# BRAIN ATLASES AND REGISTRATION

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## I. Introduction

An atlas of the brain allows us to define its spatial characteristics. Where is a given structure; relative to what other features; what are its shape and characteristics and how do we refer to it? Where is this region of functional activation? How different is this brain compared with a normal database? An atlas allows us to answer these and related questions quantitatively.

Brain atlases are built from one or more representations of brain (Toga and Mazziotta, 1996). They describe one or more aspects of brain structure and/or function and their relationships after applying appropriate registration and warping strategies (Toga, 1998), indexing schemes and nomenclature systems. Atlases made from multiple modalities and individuals provide the capability to describe image data with statistical and visual power.

Atlases have enabled a tremendous increase in the number of investigations focusing on the structural and functional organization of the brain. In humans and other species, the brain's complexity and variability across subjects is so great that reliance on atlases is essential to manipulate, analyze and interpret brain data effectively.

Central to these tasks is the construction of averages, templates and models to describe how the brain and its component parts are organized. Design of appropriate reference systems for brain data presents considerable challenges, since these systems must capture how brain structure and function vary in large populations, across age and gender, in different disease states, across imaging modalities, and even across species.

There are many examples of brain atlases. Initially intended to catalog morphological descriptions, today there is considerable diversity in composition and intent. There are atlases of brain structure based upon 3D tomographic images (Damasio, 1995; Kikinis et al., 1996), anatomic specimens (Talairach et al., 1967; Talairach and Tournoux, 1988; Ono et al., 1990; Duvernoy, 1991) and a variety of histologic preparations which reveal regional cytoarchitecture (Brodmann, 1909). There are atlases that include regional molecular content such as myelination patterns (Smith, 1907; Mai et al., 1997), receptor binding sites (Geyer et al., 1997), protein densities and mRNA distributions. Other brain atlases describe function, quantified by positron emission tomography (PET; Minoshima et al., 1994), functional MRI (Le Bihan, 1996) or electrophysiology (Avoli et al., 1991; Palovcik et al., 1992). Others represent neuronal connectivity and circuitry (Van Essen and Maunsell, 1983) based on compilations of empirical evidence (Brodmann, 1909; Berger, 1929; Penfield and Boldrey, 1937).

While the differences among these examples help provide a comprehensive view of brain structure and function collectively, none is inherently compatible with any other. Without appropriate registration and warping strategies (see Section VII), these brain maps will remain as individual and independent efforts, and the correlative potential of the many diverse mapping approaches will be underexploited.

## II. Structure of a Brain Atlas

Brain atlases provide a structural framework to address these difficulties. Most brain atlases (regardless of species) are based on a detailed representation of a single subject's anatomy (or at best a few) in a standardized 3D coordinate system, or stereotaxic space. The earliest attempts were created from *post mortem* specimens (e.g., Brodmann, 1909; Schaltenbrand and Bailey, 1959; Schaltenbrand and Wahren, 1977; Talairach et al., 1967; Matsui and Hirano, 1978; Paxinos and Watson, 1986; Talairach and Tournoux, 1988; Ono et al., 1990; Swanson, 1992). Such atlases take the form of anatomical references or represent a particular feature of the brain (Van Buren and Maccubin, 1962; Van Buren and Borke, 1972). They also may focus on the cellular architecture of the cerebral cortex (Brodmann, 1909), or even a specific neurochemical distribution (Mansour et al., 1995).

*Brain Templates.* The single subject chosen to represent a population acts as a template on which other brain maps (such as functional images) can be overlaid. The anatomic data provides the additional detail necessary to accurately locate activation sites, as well as providing other structural perspectives such as chemoarchitecture. A common 3D coordinate space is a prerequisite, as it supplies a quantitative spatial reference system in which brain data from multiple subjects and modalities can be compared and correlated.

Since there is neither a single representative brain nor a simple method to construct an *average* anatomy or to represent the complex variations around it, the construction of brain atlases to represent large human populations has become a major research focus (Mazziotta et al., 1995). Population-based atlases can be used to guide knowledge-based image analysis algorithms, and can even support pathology detection in individual subjects or groups. Single modality atlases may also be insufficient, because of the need to establish the relationship between different measurements of anatomy and physiology. In response to these challenges, *multi-modal* atlases combine detailed structural maps from multiple imaging sensors in the same 3D coordinate space (Fig. 1). Anatomic labels can be used to identify the source of functional activation sites, for example, helping in the analysis of metabolic or functional studies based on PET or functional MRI (Seitz et al., 1990; Evans et al., 1991; Lehmann et al., 1991; Tiede et al., 1993; Ingvar et al., 1994). Multi-modal atlases provide the best of all worlds, offering a realistically complex representation of brain morphology and function in its full spatial and multi-dimensional complexity.

Due to individual variations in anatomy among normal subjects, early registration approaches used proportional scaling systems to reference a given brain to an atlas brain (Talairach and Tournoux, 1988). More sophisticated elastic or fluid transformations, involving local matching, are rapidly becoming commonplace (see Section VII). These approaches locally deform a digital atlas to reflect the anatomy of new subjects.

## III. Types of Atlases

*MRI.* Beyond the anatomic atlases based upon *post mortem* and histologic material mentioned above, the application of magnetic resonance to acquire detailed descriptions of anatomy *in vivo* is a driving force in brain mapping research. MRI data have the advantage of intrinsic three-axis registration and spatial coordinates (Damasio, 1995), but have relatively low resolution and lack anatomic contrast in important subregions. Even high-resolution MR atlases, with up to 100-150 slices, a section thickness of 2 mm, and $256^2$ pixel imaging planes (Evans et al., 1991; Lehmann et al., 1991) still result in resolutions lower than the complexity of many neuroanatomic structures. However, advances in the technology continue to push improvements in spatial and contrast resolution. A recent innovation in the collection of atlas quality MRI involves the averaging of multiple co-registered scans ($N$=27) from a single subject to overcome the lack of contrast and relatively poor signal to noise (Holmes et al., 1998).

*Multi-Modality Atlases.* Characterizing a single subject with multiple imaging devices clearly combines the

strengths of each imaging modality. In the *Visible Human Project* (Spritzer, 1996), two (male and female) cadavers were cryoplaned and imaged at 1.0 mm intervals, 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 imagery has sufficient quality and accessibility to make it a test platform for developing methods and standards (Spritzer, 1996). The 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., 1994). Data from single subjects, premortem and postmortem, provides a unique view into the relationship between *in vivo* imaging and histologic assessment. Mega et al. (1997) scanned Alzheimer's patients in the terminal stages of their disease using both MRI and PET. These data were combined with 3D histologic images from the same subject *post mortem*, showing the gross anatomy (Toga et al., 1994) and a Gallyas stain of neurofibrillary tangles. This multimodal, but single subject, atlas of Alzheimer's disease relates the anatomic and histopathologic underpinnings to *in vivo* metabolic and perfusion maps of this disease (Fig. 2).

*3D Anatomical Models*. Modeling strategies currently used to represent brain data have been motivated by the need to extract and analyze the complex shape of anatomical structures, for high-resolution visualization and quantitative comparisons. Using standard 3D modeling approaches to examine often studied structures such as the ventricles, can provide a framework for mapping variation within and between different populations. Figure 3 shows models of the ventricles used to study the differences between a population diagnosed with a degenerative dementing disease and age-matched controls. Ray-tracing and surface rendering techniques can then be applied to parameterized or triangulated structure models (Payne and Toga, 1990; Toga, 1994) to visualize complex anatomic systems. An 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.

## IV. Coordinate Systems

The coordinate system used to equate brain topology with an index must include carefully selected features common to all brains. Further, these features must be readily identifiable and sufficiently distributed anatomically to avoid bias. Once defined, rigorous systems for matching, or spatially normalizing a brain to this coordinate system must be developed. This allows individual data to be transformed to match the space occupied by the atlas. In the Talairach stereotaxic system (Talairach et al., 1967; Talairach and Tournoux, 1988), piecewise affine transformations are applied to 12 rectangular regions of brain, defined by vectors from the anterior and posterior commissures to the extrema of the cortex. These transformations re-position the anterior commissure of the subject's scan at the origin of the 3D coordinate space, vertically align the interhemispheric plane, and horizontally orient the line connecting the two commissures. Each point in the incoming brain image, after it is registered into the atlas space, is labeled by an (x,y,z) address indexed to the atlas brain. Although originally developed to help interpret brain stem and ventricular studies acquired using pneumoencephalography (Talairach et al., 1967), the Talairach stereotaxic system rapidly became an international standard for reporting functional activation sites in PET studies, allowing researchers to compare and contrast results from different laboratories (Fox et al., 1985, 1988; Friston et al., 1989, 1991).

## V. Registration

Registration is not as simple as equating the origin of similar coordinate systems. Rather, registration must accommodate a diversity of atlas types, spatial scales and extents of coverage. Registration is also needed to

compare one brain atlas with another. The success of any brain atlas depends on how well the anatomies of individual subjects match the representation of anatomy in the atlas. While registration can bring the individual into correspondence with the atlas, and a common coordinate system enables the pooling of activation data and multi-subject comparisons, the accuracy and utility of the atlas is equally dependent on the anatomical template itself (Roland and Zilles, 1994). The Talairach templates were based on *post mortem* sections of a 60 year-old female subject's brain, which clearly did not reflect the *in vivo* anatomy of subjects in activation studies. The atlas plates were also compromised by having a variable slice separation (3 to 4 mm), and data from orthogonal planes were inconsistent. To address these limitations, a composite MRI dataset was constructed from several hundred young normal subjects (239 males, 66 females; age: 23.4±4.1 years) whose scans were individually registered into the Talairach system by linear transformation, intensity normalized, and averaged on a voxel-by-voxel basis (Evans et al., 1992, 1994). Although the resulting average brain has regions where individual structures are blurred out due to spatial variability in the population (Evans et al., 1992; 1994), the effect of anatomical variability in different brain areas is illustrated qualitatively by this map. Meanwhile, automated methods were rapidly being developed to register new MRI and PET data into a common space. These algorithms could be used to optimally align new MR data with the template by maximizing a measure of intensity similarity, such as 3D cross-correlation (Collins et al., 1994,1995), ratio image uniformity (Woods et al., 1992), or mutual information (Viola et al., 1995; Wells et al., 1997). Any alignment transformation defined for one modality, such as MRI, can be identically applied to another modality, such as PET, if a previous cross-modality intrasubject registration has been performed (Woods et al., 1993). For the first time then, PET data could be mapped into stereotaxic space via a correlated MR dataset (Woods et al., 1993; Evans et al., 1994). Registration algorithms therefore made it feasible to automatically map data from a variety of modalities into an atlas coordinate space based directly on the Talairach reference system.

## VI. Deformable Brain Atlases

*Anatomic Variability.* The use of spatial normalization schemes based upon deep white matter features (the AC and PC), such as outlined above, will never completely accommodate the most variable of brain structures, the cortex. The cortex is also the site of interest for most functional activation studies. Considerable normal variation in sulcal geometry are well-documented in primary motor, somatosensory and auditory cortex (Missir et al., 1989; Rademacher et al., 1993), primary and association visual cortex (Stensaas et al., 1974), frontal and pre-frontal areas (Rajkowska and Goldman-Rakic, 1995), and lateral perisylvian cortex (Geschwind and Levitsky, 1968; Steinmetz et al., 1989,1990; Ono et al., 1990). More recent 3D analyses of anatomic variability, based on *post mortem* and normal and diseased populations *in vivo*, have found a highly heterogeneous pattern of anatomic variation (Thompson et al., 1996, 1998, 1999; Fig. 4).

Given this complex structural variability between normal individuals, and particularly between different populations (healthy and diseased), a fixed brain atlas may fail to serve as a faithful representation of every brain (Roland and Zilles, 1994; Mazziotta et al., 1995). Since no two brains are the same, this presents a challenge for attempts to create standardized atlases. Even in the absence of any pathology, brain structures vary between individuals in every metric; shape, size, position and orientation relative to each other. Such normal variations have complicated the goals of comparing functional and anatomic data from many subjects (Rademacher et al., 1993; Roland and Zilles, 1994).

Numerous studies have measured how severe the inter-subject variations in anatomy are, even after transforming individual anatomic data into the Talairach stereotaxic system (Fig. 4). Clearly, direct averaging of digital brain maps, after transformation to a common 3D coordinate space, is only valid if homologous cortical regions in different subjects have been brought into register by spatial normalization transformation. Extreme variations in cortical patterns, observed in normal subjects and exacerbated in disease states by additional pathologic influence, suggest that caution is necessary in selecting the transformation system to support cross-subject and cross-group

comparisons of cortically-based observations or functional maps. The most severe challenge occurs when the topology itself is undergoing considerable dynamic change due to development or degeneration, for example. Direct digital subtraction of stereotaxic functional maps in studies of disease states, such as dementia, may lead to spurious results: maps of apparent significance may reflect differences which are anatomic, rather than functional, in character (Meltzer and Frost, 1994; Woods, 1996). These difficulties have led to the suggestion that direct reference to the sulci that frame architectonic fields may present a more reliable basis for functional mapping than reference to a single standard or idealized brain (Steinmetz et al., 1990; Watson et al., 1993; Rademacher et al., 1993; Thompson et al., 1996, 1998, 1999).

## VII. Warping

The fact that the Talairach brain fails to match individual scans stems partly from two facts. First, Talairach registration is only based on linear transformations (rotation, scaling, translation). Second, the origin of the coordinate system was selected to solve mapping and localization problems deep in the brain where individual variability is relatively low.

Atlases can be greatly improved if they are elastically deformed to fit a new image set from an incoming subject. Local warping transformations (including local dilations, contractions and shearing) can adapt the shape of a digital atlas to reflect the anatomy of an individual subject, producing an *individualized* brain atlas. Introduced by Bajcsy and colleagues at the University of Pennsylvania (Broit, 1981; Bajcsy and Kovacic, 1989; Gee et al., 1993, 1995), this approach was adopted by the *Karolinska Brain Atlas Program* (Seitz et al., 1990; Thurfjell et al., 1993; Ingvar et al., 1994), where warping transformations are applied to a digital cryosection atlas to adapt it to individual CT or MR data and co-registered functional scans.

Image warping algorithms, specifically designed to handle 3D neuroanatomic data (Christensen et al., 1993; 1996; Collins et al., 1994, 1995; Thirion, 1995; Rabbitt et al., 1995; Davatzikos, 1996; Thompson and Toga, 1996; Bro-Nielsen and Gramkow, 1996; Ashburner et al., 1997; Woods et al., 1998) can transfer all the information in a 3D digital brain atlas onto the scan of any given subject, while respecting the intricate patterns of structural variation in their anatomy. These transformations must allow any segment of the atlas anatomy to grow, shrink, twist and rotate, to produce a transformation that encodes local differences in topography from one individual to another. Deformable atlases (Seitz et al., 1990; Evans et al., 1991; Miller et al., 1993; Gee et al., 1993; Christensen et al., 1993; Sandor and Leahy, 1994; 1995; Rizzo et al., 1995) resulting from these transformations can carry 3D maps of functional and vascular territories into the coordinate system of different subjects. The transformations also can be used to equate information on different tissue types, boundaries of cytoarchitectonic fields and their neurochemical composition.

Warping algorithms calculate a 3D deformation field which can be used to non-linearly register one brain with another (or with a neuroanatomic atlas). The resultant deformation fields can subsequently be used to transfer physiologic data from different individuals to a single anatomic template. This enables functional data from different subjects to be compared and integrated in a context where confounding effects of anatomical shape differences are factored out. Non-linear registration algorithms therefore support the integration of multi-subject brain data in a stereotaxic framework, and are increasingly used in functional image analysis packages (Seitz et al., 1990; Friston et al., 1995).

Any successful warping transform for cross-subject registration of brain data must be high-dimensional, in order to accommodate fine anatomic variations (Christensen et al., 1996; Thompson and Toga, 1998). This warping is required to bring the atlas anatomy into structural correspondence with the target scan at a very local level. Another difficulty arises from the fact that the topology and connectivity of the deforming atlas have to be maintained under

these complex transforms. This is difficult to achieve in traditional image warping manipulations (Christensen et al., 1995). Physical continuum models of the deformation address these difficulties by considering the deforming atlas image to be embedded in a three-dimensional deformable medium, which can be either an elastic material or a viscous fluid. The medium is subjected to certain distributed internal forces, which reconfigure the medium and eventually lead the image to match the target. These forces can be based mathematically on the local intensity patterns in the datasets, with local forces designed to match image regions of similar intensity.

*Model-Driven Registration*. To guide the mapping of an atlas onto an individual, higher-level structural information can be invoked to guarantee the biological validity of the resulting transform (Thompson and Toga, 1996; Davatzikos, 1996; Collins et al., 1996). In one approach (Thompson and Toga, 1996) anatomic surfaces, curves and points are extracted (with a combination of automatic and manual methods), and forced to match (Fig. 5). The procedure calculates the volumetric warp of one brain image into the shape of another, by calculating the deformation field required to elastically transform functionally important surfaces in one brain into precise structural correspondence with their counterparts in a target brain. The scheme involves the determination of several model surfaces, a warp between these surfaces, and the construction of a volumetric warp from the surface warp.

Model-driven warping algorithms perform well when warping neuroanatomic data not only between subjects but also between modalities. This presents new opportunities to transfer cytoarchitectural and neurochemical maps from high-resolution 3D cryosection data onto in vivo functional scans, and digitally correlate the resulting maps within a stereotaxic atlas space. Recent studies have used a deformable cryosection atlas to correlate histologic markers of Alzheimer's Disease with metabolic PET signals *in vivo*, while correcting for tissue deformation due to *post mortem* changes and histologic processing (Mega et al., 1997). Deformable atlas approaches offer a powerful means to transfer multi-modal 3D maps of functional and neurochemical territories between individuals and neuroanatomic atlases, respecting complex differences in the topography of the cortex and deep anatomic systems. These algorithms can also be applied to high-resolution brain atlases based on 3D digital cryosection images, to produce flexible high-resolution templates of neuroanatomy that can be adapted to reflect individual subjects' anatomy (Toga and Thompson, 1997).

Automated deformable atlases promise to have considerable impact on clinical and research imaging applications. Atlas deformations can carry pre-segmented digital anatomic models, defined in atlas space, into new patients' scans, automatically labeling their anatomy (Collins et al., 1995). Non-linear registration of 3D geometric atlases onto individual datasets has been used to support automated brain structure labeling for hippocampal morphometry (Haller et al., 1997), analysis of subcortical structure volumes in schizophrenia (Iosifescu et al., 1997), estimation of structural variation in normal and diseased populations (Collins et al., 1994; Thompson et al., 1997), and segmentation and classification of multiple sclerosis lesions (Warfield et al., 1995). Projection of digital anatomic models into PET data can also serve to define regions of interest for quantitative calculations of regional cerebral blood flow (Ingvar et al., 1994).

*Measuring Structural Differences*. Deformable atlas algorithms produce extremely detailed 3D maps of regional differences that can be used to investigate dynamic structure alterations in disease or during brain development. The complex profiles of dilation and contraction required to warp a digital atlas onto a new subject's brain provide an index of the anatomical shape differences between that subject's brain and the atlas (Bookstein, 1989, 1997; Davatzikos et al., 1996; Subsol et al., 1997; Thompson and Toga, 1997). Atlas deformation maps offer a framework for pathology detection (Thompson et al., 1997; Bookstein, 1997; Thompson and Toga, 1998; Grenander and Miller, 1998), identification of gender-specific anatomic patterns (Davatzikos, 1996), and mapping of dynamic patterns of structural change in neurodevelopmental and degenerative disease processes (Toga et al., 1996; Thompson et al., 1999).

## VIII. Multiple Modalities and Dimensions

As noted earlier, due to pronounced anatomic variability between individual human brains, any atlas or clinical diagnostic system based on a single subject's anatomy cannot succeed fully. A deformable brain atlas counteracts some of the limitations of a fixed atlas by using mathematically flexible transformations. Nonetheless, its success is still based on the premise that brains resemble a prototypical template of anatomy, and can be produced by continuously deforming it.

Atlasing considerations suggest that a statistical confidence limit, rather than an absolute representation of neuroanatomy, may be more appropriate for representing particular subpopulations. Methods to create *probabilistic* brain atlases currently fall into three major categories, each differing slightly in its conceptual foundations. The three methods are: density-based, label-based, and deformation-based approaches.

1. *Density-Based Approaches*. Initial approaches to population-based atlasing concentrated on generating *average* representations of anatomy by intensity averaging of multiple MRI scans (Evans et al., 1992; Andreasen et al., 1994). The average that results has large areas, especially at the cortex, where individual structures are blurred due to spatial variability in the population. While this blurring limits their usefulness as a quantitative tool, the templates can be used as targets for the automated registration and mapping of MR and co-registered functional data into stereotaxic space (Evans et al., 1994).

2. *Label-Based Approaches.* In label-based approaches (Evans et al., 1994; also known as SPAM approaches, short for *statistical/probabilistic anatomy maps*), large ensembles of brain data are manually labeled, or 'segmented', into sub-volumes, after registration into stereotaxic space. A probability map is then constructed for each segmented structure, by determining the proportion of subjects assigned a given anatomic label at each voxel position (Evans et al., 1994; Otaky et al., 1995; Paus et al., 1996). The information which these probability maps provide on the location of various tissue classes in stereotaxic space has been useful in designing automated tissue classifiers and approaches to correct radio-frequency and intensity inhomogeneities in MR scans (Zijdenbos and Dawant, 1994). In our laboratory, we have also used SPAM probabilistic maps to constrain the search space for significant activations in PET and SPECT imaging experiments (Mega et al., 1998; Dinov et al., 1999).

3. *Deformation-Based Approaches*. As noted earlier, when applied to two different 3D brain scans, a non-linear registration calculates a deformation map (Fig. 5, 6) that matches brain structures in one scan with their counterparts in the other. In probabilistic atlases based on deformation maps (Thompson and Toga, 1997, 1998; Thompson et al., 1997), statistical properties of these deformation maps are encoded locally 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 may be a sign of disease (Thompson et al., 1997). A major goal in designing this type of pathology detection system is to recognize that both the magnitude and local directional biases of structural variability in the brain may be different at every single anatomic point (Thompson et al., 1996). In contrast to the intensity averaging of other current approaches (Evans et al., 1992; Andreasen et al., 1994), an anisotropic random vector field framework is introduced to encode directional biases in anatomic variability and map out abnormalities in new subjects (Thompson et al., 1997).

The three major approaches for probabilistic atlas construction differ only in the attribute whose statistical distribution is modeled and analyzed. Random vector fields (*i.e.*, vector distributions of deformation vectors at each point in space) are analyzed in approaches based on deformation maps, while random scalar fields are used to model MR intensity statistics in the density-based approach, and to model the incidence of binary labels in space in the label-based approach.

## IX. Atlases of Cortical Patterns

Cortical morphology is notoriously complex, and presents unique challenges in anatomic modeling investigations. In response to these challenges, much research has been devoted to developing cortical parameterization and flattening algorithms. These methods optimally transform maps of cortical features onto a simpler, non-convoluted surface such as a 2D plane (Van Essen and Maunsell, 1980; Carman et al., 1995; Schwartz and Merker, 1986; Drury et al., 1996; Drury and Van Essen, 1997), an ellipsoid (Dale and Sereno, 1993; Sereno et al., 1996) or a sphere (Davatzikos, 1996; Thompson et al., 1996, 1997, 1998, 1999; Fischl et al., 1999; see Fig. 6).

*Warping the Cerebral Cortex*. Despite the advantages provided by transformations which simplify its geometry, the cortical surface presents significant challenges for all brain mapping and registration algorithms which strive to match the anatomy of one subject's cortex with another. The need to make comparative measurements at the cortex across subjects requires a surface-to-surface warp which not only matches overall cortical geometry, but also enforces point-to-point correspondence to a higher degree. Specialized approaches have been developed to match cortical regions, so that networks of sulci and gyri are individually matched (Fig. 6; Thompson and Toga, 1996, 1998). Differences in the serial organization of cortical gyri prevent exact gyrus-by-gyrus matching of one cortex with another. Some cortical areas are particularly subject to variations in the incidence and topology of accessory gyri, and one subject may have two or three gyri where one gyrus is found in another subject. This feature is especially notable in studies of paracingulate and temporo-parietal regions, in particular the *planum temporale* and posterior perisylvian areas which form a critical part of the language representation of the left hemisphere (Ono et al., 1990; Paus et al., 1996; Leonard, 1996).

## X. Disease States

Cortical structure is severely affected in a variety of disease states such as Alzheimer's disease, Pick's disease and other dementias, by tumor growth, and in cases of epilepsy, cortical dysplasias, and schizophrenia. Cortical matching approaches can be exploited by algorithms that detect these alterations. In one approach (Thompson et al., 1997), a probability space of random transformations, based on the theory of anisotropic Gaussian random fields, encodes information on complex variations in gyral and sulcal topography from one individual to another (Fig. 6). Confidence limits in stereotaxic space are determined, for cortical surface points in a new subject's brain, and color-coded probability maps are created to highlight and quantify regional patterns of deformity in the anatomy of new subjects (*q.v.*, Thompson and Toga, *this volume*).

*Genotype vs. Phenotype*. Structural image databases from twin monozygotic versus dizygotic populations provide tremendous opportunities to investigate the relationship between genotype and phenotype. Striking similarities in brain structure for both mono- and dizygotic twins have been reported in studies of corpus callosum morphology (Oppenheim et al., 1989; Biondi et al., 1998) and gyral patterning (Noga et al., 1996). These structural affinities can be exploited in clinical studies, since twins discordant for a specific disease-linked gene may be examined for regional structural differences in a context where effects of their shared genes are factored out (Goldberg et al., 1994; Noga et al., 1996). An on-going twin study (Gatz et al., 1997) focuses on 200 MR scans acquired from elderly Swedish twin pairs, where one member of each twin pair has Alzheimer's Disease (AD) or vascular dementia. Among 12 pairs of twins discordant for AD, the affected twin had greater temporal horn dilation, temporal lobe atrophy and 3rd ventricle enlargement, while significant within-pair correlations were found for measures of intracranial area, cerebellar area, temporal lobe volume, and white matter lesions (Gatz et al., 1997).

## XI. Dynamic Brain Atlases

*4D Coordinate Systems.* Atlasing of developmental brain data presents unique challenges. Imposition of standardized coordinate systems is difficult, and their relationship to anatomic nomenclature is hard to define, when potentially drastic morphological differences exist among data sets. In Yoon et al. (1997), a photographic atlas of the human embryo was created, based on detailed observations in utero from the 4th to the 7th week after ovulation (Carnegie Stages 10-18). In Chong et al. (1997), 26 normal formalin-fixed fetal specimens with a gestational age of 9 to 24 weeks were examined with high-resolution MRI using a conventional clinical magnet and pulse sequences, and MR findings were correlated with histologic atlas data. Although templates of normal development helped to identify expected developmental features, it was noted that direct correlation of fetal MR images with anatomic atlases might result in a mistaken diagnosis of delayed development, because of a time lag in the detection of structures on MR images.

Current atlases of fetal development (O'Rahilly and Müller, 1987; England, 1990) use collections of labeled data from multiple imaging modalities to characterize specific developmental stages. The first comprehensive MRI atlas of pediatric cranial anatomy (Salamon et al., 1990) incorporates 180 MRI scans acquired parallel to the orbito-meatal anatomical plane, and 360 explanatory diagrams depicting functional neuroanatomy from birth through 16 years of age. In this collection, 3D horizontal and sagittal images facilitate identification of sulci and gyri. However, stereotaxic coordinate systems were not applied to the atlas data due to difficulties in using them to reference embryonic and pediatric data. In the spirit of the deformable atlas methods described earlier, extreme deformations could be imposed to fit all stages of development into a standardized atlas, but this would hardly meet the primary requirement of atlasing, which is to provide a natural coordinate framework in which to localize and classify structures present in developing brains. Alternatively, different atlases and coordinate systems for several discrete stages of development might be used. Numerous anatomic features, due to their emergence and disappearance during development, could be used to place individual brains into an appropriate atlas in the set. Warping approaches could then be applied to the atlas coordinate systems as a basis to compare and quantitate development (Toga et al., 1996; Thompson et al., 1998, 1999).

In many ways, static representations of brain structure are ill-suited to analyzing dynamic processes of brain development and disease. Dramatic changes in brain geometry in brain development and disease mandate the design of mathematical systems to track anatomical changes over time, and map dynamic patterns of growth or degeneration.

*Temporal Maps of Brain Structure.* Current structural brain imaging investigations typically focus on the analysis of 3D models of brain structure, derived from volumetric images acquired at a single time-point from each subject in the study. However, serial scanning of human subjects, when combined with warping and analysis algorithms, can enable disease and growth processes to be tracked 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., 1998). Serial scanning of human subjects (Fox et al., 1996; 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. These models incorporate dynamic descriptors of how the brain changes during maturation or disease.

In our initial human studies (Thompson et al., 1998; Thompson and Toga, 1998), we developed several algorithms to create 4D quantitative maps of growth patterns in the developing human brain. Time-series of high-resolution pediatric MRI scans 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. Pairs of scans were selected to determine patterns of structural change across the interval between the two scans. These scan pairs were pre-processed with a radio-frequency bias field correction algorithm, and rigidly registered using automated image registration software (Woods et al., 1993). Registered scans were then histogram-matched and a preliminary map of differences in MR signal intensities between the two scans was constructed (Fig. 7). Parameterized cortical surface models were automatically extracted from each of the mutually registered histogram-matched scans. Deformation processes recovered by the warping algorithm were then analyzed using vector field operators to produce a variety of tensor maps (Figs. 8,9). 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.

Hopefully, in the near future we will be able to create 4D atlases that map growth and degeneration in their full spatial and temporal complexity. In spite of logistic and technical challenges, these mapping approaches hold tremendous promise for representing, analyzing and understanding the extremely complex dynamic processes that affect regional anatomy in the healthy and diseased brain.

## XII. Conclusion

As we have seen, the uses of brain atlases are as varied as their construction. Their utility results from their capacity to measure, visualize, compare and summarize brain images. An atlas can take on many forms, from descriptions of structure or function of the whole brain to maps of groups or populations. Individual systems of the brain can be mapped as can changes over time, as in development or degeneration. An atlas enables comparison across individuals,
modalities or states. Differences between species can be catalogued. But in most cases, the value added by brain atlases is the unique and critical ability to integrate information from multiple sources. The utility of an atlas is dependent upon appropriate coordinate systems, registration and deformation methods along with useful visualization strategies. Accurate and representative atlases of brain hold the most promise for helping to create a comprehensive understanding of brain in health and disease.

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## Figure Legends

Fig. 1. *Multimodality Brain Atlases*. Multimodality brain atlases combine data from multiple imaging devices in a common coordinate space, providing a more comprehensive description of brain structure and function than can be obtained with a single modality. Brain structure can be mapped *in vivo* with computed tomography (CT) and magnetic resonance imaging (MRI). Full-color digital images of cryosectioned head specimens (Cryo) can be reconstructed in 3D, allowing anatomy to be delineated at an even finer scale (Toga et al., 1994). Tissue sections can be stained histologically to reveal molecular content and regional biochemistry. Optical intrinsic signal imaging (OIS) monitors reflectance changes in electrically active cortex. Due to its high spatial and temporal resolution, OIS may complement assessments of brain function based on positron

emission tomography (PET) or functional MRI. Comparison of data from multiple sources requires specialized registration approaches, which may invoke statistical dependencies between the imaging signals from different sensors (Woods et al., 1993; Viola and Wells, 1995; Wells et al., 1997).

Fig. 2. *Warping Algorithms Integrate Multi-Modality Brain Data*. Histologic tissue sections, stained here to reveal neurofibrillary tangle density in a subject with Alzheimer's Disease, can be compared with functional imaging data acquired from the same subject *in vivo* (Mega et al., 1997). Images of stained tissue sections (a) are elastically warped back into their original configuration in the cryosection blockface (b). An additional warp reconfigures the *post mortem* cryosection and histologic data back into their *in vivo* configuration, as imaged by pre-mortem MRI. All maps can then be correlated with PET data acquired *in vivo* from the same patient (c), which is aligned to the MR template using an additional cross-modality registration. [Data adapted from Mega et al., 1997].

Fig. 3. *Population-Based Maps of Ventricular Anatomy in Normal Aging and Alzheimer's Disease*. (a). 3D parametric surface meshes (Thompson et al., 1996) were used to model a connected system of 14 tissue elements at the ventricular surface (partitioned along cytoarchitectural boundaries), based on high-resolution 3D MRI scans of 10 Alzheimer's patients (age: 71.9±10.9 yrs.) and 10 controls matched for age (72.9±5.6 yrs.), gender and handedness (Thompson et al., 1998). 3-D meshes representing each surface element were averaged by hemisphere in each group. (b),(c): The color map encodes a 3D r.m.s. measure of group anatomic variability shown pointwise on an average surface representation for each group, in the Talairach stereotaxic space. Oblique side views reveal enlarged occipital horns in the Alzheimer's patients, and high stereotaxic variability in both groups. (d),(e): A top view of these averaged surface meshes reveals localized patterns of asymmetry, variability, and displacement within and between groups. Asymmetry patterns at the ventricles and Sylvian fissure (see Fig. 4) emerge only after averaging of anatomical maps in large groups of subjects. Patterns of 3D variation can be encoded probabilistically to detect structural anomalies in individual patients or groups (Thompson et al., 1997; Thompson and Toga, 1998).

Fig. 4. *Population-Based Maps of 3D Structural Variation and Asymmetry*. Statistics of 3D deformation maps can be computed to determine 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; $p<0.0005$), mapped for the first time in 3D, 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 required to map the surfaces from each of the ten patients' brains onto the average. Confidence limits on 3D cortical variation (*lower right panel*), exhibited severe increases 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. 5. *A Deformable Brain Atlas Measures Patterns of Anatomic Differences.* Structure boundaries from a patient with clinically-determined Alzheimer's disease (top left) are overlaid on a cryosection atlas (top right), which has been registered to it using a simple linear transformation. A surface-based image warping algorithm is applied to drive the atlas into the configuration of the patients anatomy (bottom left). Histologic and neurochemical maps accessible only postmortem can be transferred onto the living subject's scan (Mega et al., 1997). The amount of deformation required can be displayed as a tensor map (here only 2 components of the fully 3-dimensional 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.

Fig. 6. *Maps of the Human Cerebral Cortex: Flat Maps, Spherical Maps, and Tensor Maps*. Extreme variations in cortical anatomy (*3D Models; top left*) present challenges in brain mapping, because of the need to compare and integrate cortically-derived brain maps from many subjects. Comparisons of cortical geometry can be based on the warped mapping of one subject's cortex onto another (*top right*; Thompson et al., 1997). These warps can also be used to transfer functional maps from one subject to another, or onto a common anatomic template for comparison. Accurate and comprehensive matching of cortical surfaces requires more than the matching of overall cortical geometry. Connected systems of curved sulcal landmarks, distributed over the cortical surface, must also be driven into correspondence with their counterparts in each target brain. Current approaches for deforming one cortex into the shape of another, typically simplify the problem by first representing

cortical features on a 2D plane, sphere or ellipsoid, where the matching procedure (i.e. finding $\mathbf{u}(\mathbf{r}_2)$, above) is subsequently performed (Thompson and Toga, 1996, Davatzikos et al., 1996; Drury et al., 1996; Van Essen et al., 1997). In one approach (Thompson et al., 1997), active surface extraction of the cortex provides a continuous inverse mapping from the cortex of each subject to the spherical template used to extract it. Application of these inverse maps to connected networks of curved sulci in each subject transforms the problem into one of computing an angular flow vector field $\mathbf{u}(\mathbf{r}_2)$, in spherical coordinates, which drives the network elements into register on the sphere (*middle panel*; Thompson and Toga, 1996). The full mapping (*top right*) can be recovered in 3D space as a displacement vector field which drives cortical points and regions in one brain into precise structural registration with their counterparts in the other brain. *Tensor Maps (middle and lower left):* Although these simple 2-parameter surfaces can serve as proxies for the cortex, different amounts of local dilation and contraction (encoded in the metric tensor if 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 regularization equations for matching their features. A covariant tensor approach is introduced in (Thompson and Toga, 1998a,b; *see red box*) to address this difficulty. The regularization operator L is replaced by its covariant form L*, in which correction terms (Christoffel symbols, $\mathbf{\Gamma}^{\mathbf{i}}_{\mathbf{jk}}$) compensate for fluctuations in the metric tensor of the flattening procedure. A covariant tensor approach (Thompson and Toga, 1998a,b) allows either flat or spherical maps to support cross-subject comparisons and registrations of cortical data by eliminating the confounding effects of metric distortions which necessarily occur during the flattening procedure.

Fig. 7. *Growth Patterns in the Developing Human Brain*. 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., 1998). Scan histograms were matched, rigidly registered, and a voxel-by-voxel map of intensity differences (*left*) reveals 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). Tensor maps of growth (Thompson et al., 1998) not only map local patterns of differences or change in 3 dimensions, but also allow calculations of rates of dilation, contraction, shearing, and torsion (Toga et al., 1996; Thompson et al., 1998).

Fig. 8. *Tensor Maps of Growth*. (*top panel*:) A complex pattern of growth is detected in the *corpus callosum* of a young normal male subject in the 4-year period from 7 to 11 years of age. Vector field operators emphasize patterns of contractions and dilations, emphasizing their regional character. The color code shows values of the local Jacobian of the warping field, which indicates local volume loss or gain. The effects of the transformation are shown on a regular grid ruled over the reference anatomy and passively carried along in the transformation that matches it with the later anatomy. Despite minimal changes in overall cerebral volume, callosal growth is dramatic, with peak values occurring throughout the posterior midbody. Pronounced neuroanatomical growth in the 4-year interval (*top panel*) contrasts sharply with the negligible change detected over a 2-week time-span (*middle panel*). Rapid heterogeneous growth, with a strikingly similar topographic pattern, is also observed in a young normal female (*bottom panel*), during a 4-year period spanning puberty, from 9 to 13 years of age.

Fig. 9. *3D Patterns of Deep Nuclear Tissue Loss*. (a) 3D displacement vector maps show the deformation required to match the caudate head in the earlier scan (at 7 yrs.) with its counterpart in the later scan (11 yrs.). Stability of the caudate tail (*blue colors*) contrasts sharply with dorsolateral regression of the caudate head and ventromedial progression of the internal capsule. These surface deformations are used to derive a volumetric deformation field (*vectors*, (b)), from which local measures of 3-dimensional tissue dilation or contraction can be quantified (c). In a smaller region selected for detailed analysis (*green square*, *inset*, (d)), a local 50% tissue *loss* was detected at the caudate head, as well as a 20-30% growth of the internal capsule and a 5-10% dilation of the superior ventricular horn. Visualization (d) of these maps in a graphical format indicates the anatomical context and regional complexity of the growth and regressive processes detected during the period spanned by the two scans.

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