We review recent developments in brain mapping and computational anatomy that have greatly expanded our ability to analyze brain structure and function. The enormous diversity of brain maps and imaging methods has spurred the development of population-based digital brain atlases. These atlases store information on how the brain varies across age and gender, across time, in health and disease, and in large human populations. We describe how brain atlases, and the computational tools that align new datasets with them, facilitate comparison of brain data across experiments, laboratories, and from different imaging devices. The major methods are presented for the construction of probabilistic atlases, which store information on anatomic and functional variability in a population. Algorithms are reviewed that create composite brain maps and atlases based on multiple subjects. We show that group patterns of cortical organization, asymmetry, and disease-specific trends can be resolved that may not be apparent in individual brain maps. Finally, we describe the creation of four-dimensional (4D) maps that store information on the dynamics of brain change in development and disease. Digital atlases that correlate these maps show considerable promise in identifying general patterns of structural and functional variation in human populations, and how these features depend on demographic, genetic, cognitive, and clinical parameters.

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KEY WORDS: biomedical imaging; brain mapping; cryosection imaging; neuroanatomy; atlas; neuroimaging; Alzheimer disease

The widespread collection of normal and diseased brain images in vivo and ex vivo enables a tremendous increase in the number of investigations focusing on the structural and functional organization of the brain. The complexity and variability of human brain (in particular) across subjects is so great that reliance on maps is essential to effectively analyze and interpret brain data. Design of appropriate maps for human brain data presents considerable challenges, because these systems must capture how brain structure and function vary across age and gender, in different disease states, across imaging modalities, and even across species.

This study introduces brain maps as applied to a variety of research areas in health and disease. It includes a brief survey of the types of maps and to what questions they are applied. First, there is an overview of brain mapping, describing the elements of a map as distinct from an image. Next, there follows a discussion of coordinate systems and how they reference source data from individuals, followed by a description of deformable atlases and how they can adapt to and measure variability across subjects and systems. We introduce maps that describe relationships between different observations, such as across modalities or with a changing morphology. Finally, we describe the categorization of subpopulations.

MAPS AND ATLASES

Diversity of Brain Maps

Comprehensive maps of brain structure have been created at a variety of spatial scales. These are based upon 3D tomographic images (Damasio, 1995), anatomic specimens (Talairach and Szikla, 1967; Talairach and Tournoix, 1988; Ono et al., 1990; Duvernoy, 1991) and different histologic preparations that reveal regional cytoarchitecture (Brodmann, 1909) and 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 maps have concentrated on neuronal connectivity and circuitry (Van Essen and Maunsell, 1983), based on compilations of em-
Brain Atlases

To address these difficulties, brain atlases provide a structural framework in which individual brain maps can be integrated. Most brain atlases are based on a single subject’s anatomy in a standardized 3D coordinate system, or stereotaxic space. The chosen data set 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 localize activation sites, as well as providing other structural perspectives such as chemoarchitecture. Digital mapping of structural and functional image data into a common 3D coordinate space is a prerequisite for many types of brain imaging research, as it supplies a quantitative spatial reference system in which brain data from multiple subjects and modalities can be compared and correlated.

Given the fact that there is neither a single (accepted) representative brain nor a simple method to construct an “average”, the construction of brain atlases to represent large human populations has become the focus of intense research. Deformable atlases, which can be adapted to reflect the anatomy of new subjects, and probabilistic atlases, which retain information on population variability, are powerful approaches with a range of clinical and research applications. These atlases can be used to support pathology detection in individual subjects or groups. Single modality atlases also ultimately may 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. Multi-modal atlases provide the best of all worlds, offering a realistically complex representation of brain morphology and function in its full spatial and multidimensional complexity.

Early Brain Atlases

Brain atlases were (are) built because accurate localization of brain structure and function in any modality may be improved by correlation with higher resolution anatomic data placed in an appropriate spatial coordinate system. Three-dimensional neuroanatomic templates also have the potential to provide important reference information when planning stereotaxic surgical procedures, including radiosurgery and electrode implantations (Talairach and Szikla, 1967; Kikinis et al., 1996). Most early atlases of the human brain, and other species (Paxinos and Watson, 1986; Swanson, 1992), were derived from one, or at best a few, individual post mortem specimens (Brodmann, 1909; Schaltenbrand and Bailey, 1959; Talairach and Szikla, 1967; Schaltenbrand and Wahren, 1977; Matsui and Hirano, 1978; Talairach and Tournox, 1988; Ono et al., 1990). 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), such as a specific neurochemical distribution (Mansour et al., 1995) or the cellular architecture of the cerebral cortex (Brodmann, 1909). None, to date, establishes a relationship between any two or more features of the brain. Commonly used human atlases include those of Talairach and Tournox (1988) and the thalamic and brainstem anatomical maps of Schaltenbrand and Wahren (1977). Due to individual variations in anatomy among normal subjects, proportional scaling systems are typically employed to reference a given brain to an atlas brain (Talairach and Tournox, 1988). More sophisticated elastic or fluid transformations, involving local matching, are described below. These approaches locally deform a digital atlas to reflect the anatomy of new subjects.

MRI-Based Atlases

Recent atlases based on magnetic resonance image (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. The Harvard Brain Atlas, based on a 1 x 1 x 1.5 mm resolution 3D SPGR (spoiled gradient-recalled acquisition) scan of a 25-year-old, normal subject, was enhanced by anisotropic diffusion filtering (Kikinis et al., 1996; diffusion MRI described in Mori and Barker, 1999), before being segmented into 150 hand-labeled regions, which include white matter tracts as well as major neuroanatomic structures. Nevertheless, many high-resolution MR atlases, with up to 100–150 slices, a section thickness of 2 mm, and 2562 pixel imaging planes (Evans et al., 1991; Lehmann et al., 1991) still result in resolutions lower than the complexity of many neuroanatomic structures. A recent innovation in the collection of atlas quality MR (Fig. 1) utilizes multiple scans (N = 27) and a registered average of a single individual to overcome the lack of contrast and relatively poor signal to noise (Holmes et al., 1998). The resulting volumetric datasets can serve as the basis for generating de-
tailed 3-dimensional models of anatomical structures, represented using a variety of volumetric and graphical surface formats (Fig. 2). The models can then be viewed either interactively, or off-line, using volume rendering and ray-tracing algorithms. Selective transparency can be applied to the models and animated fly-throughs generated to assist in visualizing the complex relationships among anatomical systems.

Cryosection Imaging

Several digital atlases have been developed using photographic images of cryoplaned frozen specimens (Bohm et al., 1983; Greitz et al., 1991). Photographed material, although providing superior anatomic detail, has limitations. For accurate correlations, data must be placed in a plane equivalent to that of the image of interest. Digital imaging, however, overcomes many limitations of conventional film photography. Using 1,024², 24-bits/pixel digital color cameras, spatial resolution can be as high as 100 microns/voxel for whole human head cadaver preparations, or higher for isolated brain regions (Toga et al., 1994). Cryosectioning in micron increments permits data collection with high spatial resolution in the axis orthogonal to the sectioning plane. Acquisition of images in series directly from the consistently positioned cryoplaned blockface also avoids the need for serial image registration before reconstruction. Serial images can be reconstructed to a 3D anatomic volume that is amenable to various resampling and positioning schemes.

Multi-Modality Atlases

Characterizing a single subject with multiple imaging devices clearly combines the strengths of each imaging modality. In the Visible Human Project (Spitzer et al., 1996; Spitzer and Whitlock, 1998), two (male and female) cadavers were cryopanned 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.

Although 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 (Spitzer et al., 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 patients in the terminal stages of their disease using both MRI and PET. These data were combined with post mortem 3D histological images showing the gross anatomy (Toga et al., 1994) and a Gal- lysas stain of neurofibrillary tangles. This multimodal, but single subject, atlas of Alzheimer disease relates the anatomic and histopathological underpinnings to in vivo metabolic and perfusion maps of this disease.

REFERENCE SYSTEMS

Matching a Brain to an Atlas

In existing atlases, spatial normalization systems are typically employed to reference a given brain with an atlas.
brain (Talairach and Szklra, 1967; Talairach and Tournoux, 1988). This allows individual data to be superimposed on the data in the atlas, in other words, to be transformed to match the space occupied by the atlas. In the Talairach stereotaxic system, piecewise affine transformations are applied to 12 rectangular regions of brain, defined by vectors from the anterior and posterior commissures to the extrema of the cortex. These transformations re-position the anterior commissure of the subject's scan at the origin of the 3D coordinate space, vertically align the interhemispheric plane, and horizontally orient the line connecting the two commissures. Each point in the incoming brain image, after it is “warped” into the atlas space, is labeled by an (x,y,z) address referable to the atlas brain. Although originally developed to help interpret brain stem and ventricular studies acquired using pneumoencephalography (Talairach and Szlikra, 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). 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. The average intensity template is part of the widely used Statistical Parametric Mapping package (SPM; Friston et al., 1995). The development of automated methods to map new MRI and PET data into a common space 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., 1994a, 1995), ratio image uniformity (Woods et al., 1992), or mutual information (Viola and Wells, 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.

DEFORMABLE ATLASES

Cross-Subject Anatomic Variations

The use of spatial normalization schemes based upon deep white mat-
ter features (the AC and PC), such as outlined above, has yet to completely accommodate the most variable brain structure, the cortex. The cortex is also the site of interest for most functional activation studies. Considerable normal variation in sulcal geometry has been found in primary motor, somatosensory and auditory cortex (Missir et al., 1989; Rademacher et al., 1993), primary and association visual cortex (Stenssaa 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, in post mortem, in vivo normal, and diseased populations, have found a highly heterogeneous pattern of anatomic variation (Thompson et al., 1996b, 1998a).

In view of the complex structural variability between individuals, a fixed brain atlas may fail to serve as a faithful representation of every brain (Roland and Zilles, 1994; Mazzotta et al., 1995). Because 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 not only in shape and size, but also in their orientations relative to each other. Such normal variations have also complicated the goals of comparing functional and anatomic data from many subjects (Rademacher et al., 1993; Roland and Zilles, 1994).

Numerous studies have determined how severe the inter-subject variations in anatomy are, even after transforming individual anatomic data into the Talairach stereotactic system. 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 the spatial normalization transformation. Extreme variations in cortical patterns, observed in normal subjects and exacerbated in disease states by additional pathologic change, suggest that caution is necessary in selecting the transformation system to support cross-subject and cross-group comparisons of cortically-derived events or functional maps. The most severe challenge occurs when the topology itself is undergoing considerable 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 that 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; Rademacher et al., 1993; Watson et al., 1993; Thompson et al., 1996, 1998).

The success of any brain atlas depends on how well the ananomies of individual subjects match the representation of anatomy in the atlas.

**Atlas to Brain Transformations**

Image warping algorithms, specifically designed to handle 3D neuroanatomic data (Christensen et al., 1993; 1996; Collins et al., 1994a, 1995; Rabbitt et al., 1995; Thirion, 1995; Bro-Nielsen and Gramkow, 1996; Davatzikos, 1996; Thompson and Toga, 1996) can be used to 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, however small, to grow, shrink, twist and even rotate, to produce a transformation that represents and encodes local differences in topography from one individual to another. Such deformable atlases (Bajcsy and Kovacic, 1989; Seitz et al., 1990; Evans et al., 1991; Gee et al., 1993; Christensen et al., 1993; Miller et al., 1993; Sandor and Leahy, 1994, 1995; Rizzo et al., 1995) can be used to carry 3D maps of functional and vascular territories into the coordinate system of different subjects, as well as information on different tissue types and the boundaries of cytoarchitectonic fields and their neurochemical composition.

**How Can One Brain Be Deformed to Match Another?**

Any successful warping transform for cross-subject registration of brain data must be high-dimensional, to accommodate fine anatomic variations (Joshi et al., 1995; 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 (Fig. 3). 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 hard or simply impossible to achieve in traditional image warping manipulations (Christensen et al., 1995a,b). 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.

**SUBSYSTEM MAPS**

The development of maps for anatomical subsystems, such as the somatosensory or motor systems, is typically driven by the need to catalogue functional activation studies or to describe pathways of connectivity. With the advent of deformable maps that can incorporate variability, however, individual structures such as specific nuclei or other distinguishable anatomic features are more frequently the subject of intensive mapping ef-
forts (Paxinos and Huang, 1995). A number of pathogenic processes have selective neuroanatomic targets resulting in characteristic morphological changes. Careful population mappings of these changes can produce a neuroanatomic signature that identifies the disease. Examples include the corpus callosum (Fig. 4) in dementia or schizophrenia (Thompson et al., 1998a; Narr et al., 2000), the cerebellum in autism (Courchesne, 1997) and the cingulate gyrus in Alzheimer disease (Mega and Cummings, 1996; Mega et al., 1998) among others.

Maps of the Corpus Callosum
Neuroimaging studies of the corpus callosum, for example, are easier to understand if its elaborate internal organization is considered. The corpus callosum connects the cortical surfaces of the two brain hemispheres, and there is a topographically specific organization of callosal fibers in relation to the cortical regions they connect. Tract-tracing studies using anterograde or retrograde labels such as biocytin or rhodamine-labeled latex microspheres (Innocenti, 1994) have established the topographic distribution of callosal connections at the cortex in several species. A massive perinatal loss of callosal axons, lasting from the 35th gestational week to the end of the first post-natal month (Clarke et al., 1989; La Mantia and Rakic, 1990) is thought to lead to a restricted pattern of adult callosal connections (Innocenti, 1994). In the adult callosum, the genu (or anterior third) connects pre-frontal cortices, the midbody (middle third) connects motor, somatosensory and auditory cortices, and the splenium (posterior fifth) carries temporal, parietal, and

Figure 3. Transforming one anatomical dataset to match another. 3D image deformation, or warping algorithms (Toga, 1998; Thompson et al., 2000) have powerful applications in the analysis of anatomical and functional maps. They apply a complex pattern of dilation and contraction (top left) to a 3D dataset, which reshapes the anatomy to match the anatomy in another dataset. They can correct for distortions due to post mortem anatomical change or histologic staining, reshaping cryosection or histologic images to match their in vivo configuration. Atlases can also be deformed to equate their anatomy with individual datasets. Anatomically-based warping algorithms (Thompson and Toga, 1996) use models of anatomical surfaces and curves (top right and bottom panels) to constrain the transformation, allowing key functional boundaries (here the calcarine and parieto-occipital sulci) to be matched in both datasets. By contrast with global registration approaches, the amount of deformation applied typically varies across the brain (see magnitude of deformation, top right).
occipital (visual) fibers. Perisylvian fibers from superior temporal and parietal cortex relay information from critical language and association areas, and cross mainly in the isthmus. To a certain degree, callosal fiber types are also organized topographically. Fast-conducting, large diameter (＞3μm sensorimotor fibers are concentrated in the posterior midbody and splenium, whereas thinner, more lightly myelinated fibers are found at the genu. These fibers at the genu offer a lower conduction velocity, connecting pre-frontal regions implicated in longer-term planning and organization of behavior (Aboitiz et al., 1992). Nonetheless, the idea of a sharply-defined cortical map at the callosum has been mitigated by recent anterograde tracer studies in humans (Di Virgilio and Clarke, 1997). These suggest that heterotopic connections (i.e., between non-equivalent cortical areas in each brain hemisphere) are numerous and widespread, even in the genu and splenium where callosal axons are most highly segregated.

To avoid making arbitrary definitions, Denenberg et al. (1991) performed a factor analysis to determine a “natural” partition of the callosum. Thickness measurements were obtained from a population of 104 normal adults (by connecting 100 equally spaced points on the inner and outer callosal boundaries; Fig. 4f), and these measures were used to determine seven regions with consistent variations (7 factors). Ultimately, the partitioning scheme chosen depends on the application objectives and the scale of the expected structural effects (Bookstein, 1997). Many of the conflicts among different callosal mapping efforts may derive from the use of different anatomical mapping and partitioning techniques (see Bishop and Wahlsten, 1997; reviewed in Thompson et al., 2000a).

**Figure 4.** Common partitioning schemes for regional analysis of the corpus callosum. In view of the topographically-specific relation between callosal regions and the cortical regions they connect, several partitioning approaches have been devised to allow separate analysis of different callosal sectors. Vertical partitions subdivide the callosum based on fractions of its maximal anterior-posterior length. Vertical fifths (a) (e.g., Duara et al., 1991; Lassen et al., 1992) or equal-angular sectors, relative to the callosal centroid (labeled CG in b), are commonly used. Variants of the radial partition have used rays emanating from the midpoint of the line joining the inferior rostrum and inferior splenium (Weis et al., 1993). A variant of the widely-used Witelson partition (c; Witelson, 1989), further subdivides the anterior third (A) into rostrum, genu, and rostral midbody, using an additional vertical line (Rajapakse et al., 1996). Angular rays from the callosal centroid (CG) can be used to produce a partition with 100 equiangular elements (e) (Rajapakse et al., 1996). The center of these elements (e) can also be used to derive a curvilinear reference line (d) (Clarke et al., 1989). By using a set of nodes to partitioning this line into 5 (as in d) or 30 (Clarke et al., 1989) equal segments, a slightly different set of sectors can be defined based on the shortest line through each node connecting inner and outer callosal boundaries. These shortest lines form the basis for maximal splenial width (SW) and minimal body width (BW) measurements (Clarke and Zaidel, 1994), and derived bulbosity measures (Clarke et al., 1989) equal segments, a slightly different set of sectors can be defined based on the circumference of the expected structural effects (Bookstein, 1997). Many of the conflicts among different callosal mapping efforts may derive from the use of different anatomical mapping and partitioning techniques (see Bishop and Wahlsten, 1997; reviewed in Thompson et al., 2000a).

With the advent of deformable maps that can incorporate variability, individual structures such as specific nuclei or other distinguishable anatomic features are more frequently the subject of intensive mapping efforts.

**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, but its success remains based on the premise that brains resemble a prototypical template of anatomy, and can be produced by continuously deforming it.

To realize the quantitative potential of digital atlases, data from single subjects must be extendable to populations (Mazziotta et al., 1995, 2000). Atlasing considerations suggest that a statistical confidence limit, rather than an absolute representation of neuroanatomy, may be more appropriate for representing particular subpopulations.

Population-Based Atlasing Approaches

Methods to create probabilistic brain representations currently fall into three major categories, each differing slightly in its conceptual foundations. The three methods are: the density-based, label-based, and deformation-based approaches. Benefits of each approach are outlined below.

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). A large number of MRI scans are each linearly transformed into stereotaxic space, intensity-normalized and averaged on a voxel-by-voxel basis, producing an average intensity MRI dataset. The average brains that result have large areas, especially at the cortex, where individual structures are blurred out due to spatial variability in the population. Although 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).

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 mapping individual datasets 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 in stereotaxic space (Evans et al., 1994; Otaky et al., 1995; Paus et al., 1996). The prior information that 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 (Dinov et al., 1998; Mega et al., 1998). Statistical data on anatomic labels and tissue types normally found at given positions in stereotaxic space provide a vital independent source of information to guide and inform mathematical algorithms that analyze neuroanatomic data in stereotaxic space.

Deformation-based approaches. As noted earlier, when applied to two different 3D brain scans, a non-linear registration or warping algorithm calculates a deformation map that matches up brain structures in one scan with their counterparts in the other. The deformation map indicates 3-dimensional patterns of anatomic differences between the two subjects (Bookstein, 1989). In probabilistic atlases based on deformation maps (Thompson and Toga, 1997, 1998a), 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 (Amit et al., 1991; Callini et al., 1994b; 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; Grenander and Miller, 1998).

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.

Encoding Brain Variation

Realistically complex mathematical strategies are needed to encode comprehensive information on structural variability in human populations. Particularly relevant is 3-dimensional statistical information on group-specific patterns of variation, and how these patterns are altered in disease. This information can be encoded so that it can be exploited by expert diagnostic systems, whose goal is to detect subtle or diffuse structural alterations in disease. Strategies for detecting structural anomalies can leverage information in databased anatomic data by invoking encoded knowledge on the variations in geometry and location of neuroanatomic regions and critical functional interfaces, especially at the cortex.

Atlases of Cortical Patterns

The random vector field approach is a general strategy to construct population-based atlases of the brain (Thompson and Toga, 1997). Briefly, given a 3D MR image of a new subject, a high-resolution parametric surface representation of the cerebral cortex is automatically extracted. The algorithm then calculates a set of high-dimensional volumetric maps, elastically deforming this surface into structural correspondence with other
cortical surfaces, selected one by one from an anatomic image database. The family of volumetric warps so constructed encodes statistical properties of local anatomical variation across the cortical surface. Specialized strategies elastically deform the sulcal patterns of different subjects into structural correspondence, in a way that matches large networks of gyral and sulcal landmarks with their counterparts in the target brain.

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; Schwartz and Merker, 1986; Carman et al., 1995; Drury et al., 1996), an ellipsoid (Dale and Sereno, 1993; Sereno et al., 1996) or a sphere (Davatzikos, 1996; Thompson et al., 1996a, 1997, 1998a).

Cortical parameterization offers substantial advantages for visualizing cortical topography, and provides potentially clearer interpretations of how architectonic fields and functional loci are related in the cortex (Van Essen et al., 1997). Parameterization and flattening techniques have also been applied to cortical models derived from the Visible Human datasets (Spitzer et al., 1996), and the resulting templates have served as the foundation for developing related atlases of cortical regions (Drury and Van Essen, 1997). These cortical atlases serve as a structural framework upon which architectonic, functional, and electrophysiological data, can be compared and integrated. Parametric models of the cortex also make comparisons of cortical anatomy more tractable in disease states (Thompson et al., 1997) and even across species (Van Essen et al., 1997). They can also help overcome problems caused by wide cross-subject variations in cortical geometry, by supporting non-linear registration of cortically-derived functional data and histologic brain maps localized at the cortex (Davatzikos, 1996; Thompson and Toga, 1996; Mega et al., 1997).

Warping the Cerebral Cortex

Despite the advantages provided by transformations that simplify its geometry, the cortical surface presents significant challenges for all brain mapping and registration algorithms that 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 that 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 (Thomp-
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 paracingular and temporo-parietal regions, in particular the planum temporale and posterior perisylvian areas that form a critical part of the language representation of the left hemisphere (Ono et al., 1990; Leonard, 1996; Paus et al., 1996). Because the assumption that brains are topologically equivalent breaks down once the functional units of the cortex are finely subdivided, an important intermediate goal has been to identify and match a comprehensive network of sulcal and gyral elements that are consistent in their incidence and topology across subjects (Ono et al., 1990; Rademacher et al., 1993; Thompson et al., 1996, 1997). Because the assumption that brains are topologically equivalent breaks down once the functional units of the cortex are finely subdivided, an important intermediate goal has been to identify and match a comprehensive network of sulcal and gyral elements that are consistent in their incidence and topology across subjects (Ono et al., 1990; Rademacher et al., 1993; Thompson et al., 1996, 1997).

In surface-based approaches, 3D deformable models (Cohen and Cohen, 1992; MacDonald et al., 1993; Davatzikos, 1996; Thompson and Toga, 1996) are used to automatically extract parametric representations of each subject’s cortex, on which corresponding networks of anatomical curves are identified. The transformation relating these networks is expressed as a vector flow field in the parameter space of the cortex that indirectly specifies a correspondence field in 3D driving one cortical surface into the shape of another (Drury et al., 1996; Davatzikos, 1996; Thompson and Toga, 1996; see Fig. 5).

An advantage of this approach is that an average model of the cortex can be generated for a population that retains the major gyral and sulcal landmarks (Fig. 5f). First, a set of color-coded 2D images is generated so that each point in the 2D image indexes a point on the cortical surface (Fig. 5c). These images essentially store information on the morphology of the cortex. These images, however, can then be warped so that corresponding gyri are aligned across subjects. If the warped images (Fig. 5d) are averaged pixel-by-pixel, the resulting color-coded image can be converted back into a cortical model with the average geometry of the group, which still retains gyral features (Fig. 5f; Thompson et al., 2000b).

This cortical averaging approach can therefore retain features of the cortex that would in general be washed away by averaging brain images directly. By retaining an average geometry for the cortical pattern, other features of cortical organization emerge after group averaging, that may not be apparent in an individual, due to the large cross-subject variations in cortical patterning. The average profile of cortical asymmetry in a population can be computed, for example, by averaging geometric models of the sulcal pattern, and comparing the results in both brain hemispheres (Fig. 6; Thompson et al., 2000). The ability to compare these cortical models across groups and across time can then be used to test hypotheses about the loss of cortical asymmetry in disease (Narr et al., 2000), its progression during development (Sowell et al., 2000), and modulation by disease processes (Thompson et al., 1998a).

Disease States

Cortical structure is severely affected in disease states such as Alzheimer disease, Pick 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. 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.

POPULATION SPECIFICITY

Coordinate Systems

Atlassing 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. Stereotaxic coordinate systems, however, 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., 1996b; Thompson et al., 1998b). Temporal interpolation between atlases in the set could be used to generate additional anatomic templates, representing brains at any stage of maturity in between those stages represented in the initial inventory.

**DYNAMIC MAPS**

In many ways, static representations of brain structure are ill-suited to analyzing dynamic processes of brain development and disease. The intense interest in brain development and disease mandates 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 3-dimensional models of brain structure, derived from volumetric images acquired at a single time-point from each subject in the study. Serial scanning of human subjects, when combined with a powerful set of warping and analysis algorithms, however, can enable disease and growth processes to be tracked in their full spatial and temporal complexity.

One of the most promising applications of warping algorithms is their use as a virtual sensor (Gee et al., 1993), creating exquisitely detailed maps of anatomic differences. Maps of anatomical change can also be generated by warping scans acquired from the same subject over time (Thompson et al., 1998b). Serial scanning of human subjects (Fox et al., 1996; Freeborough et al., 1996; Thompson et al., 1998b) or experimental animals (Jacobs and Fraser, 1994) in a dynamic state of disease or development offers the potential to create 4-dimensional models of brain structure. These models incorporate dynamic descriptors of how the brain changes during maturation or disease. For a range of patient populations, 4D models of the brain can be based on imaging and modeling its 3-dimensional structure at a sequence of time-points. In a changing morphology, warping algorithms enable one to model structural changes that occur over prolonged periods, such as developmental, aging or disease processes, as well as structural changes that occur more rapidly, as in recovery after trauma or tumor growth. A 4-dimensional approach can provide critical information on local patterns and rates of tissue growth, atrophy, shearing and dilation that occur in the dynamically changing architecture of the brain (Toga et al., 1996b; Thompson et al., 1998b).

**Mapping Growth Patterns in Four Dimensions**

In our initial human studies (Thompson et al., 1998b; Thompson and Toga, 1998b), we developed several algorithms to create 4-dimensional 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.

3D (256³ × 124 resolution) T₁-weighted fast SPGR (spoiled GRASS) MRI volumes were acquired from young normal subjects (mean age: 8.6 ± 3.1 yrs.) at intervals ranging from 2 weeks to 4 years. 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. Although dif-
ference maps help to determine whether structural change has occurred in dementia (Freeborough et al., 1996), these maps do not localize change, nor do they provide 3-dimensional measures of dilation, contraction or shearing of anatomic regions. To address this, parametric mesh models (Thompson et al., 1996a, 1997, 1998a) were created to represent a comprehensive set of deep sulcal, callosal, caudate and ventricular surfaces at each time-point. Parameterized cortical surface models were also automatically extracted from each of the mutually registered histogram-matched scans. Surface models based on manually-digitized data were averaged across multiple trials ($N = 6$) to minimize error. The deformation field required to match the surface anatomy of one scan with the other was extended to the full volume using a continuum-mechanical model based on the Cauchy-Navier operator of linear elasticity (Thompson and Toga, 1998b). Deformation processes recovered by the warping algorithm were then analyzed using vector field operators to produce a variety of tensor maps. 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.

Tensor Maps of Growth

In contrast to the near-zero maps of change recovered at short time intervals (2 weeks), tensor maps of growth spanning large time intervals (4 years) showed complex and heterogeneous patterns of change. In one subject scanned at ages 7, 9 and 11, comparative stability of lobar and thalamic anatomy, and negligible changes at the cortex, were accompanied by pronounced focal growth of the callosal isthmus (up to 80%; Fig. 7a,b), ventricular enlargement and loss of caudate tissue (Fig. 7c). Similar tensor mapping approaches can reveal the complex dynamics of tissue loss in individuals or groups of patients with Alzheimer disease (Fig. 7d,e; Thompson et al., 2000f).

In the near future, these brain mapping techniques will provide the ability to map growth and degeneration in their full spatial and temporal com-
plexity. Despite 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. (See Marshall and Marshall, 1994, for a detailed review.)

**SPECIES**

An immense variety of brain maps and atlases have been created to represent non-human primates, and a variety of other species. Despite the advent of modern neuroimaging, our knowledge of the molecular, cellular, systems and functional organization of the human brain remains rudimentary compared with the vast number of neuroscientific studies conducted in other species. The systematic electrophysiologic mapping of the neocortex in a wide range of mammals has revealed how cortical specialization varies across species (Manzonni, 1997). Many specialized stereotaxic systems, atlases, and parcellation schemes have also been developed for brain mapping in non-human species (e.g., Shantha et al., 1968; Szabo and Cowan, 1984; Paxinos and Watson, 1986; Felleman and Van Essen, 1991; Martin and Bowden, 1996). In parallel with the development of international, electronic registries for human brain mapping data (e.g., BrainMap; Fox et al., 1994), similar systems are under active development for the archival and meta-analysis of brain mapping data obtained in other species.

**Multi-Modality Maps**

Neuroimaging investigations in non-human primates have also included multi-modality studies. In our laboratory (Cannestra et al., 1998), a 3D multi-modality computerized map of the *Nemestrina* monkey brain was created by combining pre-mortem CT, PET, and MRI with a reconstructed post mortem volume of high-resolution full-color crossection images, captured at 50 micron increments. The resulting data sets were repositioned into the Horsley and Clark (1908) stereotaxic coordinate system, and labeled 3D surface models were reconstructed to represent nuclei, tracts, and other neuroanatomical features.

In the future, statistical characterization of the relationships among cortical regions in human and non-human primate populations will be invaluable in investigating how architectural patterns vary across individuals and species. Because neuronal connectivity patterns have been mapped extensively in several species, brain mapping tools that support cross-species comparisons of brain maps are likely to help in elucidating the complex functional geography of the human cortex.

**CONCLUSION**

As we have seen, the use of brain maps is as varied as their construction. Their utility results from their capacity to measure, visualize, compare and summarize brain images. Maps can take on many forms, from descriptions of structure to 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. Maps enable comparison across individuals, modalities or states. Differences between species can be catalogued. But in most cases, the value added by brain maps is the unique and critical ability to integrate information from multiple sources. Although dependent upon appropriate coordinate systems, deformation methods and visualization strategies, accurate and representative brain maps hold the most promise for helping to create a comprehensive understanding of brain in health and disease.

**ACKNOWLEDGMENTS**

This work was generously supported by research grants from the National Center for Research Resources (RR13642), National Library of Medicine (LM/MH05639), NINDS (NS38753), the National Science Foundation (BIR 93-22434), and by a Human Brain Project grant known as the International Consortium for Brain Mapping, which is funded jointly by NIMH and NIDA (P20 MH/DA52176).

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