Neuroimaging Alzheimer's Disease

[1]Arthur W. Toga PhD, [1,2]Michael S. Mega MD PhD, and [1]Paul M. Thompson PhD

[1]Laboratory of Neuro Imaging and [2]Alzheimer's Disease Center
Department of Neurology
UCLA School of Medicine, Los Angeles, CA

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Please address correspondence to:
Dr. Arthur W. Toga
(Rm. 4238, Reed Neurological Research Center)
Laboratory of Neuro Imaging, Dept. of Neurology, UCLA School of Medicine
710 Westwood Plaza, Los Angeles, CA 90095-1769
Phone: (310) 206-2101 **Fax:** (310) 206-5518 **E-mail:** toga@loni.ucla.edu

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I. Challenges in Population-Based Brain Mapping

Imaging studies of clinical populations continue to uncover new patterns of altered structure and function, and novel algorithms are being applied to relate these patterns to cognitive and genetic parameters. Post mortem brain maps are also beginning to clarify the molecular substrates of disease.

As imaging studies expand into ever-larger patient populations, population-based brain atlases (Mazziotta et al., 1995; Thompson, Mega and Toga, 2000) offer a powerful framework to synthesize results from disparate imaging studies. These atlases use novel analytical tools to fuse data across subjects, modalities, and time. They detect group-specific features not apparent in individual patients' scans. Once built, these atlases can be stratified into subpopulations to reflect a particular clinical group, such as individuals at genetic risk for AD, patients with mild cognitive impairment (MCI) or different dementia subtypes (frontotemporal dementia/semantic dementia), or patients undergoing different drug treatments. The disease-specific features these atlases resolve can then be linked with demographic factors such as age, gender, handedness, as well as specific clinical or genetic parameters (Mazziotta et al., 1995; Toga and Mazziotta, 1996; Thompson et al., 2001).

New brain atlases are also being built to incorporate dynamic data (Thompson et al., 2002). Despite the significant challenges in expanding the atlas concept to the time dimension, dynamic brain atlases are beginning to include probabilistic information on growth rates that may assist research into pediatric disorders (Thompson et al., 2000) as well as revealing patterns of degenerative rates in Alzheimer's disease (Fox et al., 1996; Thompson et al., 2001, 2002; Chan et al., 2001). Imaging algorithms are also significantly improving the flexibility of digital brain templates. *Deformable brain atlases* are adaptable brain templates that can be individualized to reflect the anatomy of new subjects. These atlases may be used for automated parcellation of new brain scans (Collins et al., 1995; Iosifescu et al., 1997), to define regions of interest in functional and metabolic studies (Dinov et al, 2000), and for anatomical shape assessment (Thompson et al., 1997; Csernansky et al., 2000). *Probabilistic atlases* are research tools that retain information on cross-subject variations in brain structure and function. These atlases are powerful new tools with broad clinical and research applications (Mazziotta et al., 1995, 2001; Kikinis et al., 1996; Toga and Thompson, 1998; Thompson et al., 2001, 2002).

Disease-Specific Atlases. This chapter introduces the topic of a *disease-specific* brain atlas (Fig. 1). This type of atlas is designed to reflect the unique anatomy and physiology of a particular clinical subpopulation (Thompson et al., 1997, 2001; Mega et al., 1997, 1999, 2000; Narr et al., 2001; Cannon et al., 2002). Based on well-characterized patient groups, these atlases contain thousands of structure models, as well as composite maps, average templates, and visualizations of structural variability, asymmetry and group-specific differences. They act as a quantitative framework that correlates the structural, metabolic, molecular and histologic hallmarks of the disease (Mega et al., 1997, 2000). Additional algorithms use information stored in the atlas to recognize anomalies and label structures in new patients. Because they retain information on group anatomical variability, disease-specific atlases are a type of probabilistic atlas specialized to represent a particular clinical group. The resulting atlases can identify patterns of altered

structure or function, and can guide algorithms for knowledge-based image analysis, automated image labeling (Collins et al., 1995; Pitiot et al., 2002), tissue classification (Zijdenbos and Dawant, 1994) and functional image analysis (Dinov et al., 2000).

We present data from several on-going projects, whose goal is to create disease-specific maps and atlases of the brain in Alzheimer's disease. Since current brain templates, typically based on young normal subjects, poorly represent the anatomy of these clinical populations, the resulting atlases offer a promising framework to investigate the disease. Pathological change can be tracked over time, and disease-specific features resolved. Rather than simply fusing information from multiple subjects and sources, new mathematical strategies are introduced to resolve group-specific features not apparent in individual scans.

In AD, early neuronal loss occurs in the entorhinal, parahippocampal and temporo-parietal cortices, consistent with the spatial pattern of early perfusion deficits and metabolic change. These deficits mirror the time course of cognitive impairment, proceeding from the entorhinal, temporal and perisylvian association cortices into more anterior regions as the disease progresses. In principle, volumetric magnetic resonance imaging (MRI) scans have sufficient resolution and tissue contrast to track cortical gray matter loss in a living individual. Yet, gyral patterns are extremely variable across subjects, making it difficult to calibrate individual patterns of gray matter loss against a normative population. It is also hard to determine the average profile of early tissue loss in a group. If 3D profiles of gray matter could be compared, this could be useful (i) for early diagnosis and assessing disease modification in an individual or group and (ii) for understanding how cortical changes relate to the fundamental anatomy of the cortex. This chapter addresses these problems.

Statistical Brain Templates. Central to the construction of a disease-specific atlas is the creation of averages, templates and models to describe how the brain and its component parts are organized, and how they are altered in disease. Statistical models are created to reveal how major anatomic systems are affected, how the pathology progresses, and how these changes relate to demographic or genetic factors. To create templates that reflect the morphology of a diseased group, specialized strategies are required for population-based averaging of anatomy (Thompson et al., 1996, 2002; Grenander and Miller, 1998). In one approach (Thompson et al., 1999), sets of high-dimensional elastic mappings, based on the principles of continuum mechanics, reconfigure the anatomy of a large number of subjects in an anatomic image database. These three-dimensional deformation fields are used to create a crisp anatomical image template to represent the brain in Alzheimer's disease, with highly-resolved structures in their mean spatial location. The mappings also generate a richly detailed local encoding of anatomic variability, with up to a billion parameters (Thompson and Toga, 1997; Grenander and Miller, 1998; Miller et al., 2002). The resulting variability parameters are stored as a tensor field (Section 9) and leveraged by pattern recognition strategies that automatically identify anatomical structures in new patients' scans, and identify disease-specific characteristics (Thompson et al., 2001; Pitiot et al., 2002).

Cortical Patterns. Cortical patterns are altered in a variety of diseases. Sulcal pattern anomalies have been identified in schizophrenia and epilepsy (Kikinis et al., 1994; Cook et al., 1994; Fuh et al., 1997), and diffuse cortical atrophy is typical of Alzheimer's disease, Pick's disease and other dementias (Schmidt, 1992). Gyral anomalies, such as cortical dysplasias, have also been linked with neurodevelopmental delay (Sobire et al., 1995). Nonetheless, ratings of structural change in the cortex are still largely based on qualitative assessment (Berg et al., 1993).

To clarify how diseases affect the cortex, specialized approaches are described for averaging cortical anatomy across subjects. Gyral pattern matching (Thompson and Toga, 1996; Thompson et al., 2000, 2001) is used to create average cortical models, to measure cross-subject differences, and to encode the magnitude and principal directions of anatomical variation at the cortex. In the resulting cortical templates, subtle features emerge. Regional asymmetries appear that are not apparent in individual

anatomies. Population-based maps of cortical variation reveal a mosaic of variability patterns that are characteristic of each cortical region.

Pathology Detection. Normal anatomic complexity makes it difficult to design automated strategies that detect abnormal brain structure. Considerable research has focused on uncovering specific patterns of anatomic alterations in Alzheimer's disease and other dementias (Friedland and Luxenberg, 1988). At the same time, brain structure is so variable that group-specific patterns of anatomy and function are often obscured.

Demographic Factors. Reports of structural differences in the brain linked to gender and handedness are still controversial, and these factors may also interact with disease-specific abnormalities (Narr et al., 2001; Thompson et al., 2002). Other factors that interfere with analysis include educational level, premorbid adjustment, treatment history and response, and the duration and course of illness (Carpenter et al., 1993). Interactions of these variables make it harder to detect disease-specific patterns and relate them to clinical and genetic parameters (Laakso et al., 2000a,b).

The importance of these linkages has propelled computational anatomy to the forefront of brain imaging investigations. To distinguish abnormalities from normal variants, a realistically complex mathematical framework is required to encode information on anatomic variability in homogeneous populations (Grenander and Miller, 1998; Thompson and Toga, 2002). As we shall see, elastic registration or *warping* algorithms offer substantial advantages in creating brain atlases that encode patterns of anatomic variation and detect pathology.

Dynamic Brain Atlases. Brain atlases have traditionally relied on static representations of anatomy, many of the diseases that affect the human brain are progressive (e.g., dementia, neoplastic tumors). The progression of a disease may also be modulated by therapy, ranging from drug treatment to surgery. In response to these challenges, *dynamic* brain atlases retain spatio-temporal information on patterns of neuroanatomic change. They offer a means to analyze the dynamics of disease. Later in the chapter, we describe how atlases can be expanded to incorporate quantitative (4D) maps of growth or degenerative patterns in the brain. These maps characterize local growth or atrophic rates in development or disease. Atlases that incorporate confidence limits on growth rates, in particular, offer a new type of normative framework to analyze aberrant brain degeneration and its modification by drug treatment or demographic factors (Thompson et al., 2001).

II. Types of Brain Atlases

Coordinate Systems. Rapid progress has been made by research groups developing standardized three-dimensional brain atlases (Talairach and Tournoux, 1988; Greitz *et al*., 1991; Höhne *et al*., 1992; Thurfjell *et al*., 1993; Kikinis *et al*., 1996; Nowinski et al., 2000; Mazziotta et al., 2001). While few of these atlases aim to represent anatomy and function in disease, several commercially-available atlases of pathology combine histologic data with illustrative metabolic or structural images. The *Harvard Brain Atlas* (Johnson., 1996) is a rich source of annotated CT, MRI, SPECT and PET (single photon/positron emission computed tomography) images from a number of clinical populations. Cerebrovascular, neoplastic and degenerative diseases are represented (including stroke, vascular dementia, and Alzheimer's disease), as are inflammatory, autoimmune and infectious diseases (multiple sclerosis and AIDS). In a similar effort, the *Atlas of Brain Perfusion SPECT* has been produced by Brigham and Women's Hospital (Holman et al., 1994). This atlas presents 21 SPECT images with co-registered scans (SPECT merged with CT or MRI), and all scans are annotated with relevant clinical information and case histories. Other collections focus on post mortem data. The *On-line Neuropathology Atlas* developed by the University of Debrecen Medical School (Hegedüs and Molnár, 1996) includes labeled images of the normal brain, with an extensive collection of pathological images from patients with cerebrovascular disease, neoplasms, as well as

inflammatory and degenerative disorders.

Perhaps surprisingly, few atlases of neuropathology use a standardized 3-dimensional coordinate system to integrate data across patients, techniques, and acquisitions. Digital templates placed in a well-defined coordinate space (Evans et al., 1991; Friston et al., 1995; Drury and Van Essen, 1997), together with algorithms to align data with them (Toga, 1998), have enabled the pooling of brain mapping data from multiple subjects and sources, including large patient populations. As we shall see, standardized coordinate systems also allow parameterized, anatomical models to be statistically combined (Thompson et al., 1996). By combining anatomical models, the results of morphometric studies can be leveraged to create disease-specific brain templates. Automated algorithms can then capitalize on atlas descriptions of anatomical variance to guide image segmentation (Le Goualher, 1999; Pitiot et al., 2002), tissue classification (Zijdenbos and Dawant, 1994), functional image analysis (Dinov et al., 2000; Zeineh et al., 2001) and pathology detection (Thompson et al., 1997, 2001).

Early Anatomic Templates. Research on brain atlases was originally based on the premise that brain structure and function imaged in any modality can be better localized by correlation with higher resolution anatomic data placed in an appropriate spatial coordinate system. Because of their detailed characterization of anatomy, most early brain atlases were derived from one, or a few, *post mortem* specimens (Brodmann, 1909; Schaltenbrand and Bailey, 1959; Van Buren and Maccubin, 1962; Talairach et al., 1967; Van Buren and Borke, 1972; Schaltenbrand and Wahren, 1977; Matsui and Hirano, 1978; Talairach and Tournoux, 1988; Ono et al., 1990). These anatomical references typically represent a particular feature of the brain, such as a neurochemical distribution (Mansour et al., 1995), myelination patterns (Smith, 1907; Mai et al., 1997), or the cellular architecture of the cortex (Brodmann, 1909).

Multi-Modality Atlases. Because of the superior anatomic resolution, several digital atlases have been created using cryosection imaging. This technique allows the serial collection of photographic images from a cryoplaned specimen blockface (Bohm et al., 1983; Greitz et al., 1991; Toga et al., 1994; Mega et al., 1997, 1999). Using 1024^2, 24-bits/pixel digital color cameras, cryosection imaging offers a spatial resolution as high as 100 microns/voxel for whole human head cadaver preparations, or higher for isolated brain regions (Toga et al., 1997). Unlike paper atlases, digital cryosection volumes are amenable to a variety of resampling and repositioning schemes. Structures can therefore be rendered and visualized from any angle. In the *Visible Human Project* (Ackerman et al., 2001), two (male and female) cadavers were cryoplaned and imaged at 1.0 mm intervals (0.33 mm for the female data), and the entire bodies were also reconstructed via 5,000 *post mortem* CT and MRI images. The resulting digital datasets consist of over 15 gigabytes of image data. While not an atlas *per se*, the *Visible Human* data has served as the foundation for developing related atlases of regions of the cerebral cortex (Drury and Van Essen, 1997), and high-quality brain models and visualizations (Schiemann et al., 1996; Stewart et al., 1996). Using multi-modality data from a patient with a localized pathology, and more recently the *Visible Human* data, Höhne and co-workers developed a commercially available brain atlas designed for teaching neuroanatomy (VOXEL-MAN; Höhne et al., 1990, 1992; Tiede et al., 1993; Pommert et al., 2001).

Post Mortem Data Fusion. Fusion of metabolic and functional images acquired *in vivo* with *post mortem* biochemical maps provides a unique view of the relationship between brain function and pathology. Mega et al. (1997) scanned Alzheimer's patients in the terminal stages of their disease using both MRI and PET. Using elastic registration techniques (Thompson et al., 1996), these data were combined with *post mortem* histologic images showing the gross anatomy (Toga et al., 1994), a Gallyas stain of neurofibrillary tangles, and a variety of spatially indexed biochemical assays (Fig. 2). The resulting multimodality maps of the Alzheimer's disease brain relate the anatomic and histopathologic underpinnings of the disease in a standardized coordinate space. These data are further correlated with *in vivo* metabolic and perfusion maps of this disease. The resulting maps are key components of a growing disease-specific atlas (Mega et al., 2000).

III. Analyzing Brain Data

A driving force that made anatomical templates important in brain imaging was the need to perform brain to brain comparisons. Anatomic variations severely hamper the integration and comparison of data across subjects, and can lead to misleading results (Meltzer and Frost, 1994; Woods, 1996; Bookstein, 2001; Ashburner and Friston, 2001). Motivated by the need to standardize and pool data across subjects, and compare results across laboratories, several registration methods have been developed to align brain mapping data with an atlas. The simplest registration techniques are linear, removing global differences in brain size. Non-linear approaches, however, can eliminate even the most local size and shape differences that distinguish one brain from another. Transforming individual datasets into the shape of a single reference anatomy, or onto a 3D digital brain atlas, allows subsequent comparison of brain function across individuals (Christensen *et al.*, 1993; Ashburner et al., 1997; Zeineh et al., 2001). Interestingly, the transformations required to remove individual differences in anatomy are themselves a rich source of morphometric data (Thompson et al., 1997, 2001; Grenander and Miller, 1998; Ashburner et al., 1998). As we shall see later, this data can be used to create disease-specific atlases.

IV. Individualized Brain Atlases

Anatomic Variations. No two brains are the same, which presents a challenge in creating standardized atlases. Even without pathology, brain structures vary between individuals in every metric; shape, size, position and orientation relative to each other (Steinmetz et al., 1989, 1990). Due to the obvious limitations of a fixed atlas, new algorithms were developed to elastically re-shape an atlas to the anatomy of new individuals (Fig. 3). The resulting *deformable brain atlases* more accurately project atlas data into new scans. Their uses include surgical planning (Warfield et al., 1998; St-Jean et al., 1998), anatomical labeling (Iosifescu et al., 1997) and shape measurement (Thompson et al., 1997; Haller et al., 1997; Csernansky et al., 1998; Subsol et al., 1997). The shape of the digital atlas is adapted using local warping transformations (dilations, contractions and shearing), producing an *individualized* brain atlas (Evans et al., 1991; Miller et al., 1993; Christensen et al., 1993; Sandor and Leahy, 1994; 1995; Rizzo et al., 1995). Pioneered by Bajcsy and colleagues at the University of Pennsylvania (Broit, 1981; Bajcsy and Kovacic, 1989; Gee et al., 1993, 1995, 1998), this approach was adopted by the *Karolinska Brain Atlas* Program (Seitz et al., 1990; Thurfjell et al., 1993; Ingvar et al., 1994). Warping algorithms can transfer maps of cytoarchitecture, biochemistry, functional and vascular territories into the coordinate system of different subjects (see Toga, 1998, for a review). Intricate patterns of structural variation in anatomy can be accommodated. These transformations must allow any segment of the atlas anatomy, however small, to grow, shrink, twist and even rotate, to produce a transformation that encodes local differences in topography from one individual to another.

Non-linear mapping of raster volumes or 3D geometric atlases onto individual datasets has empowered many studies of disease. These include brain structure labeling for hippocampal morphometry in dementia (Haller et al., 1997), analysis of subcortical structure volumes in schizophrenia (Iosifescu et al., 1997; Csernansky et al., 1998), estimation of structural variation in normal and diseased populations (Collins et al., 1995; Thompson et al., 1997), and segmentation and classification of multiple sclerosis lesions (Warfield et al., 1995). Digital anatomic models can also be projected into PET data to define regions of interest for quantitative calculations of regional cerebral blood flow (Ingvar et al., 1994; Dinov et al., 2000; Mega et al., 2000). These template-driven segmentations require extensive validation relative to more labor-intensive manual delineation of structures, but show considerable promise in studies of disease (see Mega et al., 2000).

Analyzing Brain Data with an Atlas. The ability to relate atlas data to a new subject's brain images also operates in reverse. By inverting the deformation field that reconfigures an atlas to match an individual, an

individual's data can be nonlinearly registered with the atlas, removing subject-specific anatomical differences. Functional data then be compared and integrated across subjects, with confounding anatomical effects factored out. Since they transfer multi-subject data more accurately into a stereotaxic framework, non-linear registration algorithms are now increasingly used in functional image analysis packages (Seitz et al., 1990; Friston et al., 1995; Ashburner et al., 1997; Woods et al., 1998).

Because variations in structure and function are so great, and both are altered in disease, non-linear registration approaches become relevant in creating disease-specific templates. These algorithms eliminate the anatomic component of functional variation, and are required to separate variations in structure and function. They are also vital in creating deformable atlases, which offer a means to represent, and measure, variations in structure.

When extended to accommodate more subjects, deformations that match an atlas with each patient in a population can be used to create statistical maps of anatomy, revealing patterns of variability, asymmetry or abnormality in a group (Thompson et al., 1996, 1997). With a model-driven approach, graphical surface models represent each major anatomic system, so a comprehensive geometric atlas can be built. Average representations can be created for each anatomical element, along with statistical maps that can be visualized directly or used to guide subsequent image analysis.

Continuum-Mechanical Atlases. Many brain atlases have been developed to deform according to the principles of continuum mechanics (Broit, 1981; Bajcsy and Kovacic, 1989; Christensen et al., 1996; Davatzikos, 1996; Gee and Bajscy, 1998; Thompson et al., 2001). This feature is relevant to understanding how variations in structure can be encoded. In modeling the atlas deformations, differential equations are used to make the deforming atlas conform to the behavior of elastic or fluid materials. An advantage of this approach is that the well-understood mathematics enforces several desirable characteristics in the mappings. For instance, atlas-to-patient mappings should be one-to-one (i.e., the deformed atlas should not tear or self-intersect). This is surprisingly difficult to guarantee, unless continuum-mechanical or variational methods are applied (Christensen et al., 1995; Dupuis et al., 1998; Miller and Younes, 2001). The continuum-mechanical operators that govern the atlas deformations also have a spectral (or eigenfunction) representation that helps calculate the mappings rapidly (Miller et al., 1993; Ashburner et al., 1997).

Statistical Templates. The deformable template framework has also been widely tested in computer vision applications where shape variability needs to be accommodated, such as written digit identification or face recognition. This makes it easier to build a statistical theory of shape for encoding brain variation, using Gaussian fields (Thompson et al., 1996a,b, 1997; Davatzikos et al., 1996; Ashburner et al., 1997; Gee and Bajscy, 1998; Dupuis et al., 1998; Thirion et al., 1998; Cao and Worsley, 1999; Le Goualher et al., 1999) or Riemannian shape manifolds (Bookstein, 1997). Probabilistic transformations can then be applied to deformable anatomic templates to create a type of probabilistic atlas that measures variability and detects pathology (Thompson et al., 1997, 1998; Joshi et al., 1998; Grenander and Miller, 1998).

Individualizing an Atlas. To understand how deformable atlases work, consider the deforming atlas to be embedded in a 3D elastic or fluid medium (see Figs. 3, 4). The medium is subjected to distributed internal forces, which reconfigure it, and lead the image to match the target.

V. Model-Driven Deformable Atlases

The extreme difficulty of finding structures in new patients based on intensity criteria alone has led several groups to develop model-driven deformable atlases (Thompson and Toga, 1997; Toga and Thompson, 1997). Anatomic models provide an explicit geometry for individual structures in each scan, such as

landmark points, curves or surfaces. Because the digital models reside in the same stereotaxic space as the atlas data, surface and volume models stored as lists of vector coordinates are amenable to digital transformation, as well as geometric and statistical measurement (Thompson et al., 1996). The underlying 3D coordinate system is central to all atlas systems, since it supports the linkage of structure models and associated image data with spatially-indexed neuroanatomic labels, preserving spatial information and adding anatomical knowledge.

In the following sections, we show how anatomical models can create probabilistic atlases and disease-specific templates. Statistical averaging of models provides a means to analyze brain structure in morphometric projects, localizing disease-specific differences with statistical and visual power. We first describe how models can drive deformable atlases and make average models of anatomy, measuring patient-specific differences in considerable detail.

When deforming an atlas to match a patient's anatomy, mesh-based models of anatomic systems help guide the mapping of one brain to another (Fig. 3,4). Anatomically-driven algorithms guarantee biological as well as computational validity, generating meaningful object-to-object correspondences, especially at the cortex. Ultimately, accurate warping of brain data requires:

(1) matching entire systems of anatomic *surface* boundaries, both external and internal, and
(2) matching relevant curved and point landmarks, including ones within the surfaces being matched (e.g., primary sulci at the cortex, tissue type boundaries at the ventricular surface).

Anatomical Models. Since much of the functional territory of the human cortex is buried in cortical folds or *sulci*, a generic structure is built to model them (Fig. 5; Thompson and Toga, 1996). The underlying data structure is a connected system of surface meshes, in which the individual meshes are parametric. These surfaces are 3D sheets that divide and join at curved junctions to form a connected network of models. With the help of these meshes, each patient's anatomy is modeled in sufficient detail to be sensitive to subtle differences in disease. Separate surfaces model the deep internal trajectories of features such as the parieto-occipital sulcus, the anterior and posterior calcarine sulcus, the Sylvian fissure, and the cingulate, marginal and supracallosal sulci in both hemispheres. Additional gyral boundaries are represented by parameterized curves lying in the cortical surface. The ventricular system is modeled as a closed system of 14 connected surface elements whose junctions reflect cytoarchitectonic boundaries of the adjacent tissue (Fig. 6; Thompson and Toga, 1998). Information on the meshes' spatial relations, including their surface topology (*closed* or *open*), anatomical names, mutual connections, directions of parameterization, and common 3D junctions and boundaries is stored in a hierarchical graph structure. This ensures the continuity of displacement vector fields defined at mesh junctions.

Surface Parameterization. After imposing an identical regular grid structure on anatomic surfaces from different subjects (Fig. 5), the explicit geometry can be exploited to drive and constrain correspondence maps that associate anatomic points in different subjects. Structures that can be extracted automatically in parametric form include the external cortical surface, ventricular surfaces, and several deep sulcal surfaces. Recent success of sulcal extraction approaches based on deformable surfaces (Vaillant and Davatzikos, 1997) led us to combine a 3D skeletonization algorithm with deformable curve and surface governing equations to automatically produce parameterized models of cingulate, parieto-occipital, and calcarine sulci, without manual initialization (Zhou et al., 1999). Additional, manually-segmented surfaces can also be given a uniform rectilinear parameterization using algorithms described in (Thompson et al., 1996a,b), and used to drive the warping algorithm. Each resultant surface mesh is analogous in form to a uniform rectangular grid, drawn on a rubber sheet, which is subsequently stretched to match all data points.

VI. Probabilistic Atlases

Encoding Anatomic Variability. Many morphometric studies focus on identifying systematic alterations in anatomy in a variety of diseases. These studies are complicated by the substantial overlap between measures of normal and diseased anatomy. Normal anatomic complexity makes group specific patterns hard to discern. However, disease-specific variants may be easier to localize by creating average models of anatomy, rather than deriving volumetric descriptors.

In response to these challenges, *probabilistic atlases* are research tools that retain information on anatomic and functional variability (Mazziotta *et al*., 1995, 2001; Thompson et al., 2000, 2002). A probabilistic atlas solves many of the limitations of a fixed atlas in representing highly variable anatomy. As the subject database increases in size and content, the digital form of the atlas allows efficient statistical comparisons of individuals or groups. In addition, the population that an atlas represents can be stratified into subpopulations to represent specific disease types, and subsequently by age, gender, handedness, or genetic factors.

Parametric Mesh Modeling. Parametric meshes (Thompson et al., 1996a,b) offer a means to create average models of anatomy. Once anatomical data is transformed to a standardized coordinate space, such as the Talairach space, a computational grid structure can be imposed on anatomical surface boundaries. These mesh models represent boundary point locations in stereotaxic coordinates (Fig. 5,6). Averaging of corresponding grid points across subjects results in an average surface model for each structure (Fig. 6 shows an example of average ventricular anatomy). At the same time, knowledge of each subject's deviations from the group average anatomy can be retained as a vector displacement map (Fig. 5). After storing these maps from large numbers of subjects, local biases in the magnitude and direction of anatomic variability can be displayed as a map. Variability maps for deep sulcal surfaces are shown in Fig. 7. In these maps, the color shows the root mean square magnitude of the displacement vectors that map individuals to the group mean. Separate maps are displayed for elderly normals (mean age: 72.9 ± 5.6 yrs.; all 10 right-handed), and demographically matched Alzheimer's patients (age: 71.9 ±10.7 yrs.; all 10 right-handed; mean Mini-Mental State Exam score: 19.7 ± 5.7, out of 30). As expected, there is an extraordinary increase in anatomical variability from deep structures (0-5 mm at the corpus callosum) to peak r.m.s. values of 12-13 mm at the posterior Sylvian fissures (Thompson et al., 1998). In AD however, Sylvian fissure variability rose extremely sharply from an SD of 6.0 mm rostrally on the left to 19.6 mm caudally. Underlying atrophy and possible left greater than right degeneration of perisylvian gyri (Loewenstein *et al.*, 1989; Siegel *et al*., 1996) may widen the Sylvian fissure, superimposing additional individual variation and asymmetry on that seen in normal aging.

Brain Asymmetry. A third feature observable from the average anatomical models (Figs. 6 and 7) is that consistent patterns of brain asymmetry can be mapped, despite wide variations in asymmetry in individual subjects. In dementia, the increased cortical asymmetry probably reflects asymmetric progression of the disease. Fig. 6 shows average maps of the lateral ventricles, in Alzheimer's disease and matched elderly normal populations. As expected, the ventricles are significantly enlarged in dementia. Notice, however, that a pronounced asymmetry is observed in both groups (left volume larger than right, $p < 0.05$). This is an example of an effect that becomes clear after group averaging of anatomy, and is not universally apparent in individual subjects. It is, however, consistent with prior volumetric measurements. Anatomical averaging can also be cross-validated with a traditional volumetric approach. Occipital horns were on average 17.1% larger on the left in the normal group (4070.1 ± 479.9 mm^3) than on the right (3475.3 ± 334.0 mm^3; $p < 0.05$), but no significant asymmetry was found for the superior horns (*left:* 8658.0 ± 976.7 mm^3; *right:* 8086.4 ± 1068.2 mm^3; $p > 0.19$) or for the inferior horns (*left:* 620.6 ± 102.6 mm^3; *right:* 573.7 ± 85.2 mm^3; $p > 0.37$). The asymmetry is clearly localized in the 3D group average anatomic representations. In particular, the occipital horn extends (on average) 5.1 mm more posteriorly on the left than the right. The capacity to resolve asymmetries in a group atlas can assist in studies of disease-specific

cortical organization (Thompson et al., 1997, 2001; Mega et al., 1998; Zoumalan et al., 1999; Narr et al., 1998; Sowell et al., 2001; Cannon et al., 2002).

Corpus Callosum Differences. We also tested the ability of anatomical averaging to identify disease-specific patterns in clinical populations. First, the approach was used to detect pre-clinical hippocampal atrophy in patients with minimal cognitive impairment (Kwong et al., 1999; Mega et al., 2000). To identify more focal effects, we attempted to identify regionally selective patterns of callosal change in patient groups with Alzheimer's disease (Thompson et al., 1998). The mid-sagittal callosum was first partitioned into 5 sectors (Fig. 8; Duara *et al.* (1991)). This roughly segregates callosal fibers from distinct cortical regions. In AD, focal fiber loss was expected at the callosal isthmus (sector 2) whose fibers selectively innervate the temporo-parietal regions with early neuronal loss and perfusion deficits (Brun and Englund, 1981). Consistent with this hypothesis, a significant area reduction at the isthmus was found, reflecting a dramatic 24.5% decrease from 98.0 ± 8.6 mm^2 in controls to 74.0 ± 5.3 mm^2 in AD ($p <$ 0.025). Terminal sectors (1 and 5) were not significantly atrophied, and the central midbody sector showed only a trend toward significance (16.6% mean area loss; $p < 0.1$), due to substantial inter-group overlap. Average boundary representations, however, localized these findings directly. At the isthmus, average models in AD showed a pronounced shape inflection at stereotaxic location (0.0,-25.0,19.0) (see Fig. 8).

VII. Atlas-Based Pathology Detection

Deformable Probabilistic Atlases. As noted earlier, *warping* algorithms create deformation maps (Fig. 7) that indicate 3D patterns of anatomic differences between any pair of subjects. By defining probability distributions on the space of deformation transformations which drive the anatomy of different subjects into correspondence (Grenander, 1976; Amit et al., 1991; Grenander and Miller, 1994; Thompson and Toga, 1997; Thompson et al., 1997), statistical parameters of these distributions can be estimated from databased anatomic data to determine the magnitude and directional biases of anatomic variation. Encoding of local variation can then be used to assess the severity of structural variants outside of the normal range, which, in brain data, may be a sign of disease (Thompson et al., 1997). The encoding of anatomical shape and gyral pattern variation can also assist in resolving additional disease-specific features, such as average patterns of cortical gray matter loss, as described next.

Mapping Gray Matter Loss in Alzheimer's disease. In a recent report (Thompson et al., 2001) we measured cortical gray matter distribution and disease–related gray matter loss in Alzheimer's disease. Figure 9 shows a surface-based probability field that indicates the regional significance of gray matter loss across the cortex in the entire AD cohort. Red ($P < 0.005$) denotes brain regions where the average gray matter index is significantly less in the AD cohort than in the control group. All averages and comparisons are made across corresponding areas of cortex, defined by gyral pattern matching (a procedure described in the next sections). Given these statistics, two types of inference are possible. First, the *a priori* hypothesis of gray matter loss in the temporal and parietal cortices was confirmed. There was also evidence for a region of maximal loss throughout the lateral temporal surface and the parietal operculum bilaterally ($P <$ 0.0001–0.001).

Deficit Maps. Percentages may also be plotted on the cortex (Fig. 10) to visualize the average deficit in patients relative to healthy controls. A pervasive left greater than right hemisphere reduction in gray matter was found (with up to 20–30% loss locally). The pattern of gray matter loss is consistent with findings from metabolic studies (e.g. Loewenstein et al., 1989) that the left hemisphere is, on average, more severely affected at this stage of the disease. The occipital cortices were comparatively spared bilaterally, as were the sensorimotor cortices (0–5% loss, $P > 0.05$). There was also severe gray matter loss (20–30%, $P < 0.001$–0.0001) in the middle frontal gyrus, in the vicinity of areas 9 and 46 (Rajkowska and Goldman-Rakic, 1995). We further investigated whether the regions of more *significant* gray matter loss (Fig. 9) reflected a correspondingly greater average reduction in the local gray matter index (Fig. 10). This

was important, as a greater significance value can result either from (i) a genuinely greater percent reduction in the mean gray matter in AD or (ii) a local reduction in the variance of the gray matter index across the group, which translates into a greater detection sensitivity. Interestingly, a map of the percentage reduction in average gray matter (Fig. 10) followed approximately the same anatomical pattern, suggesting that there is indeed a hierarchy in the severity of gray matter loss at this stage of the disease, rather than a fluctuation in the local power of the statistical model to detect it. Temporal and temporo-parietal cortices exhibited severe (10–30%) reductions in gray matter. This contrasted with a comparative sparing of the superior margins of the central and post-central gyri and occipital poles (0–5% loss). In mild to moderate AD, diffuse gray matter loss occurs across the majority of the cortex, but it is interesting that the superior central and post-central gyri and occipital poles show very little reduction in gray matter when adjacent posterior temporal cortex and the parietal operculum are severely affected, in both the percentage loss and statistical anatomical maps.

By averaging cortical features in an AD population and matched elderly controls, mean profiles of gray matter loss (Fig. 10), as well as local patterns anatomical variation and cerebral asymmetry (Fig. 7) can be identified. Severe reductions in gray matter (up to 30% loss) were observed across the lateral temporal surfaces and temporo-parietal cortices bilaterally. Patterns of left greater than right gray matter loss also emerged, with severe gray matter loss observed bilaterally in the vicinity of Brodmann areas 9 and 46, regions of increased synaptic loss and ß-amyloid protein deposition in AD (Clinton et al., 1994). The comparative sparing of the superior post-central and central gyri and the occipital poles (0–5% loss, $P < 0.05$) is consistent with preservation of sensorimotor and visual function at this stage of the disease, at the same time as perfusion and metabolic deficits are prevalent in association cortices.

Hemispheric Differences. Patterns of greater gray matter loss in the left hemisphere corroborate earlier reports (Loewenstein et al., 1989) of predominant left hemisphere metabolic dysfunction in mild to moderate AD, when cerebral glucose utilization is measured by positron emission tomography (PET). Structural, perfusion and metabolic studies suggest that the left hemisphere may be more susceptible to neuronal loss, instead of the alternative explanation that equivalent neuronal loss may result in greater functional deficits on one side, due to asymmetrical cortical organization. Greatest gray matter loss in the temporo-parietal cortex may underlie the prominent temporal-parietal hypometabolism found consistently in early AD, often asymmetrically (Friedland and Luxenberg, 1988; Johnson et al., 1998). Although the focus of this study (Fig. 10) was to determine patterns of gray matter loss in vivo, immunocytochemical studies have reported between 11 and 50% synaptic loss in the superior temporal and inferior parietal cortices, with a comparative sparing of occipital cortices. Relatively greater atrophy is often reported in the temporal lobe relative to overall cerebral volume (Murphy et al., 1993). The early progression of AD pathology into the parietal and frontal association cortices suggests a degeneration of synaptically linked cortical pathways, and this pattern correlates with symptoms of memory impairment, aphasias, apraxias, personality changes and spatial deficits (Roberts et al., 1993). Interestingly, gray matter loss at autopsy is predominantly cortical in Alzheimer's patients under 80 years of age (Hubbard and Anderson, 1981), when volumes of subcortical nuclei are not significantly different between patients and controls (De La Monte, 1989). Nonetheless, atrophy of the amygdala and basal nuclei (Cuénod et al., 1993) may ultimately be followed by alterations in thalamic nuclei (Jernigan et al., 1991), induced perhaps by degeneration of their cortical projection areas.

At this stage, the pathological burden of AD may be greater in terms of functional deficits, and synaptic loss, in the heteromodal cortex than in the idiotypic cortex. In our prior studies AD patients exhibited significantly greater asymmetry and structural variability in the deep perisylvian cortex, relative to controls matched for age, gender, educational level and handedness ($P < 0.05$; Fig. 7; Thompson et al., 1998). Clear differences in both AD cortical variation and gray matter distribution suggest the need for disease-specific brain atlases that better reflect the disease-related anatomy of patients and calibrate individual loss against statistical data from normative populations.

Mapping Asymmetries. There is a substantial literature on Sylvian fissure cortical surface asymmetries (Eberstaller, 1884; Cunningham, 1892; Geschwind and Levitsky, 1968; Davidson and Hugdahl, 1994) and their relation to functional lateralization (Strauss et al., 1983), handedness (Witelson and Kigar, 1992), language function (Davidson and Hugdahl, 1994), asymmetries of associated cytoarchitectonic fields (Galaburda and Geschwind, 1981) and their thalamic projection areas (Eidelberg and Galaburda, 1982). The improved ability to localize asymmetries of cortical organization (Fig. 11) or tissue loss in a group atlas presents opportunities to analyze diseases with asymmetrical progression, including different stages of AD, and to map hypothesized alterations in cortical and hippocampal asymmetry in diseases such as schizophrenia (Falkai et al., 1992; Kikinis et al., 1994; Kulynych et al., 1996; Csernansky et al., 1998; Narr et al., 2001).

VIII. Cortical Modeling

Cortical morphology is notoriously complex, and presents unique challenges in anatomic modeling. The cortex is also severely affected in disorders such as Alzheimer's disease, Pick's disease and other dementias, by tumor growth, and in cases of epilepsy, cortical dysplasias, and schizophrenia.

A major challenge in investigations of disease is to determine (1) whether cortical organization is altered, and if so, which cortical systems are implicated, and (2) whether normal features of cortical organization are lost, such as sulcal pattern asymmetries. This requires methods to create (1) a well-resolved average model of the cortex specific for a diseased group, and (2) a statistical framework to compare these average models with normative data.

Averaging Images or Averaging Geometry. In an atlasing context, it would be ideal to create a disease-specific template for a clinical group with well-resolved anatomical features in their mean anatomical configuration. Unfortunately this cannot be achieved by averaging together structural images in the traditional way, after a simple linear transformation to a standard space (Evans et al., 1994). If images are averaged in this way, cortical patterns are washed away due to wide variations in gyral organization (Fig. 12, *top left*). We describe a way to avoid this. First, an average cortical surface model is created with well-resolved gyral features in the group mean configuration. Continuum-mechanical mappings are then used to bring each subject's gyral pattern into correspondence with the average cortex. Maps of cortical variation are created as a by-product (*color maps*, Fig. 12). Finally, a high-dimensional mapping (driven by 84 structures per brain) elastically deforms each brain into the group mean geometric configuration. Once elastically reconfigured, the scan intensities are averaged on a voxel-by-voxel basis to produce a group-specific atlas template with a well-resolved cortex (Fig. 12, *lower panels*). A disease-specific brain imaging template, created to represent patients with Alzheimer's disease, will be used to illustrate this method.

Cortical Matching. Cortical anatomy can be compared, between a pair of subjects, by computing the warped mapping that elastically transforms one cortex into the shape of the other. These transformations can also match large networks of gyral and sulcal features with their counterparts in the target brain (Thompson and Toga, 1996, 1997; Davatzikos, 1996; Van Essen et al., 1997; Fischl et al., 1999). Differences in cortical organization prevent exact gyrus-by-gyrus matching of one cortex with another. Nonetheless, an important intermediate goal has been to match a comprehensive network of sulcal and gyral elements that are consistent in their incidence and topology across subjects (Fig. 13; Ono et al., 1990; Leonard et al., 1996; Kennedy et al., 1998; Thompson et al., 2001).

IX. Cortical Averaging

The warping field deforming one cortex into gyral correspondence with another can be used to create an *average* model of the cortex in a patient group. To do this, all 3D curves representing gyral curves in a

group of subjects are first transferred to a flattened (Fig. 13), or spherical (Fig. 14), parameter space (see e.g. Thompson et al., 2001, for details of the method). This procedure represents the unfolded topography of the cortex on a 2D surface, so that features in the cortex can be more easily compared from one subject to another. Next, each curve is uniformly re-parameterized to produce a regular curve of 100 points in the flattened space whose corresponding 3D locations are uniformly spaced. A set of 36 average gyral curves for the group is created by vector averaging all point locations on each curve. This *average curve template* (*curves* in Fig. 15(b)) serves as the target for alignment of individual cortical patterns (*cf.* Fischl et al., 1999, for a similar approach). Each individual cortical pattern is transformed into the average curve configuration using a flow field within the flattened space (Fig. 15(a),(b)).

Cortical Variability. By using a color code (Fig. 15(d)) to identify original cortical locations in 3D space (Fig. 15(f)), displacement fields can be recovered mapping each patient into gyrus-by-gyrus correspondence with the average cortex. Anatomic variability is then defined at each point on the average cortex as the root mean square (r.m.s.) magnitude of the 3D displacement vectors, assigned to each point, in the surface maps driving individuals onto the group average (Thompson et al., 1996a,b, 1997, 1999). This variability pattern shows the magnitude of cortical pattern variation in an elderly population, and is visualized as a color-coded map (Fig. 16).

Tensor Maps of Directional Variation. Structures do not vary to the same degree in every coordinate direction (Thompson et al., 1996), and even these directional biases vary by cortical system. The principal directions of anatomic variability in a group can be shown in a *tensor map* (Fig. 17). The maps have two uses. First, they make it easier to detect cortical atrophy in an individual patient, which may be small in magnitude but in an unusual direction. Second, they significantly increase the information content of Bayesian priors used for automated structure extraction and identification (Gee et al., 1995; Mangin et al., 1995; Royackkers et al., 1996; Pitiot et al., 2002).

Fig. 17 shows a tensor map of variability for normal subjects, after linearly mapping 20 elderly subjects' data into Talairach space (all right handed, 10 males, 10 females). Ellipsoidal glyphs indicate the principal directions of variation - they are most elongated along directions where anatomic variation is greatest across subjects. Each glyph represents the covariance tensor of the vector fields that map individual subjects onto their group average. Because gyral patterns constrain the mappings, the fields reflect variations in cortical organization at a more local level than can be achieved by only matching global cortical geometry. Note the elongated glyphs in anterior temporal cortex, and the very low variability (in any direction) in entorhinal and inferior frontal areas. By better defining the parameters of allowable normal variations, the resulting information can be leveraged to distinguish normal from abnormal anatomical variants, and can map patterns of atrophy in Alzheimer's disease (Thompson et al., 1997).

X. Brain Averaging

Average Image Templates. So far we have described a scheme to create average anatomical models for specific patient groups. By assembling these average models for a wide range of systems (cortex, hippocampus, ventricles, deep sulci, and basal ganglia), an annotated atlas of structures can be built. Nonetheless, before new data to be pooled into the atlas, an average intensity image template is also required that reflects the unique morphology of the diseased population. This makes it easier for automated, intensity-based registration algorithms (e.g. Woods et al., 1993, 1998) to align new data with the atlas.

To create a mean image template for a group, several approaches are possible. Which one is used depends on the application objectives. We describe a particular approach, which guarantees that the average template has (1) well-resolved cortical features (Thompson et al., 1999), and (2) the average size and shape for a subject group (Woods et al., 1998). To create an atlas template that is consistent with an average set of anatomical models, high-dimensional model-based registration is required. If scans are mutually aligned

with only a linear transformation, the resulting average brain is blurred in the more variable anatomical regions. The resulting average brain also tends to exceed the average dimensions of the component brain images.

By averaging geometric and intensity features separately (*cf*. Ge et al., 1995; Bookstein, 1997; Grenander and Miller, 1998; Thompson et al., 1999), a template can be made with the mean intensity and geometry for a patient population. We illustrate this approach by using the cortical transformations defined above (Figs. 13-15) to create a well-resolved disease-specific image template for an Alzheimer's disease population (Fig. 12, *lower panels*).

First, a group of well-characterized Alzheimer's patients was selected, for whom a range of anatomical surface models (84 per brain) had been created in prior morphometric projects (Thompson et al., 1998). An initial image template for the group was constructed by (1) using automated linear transformations (Woods et al., 1993) to align the MRI data with a randomly selected image, (2) intensity-averaging the aligned scans, and then (3) recursively re-registering the scans to the resulting average affine image. The resulting average image was adjusted to have the mean affine shape for the group (Woods et al., 1998). Images and surface models were then linearly aligned to this template, and an average surface set was created for the group (Thompson et al., 1997). Displacement maps (Fig. 12) driving the surface anatomy of each subject into correspondence with the average surface set were then computed, and were extended to the full volume with surface-based elastic warping (see Figs. 3,4; Thompson and Toga, 1996, 1998). These warping fields reconfigured each subject's 3D image into the average anatomic configuration for the group. By averaging the reconfigured images (after intensity normalization), a crisp image template was created to represent the group (Fig. 12, *lower panels*). Note the better-resolved cortical features in the average images after high-dimensional cortical registration. If desired, this AD-specific atlas can retain the coordinate matrix of the Talairach system (with the anterior commissure at (0,0,0)) while refining the gyral map of the Talairach atlas to encode the unique anatomy of the AD population. By explicitly computing matching fields that relate gyral patterns across subjects, a well-resolved and spatially consistent set of probabilistic anatomical models and average images can be made to represent the average anatomy and its variation in a subpopulation.

Disease Progression. The anatomical templates so far described, for demented and healthy elderly populations, have been based on homogeneous patient groups, matched for age, gender, handedness, and educational level. Since AD, in particular, is a progressive disease (see next Section), the initial atlas template was created to reflect a particular stage in the disease (MMSE score: 19.3 +/- 2.0). At this stage, patients often present for initial evaluation, and MR, PET and SPECT scans have maximal diagnostic value. Nonetheless, by expanding the underlying patient database, atlases are under construction to represent the more advanced stages of Alzheimer's disease, and MCI patients, for whom neuroimaging may be maximally informative. By stratifying the population according to different criteria, different atlases can be synthesized to represent other clinically defined groups.

Image Distortion and Registration Accuracy. Since the anatomy of a dementia population is poorly reflected by current imaging templates, substantially less distortion is applied by mapping multi-modality brain data into an atlas that reflects AD morphology (Mega et al., 1997; Thompson et al., 2000). Incoming subjects deviate least from the mean template in terms of both image intensity and anatomy. Registration of their imaging data to this template therefore requires minimal image distortion. Since the template has the average affine shape for the group (Woods et al., 1998), least distortion is applied when either linear, non-linear, approaches are used. Interestingly, automated registration approaches were able to reduce anatomic variability to a greater degree if a specially-prepared image template was used as a registration target (Thompson et al., 2000).

Other Average Templates. Several approaches are under active development to create average brain templates. Many of them are based on high-dimensional image transformations. Average templates have been made for the *Macaque* brain (Grenander and Miller, 1998), and for individual structures such as the *corpus callosum*, (Davatzikos, 1996; Gee and Bajcsy, 1998), central sulcus (Manceaux-Demiau et al., 1998), cingulate and paracingulate sulci (Paus et al., 1996; Thompson et al., 1997), hippocampus (Haller et al., 1997; Joshi et al., 1998; Csernansky et al., 1998; Thompson et al., 1999) and for transformed representations of the human and *Macaque* cortex (Drury and Van Essen, 1997; Grenander and Miller, 1998; Thompson et al., 1999; Fischl et al., 1999). Under various metrics, incoming subjects deviate least from these mean brain templates in terms of both image intensity and anatomy. Registration of new data to these templates not only requires minimal image distortion, but also allows faster algorithm convergence. This is because with smaller deformations, non-global minima of the registration measure may be avoided, as the parameter space is searched for an optimal match. For these reasons, templates that reflect the mean geometry and intensity of a group are a topic of active research (Grenander and Miller, 1998; Woods et al., 1998; Thompson et al., 1999).

XI. Dynamic (4D) Brain Atlases

4D Coordinate Systems. Atlasing of data from the developing or degenerating brain presents unique challenges (Thompson et al., 2001a,b). Serial scanning of human subjects (Fox et al., 1996; Subsol et al., 1997; Freeborough et al., 1998; Thompson et al., 1998) or experimental animals (Jacobs and Fraser, 1994) in a dynamic state of disease or development offers the potential to create 4D models of brain structure. Warping algorithms can then be applied to serial scan data to track disease and growth processes in their full spatial and temporal complexity.

Maps of anatomical change can be generated by warping scans acquired from the same subject over time (Thirion and Calmon, 1997; Thompson et al., 2000). These algorithms can generate dynamic descriptors of how the brain changes during normal aging and Alzheimer's disease (Figs. 18 and 19). They are also of interest for investigating and staging brain development in childhood and adolescence, and detecting aberrant tissue loss (Thompson et al., 2000, 2001; Sowell et al., 2001). In an atlas setting, these 4-dimensional maps can provide normative criteria for early brain change in patients with dementia (Jernigan et al., 1991; DeCarli et al., 1992; Janke et al., 2001; Thompson et al., 2001), with mild cognitive impairment (Studholme et al., 2001), or in those at genetic risk for Alzheimer's disease (Small et al., 2000). An interesting application is the compilation of dynamic maps to characterize brain change in individual patients, which we illustrate next.

Mapping Brain Development and Degeneration. In our initial human studies (Thompson et al., 2000, 2001, 2002), we developed several algorithms to create 4D quantitative maps of growth patterns in development, and well as degeneration in dementia. In a pediatric neuroimaging project, time-series of high-resolution MRI scans from healthy children were analyzed. The resulting tensor maps of growth provided spatially-detailed information on local growth patterns, quantifying rates of tissue maturation, atrophy, shearing and dilation in the dynamically changing brain architecture (Fig. 18). Pairs of scans were selected to determine patterns of structural change across the inter-scan interval. Deformation processes recovered by a high-dimensional warping algorithm were then analyzed using vector field operators to produce a variety of tensor maps (Figs. 18 and 19). These maps were designed to reflect the magnitude and principal directions of dilation or contraction, the rate of strain, and the local curl, divergence and gradient of flow fields representing the growth processes recovered by the transformation.

The growth maps obtained in these studies exhibit several striking characteristics. First, foci of rapid growth at the callosal isthmus appeared consistently across puberty, and attenuated as subjects progressed into adolescence (Fig. 24). Meanwhile, rapid rates of tissue loss were also revealed at the head of the caudate, in an earlier phase of development.

Tissue Loss in Dementia. In a pilot dementia study (Thompson et al., 2001, 2002), dynamic maps of atrophic rates were generated for 17 AD patients and 14 demographically-matched controls scanned repeatedly over a 4-year period (interscan interval: 2.6±0.3 yrs.; final age: 71.3±1.8 yrs.). 4D maps of annual atrophic rates were elastically aligned across subjects, averaged, and confidence limits were computed for tissue loss at each anatomical point throughout the brain. Profiles of local atrophic rates were visualized. Left faster than right hippocampal tissue loss was detected in controls (L: -3.8±1.6%/yr.; R:-0.5±1.2%/yr.; $p<0.05$). Significantly faster loss rates were found bilaterally in AD (L: -5.9%±1.7%/yr.; R:-7.1±3.2%/yr.; $p<0.03$), and their 3D profiles were visualized. In controls, these loss rates peaked at a localized region of the medial surface of the left hippocampal head. In AD, an anterior to posterior shift was detected in the region of peak loss, which broadened to encompass the entire hippocampus, bilaterally. Local atrophic rates were significantly linked to the rate of cognitive decline, as measured by MMSE scores ($r=0.7$; $p<0.05$).

In capturing brain change, deformation-based methods can be complementary to voxel-based morphometric methods (Ashburner and Friston, 2000; Good et al., 2001), and methods that estimate whole brain atrophic rates (Subsol et al., 1997; Calmon and Roberts, 2000; Collins et al., 1995; Smith et al., 2001). Voxel-based methods typically use a simple pixel-by-pixel subtraction of scan intensities registered rigidly across time. Tensor-based methods (Thompson et al., 2000), however, can distinguish local from global effects, and true tissue loss from shifts in anatomy. These can confound image subtraction methods.

These dynamic maps show promise in charting the dynamic progress of Alzheimer's disease, and reveal a changing pattern of deficits. Applications of these dynamic mapping approaches include measuring the statistics of brain growth in development (Thompson et al., 2000), and measuring tumor response to novel chemotherapy agents (Haney et al., 2001). By building probability densities on registered tensor fields (e.g. Thompson et al., 2001), a quantitative framework can also be established to detect normal and aberrant brain change in dementia (Thompson et al., 2002), and its modulation in clinical trials. Efforts are currently underway to use these tools to map brain regions where deficit patterns are modified by drug treatment and known risk genotypes.

XII. Conclusion

Encoding patterns of anatomical variation in disease presents significant challenges. By describing an atlasing scheme that treats intensity and geometric variation separately, we described the creation of well-resolved image templates and probabilistic models of anatomy that reflect the average morphology of a group. The continual refinement of anatomic templates is likely to be leveraged by algorithms for population-based morphometry in large image databases (Fig. 20), and by next-generation probabilistic atlases. Atlas data on anatomic variability can also act as Bayesian prior information to guide algorithms for automated image registration and labeling. The resulting atlases are expandable in every respect, and may be stratified into subpopulations according to clinical, demographic or genetic criteria.

We also described approaches for creating and averaging brain models. These techniques produce statistical maps of group differences, abnormalities, and patterns of variation and asymmetry (Fig. 20). These maps and models are key components of disease-specific brain atlases. We also described registration algorithms that transfer *post mortem* maps into an atlas, to correlate them with functional and metabolic data. The result is a multi-modality atlas that relates cognitive and functional measures with the cellular and pathologic hallmarks of the disease.

Accurate mapping of gray matter changes in a living population with AD holds significant promise for genetic, longitudinal and interventional studies of dementia. In any study where staging of the disease is required, the ability to calibrate gray matter integrity against a reference population is essential.

As well as disease-specific atlases reflecting brain structure in dementia, research is underway to build dynamic brain atlases that retain probabilistic information on growth rates in development and degeneration. Refinement of these atlas systems to support dynamic and disease-specific data should generate an exciting framework to investigate variations in brain structure and function in large human populations.

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Figure Legends

Fig. 1. *Elements of a Disease-Specific Atlas.* This schematic shows the types of maps and models contained in a disease-specific brain atlas (Thompson et al., 2000, 2002; Mega et al., 2000). A diverse range of computational anatomical tools are required to generate these average brain image templates (continuum-mechanical atlas), models and maps. Disease-specific brain atlases, such as this one based on patients with Alzheimer's disease (AD), allow imaging data from diverse modalities to be compared and correlated in a common 3D coordinate space. 3D anatomical models (e.g. cortical surfaces, *bottom row*), were extracted from a database of structural MRI data from AD patients. Models of these and other structures were digitally averaged and used to synthesize an average brain template (*Continuum-Mechanical Atlas, middle*) with well-resolved anatomical features in the mean shape and size for the population (see text for details). By rotating and scaling new images to occupy the same space as this template, models of subcortical, ventricular and deep nuclear structures can be built (*lower left*). Average models for patients and controls then be used to compute average patterns and statistics of cortical variability and asymmetry (*top left*), to chart average profiles of gray matter loss in a group, and to detect atrophy in a group or individual (*probability maps; left column*). Mega et al. (1997, 1999) also fused histologic maps of *post mortem* neurofibrillary tangle (NFT) staining density, biochemical maps of beta-amyloid distribution, and 3D metabolic FDG-PET data obtained 8 hours before death, in the same patient with AD (*top middle panels*). By classifying gray and white matter (tissue classification) and unfolding the topography of the hippocampus (*right panels*), Zeineh et al. (2001) revealed the fine-scale anatomy and dynamics of brain activation during memory tasks, using high-resolution functional MRI (time course shown for activation in right parahippocampal cortex, PHC). Atlasing techniques can represent and compare these diverse datasets in a common coordinate space, enabling novel multi-subject and cross-modality comparisons.

Fig. 2. *Elastic Registration of Brain Maps and Molecular Assays*. *Post mortem* tissue sections, from patients with Alzheimer's disease, are gridded (*left*) to produce tissue elements for biochemical assays. These assays provide detailed quantitative measures of the major hallmarks of AD, including beta-amyloid and synaptophysin density. To pool this data in a common coordinate space, tissue elements are elastically warped back into their original configuration in the cryosection blockface (middle panel). Image data acquired from the same patient in vivo can then be correlated with regional biochemistry (Mega et al., 1997). When tissue sections are warped to the blockface, continuum-mechanical models are used to make the deformations reflect how real physical tissues deform. The complexity of the required deformation vector field in a small tissue region (*magnified vector map*, *right*) demonstrates that very flexible, high-dimensional transformations are essential (Thompson and Toga, 1996; Schiemann et al., 1996; Christensen et al., 1996). These deformation vector fields project histologic and biochemical data back into their *in vivo* configuration, populating a growing Alzheimer's disease atlas with maps of molecular content and histology.

Fig. 3. *Computing Anatomical Differences with a Deformable Brain Atlas*. Structure boundaries from a patient with Alzheimer's disease (b), here imaged with 3D MRI, are overlaid on a cryosection atlas (a), which has been registered to it using a simple linear transformation. A surface-based image warping algorithm then drives the atlas into the configuration of the patient's anatomy (c). When atlas is deformed, there are two useful products. The first is a high-resolution anatomical template that is customized to reflect the individual's anatomy, and the second is a mathematical record of the shape differences between the atlas and the individual (warped grid, (d)). The amount of deformation required is displayed as a tensor map (only 2 components of the fully 3D transformation are shown). Tensor maps, and derived vector or scalar fields, can be analyzed in a statistical setting to examine anatomic variation, detect pathology, or track structural changes over time (Thompson et al., 2001). Histologic and neurochemical

maps, accessible only *post mortem*, can be transferred onto a living subject's scan with a similar warping technique (Mega et al., 1997, 1999).

Fig. 4. *Continuum-Mechanical Warping*. (a) The complex transformation required to reconfigure one brain into the shape of another can be determined using continuum-mechanical models, which describe how real physical materials deform. In this illustration, two line elements embedded in a linearly elastic 3D block (*lower left*) are slightly perturbed (*arrows*). The goal is to find how the rest of the material deforms in response to this displacement. The Cauchy-Navier equations (shown in discrete form, *top*) are solved to determine the values of the displacement field vectors, **u(x),** throughout the 3D volume. (b) *Lamé Elasticity Coefficients*. Different choices of elasticity coefficients, μ and λ, in the Cauchy-Navier equations (shown in continuous form, *top*) result in different deformations, even if the applied internal displacements are the same. In histologic applications where an elastic tissue deformation is estimated, values of the elasticity coefficients can be chosen which limit the amount of curl (*lower right*) in the deformation field. Stiffer material models (*top left*) may better reflect the deformational behavior of tissue during histologic staining procedures. *Note*: To emphasize differences, the displacement vector fields shown in this figure have been multiplied by a factor of 10. The Cauchy-Navier equations, derived using an assumption of small displacements, are valid only when the magnitude of the deformation field is small.

Fig. 5. *Modeling Anatomy with Surface Meshes*. The derivation of a standard surface representation for a range of brain structures makes it easier to compare anatomical models from multiple subjects. 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. However, 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 be stored to measure variability in different anatomic systems, including ventricular and deep sulcal (Thompson et al., 1998) surfaces. A more complex method measures cross-subject variations in gyral patterns, with a surface matching procedure that better reflects anatomical variations at the cortex (see main text). These maps can be stored to measure variability (f) and detect typical (or abnormal) patterns of brain structure in different anatomic systems.

Fig. 6. *Population-Based Maps of Average Ventricular Anatomy in Normal Aging and Alzheimer's disease*. In patients and controls, 3D parametric surface meshes (Thompson et al., 1996) were used to model 14 ventricular elements (a), and meshes representing each surface element 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). Mesh averaging reveals enlarged occipital horns in the Alzheimer's patients, and 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 of anatomical maps in large groups of subjects.

Fig. 7. *Population-Based Maps of 3D Structural Variation and Asymmetry*. Statistics of 3D deformation maps help define confidence limits on normal anatomic variation. 3D maps of anatomic variability and asymmetry are shown for 10 subjects with Alzheimer's disease (AD; age: 71.9±10.9 yrs.), and 10 normal elderly subjects matched for age (72.9±5.6 yrs.), gender, handedness and educational level (Thompson et al., 1998). Normal Sylvian fissure asymmetries (right higher than left; $p<0.0005$) were significantly greater in AD than in controls ($p<0.0002$; *top panels*). In the 3D variability maps derived for each group (*lower panels*), the color encodes the root mean square magnitude of the displacement vectors that map surfaces from each of the ten patients' brains onto the average. 3D cortical variability (*lower right panel*) increased in AD from 2-4 mm at the *corpus callosum* to a peak standard deviation of 19.6 mm at the posterior left Sylvian fissure.

Fig. 8. *Corpus Callosum in Alzheimer's disease*. Midsagittal *corpus callosum* boundaries were averaged from patients with Alzheimer's disease and from elderly controls matched for age, educational level, gender and handedness. The average representations show a focal shape inflection in the Alzheimer's patients relative to normal elderly subjects of the same age. A statistically significant tissue loss is also found at the isthmus (2^{nd} sector, when the structure is partitioned into fifths). The isthmus connects regions of temporo-parietal cortex that exhibit early neuronal loss and perfusion deficits in AD (Thompson et al., 1998).

Fig. 9. *Statistical Map of Average Gray Matter Loss in Alzheimer's disease (N=46)*. Based on averaging and comparing gray matter measurements across equivalent regions of cortex in all 46 subjects, a statistical field can be generated that reflects whether the average gray matter is reduced in patients (average of 26 subjects) relative to controls (average of 20 subjects), and the signficance of this reduction at each cortical location. As hypothesized, pervasive left-greater-than-right reductions are found, with severe, more localized reductions in temporal lobe and temporo-parietal cortex. This profile of gray matter loss mirrors the anatomical distribution of early perfusion deficits and metabolic change in mild to moderate AD.

Fig. 10. *Map of Average Gray Matter Loss in Alzheimer's disease Expressed as a Percentage of Average Control Values* (*N*=46). This map expresses the same data as Fig. 9 as a percentage reduction in the measurement of gray matter, when equivalent cortical regions are averaged and compared between AD patients and controls. The percentage reduction in average gray matter followed approximately the same anatomical pattern as the significance map, suggesting that there is indeed a hierarchy in the severity of gray matter loss at this stage of the disease, rather than a fluctuation in the local power of the statistical model to detect it. Again, temporal and temporo-parietal cortex exhibited severe (10%-30%) reductions in gray matter. This contrasted with a comparative sparing of the superior margins of the central and postcentral gyri and the occipital poles (0%-5% loss).

Fig. 11. *Mapping Brain Asymmetry in a Population*. The average magnitude of brain asymmetry in a group (*N*=20, *elderly normals*) can be assessed based on warping fields that map the cortical pattern of one hemisphere onto a reflected version of the other, and then flow the observations again so that corresponding measures can be averaged across subjects (Thompson et al., 2001; see main text for methods). Variations in asymmetry are also non-stationary across the cortex (*lower left*), and a Hotelling's T^2 statistical field can be computed to map the significance of the asymmetry (*lower right*) relative to normal anatomic variations.

Fig. 12. *Average and Probabilistic Brain Templates*. Direct averaging of imaging data after a simple affine transform into stereotaxic space washes cortical features away ((a); Evans et al., 1994; *N*=305 normals; (b) shows a similar approach with *N*=9 Alzheimer's patients). By first averaging a set of vector-based 3D geometric models, and warping each subject's scan into the average configuration, a well-resolved average brain template is produced, which reflects the anatomy of patients with mild to moderate Alzheimer's disease (c). Deformation vector maps (e) store individual deviations (*brown mesh*) from a group average (white surface, (d)), and their covariance fields (f) store information on the preferred directions and magnitude (g) of anatomic variability (*pink colors, large variation; blue colors, less*).

Fig. 13. *Measuring Differences in Cortical Anatomy*. Based on an individual's 3D MRI scan (a), detailed surface models of the cerebral cortex can be generated (b),(c). A template of 3D curved lines is delineated on these surfaces, capturing the morphology of the sulcal pattern. On the lateral brain surface, important functional landmarks include the central (CENT), pre- and post-central (preCENT, poCENT), superior and inferior frontal sulci (SFS, IFS), intraparietal sulcus (IP), Sylvian fissure (SF) and superior temporal sulcus (STS). Medial surface landmarks include the corpus callosum (CC), anterior and posterior calcarine (CALCa/p), parieto-occipital, subparietal, paracentral, paracingulate, and cingulate sulci, and the superior and inferior rostral sulci. A spherically-parameterized, triangulated 3D mesh represents the cortical surface; (d) shows the grid structure around the anterior corpus callosum. When the parameter space of the surface is flattened out (e), landmarks in the folded brain surface can be reidentified (e.g. IRS, SRS, etc.). (The white patch by the *corpus callosum* is where the surface model cuts across the white matter of the brain stem). To avoid loss of 3D information in the flattening, a color code is used to store where each flat map location came from in 3D, with red colors brighter where the lateral (X) coordinate is larger, green colors brighter where the posterior-to-anterior coordinate (Y) is larger, etc. The warping of these color maps, and the averaging of the resulting images, provides a surprising strategy for creating average cortical models for a group of subjects, and for exploring cortical pattern variation.

Fig. 14. *Cortical Pattern Matching*. Cortical anatomy can be compared, for any pair of subjects (*3D Models; top left*), by computing a 3D deformation field that reconfigures one subject's cortex onto the other (*3D Matching Field, top right*). In this mapping, gyral patterns can be constrained to match their counterparts in the target brain. To do this, flattening or inflation of the extracted cortical surface provides a continuous inverse mapping from each subject's cortex to a sphere or plane. A vector field $\mathbf{u}(\mathbf{r})$ in the parameter space can then drive the gyral pattern elements into register on the sphere (*see spherical flow*). The full mapping (*top middle*) is recovered in 3D space as a displacement vector field matching cortical regions in one brain into precise structural registration with their counterparts in the other brain. *Tensor Maps (middle and lower left):* Different amounts of local dilation and contraction (encoded in the metric tensor of the mapping, $g_{jk}(\mathbf{r})$) are required to transform the cortex into a simpler 2-parameter surface. These variations complicate the direct application of 2D warping equations for matching their features. Using a covariant tensor approach (*red box*) the regularization operator L is replaced by its covariant form $L^{\sharp}$. Correction terms (Christoffel symbols, Γ^{i}_{jk}) compensate for fluctuations in the metric tensor of the inflation and flattening procedures. This (1) makes the matching field independent of the underlying gridding of the surface (spherical or planar), and (2) eliminates effects of metric distortions that occur in the inflation or flattening procedure.

Fig. 15. *Average Cortex in Alzheimer's disease*. An average cortical surface model is shown for a group of patients (here *N*=9 Alzheimer's patients) with well-defined sulcal features appearing in their average geometric configuration. If sulcal position vectors are averaged without mathematically aligning the intervening gyral patterns (*5*), sulcal features are not reinforced across subjects: a smooth average cortex is produced. By matching gyral patterns across subjects before averaging, a crisper average cortex is produced (*6*). This type of average cortical model can be created for a group of patients by first flattening each subject's cortical model to a 2D square (*panel 1*; see also Figs. 13 and 14). A color coded map (3) stores a unique color triplet (RGB) at each location in the 2D parameter space encoding the (x,y,z) coordinate of the 3D cortical point mapped to that 2D location. By averaging these color maps pixel-by-pixel across subjects, and then decoding the 3D colors into a surface model, a smooth cortical model (5) is produced. However, a well-resolved average model (6) is produced, with cortical features in their group mean location, if each subject's color map is first flowed (4) so that sulcal features are driven into the configuration of a 2D average sulcal template (2). The average curve set is defined by 2D vector averaging of many subjects' flattened curves. In this flow (4), codes indexing similar

3D anatomical features are placed at corresponding locations in the parameter space, and are thus reinforced in the group average (6).

Fig. 16. *Mapping 3D Cortical Variability in an Alzheimer's disease Brain Atlas*. The profile of variability across the cortex is shown (*N*=26 Alzheimer's patients), after differences in brain orientation and size are removed by transforming individual data into Talairach stereotaxic space. The following views are shown: oblique frontal, frontal, right, left, top, bottom. Extreme variability in posterior perisylvian zones and superior frontal association cortex (16-18 mm; *red colors*) contrasts sharply with the comparative invariance of primary sensory, motor, and orbitofrontal cortex (2-5 mm, *blue colors*).

Fig. 17. *Tensor Maps Reveal Directional Biases of Cortical Variation*. Tensor maps can be used to visualize these complex patterns of gyral pattern variation at the cortex. The maps are based on a group of 20 elderly normal subjects. Color distinguishes regions of high variability (*pink colors*) from areas of low variability (*blue*). Ellipsoidal glyphs indicate the principal directions of variation - they are most elongated along directions where there is greatest anatomic variation across subjects. Each glyph represents the covariance tensor of the vector fields that map individual subjects onto their group average anatomic representation. The resulting information can be leveraged to distinguish normal from abnormal anatomical variants using random field algorithms, and can define statistical distributions for feature labeling at the cortex (*cf.* Le Goualher et al., 1999; Vaillant and Davatzikos, 1997).

Fig. 18. *Tensor Maps of Brain Change: 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 map volumetric change at a local level, and 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 may ultimately help elucidate the dynamics of therapeutic response in an individual or a population (Thompson et al., 2000, 2001; Haney et al., 2001).

Fig. 19. *Tensor Maps of Local Volumetric Loss in Normal Elderly Individuals*. 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; see Fig. 4) 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 neuroanatomical atlas (*final 4 panels*; see Thompson *et al*., 1997, 2000, 2001 for methods and applications).

Fig. 20. *Creating Brain Maps and Anatomical Models.* An image analysis pipeline (Thompson et al., 2001) is shown here. It can be used to create maps that reveal how brain structure varies in dementia populations, and how it is modulated by genetic factors or drug treatment. This approach aligns new 3D MRI scans from patients and controls (1) with an average brain template based on a population (in young normal studies the ICBM template is used, developed by the International Consortium for Brain Mapping; in dementia studies an AD-specific template is used; see Fig. 12). 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.

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