NEUROIMAGE 2, 89–101 (1995)

A Probabilistic Atlas of the Human Brain: Theory and Rationale for Its Development

The International Consortium for Brain Mapping (ICBM)

JOHN C. MAZZIOTTA,*,†,‡ ARTHUR W. TOGA,*,† ALAN EVANS,§ PETER FOX,¶ AND JACK LANCASTER¶

*Division of Brain Mapping, Neuropsychiatric Institute and Departments of †Neurology, ‡Radiology, and Pharmacology, UCLA School of Medicine, Los Angeles, California 90024; §Departments of Neurology, Neurosurgery, and Biomedical Engineering, Montreal Neurologic Institute, McGill University, Montreal, Canada; and ¶Departments of Radiology, Neurology, and Psychiatry, Research Imaging Center, University of Texas, San Antonio, San Antonio, Texas

Received April 6, 1995

Better to light one candle than to curse the darkness.

Chinese Proverb

STATEMENT OF PURPOSE

As in geography, neuroanatomy requires accepted maps, terminology, coordinate systems, and reference spaces in order to allow accurate and effective communication within the field and to allied disciplines. Geographical atlases of the earth have an advantage over atlases that are anatomical in nature. Earth atlases can assume a relatively constant physical reality over thousands of years. On that single, stable construct an infinite number of abstract representations of features can be overlaid. For earth maps such features might include rainfall, temperature, population density, crime rates, etc.

Unlike geographical atlases, anatomical atlases cannot assume a single, constant physical reality. This is true despite the fact that standard atlases of single subjects tended to minimize this fundamental problem. Anatomical atlases must first deal with the fact that there are a potentially infinite number of physical realities that must be modeled to obtain an accurate, probabilistic representation of the entire population. Upon this anatomical representation one can then overlay an infinite set of features in a fashion analogous to that described for earth atlases (Mazziotta, 1984). In the brain, such features might include cytoarchitecture, chemoarchitecture, blood flow distributions, metabolic rates, behavioral and pathologic correlates, and many others. Like earth maps, brain maps can vary in time frames ranging from milliseconds (e.g., electrophysiologic events) to minutes (e.g., skill acquisition), years (e.g., development, maturation, aging), or millennia (i.e., evolution).

Classic atlases of the human brain and other species have been derived from a single brain, or brains from a very small number of subjects, and have employed simple scaling factors to stretch or constrict a given subject's brain to match the atlas. The result is a rigid and often inflexible system that disregards useful information about both morphometric (i.e., dimensionality) and densitometric (i.e., intensity) variability between subjects.

This article reviews the theory and rationale for defining a probabilistic atlas derived from a large series of subjects, representative of the entire species, with retention of information about variability. Such a project must take on the problems inherent in dealing with biologically variable structure and function but, when successful, will provide a system that is realistic in its complexity, has defined accuracy and errors, and that, as a benefit, contributes new neurobiological information.

The atlas is envisioned to be both visualizable (e.g., recognizable brain images) and quantitative (e.g., tabular databases). Digital in its composition, the atlas, and the tools to enter and retrieve data from it, produce probabilistic responses to queries. That is, for a given location identified in the reference space, the atlas will produce probability distributions and confidence limits for structure identification, functional variables (e.g., blood flow, metabolism, receptor density, etc.), clinical information (e.g., deficits associated with lesions at the site, behavioral states that augment functions like blood flow at the site, etc.), and bibliographic data. By defining a subpopulation of the database contents in a given query, probabilities would shift to reflect a more constrained subset of the entire population.

A Brief History of Human Brain Mapping Approaches

Examples of brain mapping can be found in ancient times, but systematic attempts at relating structure to function find their origins in phrenology. By examining

1053-8119/95 $6.00

the irregularities of the outer table of the skull, phrenologists assigned psychological, personality, and physical traits to individuals. Concerns about inaccuracies and inconsistencies of this approach, combined with more scientific methodologies, led to the emergence of the localizationists, the earliest and most well known of whom was Pierre Paul Broca. Broca's identification of the language area in a patient with damage to the left anterior sylvian cortex represents the most celebrated example of ascribing a behavioral function, namely language output, to a cerebral site (Broca, 1861).

Localization flourished throughout the late 19th century and continues to this date (Ferrier, 1875; Phillips *et al.,* 1984). While the results of this research were prolific, these investigators depended on spontaneously occurring lesions and, thus, had a limited experimental domain. Concomitantly, anatomists produced maps of ever increasing complexity and detail about brain structure (Brodmann, 1905; Flechsig, 1901). Modern localization now takes the form of distributed large-scale neural networks rather than isolated brain regions (Mesulam, 1990; Posner and Dehaene, 1994).

In the latter half of the 19th century the electrophysiological characterization of the brain began (Fritsch and Hitzig, 1870). These measurements ranged from intraoperative depth electrode recordings, with their exquisite spatial and temporal resolution but minimal sampling, to scalp electroencephalography (EEG), which samples broadly but localizes poorly. The combination of time-locked stimuli and EEG signals produced the field of evoked potentials research. More recent has been the measurement of weak magnetic signals from the surface and depth of the brain by magnetoencephalography (MEG) (Hari, 1991). These magneto- and electrophysiological techniques provide temporal resolution on the order of that known to exist for neural events (i.e., milliseconds).

The application of Kety–Schmidt tracer-kinetic techniques (Kety and Schmidt, 1948) to externally detected distributions of radioactive xenon, pioneered by Scandinavian workers in the late 1950s and 1960s, provided the first glimpse of cortical responses of cerebral blood flow in normal subjects and patients performing a wide variety of tasks (Lassen *et al.,* 1960; Ingvar, 1975). The regional, and largely cortical, application of tracer kinetic techniques from these studies was quickly applied, using a broad range of radiopharmaceuticals, to the emission computed tomographic methods of SPECT (Kuhl and Edwards, 1973) and PET (Phelps *et al.,* 1975). The number of radiopharmaceuticals and, therefore, physiological processes that can be measured with SPECT and PET revealed, for the first time, the complex macroscopic neuronal networks associated with normal behavior and disease states (Mazziotta and Gilman, 1992). The emission tomographic methods have achieved a spatial resolution of less than 5 mm and a temporal resolution ranging from approximately 30 s to many minutes or hours.

In the early 1990s, the exquisite structural anatomy and high spatial resolution of magnetic resonance imaging (MRI) was extended to the measurement of physiological events with both high spatial and temporal resolution (Belliveau *et al.,* 1991). Further, the related technique of magnetic resonance spectroscopy (MRS) provides information about the chemical state of the human brain, albeit, with much lower spatial and temporal resolution (Prichard *et al.,* 1983). The ultimate scope of methods based on the principle of nuclear magnetic resonance is still largely unexplored (Prichard and Brass, 1992).

The realization that the integration of information from a variety of methods would provide the most comprehensive data set, with complementary features optimizing spatial and temporal resolution, as well as sampling, resulted in the development of methods to combine data from many techniques (Woods *et al.,* 1993). The need for a common means of communication within the subdisciplines of neuroscience (Mazziotta and Koslow, 1987) and the lack of a standardized coordinate system and population atlas emerged as major limitations in comparing these complex data sets between subjects, populations, or different laboratories.

The Human Brain Project

In the late 1980s in the United States, the Institute of Medicine of the National Academy of Science was commissioned by the National Institute of Mental Health, the National Science Foundation, and the National Institute on Drug Abuse to establish a panel to investigate the value of integrating neuroscientific information across a variety of technologies (Pechura and Martin, 1991). This group concluded that the fields of neuroscience, computer science, and informatics could and should be combined to integrate data from enabling technologies currently used to study neuroscientific questions. This led to the establishment of the Human Brain Project (Huerta *et al.,* 1993). Developed as a consortium of federal agencies, funding was announced for the first round of feasibility projects on this topic in the spring of 1992.

In the fall of 1992, a meeting of individuals interested in the development of a probabilistic atlas for the human brain was convened at UCLA. Following a series of such meetings, the International Consortium for Brain Mapping (ICBM) evolved and received one of the initial consortium grants from the feasibility phase of the Human Brain Project to develop a probabilistic atlas. The consortium consists of representatives from UCLA, the Montreal Neurologic Institute of McGill University, and the University of Texas Health Sciences Center at San Antonio; collaborations with a

number of other centers have been established and advisory boards in the areas of neuroanatomy, computer science, and interconsortia liaisons are part of this group. Pilot data for this project are now being collected.

The Explosion in Neuroscientific Data

Any survey of the number of neuroscientific journals or the annual number of articles relevant to neuroscience demonstrates the extraordinary acceleration and proliferation in neuroscientific research that has occurred in the past few decades (Huerta *et al.,* 1993; Koshland, 1992). The Society for Neuroscience has over 17,000 members and 22,000 neuroscientists attended the 1993 annual meeting (up from 14,000 in 1992) (Barinaga, 1993). With this rapid expansion has come an overload of information and topical diversity within neuroscience. These have led, in turn, to specialization and, quite naturally, to relative isolation of different segments of the neuroscientific community. Subspecialty sessions at national and international meetings as well as narrowly focused journals (more than 200) are now the rule rather than the exception. Without a system of organization and integration, the ongoing proliferation of neuroscientific information will lead to further fragmentation of the field and isolation of information based on arbitrary divisions such as those based on brain region, physiological process, or species, to name a few. A goal of the Human Brain Project is to act as a unifying process to promote convergence and integration of neuroscientific data and theories for all species (Huerta *et al.,* 1993). The concomitant evolution of the information technologies now makes this possible.

The establishment of realistic, unifying atlases for the important species studied by neuroscientific investigators will provide a common framework for exchanging and comparing data. Further, this will make data obtained and electronically distributed in a digital format more readily accessible to the individual researcher no matter how geographically isolated or subspecialized.

WHAT CURRENTLY EXISTS IN THE WAY OF HUMAN BRAIN ATLASES?

Most atlases of the human brain and, for that matter, of the brains of other species (Paxinos and Watson, 1986) are derived from one or at best a few, individual specimens (Brodmann, 1905; Matsui and Hirano, 1978; Talairach and Tournoux, 1988). Such atlases may take the form of anatomical references (Talairach and Tournoux, 1988), or they may represent a particular feature of the brain such as a neurochemical distribution or cerebral cortical cytoarchitecture. In existing atlases, proportional scaling systems are typically employed to reference a given brain to the atlas brain. The commonly used human atlases include those of Talairach and Tournoux (1988) and of Schaltenbrand and Wahren (1977). In the former, provisions were created to attempt to make different individuals comparable by subdividing the brain into 12 volumes referenced to the anterior and posterior commissures. Linear scaling is used to stretch or constrict the 12 volumes so as to approximate the shape and position of a given brain to the atlas brain. The Talairach atlas was derived from the brain of a 60-year-old French woman. It depicts one hemisphere assuming interhemispheric symmetry. With the exception of the upper midbrain, the atlas excludes the brainstem and cerebellum.

Atlases such as that of Talairach and Tournoux (1988) have proven very useful for anatomic normalization required for surgical procedures, particularly those at brain sites close to the origins of the reference system (i.e., the anterior and posterior commissures), such as the thalami and basal ganglia. It is predictable that such an atlas will be successful for areas of the brain that have a low intersubject variability and for sites close to the landmarks of the reference system (i.e., anterior and posterior commissures). Such atlases will be progressively less accurate in more highly variable portions of the cerebral cortex (e.g., neocortex and peri-sylvian zones) and in brain regions known to be highly asymmetric between the two cerebral hemispheres (e.g., planum temporale).

Initial attempts at developing atlases and deformation tools from populations of subjects have been reported (Fig. 1) (Van Buren and Maccubbin, 1962; Bajcsy *et al.,* 1983; Bohm *et al.,* 1983; Fox *et al.,* 1985; Vries and McLinden, 1988; Steinmetz *et al.,* 1989; Friston *et al.,* 1991; Evans *et al.,* 1992; Evans *et al.,* 1994). Such atlases have typically been derived from a single modality (e.g., structural MRI studies) and have demonstrated the utility of such an approach.

WHY ARE CURRENT ATLAS TOOLS INADEQUATE?

The anatomical variability between individual human brains is well known. Given the still undefined relationship between neural structure and function, an atlas based on an unvarying anatomy cannot succeed fully. One need only look to the functional and structural specialization of the hemispheres to recognize the depth of this problem (Geshwind and Levitsky, 1968; Wada *et al.,* 1975; Galaburda *et al.,* 1978; Le May and Kido, 1978). Single modality atlases are also of limited value, as the mapping from, for example, a neurochemical atlas to a functional assay, can only lose accuracy when transformed through a third (i.e., anatomical) reference space.

Perhaps equally important is the fact that conventional atlases are typically published rather than maintained in a digital, electronic form. While printed atlases represent essentially an understanding frozen

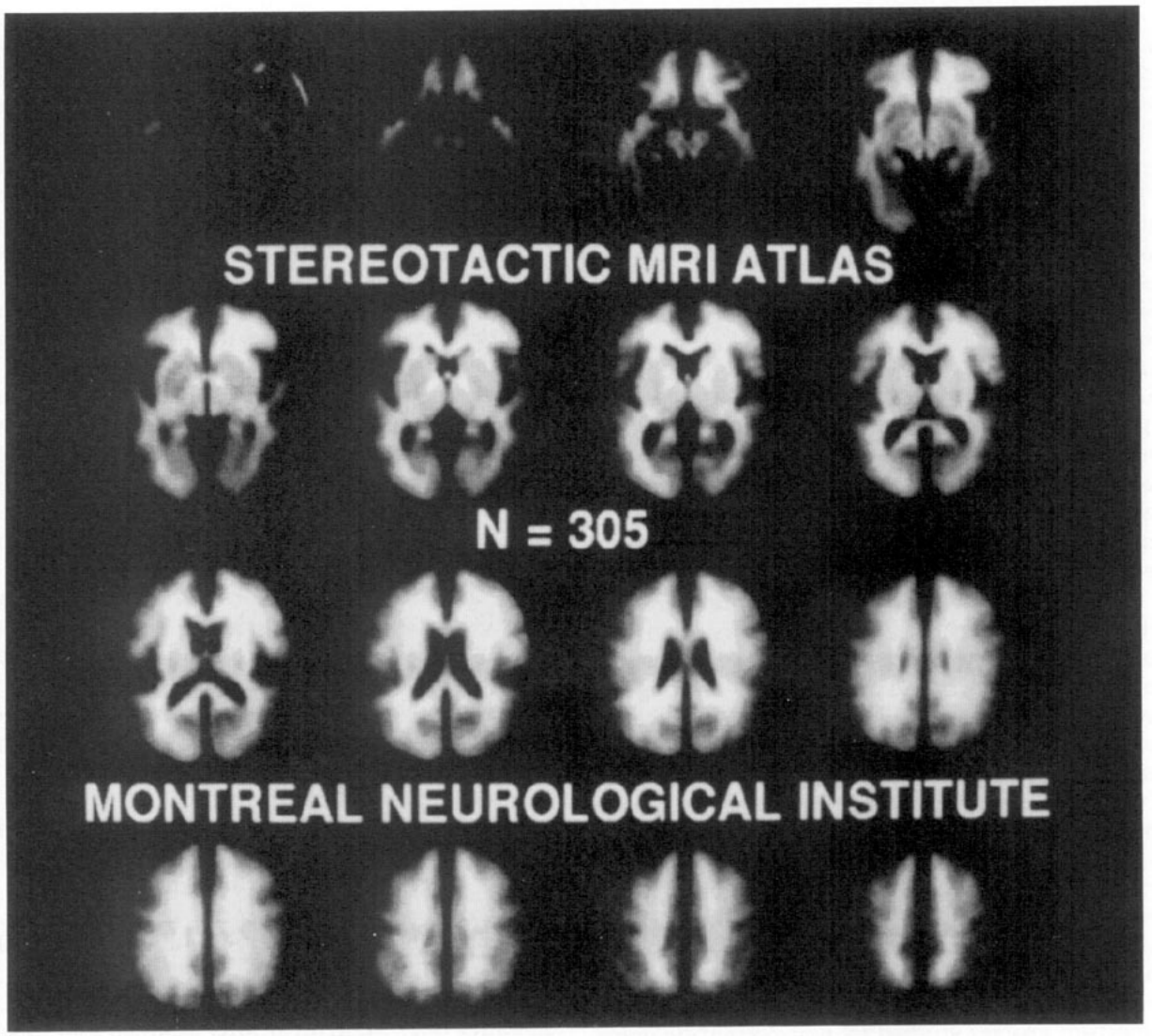


FIG. 1. Stereotaxic MRI atlas. Three hundred five MRI volumes (2-mm thick slices) were mapped by linear transformation into stereotaxic space, intensity normalized, and averaged (Evans *et al.,* 1992).

in time, a digital atlas grows and evolves. It can be resampled, annotated, or manipulated in any way. By its very nature, a probabilistic atlas improves in accuracy with time, achieving better statistics as more information is added. Furthermore, a digital atlas can be readily segmented into subpopulations by age, gender, race, behavioral abilities, handedness, or chemical composition.

WHAT ARE ADVANTAGES OF A PROBABILISTIC REFERENCES SYSTEM AND ATLAS?

A digital and probabilistic atlas based on a large population will rectify many current atlas problems. Its development from a large population provides, most importantly, retention of spatial and densitometric variance (Fig. 2). Such systems should be thought of as an ever-evolving process rather than a single solution. The evolutionary aspect of such a system recognizes the fact that as additional data are progressively added to it, its accuracy improves and the number and content of the subpopulations it depicts are increased. Landmarks will be derived from the intersubject stability of structures, rather than by simple assignment based on the anatomical features of a single brain. Since such an atlas will be fully three-dimensional and include the entire intracranial contents, as well as bony landmarks and surface features, morphometric calculations can be performed rigorously and efficiently. Its digital, electronic structure will also provide efficiency in statistical and computational comparisons between individuals or groups. The application of informatic principles, statistical methods, and mathematical approaches will make such an atlas a source of new information about the brain rather than simply a tool for localization during procedures.

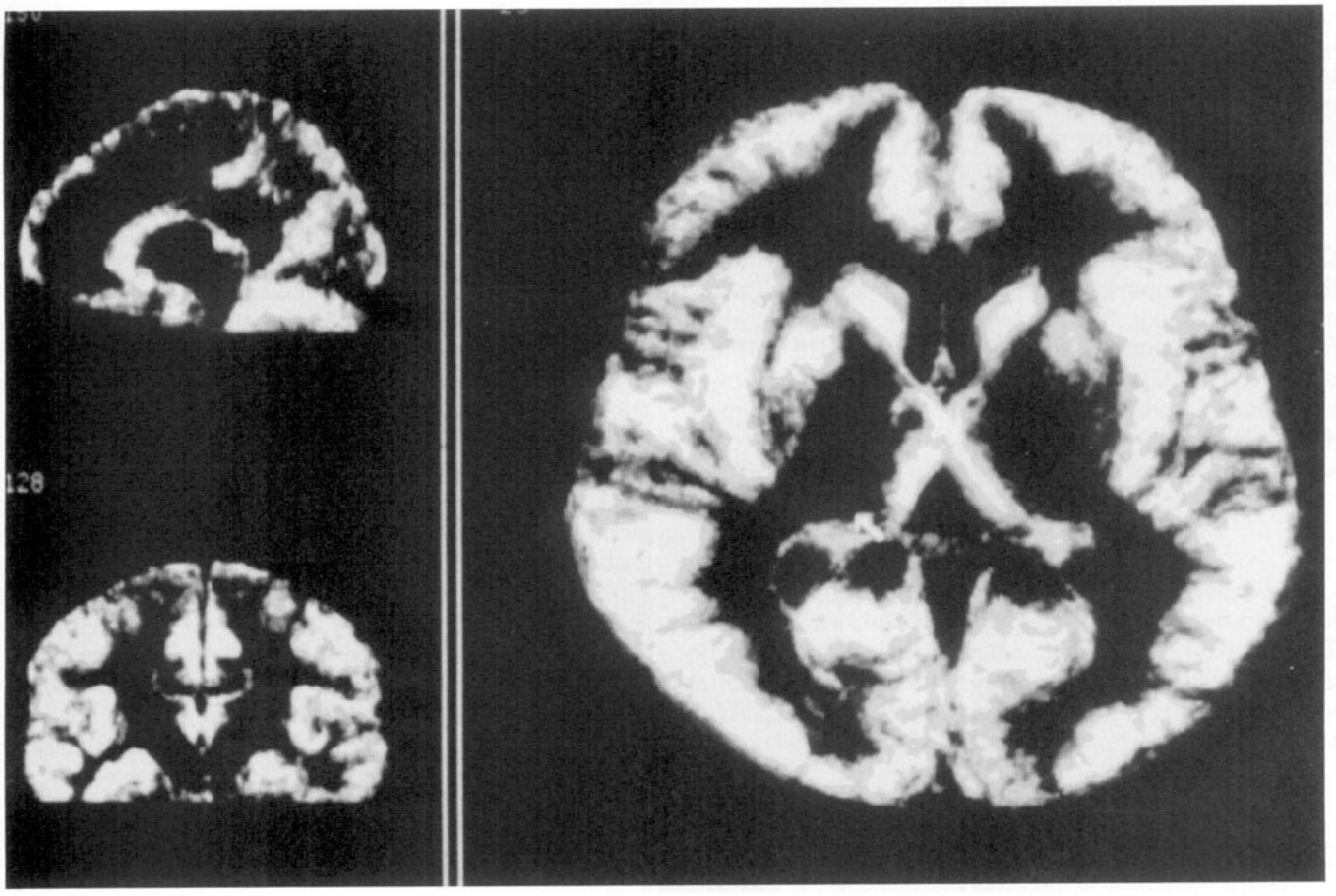


FIG. 2. Gray matter probability map in stereotaxic space. Twelve MRI volumes (3-mm-thick slices) from normal subjects were classified, using intensity and variance as features, into gray/white/CSF classes. A group probability map for each tissue type was then constructed by determining the proportion of subjects assigned a given tissue label at each voxel (Evans *et al.,* 1994).

Because the probabilistic atlas approach is tolerant of differences between subjects and modalities, past or current systems will be incorporated into it easily by digitizing the published atlases and transforming them into the newly defined probabilistic reference space (Toga *et al.,* 1989). Thus, one could interrogate the probabilistic atlas for information using its own coordinates or those from any other reference system that had been entered into the data set (e.g., the atlases of Talairach, Brodmann). In addition, information about physiology, neurochemistry, and an infinite variety of relevant maps can be layered onto the anatomic atlas as additional features that could be referenced using such a system. Interestingly, the probabilistic atlas will automatically provide variability information for data referenced by current, standard atlases.

The resulting system will become an important source of data for testing models of structure, physiology, phylogeny, ontogeny, and disease states. The addition of bibliographic references and text will enhance its utility. Knowledge of variability between ages in a population will provide important insights about development and maturation of the brain (Flechsig, 1901; Wada *et al.,* 1975), while information about evolutionarily older versus newer brain structures should provide clues to the phylogenetic history of the human brain and factors that have influenced it (Jerison, 1989; Harvey and Krebs, 1990; Rapoport, 1990). Last, such a system will provide for the valid comparison of data collected by different investigators or different laboratories through the use of a common reference system (Strother *et al.,* 1985).

WHY USE HUMANS?

Most neuroscientific information is derived from rodents, specifically, rats. Cortical studies have focused on the macaque monkey (Crick and Jones, 1993). Recent advances in imaging techniques, however, have led to a rapid expansion in the amount of functional and structural information currently available about the human brain (Mazziotta and Gilman, 1992; Prichard and Brass, 1992). Thus, human neuroscience is undergoing a rapid growth in experimental data. The human brain is particularly challenging because its presumed variance is greatest, with regard to structure and function, relative to other species.

Unlike other species, such as the rat, there is not a

vast amount of human neuroscientific data already collected using methods and systems not easily compatible with a digital, electronic atlas. Thus, newly acquired information about the human brain will be relatively easy to incorporate into the appropriate reference standards to allow use of the newly developed probabilistic atlas approach.

Perhaps most obvious, is the fact that the study of the human brain is the most relevant to understanding behavioral properties unique to humans and a few other species (e.g., language). Equally important is the fact that information about the human brain will lead to a better understanding of disorders that affect it and the means by which to rigorously analyze and compare data relevant to the treatment of neurological, neurosurgical, and psychiatric disorders.

WHAT WILL WE DO?

The first step in developing a probabilistic brain atlas is to describe the geography of the brain (Fig. 3). This leads to the natural conclusion that one must begin with structural anatomy. Ideally this anatomy would be described *in vivo*. Fortunately, modern structural imaging techniques, such as MRI, have the ability to provide three-dimensional image sets of the entire anatomy of the human head at a resolution of approximately 1 mm in all dimensions (Fig. 4). Thus, the bulk input to the development of the probabilistic atlas and reference system will be from the study of normal human subjects, obtained in large numbers, who have been carefully characterized in terms of their demographic features and their general medical, neurological, and psychiatric health. Such a data set will be macroscopic, scalable, extensible, and, presumably, manageable as a first step in the atlas building process. Importantly, it will serve as a framework for higher resolution and, ultimately, microscopic approaches that will follow.

In order to achieve neuroanatomical identifications and data sets with a spatial resolution that exceeds that of MRI, high-resolution postmortem cross-sectional (cryomacrotome) data from the entire human head will also be an important part of the feasibility studies in this project (Fig. 5) (Toga *et al.*, in press). Existing devices have the capacity to section the human head at 100-μm intervals with an in-plane spatial resolution of approximately 200 μm. In addition, sections that include neural elements as well as bone and soft tissues can be saved for future analysis. By obtain-

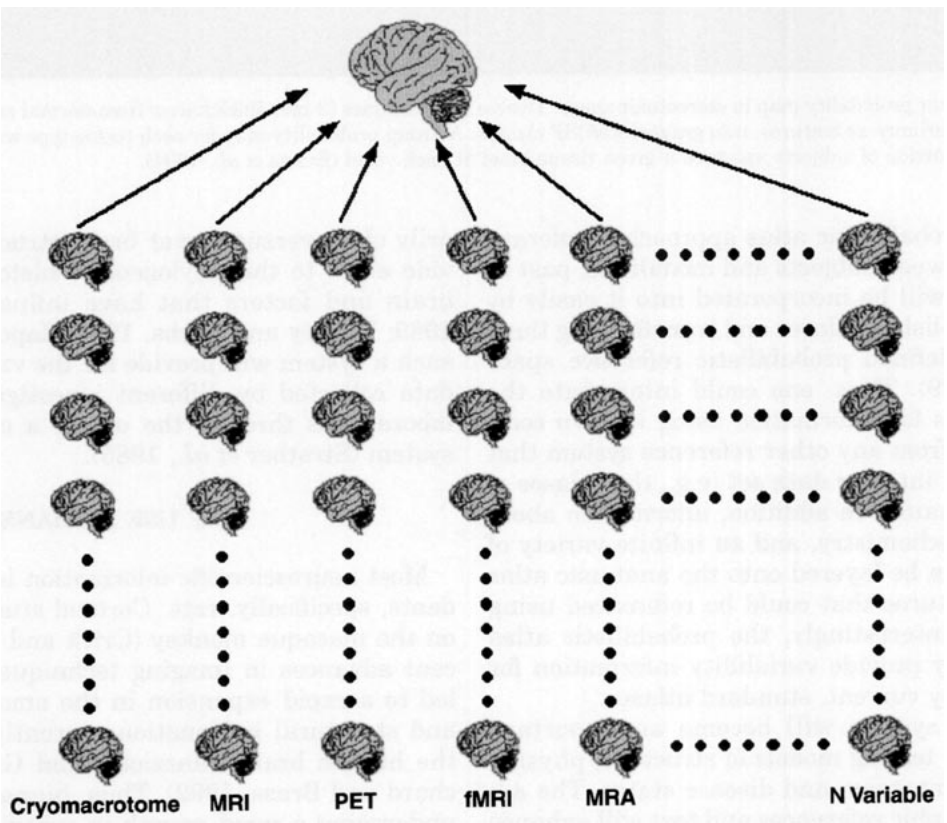


FIG. 3. Data sets incorporated in the development of a probabilistic reference system. By acquiring sets of data from subjects by a variety of input modalities we can establish the mean and variance for each feature in a probabilistic fashion and store them in the ultimate data base that would be referenced to the voxel field established for the probabilistic reference system. Core data sets include postmortem cryomacrotome human brains and structural MRI images of human subjects. Other variables that could be added might include PET, functional MRI (fMRI), MR angiography (MRA), cerebral blood volume, receptor density, electrophysiological data, and behavioral variables.

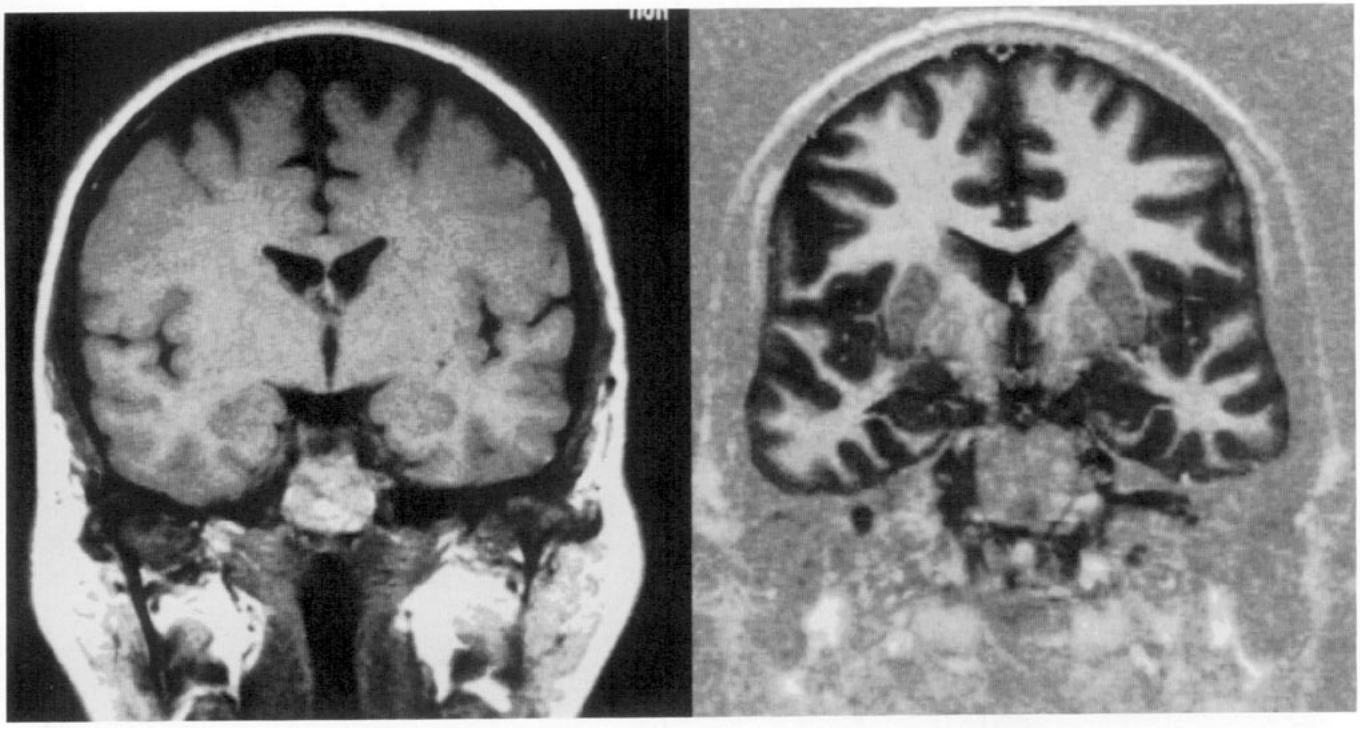


FIG. 4. Demonstration of good gray/white contrast with inversion recovery pulse sequence (right). On the left a standard T_1-weighted sequence, on the right one of a 64-slice inversion recovery acquisition (TR = 5700, TE = 21 ms, TI = 478 ms, acquisition time 24 min), demonstrating good brain–CSF separation.

ing and comparing MRI and postmortem high-resolution cryomacrotome images of nonhuman primates, the relationships between *in vivo* and postmortem anatomy can be rigorously defined.

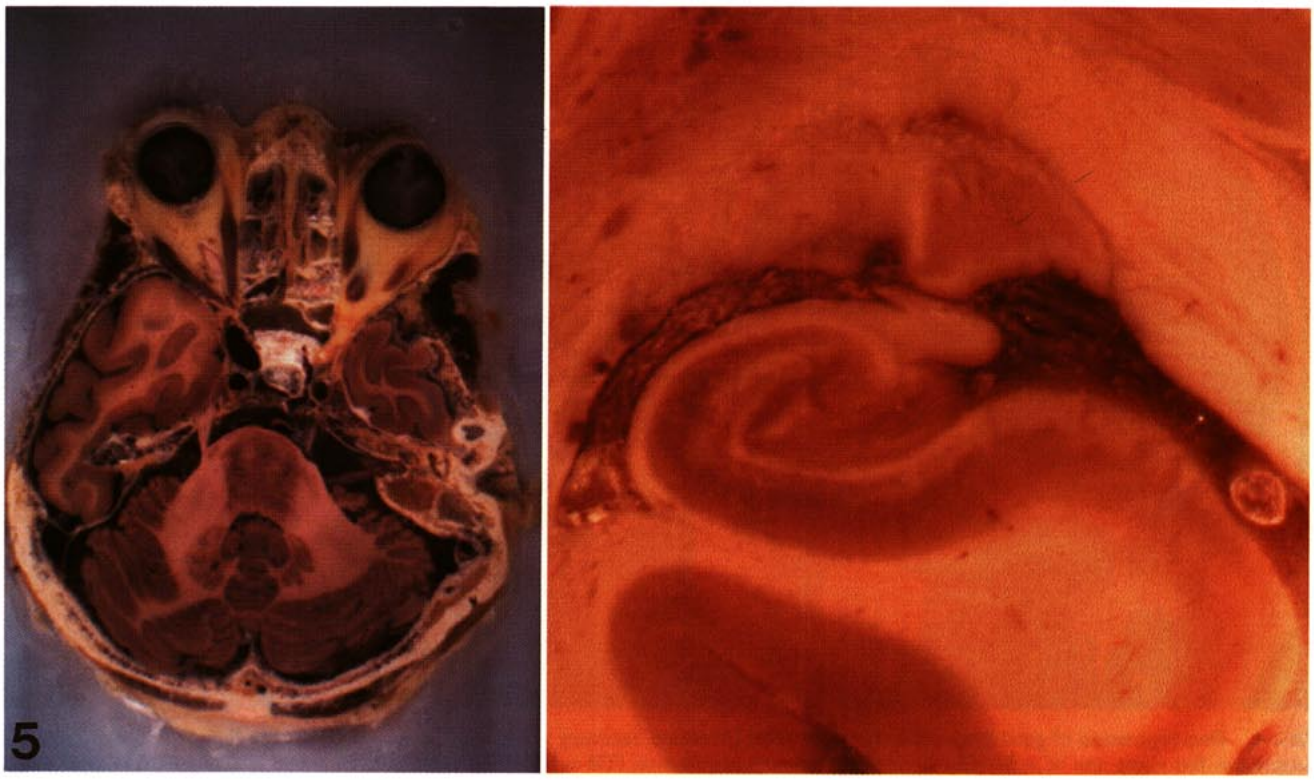
The development of the probabilistic atlas and reference system from these data sets will require an iterative approach (Fig. 6). This will be necessary on all fronts. For example, segmentation of the images into neuroanatomical structures will be hierarchical, beginning on a manual basis and, as progressively more automated approaches are developed, these will be employed. Initial segmentation will proceed from tissue characterization (e.g., gray matter, white matter, other matter) to the boundary identification of large cortical and subcortical structures and, ultimately, to nuclear and subnuclear groups. Initial data analysis will employ the macroscopic MRI data sets but progress to use of the high-resolution cryomacrotome data as the tools are developed to manage this degree of detail. Computational models and methods used to deform and warp data between subjects will progress from simple linear approaches to more complex nonlinear local deformations (Fig. 7). The reference space and coordinate system itself will iteratively evolve from an initial starting point that uses Talairach space (Talairach and Tournoux, 1988) to a newly developed three-dimensional volume.

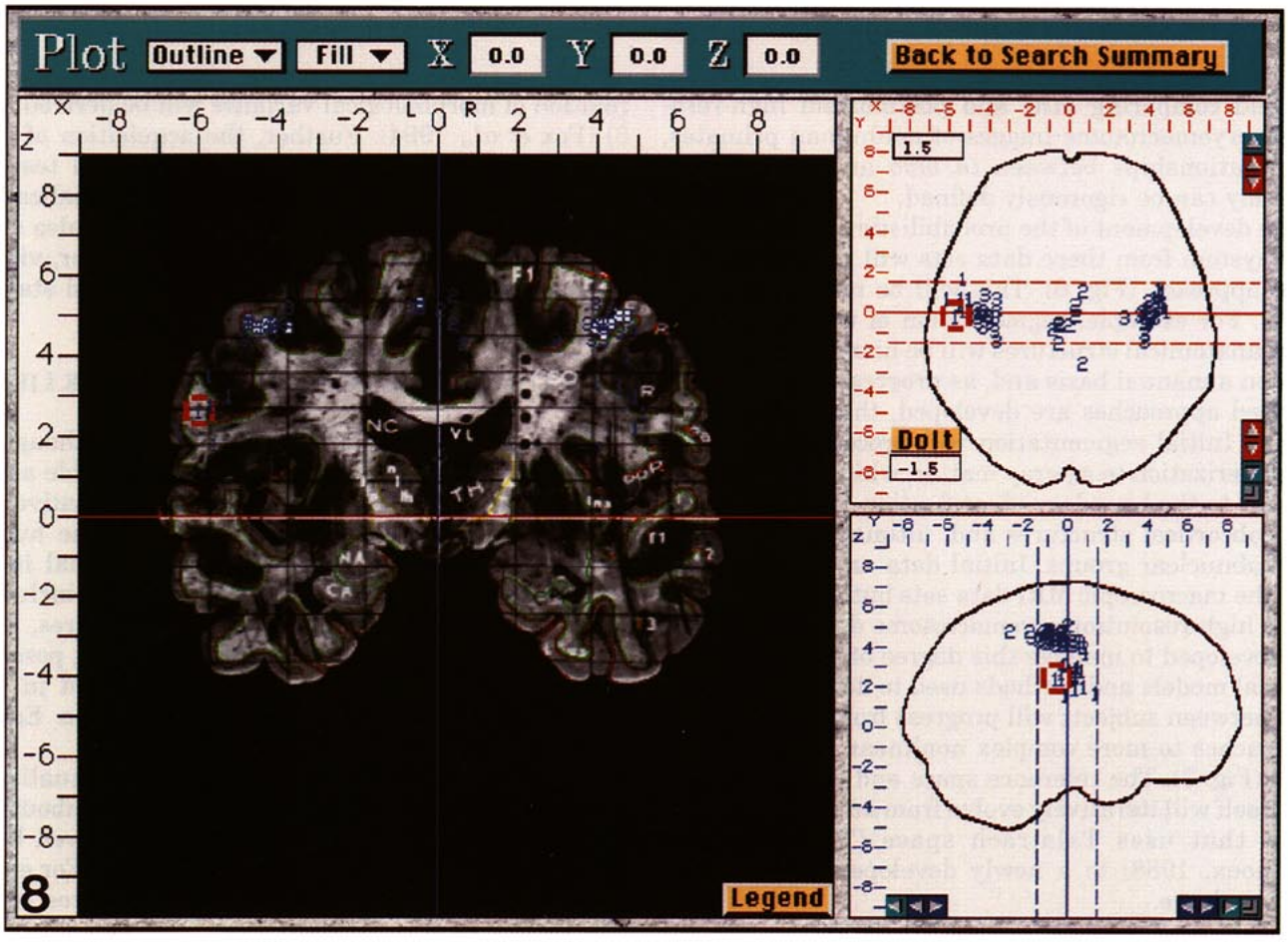
In the course of establishing the databases and reference system, initial estimates for the range and correlation of morphological variance will be derived (Fig. 8) (Fox *et al.*, 1994). Further, the acquisition of such large data sets and their management will test the capacity for data storage, compression, visualization, and communication. Thus, this project will also serve as a test bed for neuroscientific data transfer, visualization schemes, mathematical methods, and statistical approaches.

WHAT WILL THE FINAL PRODUCT LOOK LIKE?

The probabilistic reference system can be thought of in two forms. First, there will be a visualizable aspect of the atlas that allows one to see representative and neuroanatomically identifiable images of the human brain. Interrogation of this three-dimensional image will require a number of display formats including three-dimensionally rendered surface features, arbitrarily oriented planes of section (Fig. 8), and, possibly, flattening approaches such as those applied in geographical cartography (Felleman and Van Essen, 1991).

Second, highlighting a segment of this visualizable atlas will open a database of information about the region in question. Most responses for a given brain region query will be probabilistic in nature. For example, location probability would give estimates of the site in the nervous system that has been identified (e.g., 92% head of caudate, 6% anterior limb of internal


5


Plot
Outline
Fill
X 0.0
Y 0.0
Z 0.0
Back to Search Summary
Dolt
1.5
-1.5
Legend
8

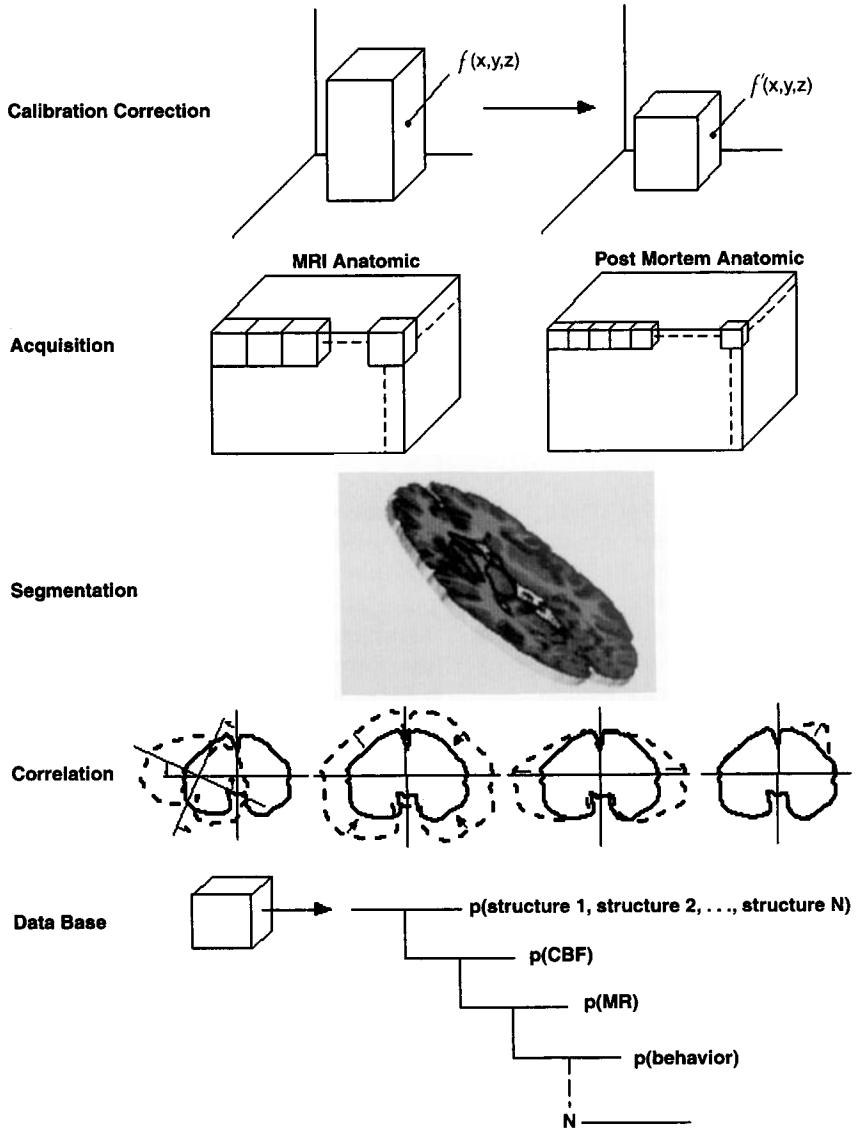


FIG. 6. The steps required to achieve the goal of developing a probabilistic reference system for the human brain. Row 1 demonstrates the requirement to calibrate acquisition instruments and correct data for acquisition-induced errors. Row 2 corresponds to the dataset acquisition at different spatial resolutions. Row 3 indicates manual, semiautomated and automatic image segmentation. This step is critical to identifying neuroanatomical structure boundaries in the high-resolution postmortem human cryomacrotome data sets as well as the lower resolution *in vivo* MRI data sets. Row 4 demonstrates the alignment and registration of images using a combination of scaling, affine, linear, and nonlinear transformations and includes local deformation required to optimize the correlation between brain data volumes, a critical component of between-subject image correlation. The bottom row depicts the data base in which all of this information will be organized into a probabilistic reference system with search and query capabilities that will allow access to any aspect of the stored data and link this data base to other existing data bases.

FIG. 5. Human brain block face sectioned with a cryomacrotome. These horizontal images are at the level of the orbits and hippocampus and illustrate the detail that can be seen. Gray and white matter differences are easy to appreciate. The inner and outer mantles of the bony skull are clearly visible. The full 1024^2 pixel resolution of the primary image is not represented in this reproduction. (Left) Note the fact that the specimen is not symmetrical. The blocking and positioning of the head in the cryomacrotome is not exact, but since the volumes are reconstructed and subsequently resampled this does not affect the final result. (Right) High-resolution primary imagery of selected human brain subregions. Here the hippocampus, alveus, taenia fibria, lateral geniculate body, and posterior cerebral artery in the ambient cystern are visible in one section of a complete cryotomy series. This approach is useful for architecturally complex regions such as hippocampus, brainstem, and cerebellum, where this approach yields detail far higher than *in vivo* imaging modalities such as MRI (Toga *et al.,* 1994).

FIG. 8. This is an example of one coronal section from the Talairach atlas used with the Brain Map data base system (Fox *et al.,* 1994). The views from above the head and from the right side of the head indicate the location (solid line) and extent for data plotting (dotted lines) of the coronal slice. Overlayed onto the gray scale atlas image are colored outlines of the cortical gray matter, white matter, and a ventricle.

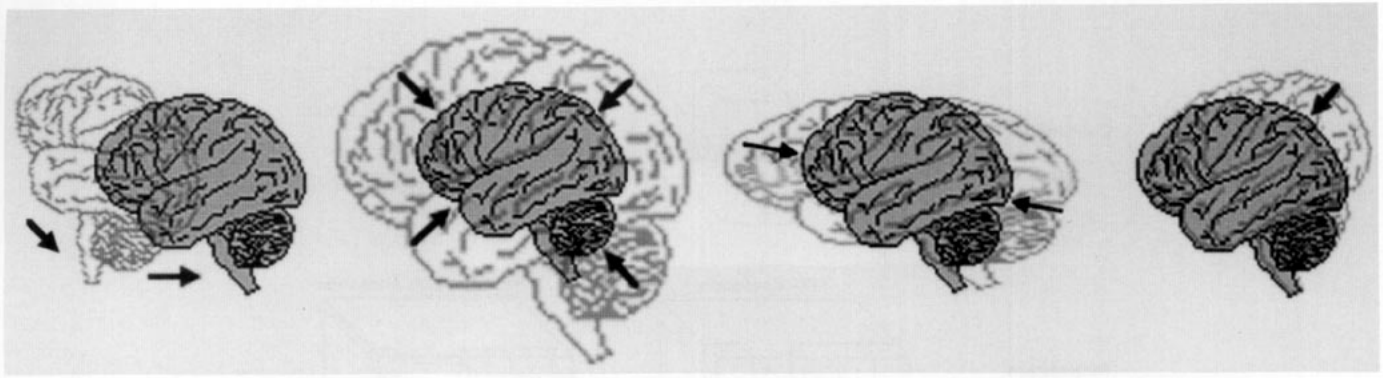


FIG. 7. Deforming and warping techniques can be either density based or spatially based. Points and contours, when available, provide spatial information for deforming. Deformations across modalities may have to rely upon spatially based methods because the density patterns may not correlate. This graphic illustrates a continuum of deformations, from pure positioning to local deformations that regionally alter the shape and form of the data set.

capsule, 1% anterior horn of lateral ventricle, <1% other regions). Average values and their variance for other features would also, ultimately, be available (e.g., blood flow ± SD, glucose metabolism ± SD, etc.). Based on anatomical site, nonprobabilistic information could also be provided. This might include a bibliography of references pertaining to that brain region.

Thus, the ultimate atlas and reference system would have both visualizable and database formats. Such an approach provides for both a visually intuitive and efficient means of interacting with the final product as well as the statistical and modeling capabilities that a database format provides (Fox *et al.,* 1994).

Access to the atlas and reference system is envisioned to come through workstations. It is predictable that the rapidly increasing speed and storage capacity of computers matched with their progressively declining cost per unit storage should result in very efficient, high capacity and low cost workstations that are commensurate with the types of data sets envisioned for such a project.

OFTEN RAISED CRITICISMS ABOUT SUCH AN APPROACH

An Average Brain System Will Not Allow Me to Study Individual Subjects

This surprisingly common misconception disregards the fact that spatial transformations conserve original data and do not destroy it. A population-based probability atlas allows an investigator to take data from an individual subject and place it into a reference system of a population that defines the anatomical uncertainty for structure and function. In our implementation, transformations are bidirectional. That is, an individual subject's brain can be deformed or warped into the reference system and then, using the same mathematical methods, be dewarped or back-transformed into its original state. In an ideal system, no data loss or distortion should occur in this process. As a result, individuals within a given experiment can be more easily and effectively studied and compared. Further, individuals or subpopulations can be compared to other populations that have been previously entered into the database by different investigators thereby facilitating the determination of interexperiment or interlaboratory reproducibility.

Such a System Might Work for Tomographically Obtained Data Sets, but I Work with Electrophysiological (e.g., EEG) Data and Thus It's Irrelevant to Me

The proposed atlas is based on neuroanatomy. This is the most fundamental language of communication in neuroscience. As such, it allows appropriate reference and localization to any structure in the brain from any signal source. In the development of the reference system, cross-sectional and tomographic data will serve as the initial data sets. Once established, however, appropriate vehicles for entering nontomographic data will be developed. For EEG data, for example, systems already exist to localize scalp electrode placement three-dimensionally, either through the use of a paired tomographic image set or by nontomographic localization methods (Gevins *et al.,* 1994).

The more difficult problem is that of entering microscopic data from brain sites that are analyzed on a regional basis (e.g., the study of the isolated hippocampus). Nevertheless, such data can also be incorporated into the probabilistic reference system and atlas. As with the EEG example above, this will require landmarks to appropriately localize regional data in the global atlas brain.

Consider the following approach. A series of postmortem cryomacrotome human brains are stained with a series of conventional and commonly used neuroanatomical "landmark" stains (e.g., Nissl, acetylcholinesterase). Using state-of-the-art imaging devices, these sections would be digitized and sampled at a 50-μm resolution. The resultant data sets would be warped

and entered into the probabilistic atlas as an additional feature. Then consider an investigator who studies GABA receptors in the human hippocampus. This investigator would like to see where the receptors from the hippocampi of a given epileptic patient population fall with regard to other data in the probabilistic reference system. In preparing the tissue, this investigator would process every *N*th section using one of the "landmark" stains that are part of the probabilistic atlas. The investigator would then digitize the information from both the GABA receptor sections as well as the "landmark" stained sections. Using alignment, registration and warping tools that are part of the atlas system, the investigator would register the "landmark" stained sections with the atlas and then use the same mathematical transformations to enter the GABA receptor information into the hippocampal region of the atlas. Once referenced, data base queries and visualization of this new data could be performed in the atlas system. A similar approach allows referencing between newly acquired *in vivo* data and stored postmortem specimens (Fig. 9) that should aid in relating functional localization with macroscopic and microscopic anatomy (Rademacher *et al.,* 1992).

These Projects Cost Too Much at a Time When Research Resources Are Shrinking

There is no question that the development of systems and tools such as the probabilistic atlas will have a specific and not insignificant cost associated with them. Also true is the fact that increments in neuroscientific research funding have not kept pace with the growth of the field in terms of numbers of investigators or the magnitude of their projects.

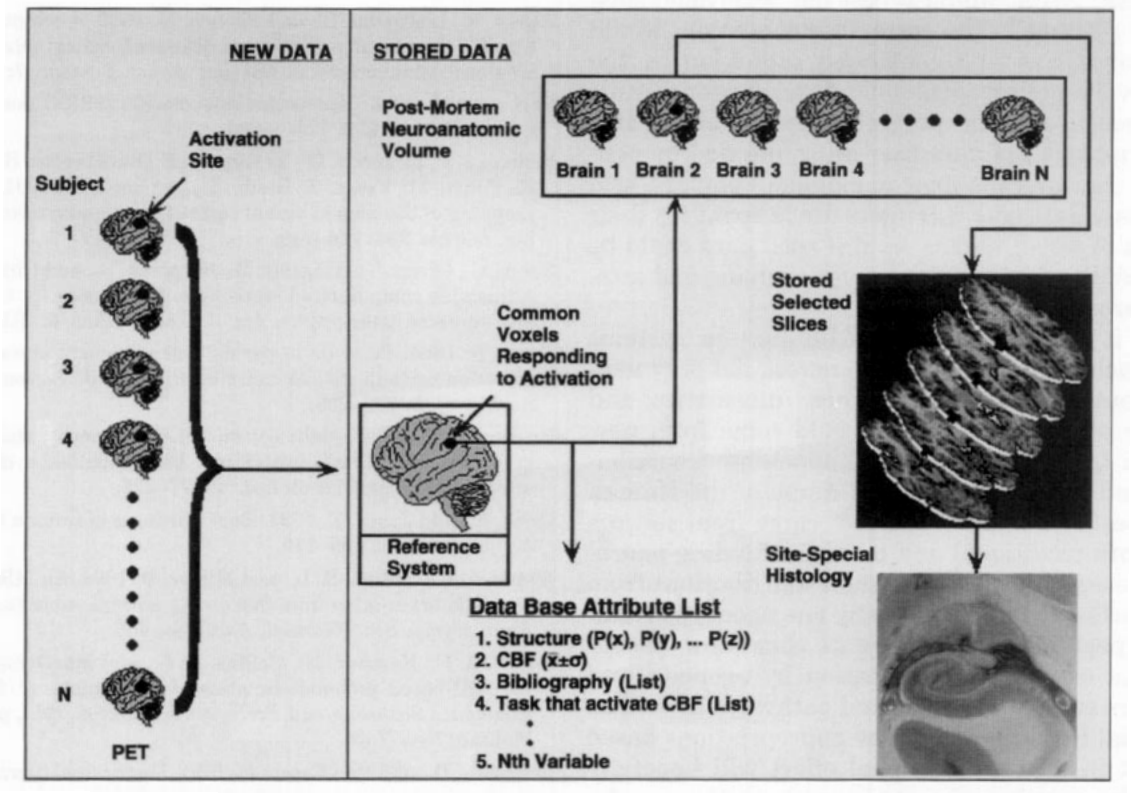


FIG. 9. Use of the Probabilistic Reference System. This figure demonstrates an invertible use of the reference system once developed. In the center is a representation of the probabilistic reference system. On the left, labeled "NEW DATA," one might envision a series of behavioral tasks performed in a group of subjects by measuring cerebral blood flow changes during the performance of a behavioral task with PET. When these new data sets are aligned, registered, and warped into the reference system, a site of common blood flow activation is identified. At this site we can query the data base for a biological feature attribute list that would tell us, as a function of probability, the location, in neuroanatomical terms, of this site, its average blood flow and variance, a bibliography related to the information known about this site, other tasks that have activated this site in terms of PET measures of cerebral blood flow and many others. In addition, using the inversion component of the reference system, one could dewarp *from* the probabilistic reference system *to* an individual cryosectioned human brain. Using the boundary coordinates obtained from the reference system one would identify the specific sections that contain this activation site and then perform detailed microscopic histology or neurochemical evaluations of the site. As such, hypothesis and data driven experiments would emerge to evaluate the site-specific microscopic structure that sustains particular functional tasks in the human brain. The concept of processing large numbers of entire human brains at a microscopic and cytoarchitectural level is a massive undertaking that, without a framework or hypothesis driven question, will be less rewarding. Finally, since the microscopic information is rigorously linked to a specific constellation of voxels in the probabilistic data base, that information can automatically be added to the feature attribute list for those voxels.

The thoughtful response to this statement requires, however, an honest appraisal of the ultimate goals of neuroscientific research. If such research is designed to produce the most accurate understanding of normal brain function and diseases that effect it, then tools that will enhance the accuracy of results, the comparison of results between subjects and laboratories, make more rigorous the confirmation or refutation of data, and guard against its loss, should have a high priority in the overall funding for the field. A system such as a probabilistic atlas for a given species, or potentially across species, provides a means by which to rigorously store, compare, and analyze data over time and between laboratories. Such a system currently does not exist. Further, by virtue of data exchange and comparison, integration within the broad field of neuroscience will begin.

One could rephrase the above statement into a question and ask, "What would it cost not to develop such integrated systems?" The costs, in our opinion, would be the progressive and continued reduction in the value of every dollar spent on future neuroscientific research because of the progressively unmanageable amounts and types of data that are generated by neuroscientist. Lacking the tools to manage, compare, and analyze these data sets will make funds spent for their acquisition of lesser impact than if such data could be preserved and referenced in an ever-evolving and integrated approach.

Clearly, it would be optimal if funding for systems and approaches to integrate data across not only neuroscience but also computer science, informatics, and potentially other related fields could come from new sources. In fact, this is already happening. Contributions to the funding of the initial round of the Human Brain Project (Huerta *et al.,* 1993) came from sources that are both traditional and novel for funding neuroscientific research. By having small contributions from many agencies, the burden on any one agency is small but the impact for the neuroscience community is significant. An expanded participation by agencies and contributors outside of traditional pathways as well as the potential for generating new appropriations based on interest in this international effort will hopefully result in the creation of systems such as the one described in this report as well as others contemplated or funded through the auspices of the Human Brain Project without detracting from traditional neuroscientific funding.

Last, it should be kept in mind that the creation of a probabilistic atlas of the human brain is not an exercise in library science. It is a series of fundamental hypothesis-driven experiments (Fig. 9) in merging mathematical and statistical approaches with morphological and physiological problems posed with regard to the nervous system. It will create new data and insights into the organization of the human nervous system in health and disease, its development, and its evolution.

ACKNOWLEDGMENTS

For their thoughtful input and suggestions, the authors thank members of the International Consortium for Brain Mapping's Advisory Board, including Karl Friston, M.D., Marsel Mesulam, M.D., George Paxinos, Ph.D., as well as Roger Woods, M.D., Mark Cohen, Ph.D., Susan Bookheimer, Ph.D., and Human Brain Project Coordinators Michael Huerta, Ph.D., and Stephen Koslow, Ph.D. Special thanks to Andrew Lee for the illustrations and to Laurie Carr for editorial preparation of the manuscript. This work was supported by the Human Brain Project jointly funded by the National Institute of Mental Health and the National Institute on Drug Abuse as well as generous contributions from the Brain Mapping Medical Research Organization, the Pierson-Lovelace Foundation, and The Ahmanson Foundation.

REFERENCES

Bajcsy, R., Lieberson, R., and Reivich, M. 1983. A computerized system for the elastic matching of deformed radiographic images to idealized atlas images. *J. Comput. Assist. Tomogr.* **7:** 618–625.

Barinaga, M. 1993. Neuroscientists reach a critical mass in Washington. *Science* **262:** 1210–1211.

Belliveau, J., Kennedy, D., McKinstry, R., Buchbinder, B., Weisskoff, R., Cohen, M., Vevea, J., Brady, T., and Rosen, B. 1991. Functional mapping of the human visual cortex by magnetic resonance imaging. *Science* **254:** 716–719.

Bohm, C., Greitz, T., Kingsley, D., Berggren, B., and Ollson, L. 1983. Adjustable computerized stereotaxic brain atlas for transmission and emission tomography. *Am. J. Neuroradiol.* **4:** 731–733.

Broca, P. 1861. Perte de la parole, ramollisement chronique et destruction partielle du lobe anterieure guache du cerveau. *Bull. Soc. Anthropol.* **2:** 235–239.

Brodmann, K. 1905. Beitrage zur histologischen lokalisation der grosshirnrinde. Dritte mitteilung: Die rindenfelder der neideren affen. *J. Psychol. Neurol. Lpz.* **4:** 177–226.

Crick, F., and Jones, E. 1993. Backwardness of human neuroanatomy. *Nature* **361:** 109–110.

Evans, A. C., Collins, D. L., and Milner, B. 1992. An MRI-based stereotactic brain atlas from 300 young normal subjects. *Proc. 22nd Annu. Symp. Soc. Neurosci. Anaheim,* 408.

Evans, A. C., Kamber, M., Collins, D. L., and MacDonald, D. 1994. An MRI-based probabilistic atlas of neuroanatomy. In *Magnetic Resonance Scanning and Epilepsy* (S. Shorvon, Ed.), pp. 263–274. Plenum, New York.

Felleman, D., and Van Essen, D. 1991. Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex* **1:** 1–47.

Ferrier, D. 1875. Experiments on the brain of monkeys. No. 1. *Proc. R. Soc. London* **23:** 409–430.

Flechsig, P. 1901. Developmental (myelogenetic) localisation of the cerebral cortex in the human subject. *Lancet* **ii:**1027–1029.

Fox, P., Perlmutter, J., and Raichle, M. 1985. A stereotactic method of anatomical localization for PET. *J. Comput. Assist. Tomogr.* **9:** 141–153.

Fox, P., Mikiten, S., Davis, G., and Lancaster, J. 1994. Brain map: A database of human functional brain mapping. In *Functional Neuroimaging: Technical Foundations* (R. Thatcher, M. Hallett, T. Zeffero, E. John, M. Huerta, Eds.), pp. 95–105. Academic Press, Orlando, FL.

Friston, K., Frith, C., Liddle, P., and Frackowiak, R. 1991. Plastic

transformation of PET images. *J. Comput. Assist. Tomogr.* **15:** 634–639.

Fritsch, G., and Hitzig, E. 1870. Uber die elektrische erregbakeit des grosshirns. *Arch. Anat. Physiol. Med.* **37:** 300–332.

Galaburda, A., Le May, M., Kemper, T., and Geshwind, N. 1978. Right–left asymmetries in the brain. Structural differences between the hemispheres may underlie cerebral dominance. *Science* **199:** 852–856.

Geshwind, N., and Levitsky, W. 1968. Human brain: Left–right asymmetries in the temporal speech areas. *Science* **161:** 186–187.

Gevins, A. S., Lee, J., Martin, N., Reutter, R., Desmond, J., and Brickett, P. 1994. High resolution EEG: 124-channel recording, spatial deblurring and MRI integration methods. *EEG Clin. Neurophysiol.* **90:** 337–358.

Hari, R. 1991. On brain's magnetic responses to sensory stimuli. *J. Clin. Neurophysiol.* **8**(2):157–169.

Harvey, P., and Krebs, J. 1990. Comparing brains. *Science* **249:** 140–146.

Huerta, M., Koslow, S., and Leshner, A. 1993. The Human Brain Project: An international resource. *Trends Neurosci.* **16:** 436–438.

Ingvar, D. 1975. rCBF in focal cortical epilepsy. In *Cerebral Circulation and Metabolism* (T. Langfitt, L. McHenry, and M. Reivich, Eds.), pp. 361–363. Springer-Verlag, Berlin/ New York.

Jerison, H. 1989. Brain size and the evolution of mind. In *Fifty-Ninth James Arthur Lecture on the Evolution of the Human Brain.* American Museum of Natural History, New York.

Kety, S., and Schmidt, C. 1948. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: Theory, procedure and normal values. *J. Clin. Invest.* **27:** 476–483.

Koshland, D. 1992. The dimensions of the brain. *Science* **258:** 199.

Kuhl, D., and Edwards, R. 1973. Quantitative section scanning using orthogonal tangent correction. *J. Nucl. Med.* **14:** 196.

Lassen, N., Feinberg, I., and Lane, M. 1960. Bilateral studies of cerebral oxygen uptake in young and aged normal subjects. *J. Clin. Invest.* **9:** 491–500.

Le May, M., and Kido, D. 1978. Asymmetries of the cerebral hemispheres on computed tomograms. *J. Comput. Assist. Tomgr.* **2:** 471–476.

Matsui, T., and Hirano, A. 1978. *An Atlas of the Human Brain for Computerized Tomography.* Igaku-Shoin, Tokyo.

Mazziotta, J. 1984. Physiologic neuroanatomy: New brain imaging methods present a challenge to an old discipline. *J. Cereb. Blood Flow Metab.* **4:** 481.

Mazziotta, J., and Gilman, S. 1992. *Clinical Brain Imaging.* Davis, Philadelphia.

Mazziotta, J., and Koslow, S. 1987. Assessment of goals and obstacles in data acquisition and analysis from emission tomography: Report of a series of international workshops. *J. Cereb. Blood Flow Metab.* **7**(2): S1–S31.

Mesulam, M-M. 1990. Large-scale neurocognitive networks and distributed processing for attention, language and memory. *Ann. Neurol.* **28:** 597–613.

Paxinos, G., and Watson, C. 1986. *The Rat Brain in Stereotaxic Coordinates.* Academic Press, Sydney.

Pechura, C. M., and Martin, J. D. 1991. *Institute of Medicine (US) Committee on a National Neural Circuitry Database.* National Academy Press.

Phelps, M., Hoffman, E., and Mullani, N. 1975. Applications of annihilation coincidence detection to transaxial reconstruction tomography. *J. Nucl. Med.* **16:** 210.

Phillips, C., Zeki, S., and Barlow, H. 1984. Localization of function in the cerebral cortex. Past, present and future. *Brain* **107:** 327–361.

Posner, M., and Dehaene, S. 1994. Attentional networks. *Trends Neurosci.* **17**(2): 75–79.

Prichard, J., and Brass, L. 1992. New anatomical and functional imaging methods. *Ann. Neurol.* **32:** 395–400.

Prichard, J., Alger, J., Behar, K., Petroft, O., and Shulman, R. 1983. Cerebral metabolic studies *in vivo* by 31P NMR. *Proc. Natl. Acad. Sci. USA* **80:** 2748.

Rademacher, J., Galaburda, A., Kennedy, D., Filipek, P., and Caviness, V. 1992. Human cerebral cortex: Localization, parcellation, and morphometry with magnetic resonance imaging. *J. Cog. Neurosci.* **4:** 352–374.

Rapoport, S. 1990. Integrated phylogeny of the primate brain, with special reference to humans and their diseases. *Brain Res. Rev.* **15:** 267–294.

Schaltenbrand, G., and Wahren, W. 1977. *Atlas for Stereotaxy of the Human Brain.* Year Book Med. Pub., Chicago.

Steinmetz, H., Furst, G., and Freund, H-J. 1989. Cerebral cortical localization: Application and validation of the proportional grid system in magnetic resonance imaging. *J. Comput. Assist. Tomogr.* **13:** 10–19.

Strother, S., Tyler, J., Peters, T., Thompson, C., Evans, A., Diksic, M., Meyer, E., Yamamoto, Y., and Feindel, W. 1985. An intercentre comparison of region-of-interest and resolution effects for normal F-18 fluorodeoxyglucose studies with PET. *J. Cereb. Blood Flow Metab.* **5**(1): S607–608.

Talairach, J., and Tournoux, P. 1988. *Co-planar Stereotaxic Atlas of the Human Brain.* Thieme Medical Publishers, New York.

Toga, A., Samaie, M., and Payne, B. 1989. Digital rat brain: A computerized atlas. *Brain Res. Bull.* **22:** 323–333.

Toga, A., Ambach, K., Quinn, B., Hutchin, M., and Burton, J. 1994. Postmortem anatomy from cryosectioned whole human brain. *J. Neurosci. Methods* **54**(2): 239–252.

Wada, J., Clarke, R., and Hamm, A. 1975. Cerebral hemispheric asymmetry in humans. *Arch. Neurol.* **32:** 239–246.

Woods, R., Mazziotta, J., and Cherry, S. 1993. MRI-PET registration with automated algorithm. *J. Comput. Assist. Tomogr.* **17**(4): 536–546.

Van Buren, J., and Maccubbin, D. 1962. An outline atlas of the human basal ganglia with estimation of anatomical variants. *J. Neurosurg.* **19:** 811–839.

Vries, J., and McLinden, S. 1988. Computerized three-dimensional stereotactic atlases. In *Modern Stereotactic Neurosurgery.* Little, Brown, Boston.