holmes, 2002). Gaussian field theory models the

distributions of features in statistical maps that would be found by accident, if the null hypothesis of no significant difference between groups were true. Experimental effects are compared with these null distributions, to check if they could have occurred by accident, or whether there is enough evidence to reject the null hypothesis of no differences between groups. Features whose distributions are modeled include (1) the maximum value (or peak height, Z_{max}) of the statistic found in the map, and (2) the size of the largest connected cluster of voxels above a given threshold. Null distributions for more complex features can also be derived mathematically, such as the number of clusters exceeding a given height and spatial extent, or the total spatial extent of these clusters. These features are thought of as measurements of 'rising swells or waves in a choppy (noisy) sea' (Lange, 1998), where the roughness of the sea is estimated from the data. To estimate the probability that the maximum value of the map (Z_{max}) is greater than a given threshold *t* under the null hypothesis (i.e., when no difference is present), Worsley et al. (1994) used the expected Euler characteristic $E[\chi(A(t))]$ of a binarized map thresholded at *t*, so that for high *t*,

$$Pr(Z_{max} > t) \cong E[\chi(A(t))] = \lambda(V)|\Lambda|^{1/2} (2\pi)^{-(D+1)/2}.He_D(t)\exp(-t^2/2). \qquad (1)$$

Here $\lambda(V)$ and *D* are the volume and dimension of the search region, and $He_D(t)$ is the *D*th order Hermite polynomial. The roughness tensor, Λ (or its inverse, the smoothness tensor, Λ^{-1}), is crucial for estimating *p*-values. It is defined as the covariance matrix of the partial derivatives of the residuals along each of the *D* coordinate axes, with variances $Var[\partial X/\partial x_i]$ on the diagonal and off-diagonal elements $Cov[\partial X/\partial x_i, \partial X/\partial x_j]$. Once these parameters are estimated, a significance level can be assigned to the overall map, so long as the theoretical assumptions are not violated.

Statistical Flattening. An underlying assumption of the above parametric approach is that the process is a *stationary* Gaussian field, i.e. its statistical characteristics, including its roughness parameter $|\Lambda|$ (or its inverse, the smoothness $|\Lambda|^{-1}$), are constant across all voxels in the image. This assumption is reasonable for functional imaging data, but is violated for structural imaging data. Binary structure masks, for example, are constant across large regions, and even after smoothing the signal changes more rapidly at the edges of structures (Worsley et al., 1999). The distribution of cluster sizes that occur by accident is therefore skewed towards larger cluster sizes in smooth image regions, resulting in more false positives (and false negatives in rough regions) than predicted by formulae for stationary fields. To address this, Worsley et al. (1999) suggested a *statistical flattening* approach in which the data are warped into a new space, which may have higher dimension than the data, so that in the new space the smoothness of the normalized residuals of the statistical model is stationary. The *p*-value for cluster sizes above a threshold can then be applied using size

measurements in the new space, or by estimating the effective resolution of the field directly from the normalized residuals (Worsley et al., 1999). Thompson et al. (2000) proposed an alternative statistical flattening approach, where a partial differential equation:

$$g^{ij}(\partial^2 \mathbf{u}/\partial r^i \partial r^j) + \partial/\partial u^j(S^{ij})\mathbf{u}_r i = 0 \qquad (2)$$

is run in the image, to generate a deformed grid $\mathbf{u}(\mathbf{r})$ whose deformation gradient tensor approximates the smoothness S^{ij} of the normalized residuals (here g^{ij} is the contravariant metric tensor of the grid). Relative to this new computational grid, the residuals are stationary and isotropic, and *p*-values for the gray matter reductions can be evaluated with standard formulae.

Non Parametric Methods: Permutation. A final approach to estimate *p*-values for significant features in statistical maps is to estimate their distribution under the null hypothesis by permutation (Bullmore et al., 1999; Sowell et al., 1999; Thompson et al., 2000, 2001, 2002). This non-parametric approach avoids assumptions about the spatial autocorrelation of the process, and has been successful in functional imaging as well (Nichols and Holmes, 2002). Subjects are randomly assigned to groups and the distribution of accidental clusters is tabulated empirically. The overall 'corrected' P value for the effect in the true grouping is given by the proportion of random maps that have an effect at least as strong as the real map (usually this is very small). In a recent study of gray matter changes in adolescence (Sowell et al., 1999), we found specific reductions in gray matter in dorsal frontal and parietal cortices (Fig. 3(b); $p < 0.05$, permutation test). Random permutations revealed that false positive clusters occurred (on average 5.8 per simulation), but the number of suprathreshold clusters (57) was significantly higher in the real experiment than predicted by the null distribution (Fig. 3(b)). In these experiments, a region of interest may also be specified in advance to constrain the search for significant results, leading to increases in statistical power (Thompson et al., 2002).

4 Anatomical Surface Modeling

Anatomical surface modeling (Thompson et al., 1996, 2002; Gerig et al., 2001) provides an alternative approach to map group differences in brain structure. 3D surface models are built to represent anatomical structures in each scan. By imposing a regular mesh structure on structures in different subjects, average models can be created to represent a particular group. Asymmetries, profiles of group variability, and individual or group differences are visualized locally.

Rather than contrasting image intensities at each image voxel across subjects (as in VBM), differences in the shapes of structures are measured and mapped. Shape measures can be sensitive to disease-specific changes, even when volumetric measures are not (Narr et al., 2000). Narr et al. (2000) observed that callosal area did not discriminate schizophrenic groups from healthy controls, while shape measures provided a distinct group separation. Wang et al. (2001) found that hippocampal shape descriptors had greater power to distinguish patients from controls than volumetry, while others have argued that each approach provides complementary information (Gerig et al., 2001; Golland et al., 2001; Thompson et al., 2001).

Surface averaging techniques have mapped local profiles of ventricular expansion and cortical asymmetries in dementia, autism, and schizophrenia (Fig. 3; Thompson et al., 2000; Blanton et al., 2000; Narr et al., 2002), as well as subtle or pre-clinical hippocampal changes (Csernansky et al., 1999; Narr et al., 2001). Thinning effects have also been localized at the callosal *isthmus* in Alzheimer's disease (Thompson et al., 1998), as have growth profiles in childhood (Thompson et al., 2000). Parametric mesh models have also visualized patterns of callosal arching in chronic and first-episode schizophrenia patients as well as high-risk relatives (Narr et al., 2000, 2002). They have also found gender x disease interactions in schizophrenia (Narr et al., 2000) and callosal alterations in fetal alcohol syndrome (Sowell et al., 2001; see also Bookstein et al., 2001).

Generating Surfaces. Some surface models are easy to extract automatically. Examples include the cortex (MacDonald et al., 2000; Shattuck and Leahy, 2001; Fischl and Dale, 2001; Ratnanather et al., 2001), cerebellar surface, corpus callosum (Pitiot et al., 2002), and hippocampus (Haller et al., 1997; Joshi et al., 1998). Structures that are more difficult to extract automatically can be traced manually in serial sections, or in 3D, using a formal anatomical protocol with quantified reliability (e.g. Sowell *et al.,* 2001; Zhou et al., 2001; Hayashi et al., 2002). Manual traces are subsequently converted to uniform mesh format using a re-gridding algorithm, which makes the sampled points spatially uniform (Thompson et al., 1996a,b). In many morphometric studies, manual and automated methods are combined, for greatest accuracy. For example, the cortex may be extracted automatically, but gyral landmarks may be traced on it manually by trained raters.

Anatomical Averaging. An average anatomical surface is generated for a group of subjects by averaging the vector locations of corresponding surface points across the subject group. This process is repeated for each point on the surface. If $\mathbf{r}_i(u,v)$ is the 3D position in stereotaxic space of the point with parametric coordinates (u,v) on the *i*th subject's mesh, a

group average surface model is given by another mesh of the form:

$$\mathbf{r}_{\cdot}(u,v) = (1/N)\sum_{i=1 \text{ to } n} \mathbf{r}_i(u,v), \text{ for all } (u,v). \qquad (3)$$

Information on anatomic variability may be shown as a *variability map* (Thompson et al., 1996, 1998). To map variability, individual deviations from the average surface are measured by computing 3D displacement maps (Fig. 4). These are patterns of 3D displacement vectors that would be required to re-shape the average surface into the shape of a specific individual. If surface locations $\mathbf{r}_i(u,v)$ in subject *i*, are indexed by parametric coordinates (u,v), then deviations of these locations in individual *i* from the mean anatomical surface are given by the set of displacement vectors:

$$\mathbf{d}_i(u,v) = \mathbf{r}_i(u,v) - \mathbf{r}_{\cdot}(u,v), \qquad (4)$$

for all pairs of corresponding grid points $\mathbf{r}_i(u,v)$ and $\mathbf{r}_{\cdot}(u,v)$. For each (u,v), the associated displacement maps $\mathbf{d}_i(u,v)$ represent a sample of (vector) observations from a zero-mean, spatially anisotropic probability distribution (Thompson et al., 1996). The variability of the surface points can be encoded using the covariance matrix, or tensor, of the deformation maps:

$$\mathbf{\Psi}(u,v) = [1/(N-1)] \, \Sigma_{i=1 \text{ to } N} \, \mathbf{d}_i(u,v)\mathbf{d}_i(u,v)^T \qquad (5).$$

This matrix stores the shape, or preferred directions, of anatomic variability in the brain (Thompson et al., 1996; Cao and Worsley, 1999). The simplest measure of anatomic variability is the root mean square magnitude of the 3D displacement vectors, assigned to each point, in the surface maps from individual to average. This variability pattern can be visualized as a color-coded map. This map picks out highly variable regions, such as the occipital horns of the ventricles (Fig. 5), and the gyral patterns of the perisylvian cortices.

Application to Alzheimer's Disease. An illustrative application of surface modeling is the analysis of ventricular anatomy in Alzheimer's disease. Two features emerge in the average anatomical maps (Fig. 5) that may be difficult to localize with conventional volumetry. First, the ventricles are larger in Alzheimer's disease than in healthy controls; second, a marked ventricular asymmetry (left larger than right) appears in the occipital horns. Considerable anatomic variation (*red colors*), in occipital horn regions, obscures these average patterns in individual datasets. Once identified, these features can be assessed statistically in new datasets, or an individual anatomy can be compared with the average maps in the atlas.

Corpus Callosum Shape in Schizophrenia. The averaging of parametric mesh models can also be used to understand how shape modeling relates to voxel based morphometry. Narr et al. (2000) created average models of the *corpus callosum* in 25 chronic schizophrenia patients and 28 matched normal controls (in this case anatomical curves were averaged rather than surfaces but the principle is the same). An increased curvature, or arching, of the *corpus callosum* was observed in patients, with stronger effects in males than females (see Fig. 6). These findings complement the periventricular changes mapped in the childhood onset cohort using VBM (Fig. 3; Sowell et al., 2000). Both techniques suggest that the bowing effect may be secondary to third ventricle enlargement. While VBM surveys the whole brain at once, and does not require *a priori* assumptions about the location or extent of the regions of interest, shape averaging produces a crisp average anatomical boundary that reveals a clearly localized shape difference in patients. In the next section we see how analysis of shape (through deformations) may be combined with a simultaneous analysis voxel-level differences in gray matter, so that the two effects can be studied in tandem.

5 Cortical Mapping

Individual variations in gyral patterns are so extreme that it is difficult to identify group patterns of cortical organization or pinpoint disease effects. The cortex also changes over time, as in aging, Alzheimer's disease (Mega et al., 2000), or development (Sowell et al., 1999; Thompson et al., 2000, 2001; Blanton et al., 2001). Cortical pattern matching methods, which encode both gyral pattern and gray matter variation, can substantially improve the statistical power and ability to localize these changes. In schizophrenia, cortical mapping reveals a progressive spread of cortical gray matter deficits in childhood onset cases (Thompson et al., 2001), and deficits can be related to genetics (Cannon et al., 2002), symptoms (Vidal et al., 2002), and underlying functional activations (Rasser et al, 2003). These cortical analyses tease apart the effects of gyral shape variation from gray matter change, as well as cortical asymmetries. As such, these techniques are hybrids between voxel-based methods (like VBM) that assess tissue distribution, and deformation-based methods that map shape differences using high-dimensional warping transforms. To illustrate these techniques, we describe how to compare and average sulcal patterns and gray matter maps across subjects, groups, and over time, and map their variations and asymmetries.

Cortical Parameterization. Many automated algorithms have been developed to extract cortical surface models from 3D MRI data (MacDonald, 1998; Fischl et al., 2000; Shattuck and Leahy, 1999). Some of these impose a tiled,

parametric grid structure on the anatomy, which supplies a coordinate framework for subsequent computations. In several approaches (Fischl *et al.*, 1999; Haker *et al.*, 1999; Shattuck and Leahy, 2001), a white matter segmentation is generated first. Its topology is then corrected using graph theoretic methods that remove holes, or artifactual bridges between white matter regions that are not truly connected (Shattuck and Leahy, 2001; Xiao Han et al., 2001). The surface is tiled using triangulation methods such the *Marching Cubes* algorithm (Lorensen and Kline, 1987; analogous methods can be used to recover the gray matter-CSF interface). The gridded surface is then inflated, using iterative smoothing, to a spherical shape. By inverting this inflation mapping, a spherical coordinate system can be projected back onto the 3D model, or the 3D surface may be flattened to a 2D plane prior to computing group differences (Fig. 7; Drury and Van Essen *et al.*, 1997; Thompson *et al.*, 1997, 2001; Angenent *et al.*, 1999).

Matching Cortical Patterns. Cortical anatomy can be compared, between any pair of subjects, by computing the warped mapping that elastically transforms one cortex into the shape of the other. Due to variations in gyral patterning, cortical differences among subjects will be severely underestimated unless elements of the gyral pattern are matched from one subject to another. This matching is also required for cortical averaging; otherwise, corresponding gyral features will not be averaged together.

To find good matches among cortical regions we perform the matching process in the cortical surface's parametric space, which permits more tractable mathematics (Fig. 7). This vector flow field in the parametric space indirectly specifies a correspondence field in 3D, which drives one cortical surface into the shape of another. This mapping can also be constructed so it exactly matches a network of consistently occurring landmark curves (Thompson and Toga, 2002) with their counterparts in the target brain, producing a transform that stores detailed information on morphometric differences.

Sulcal Alignment. Fig. 7(e) shows 3D sulcal landmarks in an individual subject that have been flattened into a 2D square. With the shape averaging techniques introduced earlier (to average models of the *corpus callosum*), an average set of flattened sulci can be created for the group of subjects under study (Fig. 7). An elastic warp is then applied to each individual's flat map that drives individual landmarks onto this average set of curves (see Thompson et al. 2002 for the mathematics). This warping adjusts for cortical patterning differences. Cortical data, such as gray matter density mapped in each individual (Fig. 8), or even functional imaging data (Zeineh et al., 2001; Rex et al., 2001; Rasser et al., 2003), can then be carefully aligned across subjects before averaging and comparison. Fig. 8 shows how this technique aligns maps of gray matter density from homologous cortical regions across subjects. The resulting maps of gray matter density

can be analyzed for group differences using VBM style techniques (examples in dementia and schizophrenia are described in Section 6). Cortical pattern matching can also increase detection sensitivity for group effects (Thompson et al., 2001; Davatzikos et al., 2001), while retaining quantitative measures of gyral pattern differences.

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Cortical Averaging. In the processing sequence shown in Fig. 7, a well-resolved average 3D cortical model can also be created for a group of subjects. A color code, storing 3D cortical locations in each individual, is plotted in flat space, and this color image is convected along with the warp that aligns that individual flattened data to the average. The resulting warped color images can be averaged across subjects and decoded to produce a crisp cortical model, with well-defined sulcal features in their mean geometric locations (Thompson et al., 2000).

Deformation-Based Morphometry. Deformations that align individual anatomies with an average template or an atlas standard can be analyzed to detect group differences in anatomy (a technique called 'deformation-based morphometry'; Thompson et al., 1997; Ashburner et al., 1999; Gaser et al., 1999; Gaser, 1999; Ashburner, 2001; Good et al., 2001). Deformation fields are a rich source of morphometric data and their statistics can be stored in an atlas, providing criteria for abnormal anatomy (Fig. 9). Depending on the approach, warping fields may be computed by matching cortical surfaces (as is the case in Fig. 9), or by algorithms that warp the entire 3D image onto a neuroanatomic template (e.g. Ashburner et al., 1998; see also Toga, 1998 for a review). Depending on whether these fields are stored as 3D deformation *vectors* (Thompson et al., 1997; Cao and Worsley, 1999), or as a set of *basis function coefficients* that parameterize the nonlinear warp (Csernansky et al., 1999; Ashburner, 2001), the analysis of structural differences proceeds a little differently. Deformation fields represented as basis function coefficients can be analyzed using a spectral methods (Miller et al., 2002; Joshi et al., 1998; Csernansky et al., 1999), Riemannian shape manifolds (Bookstein, 1997), or with multivariate methods such as canonical variates analysis (Ashburner et al., 1998). Most approaches perform statistical analysis on the coefficients of functions that warping algorithms use to represent the deformation fields, such as discrete cosines (Ashburner et al., 1998), polynomials (Woods et al., 1998), spherical harmonics (Thompson et al., 1996; Gerig and Styner, 2001), or eigenfunctions of self-adjoint differential operators (Miller et al., 2002). We describe two such approaches next (others are reviewed in Thompson and Toga, 2002).

Multivariate Analysis of Deformation Fields. Ashburner et al. (1998) developed a multivariate statistical approach, based on deformations that match individual anatomies to an atlas, to compare the gross morphometry of male and female brains. They also studied the effects of handedness on brain asymmetry and brain structure. The set of deformation

mappings was compacted using principal components analysis, producing a set of vectors with new coefficients (20 parameters accounting for 96% of the variance of the estimated mappings). By performing MANCOVA (multivariate analysis of covariance) on these new vectors, effects of confounding factors that might affect brain structure (e.g. age), and even interactions between variables, were quantified or discounted. If the data vectors, covariates of interest, and confounds are represented by matrices **A** ($m \times n$), **C** ($m \times c$) and **G** ($m \times g$), then variance due to the confounds **G** is eliminated with $\mathbf{A_a = A - G(G^TG)^{-1}G^TA}$, and the design matrix is orthogonalized with respect to **G** with $\mathbf{C_a = C - G(G^TG)^{-1}G^TC}$. The decrease in predictability of the deformations, once the effects of interest are discounted, is measured using the *Wilk's Lambda* statistic (Krzanowski, 1988):

$$\Lambda = \det(\mathbf{W})/\det(\mathbf{B}+\mathbf{W}) \text{ , where } \mathbf{B}=\mathbf{T}^{\mathbf{T}}\mathbf{T},\ \mathbf{W}=(\mathbf{A_a}-\mathbf{T})^{\mathbf{T}}(\mathbf{A_a}-\mathbf{T}),\ \mathbf{T}=\mathbf{C_a}((\mathbf{C_a}^{\mathbf{T}}\mathbf{C_a})^{-1}\mathbf{C_a}^{\mathbf{T}}\mathbf{A_a} \qquad (6).$$

Here Λ has an approximate null distribution of $\exp[\chi^2_{nc}/((n-c-1)/2 - (m-c-g))]$, where χ^2_{nc} is a χ^2 statistic with nc degrees of freedom. The results of such analyses are a significance value (p-value) for the effect (e.g. of disease or handedness, on anatomy), and one or more canonical vectors (or deformations that are eigenvectors of the fitted effects, **B**) which caricature the effect (Ashburner et al., 1999).

Random Vector Fields. A second approach for analyzing deformation fields compiles statistics on the deformation vectors required to align each individual anatomy with an atlas standard. In a *random vector field* approach (Thompson et al., 1997; Cao and Worsley, 1999), affine components of the deformation fields are first factored out. After this, the deformation vector required to match the structure at position **x** in the average cortex with its counterpart in subject i can be modeled as:

$$\mathbf{W}_i(\mathbf{x}) = \boldsymbol{\mu}(\mathbf{x}) + \boldsymbol{\Sigma}(\mathbf{x})^{1/2}\boldsymbol{\varepsilon}_i(\mathbf{x}). \qquad (7)$$

Here $\boldsymbol{\mu}(\mathbf{x})$ is the mean deformation vector for the population (which approaches the zero vector for large N), $\boldsymbol{\Sigma}(\mathbf{x})$ is a non-stationary, anisotropic covariance tensor field estimated from the mappings, $\boldsymbol{\Sigma}(\mathbf{x})^{1/2}$ is the upper triangular Cholesky factor tensor field, and $\boldsymbol{\varepsilon}_i(\mathbf{x})$ is a trivariate random vector field whose components are independent zero-mean, unit variance, stationary random fields. This 3D probability distribution makes it possible to visualize the principal directions (eigenvectors) as well as the magnitude of gyral pattern variability, as a 'tensor map' (Fig. 12(b)). The significance of a difference in brain structure between two subject groups (*e.g.*, patients and controls) of N_1 and N_2 subjects is assessed by

calculating the sample mean and variance of the deformation fields (j=1,2):

$$\mathbf{W}^{\mu}_{j}(\mathbf{x}) = \sum_{i=1 \text{ to } Nj} \mathbf{W}_{ij}(\mathbf{x}) / N_j$$

$$\mathbf{\Psi}(\mathbf{x})=(1 / [N_1+N_2-2])\{ \sum_{j=1 \text{ to } 2} \sum_{i=1 \text{ to } Nj} [\mathbf{W}_{ij}(\mathbf{x})- \mathbf{W}^{\mu}_{j}(\mathbf{x})][\mathbf{W}_{ij}(\mathbf{x})- \mathbf{W}^{\mu}_{j}(\mathbf{x})]^{\mathbf{T}}\}. \quad (8)$$

and computing the following statistical map (Thompson et al, 1997; Cao and Worsley, 2001):

$$T^2(\mathbf{x})= \{N_1N_2 / (N_1+N_2) (N_1+N_2-2)\} [\mathbf{W}^{\mu}_{2}(\mathbf{x}) - \mathbf{W}^{\mu}_{1}(\mathbf{x})]^{\mathbf{T}} [\mathbf{\Psi}(\mathbf{x})]^{-1}[\mathbf{W}^{\mu}_{2}(\mathbf{x}) - \mathbf{W}^{\mu}_{1}(\mathbf{x})], \quad (9)$$

Under the null hypothesis, $(N_1+N_2-2)T^2(\mathbf{x})$ is a stationary Hotelling's T^2-distributed random field. At each point, if we let $\nu=(N_1+N_2-2)$ and we let the dimension of the search space be d=3, then:

$$F(\mathbf{x})=((\nu-d+1)/d)T^2(\mathbf{x}) \sim F_{d,(\nu-d+1)}. \quad (10)$$

In other words, the field can be transformed point-wise to a Fisher-Snedecor F distribution (Thompson et al., 1997), and these statistics of abnormality can be plotted in color across the cortex. Fig. 9 shows the approach applied to detect atrophy in Alzheimer's disease (Thompson et al., 1997). Note the broad region of abnormality detected in orbitofrtonal cortex (Fig. 9). Validation studies on normal elderly subjects revealed that these atrophic changes were specific to patients, and were not detected in controls.

Mapping Brain Asymmetry. Brain asymmetry may also be studied by analysis of variance in 3D deformation fields. Structural brain asymmetry is linked with functional lateralization (Toga and Thompson, 2003), handedness (Witelson, 1989), and language function (Davidson and Hugdahl, 1994), and may be diminished in some brain disorders, including schizophrenia (cf. Crow, 2002, Kikinis et al., 1994, Narr et al., 2001). To visualize the average magnitude of brain asymmetries in a group of subjects, 3D deformation fields can be recovered for each subject, matching each brain hemisphere with a reflected version of the opposite hemisphere (cf. Thompson et al., 1998; Wang et al., 2001). The pattern of mean brain asymmetry for a group of 20 subjects is shown in Fig. 10. The resulting asymmetry fields $\mathbf{a}_i(\mathbf{r})$ (at parameter space location $\mathbf{r}$ in subject i) can be treated as observations from a spatially-parameterized random vector field, with mean $\boldsymbol{\mu}_{\mathbf{a}}(\mathbf{r})$ and a non-stationary covariance tensor $\boldsymbol{\Sigma}_{\mathbf{a}}(\mathbf{r})$. The significance α of deviations from symmetry can be assessed using a T^2 or F statistic, and ultimately a p-value, that indicates evidence of significant asymmetry in cortical patterns between hemispheres (Fig. 10).

Using this mapping technique, we showed that brain asymmetry increases during childhood and adolescence (Sowell et al., 2001). There are also significant asymmetries in distribution of gray matter in the brain (Watkins et al., 2001; Thompson et al., 2002), and in the degree to which genes affect brain structure (Thompson et al., 2001; Geschwind et al., 2002). Encoded knowledge on the statistics of brain asymmetry can also help detect departures from normal asymmetry and even the emergence of lesions (sometimes termed '*dissymmetry*': see Thirion et al., 2000; Joshi et al., 2001).

Applications of Deformation-Based Morphometry. Gaser et al. (1999, 2001) have used deformation-based morphometry to study differences in brain shape and ventricular expansion in schizophrenia. In a validation study, Gaser et al. (2001) used the image deformation algorithm of Ashburner et al. (1998) to warp MRI datasets onto a standard brain template. They compared ventricle to brain ratios derived from manual tracings with those derived by integrating the Jacobian determinant (i.e. the 'expansion factor') of the deformation fields, computed automatically, over the ventricular region. The high intraclass correlation between manual and automated measures of ventricular volume (r=0.96) supported the validity of using DBM to examine local and global brain morphology.

6 Applications in Dementia and Schizophrenia

Dynamically Spreading Tissue Loss in Dementia. Fig. 11 shows the cortical pattern matching method applied to a longitudinal study of brain change. A dynamically spreading wave of gray matter loss is visualized in the brains of patients with Alzheimer's Disease (AD) as it spreads over time from temporal and limbic cortices into frontal and occipital brain regions, sparing sensorimotor cortices. The maps are based on 52 high-resolution MRI scans of 12 AD patients (age: 68.4±1.9 yrs.) and 14 elderly matched controls (age: 71.4±0.9 yrs.), scanned longitudinally (two scans; interscan interval: 2.1±0.4 years). Three key features are apparent: overall, gray matter loss rates were faster in AD (5.3%±2.3%/year) than in healthy controls (0.9±0.9%/year in controls). Second, these shifting deficits are asymmetrical (left hemisphere > right), and correlate with progressively declining cognitive status (see map of voxelwise correlations with MMSE scores). Finally, cortical tissue is lost in a well-defined sequence as the disease progresses, approximately mirroring the sequence of metabolic decline in PET studies and neurofibrillary tangle accumulation seen cross-sectionally at autopsy. These processes can be observed in video format on the Internet (Thompson et al., 2002; see

URL). The goal of these dynamic maps is to uncover the path of degeneration for different brain systems, and define possible MRI-based markers for drug trials.

Childhood Onset Schizophrenia. Fig. 12 shows a similar application of cortical pattern matching to detect a spreading wave of gray matter loss in childhood onset schizophrenia (Thompson et al., 2001, 2002). 12 very-early onset schizophrenic patients were scanned three times over a period of 5 years, as were 12 healthy controls matched for age, gender, and demographics. At each scan, a measure of the local quantity of gray matter density was made at each point on the cerebral cortex. The average pattern of changes was mapped in both patients and controls, using cortical pattern matching to help compare data across time, and average data from corresponding regions of cortex. At their first scan (an average of 1.5 years after initial diagnosis, at age 13), patients showed a 10% gray matter deficit in a small region of the parietal cortex. Over the 5 succeeding years, this brain tissue loss swept forward into dorsolateral prefrontal and temporal cortices, where deficits were not found initially. Male and female patients showed similar patterns of spreading deficits, reaching a 20%-25% average loss in some regions. Group differences were highly significant ($p < 0.01$, *permutation test*), relative to both healthy controls and non-schizophrenic controls matched for medication and IQ. The mapping technique also agreed with more conventional methods, in which the lobar gray matter volumes were compared over time. Rapoport et al. (1999) found that the healthy controls lost cortical gray matter in the frontal (2.6%) and parietal lobes (4.1%); patients had faster losses in frontal (10.9%) and parietal (8.5%) regions, and they also suffered a decrease in temporal gray volume (7%), which remained stable in the controls.

Genetic Brain Maps. Cortical mapping can also identify deficit patterns associated with genetic risk for schizophrenia. Genetic brain maps (Fig. 13) use twin data to fit genetic models to imaging data at each voxel (Thompson et al., 2001, 2002). This can show which aspects of brain structure are under strongest genetic control. In disease studies (Cannon et al., 2002), they can also reveal brain regions at genetic risk for deficits. To see how this approach works, consider the maps in Figure 13(a),(b). These are computed from MRI scans of normal twins. Fig. 13(a) shows the correlation in gray matter density between identical (monozygotic) twins, who have exactly the same genes. Red colors denote regions where twins are extremely similar in their quantity of gray matter. Fig. 13(b) shows the gray matter correlations for fraternal (dizygotic) twins, who share on average half their genes. These correlations are substantially less. If only the environment were important in determining these differences (rather than genetic factors), it would not matter whether the twins were identical or fraternal. However, the heritability map (Fig. 13(c)) shows that gray matter density in certain parts of the brain is statistically more closely matched in the identical twins than in twins who were less

similar genetically. Frontal gray matter volumes were found to be under strong genetic control, and correlated with individual differences in intellectual function (IQ; Plomin and Kosslyn, 2001; Posthuma et al., 2002).

Discordance Maps and Allelic Variation. In a discordant twin study (Cannon et al., 2002), we also measured differences in cortical gray matter distribution between monozygotic (MZ) twins discordant for schizophrenia, averaging the results across discordant pairs. In the identical twins we examined, the schizophrenic member of each pair showed statistically significant deficits (between 5-8%) in superior parietal and dorsolateral prefrontal cortices, and in the left superior temporal gyrus (Fig. 13(d)). No significant differences were found between discordant co-twins in primary somatosensory or primary motor areas. In the frontal and temporal regions, deficits were found to be highly heritable. The liability map shows regions where deficits were found in healthy relatives of patients. These deficits were statistically linked with the degree of genetic affinity to a patient (i.e., worse deficits in MZ than DZ relatives). This shows that these particular deficits are mediated in part by genetic differences. Similarly, genetic liability was shown to result in increased bowing of the *corpus callosum*, using shape averaging methods (Section 4; Narr et al., 2002; cf. Hulshoff Pol et al., 2002).

7 Tensor Maps of Brain Change

Strategies to map brain changes are of immense value in basic and clinical neuroscience. For longitudinal studies, specialized algorithms have been developed to map patterns of brain change over time, in individuals scanned at multiple time points. These techniques can capture the dynamics of brain growth and loss in development and aging. If they are sufficiently sensitive, they can also assess drugs that aim to decelerate or arrest these changes, pinpointing where tumor growth, gray matter loss, or other atrophic processes are speeding up or slowing down.

Tensor Maps. Maps of brain change over time may also be based on a *tensor mapping* concept. In this approach, a high dimensional elastic deformation, or warping field, is calculated, typically with millions of degrees of freedom, which drives an image of a subject's anatomy at a baseline timepoint to match its shape in a later scan (see Fig. 14). The tensor that is mapped, in this context, is the gradient of the deformation field: mathematically it is equivalent to a 3x3 matrix attached to each point in the anatomy, which describes the principal directions of deformation at that point. The determinant of this matrix, called the Jacobian, is often used to summarize the transformation: this single number represents the local expansion factor (plotted in color in Fig. 14), and can be converted into a growth rate based on the

time interval between scans. A notable feature of *tensors*, relative to displacement vectors, is that they distinguish intrinsic volumetric changes from bulk shifts in anatomy: unlike displacement vectors, tensors are invariant to translational shifts of a structure in stereotaxic space, but they are still sensitive to intrinsic volumetric changes. This distinction can help in studying disease effects, as intrinsic changes in some structures may cause other structures to shift translationally. These two types of changes will usually not be distinguished by voxel based methods, unless structures are perfectly aligned using high dimensional registration (Bookstein, 2001).

Fig. 15 shows typical results of a tensor mapping approach we developed to map brain growth in young children. An anterior-to-posterior wave of growth was found in the brains of children scanned repeatedly between the ages of 3 and 15 (Thompson et al., 2000). Parametric surface meshes were built to represent anatomical structures in a series of scans over time, and these were matched using a fully volumetric deformation. Dilation and contraction rates, and even the principal directions of growth, can be derived by examining the eigenvectors of the deformation gradient tensor, or the local Jacobian matrix of the transform that maps the earlier anatomy onto the later one (Fig. 14). By analyzing the deformation fields, *tensor* maps can be created to reflect the magnitude and principal directions of tissue dilation or contraction. This mapping process is illustrated in Fig. 15. The validity of the approach can also be assessed by visualizing 'null maps' of brain change over short intervals. Of particular interest is the pattern of rapid volumetric loss, adjacent to a region of rapid volumetric gain, in the caudate nucleus of a child scanned at ages 7 and 11. The increased spatial detail afforded by these mapping approaches makes them of particular interest for assessing fine-scale caudate changes in response to antipsychotic medications. These drug effects have been reported volumetrically but are currently poorly understood (Chakos et al., 1995).

Voxel Compression Mapping. Tensor maps may also be used to map tissue loss rates over time in patients with dementia (Fig. 16; Thompson et al., 2001; Janke et al., 2001; Thompson et al., 2001) and multiple sclerosis (Janke et al., 2001). Freeborough et al. (1997) implemented a fluid matching algorithm to visualize how brain structure locally contracts and expands in a longitudinal study of Alzheimer's disease. Calling the technique '*voxel compression mapping*', they also used the Jacobian of the deformation field to compute local atrophy and expansion (see also Thompson et al., 2000; Crum et al., 2001). These changes were displayed as a color-coded map overlaid on the original scan, which indicates where tissue is lost. In clinical studies using this method, Fox et al. (2001) found characteristic patterns of atrophy in the different dementias. Alzheimer's disease patients showed diffuse atrophy, but more regionally selective atrophy was found in individuals with frontotemporal dementia. Janssen et al. (2002) suggested that voxel

compression maps may even identify regional brain atrophy prior to clinical diagnosis in both Alzheimer's disease and frontotemporal dementia, underscoring the clinical potential of these methods. Strategies for pooling these maps across subjects, in dynamic brain atlases, are reviewed in Toga and Thompson (2003). Once registered across subjects, the resulting Jacobian determinant images may be analyzed using voxel based methods, an approach known as *tensor based morphometry* (TBM; Davatzikos et al., 1996; Chung et al., 2001; Ashburner et al., 2003).

8 Conclusion

In this chapter, we reviewed some of the major types of morphometric methods for mapping disease-related alterations in brain structure. As image analysis methods become increasingly automated, and as the scope and power of brain imaging studies expands to larger and more complex studies, substantial benefits will accrue. For schizophrenia research in particular, key information is likely to come from the large-scale integration of neuroimaging data across patient cohorts. These include chronic, first-episode, and early-onset patients, as well as data from at-risk relatives and those in the prodromal phase of the disorder. Automated tools can then further stratify these cohorts by symptom profiles, therapeutic response, and currently identified risk factors to better understand the links between neuroimaging markers and the clinical course of the illness.

In addition, genetic brain maps combine mathematical methods from neuroimaging and genetics. They fit genetic models to voxel-based measures, and assess the results with techniques from imaging statistics and random field theory (Thompson et al., 2002). They are also beginning to provide biological markers for brain regions at risk in schizophrenia. In future, similar statistical maps may be useful in large cohort studies to assess how brain structure depends on allelic variation at candidate susceptibility loci (Thompson et al., 2002a,b). Continued hybridization of methods from genetics and brain imaging is likely to accelerate our understanding of genetic risks and the time-course of schizophrenia, including its development and progression.

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Figure Legends

Fig. 1. *Taxonomy of Methods for Analyzing MRI Data*. This schematic illustrates six major types of analysis of structural images, showing some of the data used in each case (see Table 1 for the key concepts underlying each method). Voxel based morphometry (VBM; top left panels) compares anatomy voxel by voxel to find voxels (shown here in blue) where the tissue classification (gray, white matter, CSF) depends on diagnosis or other factors. Results are typically plotted in stereotaxic space (lower panel), and their significance assessed using random field or permutation methods (see text for details). Deformation based morphometry (DBM) can be used to analyze shape differences in the cortex, or brain asymmetries (colored sulci: red colors show regions of greatest asymmetry). Tensor based morphometry (TBM) uses 3D warping fields with millions of degrees of freedom (top) to recover and study local shape differences in anatomy across subjects or over time (red colors indicate growth rates in the corpus callosum of a young child). Other methods focus on structures such as the cerebral cortex, which can be flattened to assist the analysis (bottom left), or the lateral ventricles ('Shape Modeling'). If anatomic structures are represented as parametric surface meshes (Thompson et al., 2000), their shapes can be compared, their variability can be visualized, or they can be used to show where gray matter is lost (e.g., in Alzheimer's disease: bottom left panel, red colors denote greatest gray matter loss in the limbic and entorhinal areas). Fine scale anatomical parcellation (lower right) can be used compare structure volumes across groups, or to create hand labeled templates that can be automatically warped onto new MRI brain datasets, creating regions of interest where analyses are performed. [VBM data courtesy of Elizabeth Sowell, Ph.D. (adapted from Sowell et al., (2000)), and parcellation data courtesy of Jacopo Annese, Ph.D., UCLA Laboratory of Neuro Imaging].

Fig. 2. *An Image Analysis Pipeline*. This schematic illustrates the sequence of analysis steps in an MRI study (Thompson et al., 2001). By using several of these processing modules, an investigator can create maps that reveal how brain structure varies in large populations, differs in disease, and is modulated by genetic or therapeutic factors. This approach aligns new 3D MRI scans from patients and controls (1) with an average brain template based on a population (here the ICBM template is used, developed by the International Consortium for Brain Mapping). Tissue classification algorithms then generate maps of gray matter, white matter and CSF (2). To help compare cortical features from subjects whose anatomy differs, individual gyral patterns are flattened (3) and aligned with a group average gyral pattern (4). If a color code indexing 3D cortical locations is flowed along with the same deformation field (5), a crisp group average model of the cortex can be made (6), relative to which individual gyral pattern differences (7), group variability (8) and cortical asymmetry (9) can be computed. Once individual gyral patterns are aligned to the mean template, differences in gray matter distribution or thickness (10) can be mapped, pooling data from homologous regions of cortex. Correlations can be mapped between disease-related deficits and genetic risk factors (11). Maps may also be generated visualizing linkages between deficits and clinical symptoms, cognitive scores, and medication effects. The only steps here that are currently not automated are the tracing of sulci on the cortex (3a). Some manual editing may also be assist algorithms that delete dura and scalp from images, especially if there is very little CSF in the diploic space (e.g. in nomal children).

Fig. 3. *Voxel Based Morphometry*. [Figure courtesy of Elizabeth Sowell, Ph.D.; data from Sowell et al., 1999, 2000]. Changes in stereotaxic tissue distribution can be assessed by comparison of binary maps of each tissue class (gray matter, white matter, CSF), after alignment of individual data

into stereotaxic space. In (a), voxels with significant differences were assessed between patients with childhood-onset schizophrenia (N=9) and matched controls (N=10; Sowell et al., 2000). Voxels with significant differences in each tissue class were mapped onto orthogonal slices from the averaged patient image (top row), and the same slices of the average control image. In (b), regions of profound gray matter reduction are observed between childhood and adolescence (top panels; $p < 0.05$, *permutation test;* data from Sowell et al., 1999). Differences in local gray matter content are assessed by fitting a linear statistical model at each voxel, to assess the significance of gray matter reductions with increasing age. The significance of the effect is then assessed by creating a voxel-by-voxel map of these statistics, and examining the null distribution of features that occur in these maps under the null hypothesis of no difference between groups (see Bullmore et al., 1999; Thompson et al., 2000). To control for false positives, distributions for peak values in the maps, or extents of clusters above a given threshold, can be derived from the theory of stationary Gaussian fields. If the stationarity assumption is violated, some small regions may appear to be significantly different (*null map;* bottom panels), even if the groups are randomized and there are no true differences. To avoid this, the empirical distribution of different statistical features can be assessed directly from the data by randomly assigning subjects to groups and tabulating a reference distribution, relative to which experimental differences can be assessed.

Fig. 4. *Surface Mesh Models, Anatomical Averaging, and Deformation Maps*. Parametric surface modeling is a morphometric approach that makes it easier to compare anatomical models from multiple subjects, as well as make average models for disease and control groups. An algorithm converts a set of digitized points on an anatomical structure boundary (e.g., deep sulci (a)) into a parametric grid of uniformly spaced points in a regular rectangular mesh stretched over the surface ((b); Thompson et al., 1996). By averaging nodes with the same grid coordinates across subjects (c), an average surface is produced for the group. Information on each subject's individual differences is retained as a vector-valued displacement map (d,e). This map indicates how that subject deviates locally from the average anatomy. The root mean square magnitude (e) of these deviations provides a variability measure whose values can be visualized using a color code (f). These maps can illustrate variability in different anatomic systems (f) and detect typical (i.e., average) patterns of brain structure in different anatomic systems.

Fig. 5. *Anatomical Averaging, Applied in a Study of Aging and Alzheimer's Disease*. In a group of elderly Alzheimer's disease patients and matched healthy controls, 3D parametric surface meshes (Thompson et al., 1996) were used to model 14 ventricular elements (a). Surface meshes were averaged by hemisphere in each group. (b) An average model for Alzheimer's patients (*red;* AD) is superimposed on an average model for matched normal controls (*blue;* NC). Occipital horns are enlarged in the AD patients, and there is high stereotaxic variability (c) in both groups. Extreme variability at the occipital horn tips also contrasts sharply with the stability of septal and temporal ventricular regions. A top view of these averaged surface meshes reveals localized asymmetry, variability, and displacement within and between groups. These subcortical asymmetries emerge only after averaging anatomical maps in groups of subjects.

Fig. 6. Averaging *Corpus Callosum Models in Schizophrenia*. [Data from Narr et al., 2000, courtesy of Katherine Narr]. Midsagittal *corpus callosum* boundaries were averaged from 25 patients with chronic schizophrenia (DSM-III-R criteria; 15 males, 10 females; age: 31.1 +/- 5.6 yrs.) and from 28 control subjects matched for age (30.5 +/- 8.7 yrs.), gender (15 males, 13 females) and handedness (1 left-handed subject per group). Profiles of anatomic variability around the group averages are shown (*in color*) as an r.m.s. deviation from the mean. Anatomical averaging reveals a significant bowing effect in the schizophrenic patients relative to controls. Male patients show a significant increase in curvature for superior and inferior callosal boundaries ($p < 0.001$), with a highly significant Sex by Diagnosis interaction ($p < 0.004$). Separate group averages show that the disease induces less bowing in females (*panel 1*) than in males (*panel 2*). A gender differences are not apparent in controls (*panel 3*), but a clear gender difference is seen in the schizophrenic patients (*panel 4*). Abnormalities localized in a disease-specific atlas can therefore be analyzed to reveal interactions between disease and demographic parameters.

Fig. 7. *Cortical Mapping Techniques Used to Measure Differences Across Subjects and Across Time*. Using cortical flattening (a-f), and sulcal matching (g-l), an average model of the cortex (l) can be built for a group of subjects. Sulcal landmarks are defined on individual cortices, and this

enables data to be averaged from corresponding regions of cortex across subjects, reinforcing systematic features. See text for details of this procedure. [Sulci shown in (b),(c) include the superior and inferior frontal (SFS, IFS), pre- and postcentral (preCENT, poCENT), central (CENT), intraparietal (IP), superior temporal (STS), Sylvian fissures (SF), paracentral (paCENT), cingulate (CING) and paracingulate (paCING), subparietal (subP), callosal (CC), superior and inferior rostral (SRS, IRS), parieto-occipital (PAOC), anterior and posterior calcarine (CALCa/p) sulci.]

Fig. 8. *Image Processing Steps applied in a Cortical Pattern Matching Study***.** This flow chart illustrates the key steps used to process the MRI brain scans in a study of cortical gray matter differences between patients and controls. This study uses cortical pattern matching (Thompson et al., 2001) to control, as far as possible, for individual sulcal pattern differences. Example brain MRI datasets are shown from a healthy control subject (*left column*) and from a patient (in this case, a patient with Alzheimer's disease; *right column*). First, the MRI images (*stage 1*) have extracerebral tissues deleted from the scans and the individual pixels are classified as gray matter, white matter or CSF (shown here in green, red, and blue colors; *stage 2*). After flattening a 3D geometric model of the cortex (*stage 3*), features such as the central sulcus (*light blue curve*), and cingulate sulcus (*green curve*) may be reidentified. An elastic warp is applied (*stage 4*) moving these features, and entire gyral regions (*pink colors*), into the same reference position in flat space. After aligning sulcal patterns from all individual subjects, group comparisons can be made at each 2D pixel (*yellow cross-hairs*) that effectively compare gray matter measures across corresponding cortical regions. In this study, the cortical measure that is compared, across groups, and over time, is the amount of gray matter (*stage 2*) lying within 15 mm of each cortical point. The results of these statistical tests can then be plotted back onto an average 3D cortical model made for the group (Fig. 7), and the findings can be visualized as a color coded map.

Fig. 9. *Mapping Abnormal Cortical Shape with Deformation Based Morphometry.* Due to individual anatomical differences, an individual subject's brain will deviate from an anatomic atlas or from an average cortical model prepared for a group (a); white mesh). However, elastic warping algorithms can apply local dilations and contractions to the average brain model, deforming its shape to match the individual anatomy so that key surfaces and landmarks correspond. These deformations also store detailed information on how specific individuals (e.g. *brown mesh*, (a)) deviate from the atlas. Mean anatomical shapes and confidence limits on normal variation (b) can be computed. If individual deviations (a) are calibrated against the probability distributions that capture normal variation, abnormality maps (c) may be generated. These indicate the probability of finding the anatomy in its observed configuration in a normal population. Here, in a patient with mild Alzheimer's disease, atrophic changes are easiest to detect in orbitofrontal regions where normal variation is least (*labeled F in* (b); *red colors* in (c); data from Thompson et al., 1997, 1998).

Fig. 10. *Multi-Subject Maps of Brain Asymmetry*. Image analysis techniques make it possible to distinguish systematic asymmetries in a population, or a specific group of subjects, from random fluctuations in anatomy (Thompson et al., 2001). After aligning and scaling individual MRI scans into a standard 3D space, 3D curves representing the primary sulcal pattern are digitized (a). [Sulci include central (CENT), precentral (preCENT), postcentral (poCENT), intraparietal (IP), superior frontal (SFS), inferior frontal (IFS), superior temporal (STS) and Sylvian fissures (SF)]. Averaging these curves across 20 normal subjects (b), the magnitude of asymmetry in the average anatomy is shown in color (red colors denote greater asymmetry; note this is a slightly different concept from the averaged 'individual asymmetry', which would also incorporate a measure of random variability; see next panels). Extension of these methods to surfaces (c,d) reveals prominent asymmetries in Broca's anterior speech area and in language regions surrounding the Sylvan fissure. By comparing the average magnitude of the individual asymmetries to their standard error, regions of significant asymmetry are identified (f).

Fig. 11. *Mapping Disease Progression and Linking Structural Change with Cognitive Decline in Dementia*. Gray matter deficits occurring during the development of Alzheimer's Disease are detected by comparing average profiles of gray matter between patients and controls at a baseline

scan (mean mini-mental state exam (MMSE) score=18; panels (a),(b)) and at their follow-up scan 1.5 years later (mean MMSE=13; (c)). The average percent loss in patients is shown, for a gray matter density measure derived automatically from each scan (d). Profound loss engulfs the left medial wall (>15%; (b)). On the right however, the deficits in temporo-parietal and entorhinal territory (a) spread forwards into the cingulate 1.5 years later (c), after a 5 point drop in average MMSE. Note the division between limbic and frontal zones, with different degrees of impairment (c). The corpus callosum is indicated in white; maps of gray matter change are not defined here, as it is a white matter commissure. Maps (d) and (e) show the significance of the linkage between gray matter reductions and cognition, as measured by MMSE score. Variations in temporal, parietal, and ultimately frontal (f) tissue are linked with cognitive status. Less gray matter is strongly correlated with worse cognitive performance, in all regions with prominent deficits. Linkages are most strongly detected in the left hemisphere medial temporo-parietal zones. As expected, no linkages are found with sensorimotor gray matter variation (*blue strip* in (f)), which is not significantly in deficit in late AD.

Fig. 12. *Dynamic Brain Maps: Mapping Brain Changes in Schizophrenia*. Derived from high-resolution magnetic resonance images (MRI scans), the above images were created after repeatedly scanning 12 subjects with childhood onset schizophrenia over five years, and comparing them with matched 12 healthy controls, scanned at the same ages and intervals. Severe loss of gray matter is indicated (*red and pink colors*), while stable regions are in blue. STG denotes the superior temporal gyrus, and DLPFC denotes the dorsolateral prefrontal cortex. Video sequences showing these dynamic changes can be viewed on the Internet at: http://www.loni.ucla.edu/~thompson/MOVIES/SZ/sz.html (Reprinted with permission from Thompson et al., *Proceedings of the National Academy of Sciences of the USA*, 98[20]:11650-11655, 2001).

Fig. 13. *Genetic Influences on Brain Structure: Mapping Heritability and Liability*. Color-coded maps (a,b) show local gray matter correlations between MZ and DZ twins. (c): A map of heritability statistics (h^2, computed from Falconer's heritability formula) estimates the proportion of anatomic variation attributable to genetic factors. An anatomical band encompassing frontal, sensorimotor, and parietal cortices (*red colors*) is under strong genetic control. In (d), the liability map (*green colors*) reveals frontal brain regions where gray matter deficits are found in healthy MZ and DZ twins of schizophrenia patients. Greater deficits are found in relatives who are genetically closer to a patient. Red colors show regions with deficits in schizophrenic twins relative to their genetically identical healthy MZ co-twins. Disease-specific differences must be due, in part, to non-genetic factors. (Panels a-c adapted with permission from Thompson PM et al., *Nature Neuroscience* 4(12):1253-1258 (2001); panel (d) adapted from Cannon TD et al., *Proceedings of the National Academy of Sciences of the USA* 99(5):3228-3233 (2002)).

Fig. 14. *Tensor Based Morphmetry*. Patterns of local volumetric growth and loss can be estimated from a deformation map that captures brain changes over time, or even shape differences between an individual or a brain atlas. The determinant of the deformation gradient, i.e. the Jacobian or local expansion factor, is shown in color. Tensor maps distinguish local volume changes from volume-preserving shifts in anatomy.

Fig. 15. *Visualizing Growth and Atrophy*. If follow-up (longitudinal) images are available, the dynamics of brain change can be measured with *tensor mapping* approaches (Thompson et al., 2000). These maps show local rates of tissue growth or loss. Fastest growth is detected in the isthmus of the corpus callosum in two young girls identically scanned at ages 6 and 7 (a), and at ages 9 and 13 (b). Maps of loss rates in tissue can be generated for the developing caudate ((c), here in a 7-11 year old child), and for the degenerating hippocampus [(d),(e)]. In (e), a female patient with mild Alzheimer's disease was imaged at the beginning and end of a 19 month interval with high-resolution MRI. The patient, aged 74.5 years at first scan, exhibits faster tissue loss rates in the hippocampal head (10% per year, during this interval) than in the fornix. These maps can elucidate the dynamics of therapeutic response in an individual or a population (Haney et al., 2001), and may be useful in mapping acute changes in the basal ganglia secondary to antipsychotic medication (Chakos et al., 1995).

Fig. 16. *Spatial Normalizaation of Tensor Maps for Group Comparisons*. Local volume loss patterns in the hippocampus of an elderly subject (here, over a 6 month interval) are hard to appreciate from raw MRI data (*left*). They can be localized by using 3D surface models to drive a 3D continuum-mechanical partial differential equation (PDE) from which dynamic statistics of loss are derived. Comparison and averaging of this

loss rate data across subjects requires a second PDE to convect the attribute data onto an average neuroanatomic atlas (*final 4 panels*).

Table 1. *Classes of Morphometric Methods*. While not an exhaustive list, this table describes some key methods for analyzing MRI data. Each of these methods can be used to identify group differences in brain structure. [Abbreviations. VBM: voxel based morphometry; DBM: deformation based morphometry; TBM: tensor based morphometry].

Method	**Principle**	**Methods Papers**
VBM	Maps group differences in gray matter, white matter, CSF at each voxel in stereotaxic space	Ashburner and Friston, 2000; Davatzikos et al., 2001; Good et al., 2001
DBM	Analyzes brain shape differences based on deformations that map each brain to a common anatomic template	Ashburner et al., 1998; Miller et al., 2002; Gaser, 1999; Thompson et al., 2000
TBM	Analyzes local compression or dilation required to warp a baseline image onto an atlas or onto a later one from the same subject	Davatzikos et al., 1996; Fox et al., 1998; Thompson et al., 2000
Cortical Mapping	Sulcal matching is performed on extracted cortical surface models prior to comparing gray matter measures, shape differences, asymmetries	MacDonald, 1998; Thompson et al., 2001; Fischl et al., 2000
Shape Modeling	3D geometric models of anatomical curves or surfaces are averaged and compared	Thompson et al., 1996; Joshi et al., 1998; Csernansky et al., 1999; Gerig et al., 2001
Parcellation	Regions of interest are manually traced or automatically labeled on images, and volumes are compared across groups	Collins et al., 1995; Kennedy et al., 1998; Fischl et al., 1999

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