# TEMPORAL DYNAMICS OF

# BRAIN ANATOMY

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# TEMPORAL DYNAMICS OF BRAIN ANATOMY

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**Abstract**

The brain changes profoundly in structure and function during development, and as a result of diseases such as the dementias, schizophrenia, multiple sclerosis and tumor growth. Strategies to measure, map, and visualize these brain changes are of immense value in basic and clinical neuroscience. Algorithms that map brain change with great spatial and temporal sensitivity can also assess drugs that aim to decelerate or arrest these changes. In neuroscience studies, these tools can reveal subtle brain changes in adolescence and old age, and link these changes with measurable differences in brain function and cognition. Early detection of brain change, in patients at risk for dementia, tumor recurrence, or relapsing-remitting conditions such as multiple sclerosis, is also vital for optimizing therapy. We review a variety of mathematical and computational approaches to detect structural brain change with unprecedented sensitivity, both spatially and temporally. The resulting four-dimensional (4D) maps of brain anatomy are warehoused in *population-based brain atlases.* Here statistical tools compare brain changes across subjects and across populations, adjusting for complex differences in brain structure. Brain changes in an individual can be compared with a normative database, based on subjects matched for age, gender, and other demographic factors. These dynamic brain maps offer key biological markers for understanding disease progression and testing therapeutic response. The early detection of disease-related brain changes is also critical for possible pre-emptive intervention before the ravages of disease have set in.

## 1. Introduction

*Applications of Mapping Brain Change.* The brain changes dramatically over the human lifespan. Normal anatomical changes occur in brain development and aging, and these can be abnormally accelerated, delayed, or otherwise modified by the onset and progression of disease.

The last decade has seen tremendous advances in image analysis tools to detect, visualize and compare these brain changes. These tools have uncovered developmental growth spurts in childhood and the teenage years, pointing to regions of rapid growth and tissue loss (Thompson et al., 2000). In studies of disease, they have revealed the dynamic path of Alzheimer's disease in the brain (Fox et al., 2000; Janke et al., 2001; Thompson et al., 2002). They have also mapped a dynamically spreading wave of gray matter loss as patients develop schizophrenia, which is correlated with increasing symptom severity (Thompson et al., 2001). In drug studies, the slowing of tumor growth with chemotherapeutic agents has also been mapped (Haney et al., 2001).

*Novel Algorithms*. The major thrust of these efforts is to design tools that map brain changes with unprecedented sensitivity (Subsol et al., 1999; Thompson et al., 2000; Studholme et al., 2001; Rey et al., 2002; Smith et al., 2002). When subjects are studied longitudinally with magnetic resonance imaging, different image analysis approaches can be applied that are sensitive to different aspects of brain change. Simple volumetric approaches, for example, produce global measures of change (e.g., 'the hippocampus lost 4% of its volume in a year'). Mapping approaches, however, visualize these changes in detail, pinpointing where the losses occur (*tensor-based morphometry*; Thompson et al., 2000).

*Dynamic Brain Atlases*. Approaches to map brain change can be greatly enhanced if they are used in conjunction with a population-based brain atlas (Mazziotta et al., 1995, 2001; Thompson and Toga, 2002). Digital

atlases can compile data from hundreds or even thousands of subjects (Mazziotta et al., 2001), in a standardized coordinate system. This information can include dynamic data on rates of brain change. Statistics can then be developed to detect how these changes are modulated in disease or by risk genes (Thompson et al., 2002a,b). These statistical atlases can provide normative criteria to help detect early brain change in patients with dementia (Jernigan et al., 1991; DeCarli et al., 1992; Janke et al., 2001; Thompson et al., 2001), or in those at genetic risk for Alzheimer's disease (Small et al., 2000; Lehtovirta et al., 2000). The ability to stratify these atlases by demographic or clinical criteria shows promise in uncovering how brain changes vary by age-group, gender, and in disease. Subpopulations can also be selected from the underlying database to compare brain changes in different groups with similar or overlapping symptom profiles (Thompson et al., 2001). This is advantageous for studying populations of patients with complex disorders such as schizophrenia. As longitudinal studies are performed in different neuroimaging centers worldwide, the growing dynamic atlas provides a basis to contrast chronically-medicated and first-episode patients (Narr et al., 2001), childhood-onset and adult patients (Rapoport et al., 1999; Giedd et al., 1999; Thompson et al., 2001), schizoaffective and bipolar patients, patients receiving different medications, and even family members at increased genetic risk (Cannon et al., 2001).

*Organization of this Paper*. In the next sections, we describe the key approaches for mapping brain change. They are broadly divided into (1) image subtraction methods (which detect changes in MRI signal); (2) image deformation and tensor mapping methods (these detect changes in brain shape); and (3) specialized approaches to map *cortical* change. Following the description of these major classes of algorithms, we describe additional non-linear registration and statistical mapping techniques required to register profiles of brain change across subjects, and optimize detection of disease effects.

## 2. Approaches to Map Brain Change

*Image Acquisition*. *Parametric imaging* (Jolesz, 1994; Sbarbati et al., 2002) is a type of magnetic resonance imaging that is ideal, in some respects, for longitudinal studies of brain change. It produces quantitative maps of tissue parameters that can be compared over time. This differs from conventional MR imaging, in which T1-weighted or T2-weighted images are optimized for tissue contrast, but are not typically designed for absolute quantitation of MR signal across time or even across subjects. As such, the absolute signal values in conventional MR images can change arbitrarily due to fluctuations in scanner calibration from one acquisition to another. Parametric images, however, display scanner-independent parameters (usually the MRI signal decay constants, $T_1$ and $T_2$). These reflect changes in the underlying tissue lipid content, hydration, and physiology. Parametric scans are of special interest for studying developmental brain change, as well as steroid effects and edema in glioma patients (Haney et al., 2001). Brain development produces complex changes in brain shape, but changes that affect the MRI signal itself, including myelination from before birth into old age and decreases in brain proton density, $T_1$ and $T_2$. These changes can be studied using relaxometry, which measures absolute changes in MR signal parameters. In a recent study of brain changes in glioma (Frew et al., 2002), 21 parametric $T_2$ images were acquired from two cancer patients over 24 weeks. Consistent linear trends as small as 0.01 msec/day were statistically detectable. The direction and consistency of these changes was validated using jackknifing. Tumor changes due to radiation treatment were also mapped. Such quantitative MRI approaches show promise for detecting subtle tissue changes due to brain disease progression or therapy (Frew et al., 2000, 2002).

*Volumetric Studies*. By far the commonest, and oldest, approach to study brain change has been volumetric image analysis. It requires only relatively simple image processing. Many groups have used manual or automated approaches, or both, to create 3D models of brain substructures, based on MRI, computed tomography (CT) or 3D cryosection data (Toga et al., 1994; Thompson et al., 1996; Csernansky et al., 2000; Van Essen et al., 2002). A variety of morphometric statistics have been derived from these 3D models, including shape statistics based on averaging parametric meshes (Thompson et al., 1996), using Riemannian shape theory (Bookstein, 1997), eigenfunction decomposition (Joshi et al, 1998; Csernansky et al., 2000), or medial representations (Gerig and Styner, 2001).

In the simplest approaches, the volume, or cross-sectional area, is computed for structures such as the corpus callosum (Thompson et al., 2002), hippocampus (Narr et al., 2001), ventricular system (Thompson and Toga, 2002), basal ganglia (Narr et al., 2001), cerebellum (Blanton et al., 2001) or individual lobes of the brain. The resulting volumes are subjected to volumetric analyses, such as multivariate analysis of covariance (MANCOVA) or discriminant function analysis. By fitting statistical models, disease, gender, and systematic changes in these structures over time, are distinguished from fluctuations due to sampling and measurement error.

*Anatomical Surface Modeling*. An extension of this approach is *parametric mesh modeling* (Thompson et al., 1996, 1997, 2002; Joshi et al., 1998; Gerig and Styner, 2001). This approach applies a regular computational grid over the 3D boundary of a structure, in the form of a triangulated mesh. By modeling the same brain structures in multiple subjects with parametric meshes, average shape representations can be developed for particular structures. Patterns of changes over time can be mapped locally using deformation maps (described later). The surface grid format is a data type that can be graphically visualized with surface rendering or animation techniques (Thompson et al., 1996). Surface models can also be averaged across subjects. They also support additional computations on surface attributes such as curvature and complexity. Parametric surface approaches are highly effective for studying changes in more complex surface attributes on the highly folded cerebral cortex (Thompson et al., 1996; Sereno et al., 1996; Fischl et al., 1999). Strategies are discussed later to compute and compare dynamic changes in cortical shape (Thompson et al., 1997, 2000), cortical gray matter density and thickness, and surface-based functional imaging signals (Zeineh et al., 2001; Rasser et al., 2003). Studies using these tools reveal increases in cortical surface complexity and cortical expansion during childhood (Thompson et al., 2000; Blanton et al., 2001; Sowell et al., 2002), increases in brain asymmetry over the human lifespan (Thompson et al., 2001; Sowell et al., 2002), as well as progressively spreading waves of cortical gray matter loss in dementia and psychosis (Thompson et al., 2001, 2002).

*Cross-Sectional and Longitudinal Designs*. Brain changes in development, aging, and most degenerative diseases are subtle compared with the current resolution of MRI. Often these changes play out over time-spans longer than a typical research study, even over entire lifetimes (Sowell et al., 2002). By contrast, *longitudinal studies*, in which the same individuals are scanned over time, typically use interscan intervals of only one to two years (e.g. in development and dementia; Fox et al., 2000; Thompson et al., 2000, 2001, 2002). Intervals as short as a week may evidence significant tumor growth in glioma studies (Haney et al., 2001; Frew et al., 2001).

To capture brain changes occurring over longer periods, *cross-sectional* data is typically used. Here subjects of different ages are scanned once only. Due to the large variability in brain structure across subjects, underlying brain changes over time are harder to detect. Typically multivariate modeling and large sample sizes are used (Paus et al., 1999 (N=111); Giedd et al., 2000; Sowell et al., 2002). These multivariate models partition the variance in the observed data into that due to the effects of time (or age), and other influential factors, such as gender or disease. Longitudinal studies typically have higher statistical power to detect brain change, but cross-sectional studies have easier logistics, smaller cost, and a lower subject attrition rate. To accommodate both styles of data acquisition, so-called '*mixed'* or '*random effects' models* have been developed that can combine information from both types of data in a single analysis (Davidian and Giltinan, 1995; Verbeke and Molenberghs, 1997; Lange et al., 2000).

*Serial Image Registration*. Serial image registration, or digital overlay of consecutive 3D MR images from the same subject, has resulted in a variety of related approaches to compare anatomy over time. At the simplest level, images can be overlaid, using a rigid-body transformation, histogram equalized, and subtracted voxel-by-voxel. This produces a difference image (see Fig. 1, *left panel*). If perfect registration occurs, and if no changes in brain shape or MRI signal occur across the interval between the two scans, the difference image is largely noise (Fig. 1, *right panel*), due to temporally uncorrelated noise in the reconstructed MR signal from one acquisition to the next. When subtracting images acquired during a period of significant biological change, often anatomical features can appear in the difference images. Unfortunately, these difference images cannot usually provide reliable spatial information on where atrophy is occurring. The features they contain that appear may indicate localized anatomical

change, but they may also indicate registration error, or an arbitrary combination of each (Bookstein, 2001). If brain size is changing overall, for example, a rigid body transform will best align the central regions of the brain, with more peripheral regions successively more displaced, although the anatomical change may be no greater there. Subsequent linear and non-linear deformation algorithms are therefore essential to model more localized brain change. Nonetheless, accurate rigid-body registration is usually a prerequisite before more sophisticated methods can be applied to measure brain change.

*Image Subtraction Methods*. Image subtraction is used in many areas of computer vision, such as video surveillance and motion tracking, to measure changes in consecutive pairs of images. Various image subtraction methods have been used to measure brain changes in development (Rutherford et al., 1997), aging, and dementia (Nelson et al, 1994; Hajnal et al, 1995a,b; Freeborough et al., 1996; Fox and Freeborough, 1997; Chan et al., 2001). Bromiley et al. (2000) noted that interpretation of the resulting difference image can be problematic since the pixel values have no objective meaning (typically they are in gray level units, unless parametric imaging is used). To determine if changes in a subtraction image are statistically significant, Bromiley et al. developed a non-parametric statistical test, which visualizes altered regions as a probability map. Pixel values in this map represent the probability that the pairing of pixel values at that position in the original aligned images was drawn from the bulk distribution for pixel values in the images. This distribution is estimated non-parametrically using the grey-level scattergram, or co-occurrence matrix, of the original images. This data structure is often used in entropy-based methods for image registration. The resulting joint distribution is invariant to differences in mean intensity between the two images, and can be used to distinguish local effects from global differences or background noise.

Fox and Freeborough (1997) describe a variant of image subtraction, known as the Brain Boundary Shift Integral (BBSI). They first isolate the brain is from each serial scan by morphological operations and manual editing, prior to rigid body registration and intensity normalization. Because the scan intensities may also be changing over time, scan intensities are typically normalized first based on the mean intensity of a relatively unchanging brain region, typically the white matter. In other approaches, image intensities are first equalized across scans using histogram-matching and relative bias field correction (Lemieux et al., 1998; Thompson et al., 2000).

Image subtractions of pairs of registered scans often show intensity loss at tissue boundaries (see Fig. 1). The BBSI approach (Freeborough and Fox, 1997) notes that the intensity loss corresponds to the positional shift at image edges and structure boundaries. The volume of lost tissue can therefore be computed by estimating the volume through which the boundary has shifted. This volume, known as the BBSI, is derived by integrating intensity loss, within a pre-defined intensity range, over the external boundary between cerebro-spinal fluid (CSF) and the brain (Freeborough et al., 1997). Strictly speaking, the area under the intensity profile across a boundary in image 1 is subtracted from that for image 2, and this difference is divided by the boundary height. This provides an accurate measure of lateral boundary shift, so long as the image contrasts are well-matched in the two images (Smith et al., 2002).

*Brain Boundary Shift Integral*. Global rates of brain atrophy based on the BBSI were found to be linked with the rate of cognitive decline in dementia patients (Fox et al., 1999). Mean atrophic rates were significantly faster in Alzheimer's disease patients, at 2.8%/year (±0.9% SD), than in age-matched controls (at only 0.2%/year ±0.3% SD; Fox and Freeborough, 1997). Power calculations (Fox et al., 2000) also suggested that the BBSI measure requires a smaller sample size to detect treatment effects than conventional measures based on manually segmenting individual brain structures.

*Optimizing Serial Image Registration*. Successful monitoring of brain change using image registration depends on the algorithm used and the quality of the images. Many of the key algorithms for rigidly aligning serial images are the same ones that are routinely used for motion correction in functional MRI, and for re-aligning pre- and post-contrast radiological exams. These registration approaches typically tune the parameters of the alignment transformation (here three translations and three scales, for a rigid body transform) until a measure of the scan overlap is optimized (e.g., squared intensity difference, cross-correlation, or mutual information; see e.g. Woods et

al., 1993; Hajnal et al., 1995; Lemieux et al., 1998; Studholme et al., 1999). In functional MRI, a time-series of images is typically acquired from each subject over a period of several minutes, and retrospective image alignment is used to adjust for subject motion (Woods et al., 1993; Friston et al., 1995). Oatridge (1999) noted that the accuracy of serial image registration depends heavily on the SNR of the images. Subvoxel accuracy is, however, often achievable if a high-order resampling method is used, such as sinc or 'chirp-Z' interpolation (Hajnal et al., 1995). Matching accuracies of better than 0.01 mm per axis and 0.01 degrees for each rotation angle can be routinely achieved in least-squares registrations of phantoms (Oatridge, 1999).

*Edge-Based Methods*. Smith et al. (2002) describe a related approach to estimate brain atrophy over time. Their technique is known as *SIENA* (Structural Image Evaluation, using Normalization, of Atrophy). SIENA also estimates boundary shift, but with several modifications that correct for problems in prior approaches and provide greater accuracy.

To measure brain change over time, SIENA first segments brain from non-brain tissue, and automatically extracts models of the exterior skull surfaces, which are used to register the two scans. Skull surfaces are registered rather than the brain itself, because they are more likely to be static over time, while the brain may change in overall size and shape. In aligning one scan to the other, geometric scaling is also allowed, i.e. the transform is not constrained to be rigid. This compensates for any errors in the spatial calibration of the scanner (e.g., due to gradient calibration drift, local field distortions, or varying head placement in the scanner). A 12-parameter (affine) registration is performed, using cross correlation to align the second scan to the first (Jenkinson and Smith, 2001). Using the square root of the alignment matrix, both images are then resampled to a position 'half way' between them. This avoids differences in the level of blurring that would occur if only one scan were resampled. Brain change is then estimated from the movement of all brain surface edge points (including those on the internal brain-CSF boundary). Candidate edge-points are recovered with sub-voxel accuracy in both images using a gradient-based edge detector with non-maximum suppression. The use of an edge detector avoids the need for intensity normalization, and makes the approach more robust to overall changes in tissue intensity and radio-frequency bias between scans. The apparent motion of each brain edge point is computed perpendicular to the local edge. Using the recovered edge points only, the average motion perpendicular to the brain surface is computed. Finally, this average surface shift is converted into an estimate of brain volume change, using an estimate of the brain's volume divided by its surface area. The resulting method measures overall brain change extremely accurately in longitudinal studies of dementia. Validation studies reported a 0.5%-1% error in estimating brain volume, and brain change is estimated with an error around 0.15% of total brain volume (Smith et al., 2002).

*Serial MRI in Multiple Sclerosis*. A common application of serial image subtraction is tracking disease progression in patients with multiple sclerosis (MS; Zijdenbos et al., 1996; Oatridge, 1999; Rey et al., 2002). In MS, changes of 5%-10% per year in lesion burden can be seen in longitudinally acquired MR images. Localized lesions differ in intensity, and can be detected using tissue classification techniques (Zijdenbos et al., 1996), especially if an intravenous MRI contrast agent is used, such as GdDTPA. In MS research, the focus is on changes in image *intensity* observed over time, rather than changes in brain shape. Nonetheless, some transient brain shrinkage is seen patients undergoing steroid treatment. Lesions are usually better detected using serial image registration instead of manual segmenting the lesions. Remitting and worsening lesions can often be identified in close proximity (Oatridge, 1999). In large scale studies, image processing pipelines (Toga et al., 2001) make it easier to evaluate how lesions vary over time in clinical trials.

*Deformation-Based Methods*. Maps of brain change over time may also be based on a *deformation mapping* concept. In this approach, a 3D elastic deformation is calculated. This deformation, or warping field, drives an image of a subject's anatomy at a baseline timepoint to match its shape in a later scan (see Fig. 2). Image warping techniques have evolved over many years (Toga, 1998). Now mappings can be calculated in a very exact way that matches a large number of the key functional and anatomic elements in the scans to be matched. This results in a very complex transformation, often with up to a billion parameters, from which local volume changes in tissues can be calculated (Fig. 3; Miller *et al.,* 1993; Christensen *et al.,* 1993, 1996; Collins et al., 1994; Davatzikos, 1996;

Thompson and Toga, 1996; Davis et al., 1996, 1997; Bro-Nielsen and Gramkow, 1996; Dupuis et al., 1998; Gee and Bajcsy, 1998; Freeborough and Fox, 1997; Thompson *et al.,* 1999, 2001; Cachier *et al.,* 1999; Haker et al., 2000; Janke *et al.,* 2001; Miller and Younes, 2001).

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; Smith et al., 2002). Voxel-based methods typically use a simple pixel-by-pixel subtraction of scan intensities registered rigidly across time. Deformation methods, however, can distinguish local from global effects, and true tissue loss from translational shifts in anatomy, which can confound image subtraction methods (Bookstein, 2001; Ashburner and Friston, 2001).

*Mapping Growth Patterns*. Fig. 4 shows some typical results of a deformation-based 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. 3). By applying local operators to 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. 4. The validity of the approach can also be assessed by visualizing 'null maps' of brain change over short intervals. Circadian rhythms in brain hydration, positioning in the scanner, and even hormonal effects, can have small effects on brain morphology. Oatridge (1999) used repeat MRI scanning of four female subjects to observe slight ventricular enlargement and CSF volume increases in the second half of the menstrual cycle. They also observed that during normal pregnancy the brain of the mother decreases in size reaching a maximum reduction at term. After delivery it regains its original size over a period of 4-6 months (Oatridge et al., 1998, 1999).

In studies of brain growth using these techniques, after the age of 6, peak growth rates were consistently found in regions of the *corpus callosum* that connect linguistic and association cortices of the two brain hemispheres. After puberty, these growth rates were considerably reduced, and tissue loss was also identified in subcortical regions. By characterizing the dynamics of brain development, statistical criteria can be developed to estimate the rates at which specific brain regions normally develop. In developmental disorders, for example, a child may display a normal phenotype with an aberrant time-course. Similarly, if growth rates are abnormal, morphology may not be detectably different at any time-point, due to the wide variations in normal anatomy. Current developmental atlasing projects make it possible to compare the dynamics of brain growth and tissue elimination in an individual or group against a database of dynamic normative data.

Applications of these deformation maps of change include measuring the statistics of brain growth (Thompson et al., 2000), mapping tissue loss rates in dementia (Thompson et al., 2001), and measuring tumor response to chemotherapy agents (Haney et al., 2001). By building probability densities on registered tensor fields (e.g. Thompson et al., 2000; Chung et al., 2001), a quantitative framework can be established to detect normal and aberrant brain change, and its modulation by medication in clinical studies.

*Mathematical Details*. Deformation-based methods to track brain change have often been based on continuum mechanics, which describes physical models of elastic or fluid bodies (see Fig. 4; reviewed in Toga, 1998; Thompson and Toga, 2000; *cf*. Freeborough and Fox, 1998; Haney et al., 2001a,b; Chung et al., 2001). The 3D shape of one brain, imaged with MRI at one time-point, is imagined to be embedded in a physical medium, such as an elastic block or a fluid. This deformable template is reconfigured to match its shape in a later image (intensity changes over time may also be modeled; q.v. Joshi et al., 2001). In some approaches, a complex 3D deformation field is computed that matches large numbers of surface, curve, and point landmarks in the two brains (see Thompson *et al.,* 2000 for details, and a review of similar methods by other groups). By adding anatomical features to constrain the deformation, key anatomic and functional interfaces can be matched up when one scan is deformed into the shape of the other. In one approach

(Thompson and Toga, 1996, 2002), parametric mesh models of brain structures are used to drive a 3D deformation vector map $U$:$\mathbf{x} \mapsto \mathbf{u}(\mathbf{x})$ which is derived from the Navier equilibrium equations for linear elasticity:

$$\mu \nabla^2 \mathbf{u} + (\mu+\lambda) \nabla (\nabla \bullet \mathbf{u}(\mathbf{x})) + \mathbf{F}(\mathbf{x}-\mathbf{u}(\mathbf{x})) = \mathbf{0}, \quad \mathbf{x} \in R \qquad (1).$$

All the terms in this equation just describe forces and distortions in a 3D material, in which the image considered to be embedded. R is a discrete lattice representation of the scan to be transformed, $\nabla \bullet \mathbf{u}(\mathbf{x}) = \sum \partial u_j / \partial x_j$ is the divergence, or cubical dilation of the medium, $\nabla^2$ is the Laplacian operator which measures the irregularity of the deformation, $\mathbf{F}(\mathbf{x})$ is the internal force vector, and Lamé's coefficients $\lambda$ and $\mu$ refer to the elastic properties of the medium. Matching of cortical surfaces, across time and subsequently across subjects (for data averaging) can also be enforced. Mappings based on high-dimensional elastic and fluid models can recover extremely complex patterns of change (Fig. 4; see also Freeborough and Fox, 1998; Rey et al., 2002); their mathematics is reviewed elsewhere (Thompson et al., 2000).

*Fluid Modeling of Brain Change.* Building the work on elastic image registration, Christensen et al. (1996) developed a compressible fluid deformation model for image registration, which forces the deformation matching the scans to be smooth and topology preserving, even under large deformations. Strictly speaking, the Navier equations (1) are derived under a small deformation assumption (which is valid for growth and atrophic processes), but the fluid model uses a re-gridding approach when necessary to ensure a smooth final solution. The forces that drive one image to match the other were also designed to match regions in each dataset with high intensity similarity. Transformation parameters were determined by gradient descent on a cost functional (2) that penalizes squared intensity mismatch between the deforming template $T(\mathbf{x}-\mathbf{u}(\mathbf{x},t))$ and target $S(\mathbf{x})$, while guaranteeing the smoothness of the transformation:

$$C(T(\mathbf{x}), S(\mathbf{x}), \mathbf{u}) = (1/2) \int_\Omega \left| T(\mathbf{x}-\mathbf{u}(\mathbf{x},t))-S(\mathbf{x}) \right|^2 d\mathbf{x} \qquad (2)$$

The driving force, which deforms the anatomic template, is defined as the variation of the cost functional with respect to the displacement field:

$$\mathbf{F}((\mathbf{x},\mathbf{u}(\mathbf{x},t)) = -(T(\mathbf{x}-\mathbf{u}(\mathbf{x},t))-S(\mathbf{x})) \nabla T \Big|_{\mathbf{x}-\mathbf{u}(\mathbf{x},t)} \qquad (3)$$

$$\mu \nabla^2 \mathbf{v}(\mathbf{x},t) + (\mu+\lambda) \nabla (\nabla^T \bullet \mathbf{v}(\mathbf{x},t)) + \mathbf{F}(\mathbf{x},\mathbf{u}(\mathbf{x},t)) = \mathbf{0} \qquad (4)$$

$$\partial \mathbf{u}(\mathbf{x},t)/\partial t = \mathbf{v}(\mathbf{x},t) - \nabla \mathbf{u}(\mathbf{x},t)\mathbf{v}(\mathbf{x},t) \qquad (5)$$

The deformation velocity (4) is governed by the creeping flow momentum equation for a Newtonian fluid and the conventional displacement field in a Lagrangian reference system (5) is connected to a Eulerian velocity field by the relation of material differentiation. Experimental results were excellent (Christensen *et al*., 1996). Because fluid matching is computationally intensive, subsequent work focused on deriving separable (and therefore computationally fast) filters to approximate the continuum-mechanical filters derived above (Nielsen et al., 1994; Gramkow, 1996; Lester et al., 1999; Cachier et al. 1999; Miller et al., 2002; see Thompson et al., 2000 for a review of these approaches). Some elastic matching algorithms are now fast enough to track brain change in real-time, in surgical applications that use intraoperative scanning (Warfield et al., 1998).

*Voxel Compression Mapping.* Freeborough et al. (1997) implemented a fluid matching algorithm to visualize how brain structure locally contracts and expands in a longitudinal study of dementia. 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. 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.

*Population-Based Atlasing of Brain Change*. In different individuals, growth processes or tissue losses occur in anatomies that are geometrically different. Additional warping techniques are needed to compare growth profiles across subjects. This additional warping is needed to compute average profiles of growth in a group, and to define statistical differences in rates of growth or loss. Mathematically, if $U^i(\mathbf{x},t_i)$ is the 3D displacement vector required to deform the anatomy at position **x** in subject *i* at reference time 0 to its corresponding homologous position at time $t_i$, then a linear approximation the local rate of volumetric growth (Chung et al., 2001) can be written in terms of the identity tensor and displacement gradient tensor as:

$$\Gamma^i(\mathbf{x}) = \partial J^i/\partial t = det\,(I + \nabla U^i) / t_i, \qquad (6)$$

If $A^i$ is the secondary deformation mapping transforming the baseline anatomy of individual *i* onto the atlas ('*Warping Field*', in Fig. 5), then the set of registered growth maps $\Gamma^i(A^i(\mathbf{x}))$ (*shown in the final panel of Figure 5*) can be treated as observations from a spatially-parameterized random field, whose mean and variance can be estimated. Statistical effects of age, gender, genotype or medication can then be detected using random field theory to produce statistical maps (Thompson et al., 2001; Ashburner, 2001).

*Improved Dynamic Models*. In developing dynamic atlases for clinical applications, there is a particular interest in modeling developmental processes that speed up or slow down. Diseases may accelerate, or their rate of progression may be slowed down by therapy. If individuals are scanned more than twice over large time-spans, this presents the opportunity for more accurate detection of brain change, and encoding of these changes in a group atlas. To compare growth patterns in different groups of subjects, the 'general linear model' (Friston et al., 1995; Frackowiak et al., 1997) can be used to analyze the registered growth profiles (or degenerative profiles). For the *i*th individual's *j*th measure we have:

$$Y_{ij} = f(\mathrm{Age}_{ij},\beta) + \varepsilon_j \qquad (7).$$

Here $Y_{ij}$ signifies the outcome measure at a voxel or surface point, such as growth or tissue loss, $f()$ denotes a constant, linear, quadratic, cubic, or other function of the individual's age for that scan, and $\beta$ denotes the regression/ANOVA coefficients to be estimated. Age ($\mathrm{Age}_{ij}$) may be replaced by time from the onset of disease, the start of medication, or the time from the onset of puberty (Giedd et al., 1999). This flexibility in parameterizing the time axis allows one to temporally register dynamic patterns using criteria that are expected to bring into line temporal features of interest that appear systematically in a group (Janke et al., 2001). For example, the independent variable could be a cognitive score such as Mini-Mental status (Thompson et al., 2002), which declines over time in disease. In a developmental study, this independent variable could be a measure of physical or psychological maturity that may better reflect the developmental stage of the subject than age alone. Parameterization of dynamic effects using measures other than time (e.g. clinical status) also provides a mechanism to align new patients' time series with a dynamic atlas (Janke et al., 2001).

*Random Effects Modeling*. In the above statistical model of brain change (Eq. 7), the coefficient vector, $\beta$, is assumed to be constant, i.e. a fixed effect. The $\varepsilon_j$ are assumed normally distributed and uncorrelated both between and within individuals. If multiple scans are available over time, a random effects model can also model brain changes in a population:

$$Y_{ij} = \eta_i + f(\mathrm{Age}_{ij},\beta) + \varepsilon_j \qquad (8).$$

Here the model is the same as the General Linear Model except for the $\eta_i$ term, which is called a *random effect* (Pinheiro and Bates, 2000). It describes the correlation between an individual's multiple scans. Random effects models may also be fitted with *correlated* errors (Davidian and Giltinan, 1995; Verbeke and Molenberghs, 1997). If this is done, $\varepsilon_j$ and $\varepsilon_k$ ($k$ not equal to $j$) are assumed correlated with the correlation a function of the time elapsed between the two measurements (Giedd et al., 1999). In models whose fit is confirmed as significant, e.g. by permutation, loadings on nonlinear parameters may be visualized as attribute maps $\beta(\mathbf{x})$. This reveals the topography of accelerated or decelerated brain change (Thompson *et al.,* 2001). The result is a formal approach to assess whether, and where, brain change is

speeding up or slowing down. This is key feature in developmental or medication studies, and a key element of developmental atlases currently being built.

*Mapping Brain Change in Alzheimer's Disease.* The brain mapping approaches described so far have been applied to study brain structure in Alzheimer's disease (Thompson et al., 2000a,b; Mega et al., 1999), chronic, first-episode, and childhood-onset schizophrenia (Narr et al., 2000, 2001a,b; Cannon et al., 2001), fetal alcohol syndrome (Sowell et al., 2001), and brain changes during childhood and adolescence (Thompson et al., 2000, 2001; Sowell et al., 2001a,b; Blanton et al., 2001).

A key clinical application is in visualizing the average profile of gray matter loss across the cortex in Alzheimer's disease, based on serial MR images from a large number of subjects. Everyone's brain shrinks with age, although not in a uniform way. Diseases such as Alzheimer's cause changes in the overall rates and patterns of brain change. They also cause a regional pattern of gray matter loss, which spreads in the brain over time. Mapping techniques can be used to visualize, or even animate, how these deficits spread dynamically in the brain (Thompson et al., 2002; *see URL for animations*). The resulting temporal maps provide a dynamic model of the disease, and a potential biological marker for drug studies.

*Cortical Maps*. Understanding cortical anatomy and function is a major focus in brain research, and many diseases cause profound changes in the cortex. Cortical changes are found in Alzheimer's disease and other dementias (Thompson et al., 2000, 2002; Studholme et al., 2001), early-onset schizophrenia (Thompson et al., 2001), and a variety of developmental disorders, such as fetal alcohol syndrome (Sowell et al., 2002). Since most imaging studies of brain function focus on the cortex, it is especially important to be able to pool cortical brain mapping data from subjects whose anatomy is different (Zeineh et al., 2001). Gyral pattern variation in particular (1) makes general patterns of organization and disease effects hard to discern, and (2) complicates attempts to define statistical criteria for abnormal cortical anatomy. To simplify computation of differences across individual and changes over time, many investigators have developed surface parameterization approaches, which we briefly describe next.

*Cortical Parameterization*. Several methods exist to generate surface models of the cortex from 3D MRI scans. Some of these impose a tiled, parametric grid structure on the anatomy, which is used as a coordinate framework to support subsequent computations. In '*bottom-up'* approaches (e.g. Fischl *et al.,* 1999; Haker *et al.,* 2000; Shattuck and Leahy, 2001), a voxel-based segmentation of white matter is generated first, using a tissue classifier or level set methods (Sapiro, 2001). Its topology is then corrected using graph theoretic methods (Shattuck and Leahy, 2001). This creates a single, closed, simply connected surface homeomorphic to a sphere (Fischl et al., 1999; Hurdal et al., 1999; Rettman et al., 2000; Shattuck and Leahy, 2001). The surface is tiled using triangulation methods such the *Marching Cubes* algorithm (Lorensen and Kline, 1987). The gridded surface is then inflated, using iterative smoothing, to a spherical shape. By inverting this inflation mapping, this allows a spherical coordinate system to be projected back onto the 3D model, for subsequent computations. Alternatively the 3D surface may be flattened to a 2D plane (Fig. 6; Drury and Van Essen *et al.,* 1997; Van Essen et al., 1997; Thompson *et al.,* 1997; Angenent *et al.,* 1999; Hurdal *et al.,* 1999), inducing an alternative 2D parameterization onto the original 3D surface.

A second ('*top-down'*) type of surface extraction method (Davatzikos, 1996; MacDonald, 1998; Kabani et al., 2000) begins with a spherical or ellipsoidal surface that is already tiled. This parametric surface is successively moved, under image-dependent forces, reshaping it into the complex geometry of the cortical boundary (see Xu *et al.,* 1999, for work on *gradient vector flow*). This avoids the need for topology correction, as a single, fixed, grid structure is established at the start, and mapped with a continuous deformation onto each anatomy. Complex constraints are, however, required while deforming the surface. These ensure that the surface does not self-intersect and adapts fully to the target geometry. The first (bottom-up) strategy turns the cortex into a sphere, while this latter approach deforms a sphere onto the cortex. Both approaches allow project a coordinate-system onto the anatomy, so that cortical locations can be referred to in surface-based coordinates.

*Mapping Gyral Pattern Differences in a Population.* Once cortical models are available for a large number of subjects, in a common 3D coordinate space, patterns of cortical variability and cortical change over time can be calculated. 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. Fortunately, the major gyri and sulci of the cortical surface have a similar spatial layout across subjects (Ono et al., 1990; Regis, 1994; see Thompson et al., 2002 for some caveats), even though their geometry varies substantially. Transformations can therefore be developed that 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).

In one approach (Thompson et al., 2000), a maximal set, or template, is specified, containing all primary sulci that consistently occur in normal subjects (Fig. 6(b),(c) shows some of these). 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 many groups perform the matching process in the cortical surface's parametric space, which permits more tractable mathematics (Fig. 6, *right panels*). 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 not only matches overall cortical geometry, but matches the entire network of the 38 landmark curves with their counterparts in the target brain, and thus is a valid encoding of cortical variation. The flow in parameter space (Fig. 6) can be represented by spherical harmonics (Thompson and Toga, 1996; Gerig and Styner, 2001), which are eigenfunctions of the spherical Laplacian, or by solving an elastic or fluid PDE that aligns sulcal/gyral landmarks (Bakircioglu et al., 1999; Miller et al., 2002) or curvature maps (Fischl et al., 1999). In one approach, based on covariant PDEs, these flows are made invariant to the way the cortical surfaces are parameterized (Thompson et al., 2000). When the self-adjoint differential operator governing the PDE is discretized, fields of Christoffel symbols are derived from the metric tensor of the surface domain and added as correction terms. The matching fields are then independent of the surface metrics, and can be used to associate signals from corresponding cortical regions across subjects.

On the sphere, the parameter shift function $\mathbf{u}(\mathbf{r})$:□ □ □, is given by the solution F:$\mathbf{r}$□ $\mathbf{r}$-$\mathbf{u}(\mathbf{r})$ to a curve-driven warp in the spherical parametric space □=[0,2□)□[0,□). For points $\mathbf{r}$=(r,s) in the parameter space (Fig. 7), a system of simultaneous partial differential equations is written for the flow field $\mathbf{u}(\mathbf{r})$:

$$L^{\ddagger}(\mathbf{u}(\mathbf{r})) + \mathbf{F}(\mathbf{r}-\mathbf{u}(\mathbf{r})) = \mathbf{0}, \ \forall \mathbf{r} \in \square, \text{ with } \mathbf{u}(\mathbf{r}) = \mathbf{u_0}(\mathbf{r}), \ \forall \mathbf{r} \in M_0 \subset M_1. \qquad (9)$$

Here $M_0$, $M_1$ are sets of points and (sulcal or gyral) curves where displacement vectors $\mathbf{u}(\mathbf{r})=\mathbf{u_0}(\mathbf{r})$ matching corresponding anatomy across subjects are known. The flow behavior is modeled using continuum-mechanical equations. L can be any second order self-adjoint differential operator; a common example is the Cauchy-Navier differential operator $L = \mu\nabla^2+(\lambda+\mu)\nabla(\nabla^T\bullet)$ with body force $\mathbf{F}$ (*cf.* Gee and Bajscy, 1998; Christensen et al., 1996). To create mappings that are independent of the surface metrics (parameterizations), we use $L^{\ddagger}$, the *covariant* form of the differential operator $L$. $L^{\ddagger}$, all $L$'s partial derivatives are replaced with *covariant* derivatives with respect to the metric tensor of the surface domain where calculations are performed. The covariant derivative of a (contravariant) vector field, $u^i(\mathbf{x})$, is: $u^i{}_{,k} = \partial u^j/\partial x^k + \Gamma^j_{ik}\, u^i$ where the *Christoffel symbols of the second kind*, $\Gamma^j_{ik}$, are computed from derivatives of the metric tensor components $g_{jk}(\mathbf{x})$:

$$\Gamma^i_{jk} = (1/2)\, g^{il}\, (\partial g_{lj}/\partial x^k + \partial g_{lk}/\partial x^j - \partial g_{jk}/\partial x^i). \qquad (10)$$

These correction terms are then used in the solution of PDE, producing a family of 3D deformation maps, $\mathbf{U}_i(\mathbf{r})$ matching each individual cortex in 3D to the average cortex for a group. Here $\mathbf{U}_i$ is a 3D location on the $i$th subject's cortex, and $\mathbf{r}$ is the location it maps to, after warping, in the cortical parameter space.

*Mapping Gray Matter Deficits*. To help understand the approach, first we describe a cross-sectional study of gray matter deficits in dementia, in which each subject is imaged once; longitudinal data described next. Even in a study with a single scan from each subject, gyral pattern variation across subjects makes it difficult to infer precisely where gray matter is lost in a group. If gray matter maps are directly averaged together in stereotaxic space, it is difficult to localize results to specific cortical regions. To address this, cortical pattern matching can help in computing group averages and statistics. As a first step, all MRIs are RF-corrected and segmented with a Gaussian mixture classifier, producing binary maps of gray matter. Let $g_{i,r}(\mathbf{x})$ be the '*gray matter density*', i.e. the proportion of voxels classified as gray matter falling within a sphere (center $\mathbf{x}$, radius $\mathbf{r}$) in the $i$th subject's scan. Then for a point at parameter location $\mathbf{r}$ on the group average cortex, $g_{i,r}(\mathbf{U}_i(\mathbf{r}))$ is the gray matter density at the corresponding cortical point in subject $i$.

After averaging the aligned maps of gray matter density across groups of patients with Alzheimer's disease and healthy controls, Fig. 7 reveals the spatial profile of gray matter deficits in disease. By averaging the aligned maps, and texturing them back onto a group average model of the cortex, the average magnitude of gray matter loss was computed for the Alzheimer's disease population (Fig. 7, *top row*). Regions with up to 10-20% reduction in the measure are demarcated from adjacent regions with little detectable loss. The group effect size can also be measured by attaching a field of $t$ statistics, $t(\mathbf{r})$, to the cortical parameter space, and computing the area of the $t$ field on the group average cortex above a fixed threshold ($p < 0.01$, uncorrected). For groups that are not demographically matched, more sophisticated regression models could be applied, resulting in $F$ fields (or other non-parametric fields) that indicate the significance of the overall fit, and of how individual model parameters help explain the loss. If whole surfaces of statistics are surveyed, there are several approaches that are routinely used to make a multiple comparisons correction, which is required to confirm the significance of the overall effect. In permutation approaches, the significance of the deficits can be confirmed, by permuting the assignment of subjects to groups repeatly, and estimating the null distribution of statistics on the surface. Under stronger assumptions, Gaussian field methods may also be used, which analyze the topology and smoothness of the statistical fields and their level sets (see Thompson et al., 2001 for a review).

*Dynamically Spreading Tissue Loss in Dementia*. Fig. 7 shows these methods 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. Finally, cortical tissue is lost in a well-defined sequence as the disease progresses, 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.

*Mapping Surface Area Changes*. A similar cortical matching approach has been used to map localized changes in cortical surface *area*, over time (Thompson et al., 2000; Chung et al., 2001). Chung et al. (2001) noted that if $X = X(v_1,v_2,t)$ is a parameterization of the cortical surface $S_t$, its surface metric tensor is $g_{ij} = X_i'X_j$, where $'$ indicates the matrix transpose and $X_i=dX/dv_i$ denotes the partial derivative vector. The rate of local surface-area change per unit surface area or *area-dilatation rate* is then approximated by:

$$d(\ln L)/dt = tr[g^{-1}(DX)'(d(DU)/dt)DX], \quad (11)$$

where the *local surface area element*, $L(t)$, is given by:

$$L(t)=det^{1/2}(g)=(g_{11}g_{22}-g_{12}g_{21})^{1/2} \quad (12).$$

Here $DX = (X_1,X_2)$ is 3 x 2 matrix and $DU$ is a 3 x 3 displacement gradient matrix. Approximating the resulting surface-based parameters as *t*-distributed random fields (Chung et al., 2001), or chi-squared and Hotelling's $T^2$–distributed random fields (Thompson et al., 1996, 1997), null distributions and statistical criteria can be developed to tell where significant brain change has occurred (Thompson et al., 2000). Laplace–Beltrami smoothing (Chung et al., 2001) and statistical flattening (Worsley et al., 1999; Thompson et al., 2000) can also help to optimize signal detection in the resulting surface-based fields.

*A Spreading Wave of Brain Change in Schizophrenia.* An interesting application, detecting surface–based brain changes, is compiling dynamic maps to characterize diseases with childhood or adolescent onset. In a schizophrenia study (Thompson et al., 2001; Fig. 8), the gray matter mapping procedure, described above, was applied to longitudinal MRI data from 12 schizophrenic patients and 12 adolescent controls scanned at both the beginning and end of a 5-year interval. The average rate of gray matter loss was estimated throughout the cortex, by matching cortical patterns and comparing changes in disease with normal changes in controls. Cortical models and gray matter measures were elastically matched first within each subject across time, to compute individual rates of loss, and then flowed into an average configuration using flat space warping (Fig. 8). The resulting maps (Fig. 8) show dynamic gray matter loss in superior parietal, sensorimotor and some frontal brain regions (up to 5% annually), in a pattern that sweeps forwards across the brain over time. Group differences were highly significant ($p < 0.01$, *permutation test*), relative to healthy controls and non-schizophrenic controls matched for medication and IQ, and were linked with psychotic symptom severity (for details, see Thompson et al., 2001; see also Fig. 9).

## Conclusion

The ability to detect changes in the human brain is of great interest in basic and clinical neuroscience. Engineering challenges occur at many stages of the analysis, even after serial images are acquired. Different image analysis approaches, some based on image subtraction, deformation mapping, random field theory, and anatomical surface modeling have been developed that are sensitive to different features of brain change. Specialized approaches have also been developed to measure changes in the human cortex. Statistical atlases can then store these dynamic data and make comparisons across individuals and populations. The resulting armory of tools shows enormous promise in charting the dynamics of disease, and in revealing how the brain changes over the human lifespan.

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## Figure Legends

**Figure 1.** *Image Subtraction***.** A young normal subject was scanned at the age of 7, and again four years later, aged 11, with the same protocol (data from Thompson et al., 2000). Scan histograms were matched, rigidly registered, and a voxel-by-voxel map of intensity differences (*left*) suggests global growth. In a control experiment, identical procedures were applied to two scans from a 7 year old subject acquired just two weeks apart, to detect possible artifactual change due to mechanical effects, and due to tissue hydration or CSF pressure differences in the young subject between the scans. These artifacts were minimal, as shown by the difference image, which, as expected, is largely noise. Rigid registration of the scans does not localize anatomic change, but is a precursor to more complex tensor models of

structural change (see main text), which not only map local patterns of differences or change in 3 dimensions, but also allow calculations of rates of dilation, contraction, shearing, and torsion (Thompson et al., 2000).

**Figure 2.** *Deforming Anatomical Templates with Neural Nets and Continuum Mechanical Flows.* The complex transformation required to model brain change over time can be determined using radial basis function neural networks [(a), Davis et al., 1997; see Thompson et al., 2000 for details], or continuum-mechanical models (b). In Davis et al. (1997), each of the 3 deformation vector components, $\mathbf{u}^k(\mathbf{x})$, is the output of the neural net when the position in the image to be deformed, $\mathbf{x}$, is input to the net. Outputs of the hidden units ($G_i$, $\square_m$) are weighted using synaptic weights, $w_{ik}$. If landmarks constrain the mapping, the weights are found by solving a linear system. Otherwise, the weights can be tuned so that a measure of similarity between the deforming image and the target image is optimized. Continuum-mechanical models, (b), can also be used to compute these deformation fields (Davatzikos et al., 1996; Christensen et al., 1996; Gee et al., 1998; Thompson et al., 2000; Miller et al., 2002). In (b), two line elements embedded in a linearly elastic block are slightly perturbed. The goal is to find how the rest of the material deforms in response to this displacement. The Navier equations (shown in continuous form, (b), and in discrete form, (d)) are solved to determine the values of the displacement field vectors, $\mathbf{u}(\mathbf{x})$, throughout the 2D or 3D image. (b) *Lamé Elasticity Coefficients.* Different choices of elasticity coefficients, $\square$ and $\square$, in the Cauchy-Navier equations (shown in continuous form, *top*) result in different deformations, even if the applied internal displacements are the same. Elasticity coefficients can be chosen which limit the amount of curl (*lower right*) in the deformation field. To emphasize differences, the displacement vector fields shown in (b) 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. Using parametric meshes to model anatomical surface in registered pair of anatomical scans, patterns of local displacement can be computed over time (caudate nucleus, bottom left panel). These displacement vectors are used to drive a complex 3D volumetric deformation of anatomy (deformed grid, (d)), which can be thought of as a vector field (c). From this field, measures of local volumetric loss and gain can be computed. (e) shows the caudate nucleus of a young child, imaged at the age of 7 and again at age 11, with a growth map overlaid in color. Note regions of tissue loss (*blue colors*) are found immediately adjacent to regions of dramatic tissue growth (*red colors*).

**Figure 3**. *Deformation Mapping*. Patterns of local volumetric growth and loss can be estimated from a deformation map that captures brain changes over time. The determinant of the deformation gradient, i.e. the Jacobian or local expansion factor, is shown in color. Unlike with image subtraction (Fig. 2), the maps distinguish local volume changes from volume-preserving shifts in anatomy.

**Figure 4.** *Tensor Maps of Brain Change: Visualizing Growth*. If follow-up (longitudinal) images are available from the same subject, the dynamics of brain change can be measured with *tensor mapping* approaches. These map volumetric change at a local level, and show local rates of tissue growth or loss (red colors denote fastest growth). In children around the age of puberty, fastest growth is detected in the isthmus of the *corpus callosum*, which connects the language regions of the two brain hemispheres.

**Figure 5**: *Tensor Maps of Local Volumetric Loss*. 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 PDE (Gee and Bajcsy, 1998; Christensen *et al.,* 1996; Thompson *et al.,* 2000) 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*).

**Figure 6.** *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 Methods 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.]

**Figure 7.** *Asymmetric Progression of Alzheimer's Disease*. These maps show the average profile of gray matter loss in a group of 17 patients with mild to moderate Alzheimer's disease (Thompson et al., 2002). Average percent reductions in the local amount of gray matter are plotted, relative to the average values in a group of 14 healthy age and gender matched elderly controls. Initially, the left hemisphere is much more severely affected (b) than the right (a), but the deficits progress to encompass more of the left hemisphere (c). Maps of regional gray matter (*green colors*, (d)) are here computed from MRI brain scans acquired longitudinally over a 1.5 year period from both patients and controls.

**Figure 8.** *Spreading Wave of Gray Matter Loss in Schizophrenia*. Derived from high-resolution magnetic resonance images (MRI scans), the above images were createdafter repeatedly scanning 12 schizophrenia subjects over five years, and comparing them with matched 12 healthy controls, scanned at the same ages and intervals. Statistically signficant loss of gray matter is indicated by red and pink colors, while stable regions are shown in blue. STG denotes the superior temporal gyrus, and DLPFC denotes the dorsolateral prefrontal cortex.

**Figure 9.** *Data, Statistical Models and Maps*. This schematic shows some of the steps used in mapping cortical change. First, measures ($Y_{ij}$) are defined that can be measured longitudinally (green dots) or once only (red dots) in a group of subjects at different ages. Fitting of statistical models to these data (Statistical Model, lower right) produces estimates of parameters that can be plotted onto the cortex, using a color code. These parameters can include age at peak (see arrow at peak of the curve), significance values, or estimated statistical parameters such as rates of change, and effects of demographic factors or risk genes.

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