Informatics and Computational Neuroanatomy

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Rapid and convenient access to digital image archives, as well as archive-based computational tools, are fundamental to many hypothesis-driven investigations of brain anatomy and function in health and disease. The complexity and density of brain image data requires the design of intelligent tools which allow scientific and clinical data, collected at numerous research centers, to be compared, integrated, and disseminated. We describe our results in the development of image data navigational tools, a World Wide Web repository of image analysis software, and strategies to represent populations of brain image data involving atlas descriptions of its variance.

INTRODUCTION

Informatics and Human Brain Mapping. Brain mapping is a multidisciplinary science whose goal is the integration of information describing brain structure and function. From microscopic to whole brain organization, data are acquired at many scales from subjects in various experimental conditions, at differing ages and in a range of developmental or disease states. Very high resolution *post mortem* techniques, such as cryosectioning, can be used to bridge the gap between lower resolution *in vivo* techniques, such as magnetic resonance imaging (MRI), and ultra high resolution methods, such as neurochemical and molecular mapping. In this manner, brain mapping permits the characterization of regional anatomy and the integration of functional information at a very fine structural level.

Unlike most reductionistic approaches in medical science, where an explosion of information has resulted in ever increasing subspecialization and diversity, brain mapping integrates many sources of information to produce a holistic view, combining the technical skills of experts in neuroscience, computer science and informatics. A pre-requisite to the success of such an effort is the development of advanced technologies to open information superhighways to brain researchers and clinicians, by providing an array of information tools for the analysis and representation of brain structure and function [1]. These include digital brain atlases, mathematical and computational tools for analyzing multi-modality image databases, and technologies for such information to be managed, integrated, and shared over networks.

The ultimate goal of brain mapping is to provide a means by which investigators and students can learn about brain function in health and disease, through the integrated data sets collected and stored in digital brain libraries. In this paper, we describe the development of a battery of internet-based resources, ranging from new computational tools to digital image archives. These resources are designed to allow rapid and convenient access to archives of brain images in various modalities, while the accompanying software provides methods for comparing and integrating brain data obtained at geographically disparate research centers. Archive-based computer algorithms are described which allow globally-networked sites to benefit directly from large repositories of image data collected at remote research centers. Applications include the detection and quantification of structural abnormalities in brain scans from incoming patients, and the complex transformation of neuroanatomic atlases onto new patients' scans to compensate for the normal structural variations of different individuals. With these methods, computer databases which continually benefit from the addition of new information, as well as new tools for analyzing this information, will better characterize normal brain function, disease states, and the detailed circuitry of the brain's component parts.

I. Digital Image Archives. The World Wide Web server at the UCLA Laboratory of Neuro-Imaging (http://www.loni.ucla.edu/) provides public access to various types of image data, and source code for tools to interact with it. The source code archive provides hypertext documentation on the functionality and use of the available programs. These programs include tools for volume warping and resampling, structure/function delineation, and surface construction.

Access to the image data is provided by a forms-based browser, for viewing digitally-reconstructed images of the brain. Slice number and orientation of cut can be controlled by the user. Interactivity, particularly over low bandwidth connections, is improved by two mechanisms. First is the control of image resolution, which ensures that only the desired amount of information is sent. Second is the use of interleaved *gif*s as the image format, which enables image display to proceed incrementally. Even faster transmission may be possible for abstracted graphics, such as 1-bit black and white outlines of structure boundaries. If several slices are to be sent or if continuous sweeps through the

volume are required, bulk transfer of volume data can be carried out via ftp. Online volumes are in stereotaxic space, a standard brain-based coordinate system which allows meaningful comparisons of different 3D data sets. Some volumes have associated anatomical region of interest and label information; such datasets can be viewed with or without their labels.

II. Braintree The application of these and other methods has resulted in an explosion of online brain maps and atlas-oriented databases. One central doctrine that makes this multitude accessible is the use of a standard 3D space, arrived at by applying a well-defined transformation to each input brain volume. The most commonly used space is that of Talairach [2], whose coordinate system has become familiar enough for some brain structures to be referenced using their (X,Y,Z) triplets. While the use of this space has greatly simplified the exchange of data between investigators, traditionally, neuroscientists rely on the usage of commonly understood anatomical terms to describe regions of interest. Although variability still exists in the usage of neuroanatomical terminology, standards have been set out and accepted (*e.g., Nomina Anatomica* [3]). In general these nomenclatures do not contain spatial information in the sense of a defined 3D coordinate space, leaving it up to the investigator to apply a name to a particular region in such a space. This makes the task of clearly describing anatomy quite difficult. Imagine, for instance, being asked to describe a city and its suburbs using only latitude and longitude, rather than place and street names.

As an initial attempt to merge standard nomenclature with computational methods, the NeuroNames program [4], uses a hierarchical tree of neuroanatomical nomenclature drawn from *Nomina Anatomica*, among other sources. While providing a readily accessible nomenclature in a computationally familiar form (a tree), NeuroNames does not allow for individual variations in usage or structure, nor does it link the nomenclature to a 3D space. We developed the Braintree hierarchical editor to address these two concerns.

Braintree is a simple interface to an anatomical hierarchy stored independently in a database. Braintree retrieves and displays hierarchies in an X11-based window using the TCl/Tk interpreter. Each node in the hierarchy can be relocated in the tree using prune and graft operators, and the newly configured hierarchy can be saved to disk. By providing an editable interface to the hierarchical data, Braintree permits customization of the relationships between structures, while preserving the underlying nomenclature itself (Fig. 1).

In order to link the developed nomenclature to 3D space, Braintree relies on a 2-coordinate bounding-box for each node, defining a region of 3D space that entirely contains

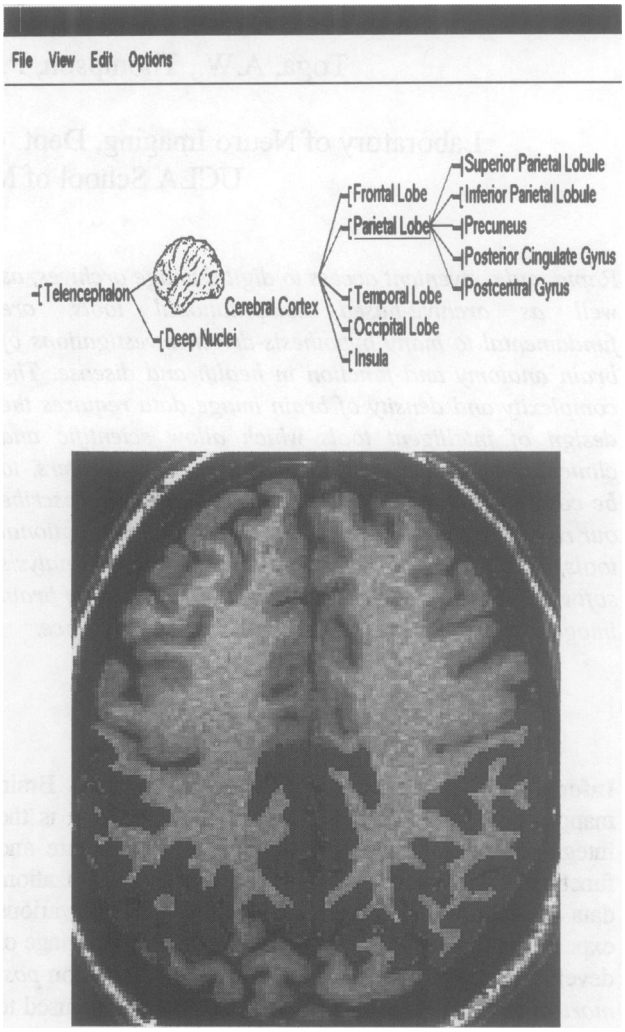

Fig. 1. The Braintree hierarchy has been opened to the level of cortical lobes and gyri. The user has selected the parietal lobe, whose constituents are displayed (*top panel*). Information about the boundaries of the parietal lobe has been passed to an auxiliary viewing tool (*bottom panel*) where the cortex of the parietal lobe (*solid gray*) has been identified in a T_1-weighted MR image.

(*cont'd..*)
the structure named. The bounding boxes for 'branch' nodes are constructed online from the logical AND of each of the 'leaf' nodes, and are recalculated with each change to the tree structure. The user can select a structure on the basis of its standard nomenclature, and have its coordinates passed to external tools. Hence, the Braintree program provides a facile interface between editable nomenclatures and standard 3D stereotaxic space. By maintaining a centralized repository of the most up-to-date leaf node coordinates, each investigator can be assured that he/she is referring to the same place in standard space as everyone else, while using the familiar neural place-names instead of obscure three dimensional coordinates.

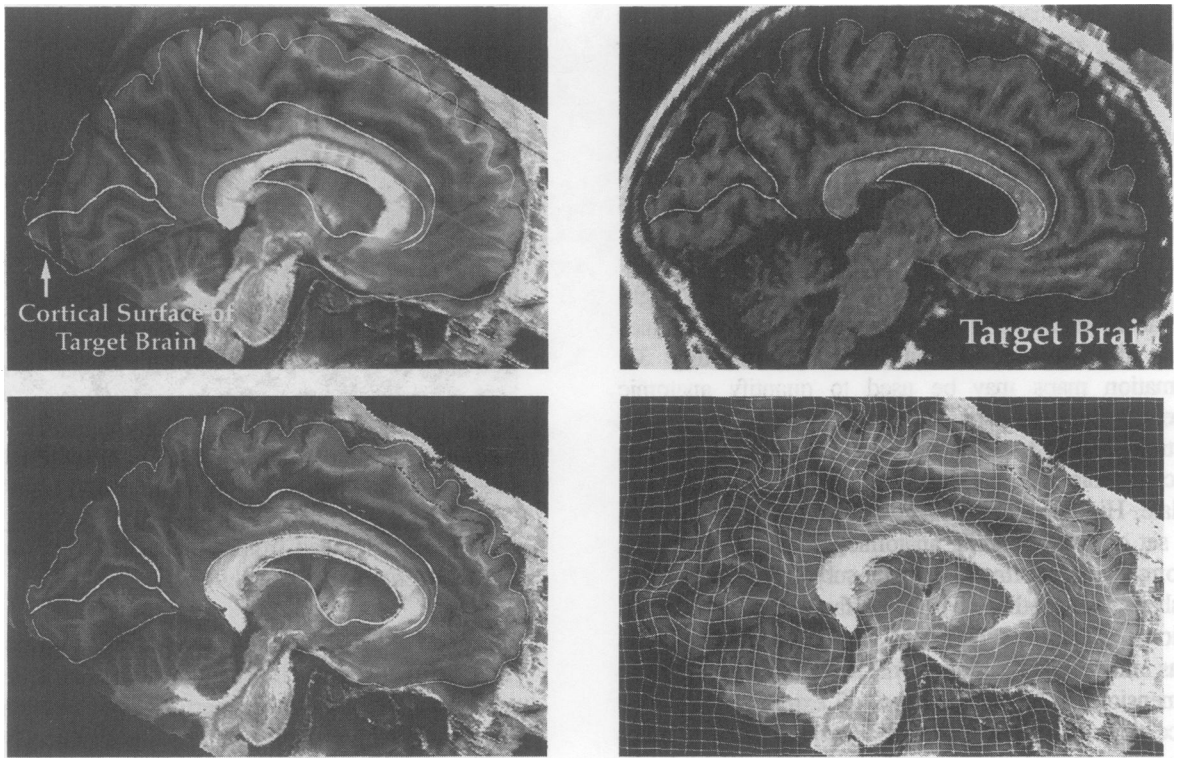

Fig. 2. Inter-Modality Data Fusion: 3D Digital Cryosection Volumes mapped onto 3D MRI volumes. Sagittal brain slice images from (*top left:*) a digitally-imaged, cryosectioned whole human head, and (*top right:*) a 3D SPGR T_1-weighted MR target scan. Also shown are the result (*bottom left*) of warping the cryosection image into structural correspondence with the MR scan, and the same transformation (*bottom right*) applied to a regular grid in the reference coordinate system. Note the reconfiguration of the major sulci, and the degree to which the reference *corpus callosum* is transformed into the shape of the target *callosum*. The continuous 1-to-1 mapping property of the warping transformation preserves the structural integrity of the data, and ensures the smooth continuation of the warping field from the complex anatomic surfaces into the surrounding brain architecture. Recent investigations in our laboratory have involved high-resolution cryosection imaging of whole human heads from subjects whose pre-mortem PET and MR scans are also available [10]. High-dimensional transformation tools enable the integration of cytoarchitectural and molecular maps with functional data obtained from the same individual *in vivo*.

III. Brain Atlas Databases.

Accurate clinical diagnosis often requires the severity of subtle deviations from normal brain structure and function to be quantified precisely. This exercise is especially difficult in the brain, because its internal geometry is highly individual in character. Striking variations exist, across normal subjects, in the size, configuration, and complexity of brain substructures [5]. These complex variations have complicated the goals of comparing and integrating functional data from many subjects, and of developing standardized atlases of the human brain. In what follows, we describe recent developments in neuroscience and informatics which may offer viable solutions to each of these two problems. First, we describe the design of software tools, available to globally-networked research centers via the Internet, which make it easier to compare and integrate experimental findings about brain structure and function across subjects and imaging modalities. Secondly, we describe research projects directed towards the eventual development of publicly available anatomical templates and expert diagnostic systems which retain comprehensive information on inter-subject variations in brain architecture.

(i). Deformable Brain Atlases. In view of the complex structural variability between individuals, a fixed digital atlas, representing the anatomy of a single human brain, will fail to serve as a faithful representation of the brains of new subjects. It would, however, be ideal if an atlas could be elastically deformed to fit a new image set from an incoming patient. Transforming individual datasets into the shape of a single reference anatomy, or onto a 3D digital brain atlas, removes subject-specific shape variations, and allows subsequent comparison of brain function between individuals [6]. Conversely, high-dimensional warping algorithms can also be used to transfer all the information in a 3D digital brain atlas onto the scan of any given patient, while respecting the intricate patterns of structural variation in their anatomy. Such *deformable atlases* [7,8]

can be used to carry 3D maps of functional and vascular territories into the coordinate system of different patients, as well as information on different tissue types and the boundaries of cytoarchitectonic fields and their neurochemical composition.

Deformable atlases rely on high-dimensional warping algorithms to drive them into precise structural correspondence with target brain images. Fig. 2 illustrates the behavior of a surface-based warping procedure, recently devised and implemented in our laboratory [9]. This algorithm was designed to calculate the high-dimensional deformation field relating the brain anatomies of an arbitrary pair of subjects. The resulting 3D deformation maps may be used to quantify anatomic differences between subjects or within the same subject over time, and to transfer functional information between subjects or integrate that information on a single anatomic template. High spatial accuracy is guaranteed by using a large set of corresponding anatomic surfaces to constrain the complex transformation of one subject's anatomy into the shape of another. These surfaces include critical functional interfaces such as the ventricles and cortex, as well as numerous cytoarchitectonic and lobar boundaries in 3 dimensions. The construction of extremely complex surface deformation maps on the internal cortex is made easier by building a generic surface structure to model it. Connected systems of parametric meshes model several deep internal fissures, or *sulci*, whose trajectories represent critical functional boundaries. These sulci are sufficiently extended inside the brain to reflect subtle and distributed variations in neuroanatomy between subjects. The parametric form of the system of connected surface elements allows us to represent the relation between any pair of anatomies as a family of high-resolution displacement maps carrying the surface system of one individual onto another in stereotaxic space. The algorithm then calculates the high-dimensional volumetric warp (typically with 384^2x256x3 $\approx$ 0.1 billion degrees of freedom) deforming one 3D scan into structural correspondence with the other. Integral distortion functions are used to extend the deformation field required to elastically transform these surface systems into structural correspondence with their counterparts in the target scan.

3D warping algorithms provide a method for calculating local and global shape changes and give valuable information to scientists studying normal and abnormal growth and development. Deformable atlases not only account for the anatomic variations and idiosyncrasies of each individual patient, but they offer a powerful strategy for exploring and classifying age-related, developmental or pathologic variations in anatomy. More fundamentally, they also provide a method for spatially normalizing the anatomies of different brains. Further automation of warping algorithms may ultimately allow extramural users to submit their own images for normalization, instead of downloading the source code directly. Such normalization software supplies a basis for comparing experimental or clinical data obtained from different subjects or different research centers.

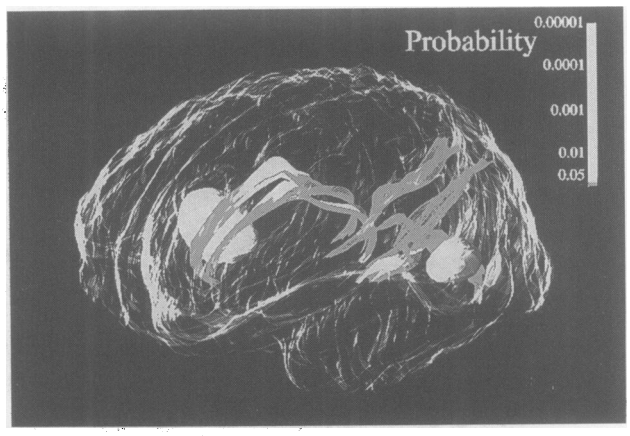

Fig. 3. Probability maps quantify the impact of two focal metastatic tumors on adjacent callosal and occipital sulci.

(ii). Probabilistic Brain Atlases. Probabilistic atlasing [11,12,13] is a research strategy whose goal is to generate anatomical templates and expert diagnostic systems which retain quantitative information on inter-subject variations in brain architecture. The recent interest in comprehensive brain mapping also stresses that the comparisons between subjects, both within and across homogeneous populations, are required to understand normal variability and genuine structural and functional differences. Initial attempts to derive average representations of neuroanatomy have underscored the power of this approach in both clinical and research settings [14,15].

We have developed and implemented an approach for constructing a probabilistic surface atlas of the brain. This performs a statistical analysis of deep surface structures in the brain (in a reference database of normal scans), and then automatically quantifies and maps distributed patterns of abnormality in the same system of anatomic surfaces in new subjects. Once again, connected systems of parametric meshes model deep fissures in the brain, whose trajectories represent critical functional and lobar boundaries. Additional surface analysis algorithms construct a probability space of random transformations (based on the theory of 3D Gaussian random fields) reflecting the variability in stereotaxic space of the connected system of anatomic surfaces. Automatic parametrization of the surface anatomy of new subjects has enabled the detection and mapping of subtle shape and volume abnormalities in the brains of patients with metastatic tumors (Fig. 3). These shape changes can be visualized in the form of probability maps on a graphical surface model of the subject's anatomy. The resulting surface system can be rotated, magnified and animated interactively for detailed examination and clinical diagnosis.

Publicly available computer algorithms, defined on a large

database of anatomic data, permit rapid detection and exploration of trends in vast ensembles of 3D images. Archive-based computer algorithms such as these enable deviations in the anatomy of new subjects to be analyzed and quantified at an extremely local level [5,7,13]. Any discrepancies, which may be of clinical or scientific relevance, can therefore be mapped in 3-dimensional space, quantified and evaluated, at a site which may be geographically distant from the reference image archives.

DISCUSSION

In the future, rapid access to digital image archives, as well as archive-based computational tools, will be fundamental to many hypothesis-driven investigations of brain anatomy and function in health and disease. The establishment of powerful brain atlasing approaches, together with methods for guaranteeing the comparability of research findings from different laboratories, are central to the task of comprehensive brain mapping. Internet repositories of software tools, such as those for creating deformable neuroanatomic atlases [6,8,9], will enable the transfer of multi-subject 3D functional, vascular and histologic maps onto a single anatomic template, the mapping of 3D brain atlases onto the scans of new subjects, and the rapid detection, quantification and mapping of local shape changes in 3D medical images in disease, and during normal or abnormal growth and development.

Digital probabilistic atlases based on large populations will also rectify many current atlasing problems, since they retain quantitative information on the variability inherent in anatomic populations. As the underlying database of subjects increases in size and content, the digital, electronic form of the atlas provides efficiency in statistical and computational comparisons between individuals or groups. The atlas also improves in accuracy over time achieving better statistics as more information is added. In addition, the digital form of the source data enables the population on which probabilistic atlases are based to be stratified into subpopulations by age, gender, by stage of development or to represent different disease types. Such archive-based atlasing approaches will therefore allow globally-networked sites to benefit directly from vast repositories of image data collected at remote research centers.

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