CHAPTER 4.1

Interactive Brain Maps and Atlases

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Abstract

The emergence of powerful and practical computer graphics applications in the last decade is revolutionizing the production and use of brain maps for summarizing the results of experimental neuroanatomy. Perhaps the most far-reaching consequence of electronic or digital brain maps will be their use in databases of graphically presented structural information that may be queried via the World Wide Web. The design of such databases is a major goal of the USC Brain Project, and they will be most powerful if results are presented on, or indexed in a systematic way to, standard or reference atlases of the brain. In practice, however, direct comparisons of histological structural data (as opposed to tomographic scans) obtained from different brains are problematic because of possible differences in plane of section, shrinkage or swelling, and nonlinear warping that has a different pattern for each histological section as it is mounted on glass for microscopic observation. Computer graphics applications also can be used to create three-dimensional models of the brain, as well as two-dimensional flatmaps, and they also may serve as templates for electronic databases.

4.1.1 General Features of Maps

In principle, there is little if any difference between maps of the Earth's surface, which we are all familiar with, and maps of the nervous system—and of the brain, in particular (see Robinson and Petchenik, 1976; Swanson, 1992). First and foremost, maps are *representations* of some part of the environment on a flat surface; that is, maps are an abstraction or simplification of an object (such as the Earth), typically from three dimensions to two. Traditional maps provide three obvious advantages. First, three-dimensional objects can be represented in two dimensions for publication. Second, large or small objects can be scaled to convenient sizes. And, third, the essential features of a complex object can be represented in a simplified, abstract way. The most obvious disadvantages of maps are that by their very nature they cannot reproduce all of the features of the mapped object and they impart misinformation if errors are made during the process of abstraction. In the end, the usefulness of any map is a function of its accuracy, clarity, and ability to display a particular type of information. It should be obvious that there is no one "correct" way to produce a map; after all, over 200 different projections of the Earth's surface onto a flat plane have been devised over the years, and none is ideal (Snyder, 1993). This is a consequence of the fact that in transferring a pattern from any curved surface (except a cone) onto a flat surface, only one of the three important features of distance, area, and shape can be maintained accurately.

While this is all well and good, it is obvious that mapping a complex three-dimensional solid such as the brain is immensely more difficult than mapping the surface of an approximate sphere (the Earth) onto paper. One might think that mapping the brain is more like mapping the Earth considered as a solid sphere, but even this is a gross oversimplification because the Earth is formed essentially of concentric layers, whereas the central nervous system (CNS—the brain and spinal cord) is essentially a hollow tube whose walls contain

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irregularly stacked cell groups that are differentiated to wildly different extents along the longitudinal axis (see Alvarez-Bolado and Swanson, 1996).

The history of attempts to map the CNS is very long indeed—it can be traced back some 2500 years—and many highly ingenious procedures have been developed (Swanson, 1999). Nevertheless, the widespread availability of personal computers in the 1990s has stimulated a radically new approach to cartography, in general, and to brain mapping in particular. The purpose of this chapter is to explore some of the new ways that brain maps can be produced and used in electronic formats and to introduce the reader to specific developments in the USC Brain Project. However, to place these developments in context, it is important first to review certain general problems faced by brain mappers: the overall structure of the brain and methods used to determine the architecture of brain circuits.

4.1.2 Overall Structure of the Brain

As mentioned above, from a topological perspective the vertebrate CNS has a rather simple shape and location: a dorsal midline tube that is closed at both ends, and that starts in the head (as the brain) and ends in the abdomen (as the spinal cord). However, the actual geometry of the adult CNS is very complex, mainly because: (1) the longitudinal axis of the tube is highly curved; (2) the walls of the tube are highly differentiated in each "segment" of the tube (endbrain, interbrain, midbrain, hindbrain, and spinal cord); and (3) connections between cell groups stacked within the walls are exceedingly complex, showing massive divergence and convergence. To gain some appreciation for the task faced by brain mappers, it is helpful to consider some of the major physical features of the mammalian brain, and for this we shall compare certain features of this organ in the rat and human.

Organization and Number of Parts

As a general organizing principle, it is useful to start by pointing out that a great deal of embryological and neuroanatomical work over the last century (well reviewed in Nieuwenhuys *et al.*, 1997) suggests that the brains of all mammals share the same basic architectural plan, with secondary variations on a common theme being characteristic of individual species (and tertiary variations being characteristic of individual members of a species). It goes without saying that brain circuits are formed by individual nerve cells or neurons (the neuron doctrine), and that in general information is received by a neuron's cell body and dendrites and then is transmitted to other cells by its axon (the theory of functional polarity). What, then, about a comparison of the human and rat brain (for further references, see Swanson, 1995)?

Based on round numbers (usually order of magnitude estimates), the following comparisons are useful. To begin with, the human brain weighs about 750 times as much as the rat brain (about 1500 g vs. 2 g; with overall dimensions of about $15 \times 15 \times 10$ cm vs. $2 \times 1 \times 1$ cm). Within those volumes, the human brain contains on the order of 10^{11} neurons (and 10^{12} glial or support cells), whereas the rat brain contains on the order of 10^3 fewer cells of either type (10^8 neurons and 10^9 glial cells).

For mapping purposes, it is also important to appreciate the dimensions of individual neurons: in humans, the cell body (the soma) ranges between 5 to 50 μm in diameter, whereas this range is 5 to 25 μm in rats. Of perhaps more interest, the length of individual axons in humans can reach on the order of a meter and on the order of 0.1 m in rats, whereas figures for the diameter of axons range between 0.1 and 15 μm in humans and 0.05 to 5μm in rats. Thus, there is a scaling factor between nerve cell diameter and axon length of 10^7 in humans and 10^6 in rats. Obviously, this places severe limitations on brain mappers in terms of accurate depiction of results—this is simply not possible when dealing with pathways between different cell groups. These results must be presented schematically.

Luckily for brain mappers, neurons tend to cluster into more or less distinct cell groups, which have been referred to variously as centers, nuclei, cortical areas, and so on. There appear to be on the order of 500 such major centers (which themselves may be subdivided) in the mammalian brain (typically, each center is found on the right and on the left side), and on average each cell group may contain on the order of five different cell (neuronal) types, based primarily on connections and secondarily on neurochemistry and physiology (see Swanson, 1996). Simple multiplication indicates that there are on the order of 2500 major types of neurons in the mammalian brain.

One reason that the circuits formed by these neurons are so complex is that parent axons typically branch (collateralize) extensively, and it seems reasonable based on a broad survey of the literature to assume that, on average, the axon of each type of neuron branches to innervate on the order of 10 different cell groups. If there are 2500 different cell types, this would imply that there are on the order of 25,000 different macroconnections or macropathways making up the circuitry of the brain. However, the true complexity of brain circuitry is fully appreciated only by realizing that each macroprojection typically branches prolifically within its target cell group, so that it has been estimated that the human brain contains on the order of 10^{14} synapses (functional contacts between an axon terminal and another cell, usually a neuron, in the brain), and the rat brain 10^{11}. The fact that the physiological effectiveness ("strength"), and total number, of individual

synapses in a terminal field (the microcircuitry) may depend on their previous history of activity—the biological foundation of learning and memory—only adds another level of complexity to the challenge faced by brain mappers.

4.1.3 Experimental Circuit-Tracing Methods

The structural complexity just reviewed has forced neuroscientists to develop over the last century experimental methods for dissecting and characterizing the structural organization and chemical content of neural circuits. Very briefly, contemporary neuroscientists rely on combining two classes of methods for characterizing the structural organization of connections between cell groups, and use brain maps to summarize the results for publication (for references to these and other neuroanatomical methods see Dashti *et al.*, 1997; Swanson, 1998–1999, 1999). One class involves the physiological transport of injected markers (tracers) up and/or down the interior of the axon. These tract-tracing methods rely on the physiological transport of markers from axon terminals to neuronal cell bodies of origin (retrograde tracing), or on transport from cell bodies to axon terminals (anterograde tracing).

The other class of methods involves performing chemical reactions on histological sections of brain tissue (histochemistry), which allows the cellular localization of molecules. The most widely used methods at this time involve *immunohistochemical* localization of neurotransmitter-related molecules within specific circuits and *hybridization histochemical* localization of messenger RNAs (mRNAs) encoding molecules of interest. Immunohistochemistry involves localizing specific molecules (antigens) in tissue sections with antibodies that have been tagged with markers that can be seen under the microscope, whereas hybridization histochemistry involves localizing nucleic acid molecules (especially mRNAs) in tissue sections with complementary strands of nucleic acids that have been tagged with markers that can be seen under the microscope.

As we shall now discuss, one major challenge to brain mappers is how to represent histochemical staining patterns, and the results of axonal transport experiments, on schematic representations of histological sections—bearing in mind the physical characteristics outlined above.

4.1.4 Atlases: Slice-Based Sampling and Standard Brains

The traditional method of representing information about brain structure on a series of slices through the organ actually dates back to Vesalius's revolutionary work in 1543 (Fig. 1a) and has been refined progressively ever since (Swanson, 1999). Because histological sections for experimental neuroanatomy are relatively thin (e.g., 30 μm thick) to increase microscopic resolution, serial sections are virtually never illustrated in publications (a rat brain cut in the transverse plane has almost 700 frozen sections 30 μm thick). Instead, evenly spaced (e.g., 1-in-10) series of sections might be illustrated, or, alternatively, unevenly spaced series of sections might be used more efficiently if data are clustered in certain regions of the brain (Fig. 1b). The neuroanatomist chooses a sampling method that best represents the data. It should be noted in passing that whereas confocal microscopy now can be used to reconstruct three-dimensional datasets from thick histological sections, the volume of tissue involved is always very tiny compared to the volume of the entire brain.

Vesalius produced a series of maps (an atlas) of progressively deeper horizontal slices through the human brain, and over the years atlases of slices cut in one or another of the three standard anatomical planes (horizontal, sagittal, and frontal or transverse) in many different species have been prepared. Nevertheless, it is worth stating the obvious: any particular brain (or brain block) can be sliced physically only in one plane; therefore a decision has to be made as to the most appropriate or useful plane in which to section a particular brain or brain block. Approaches based on using multiple brains, each cut in a different plane of section, to reconstruct three-dimensional datasets or atlases will be discussed below.

Many factors go into determining the most appropriate plane of section for a particular brain or brain feature. However, the factor that concerns us here is the ability to compare easily the results of different experiments, that is, results obtained from different animals. Direct comparisons are always easiest to make when patterns of data are viewed in the same plane of section using a standard format. For example, in comparing the distribution pattern of two neurotransmitter receptors in a complex region such as the visual cortex, it is better to compare the patterns in adjacent sections cut in the same plane rather than in one frontal section and one horizontal section. These considerations assume even more importance when graphical databases are a goal. In principle, an electronic database of graphical neuroanatomical information would be most efficient and accurate if all results were plotted in a standardized way on a standard brain with standardized nomenclature, because under these circumstances queries could be stated precisely, and the results of searches would be unambiguous.

As discussed elsewhere we are far from this state of affairs at the present time (Swanson 1992, 1998–1999). In a nutshell, we are still profoundly ignorant about the fundamental organizing principles of brain architecture and circuitry because of the bewildering complexity outlined above. As a result, there is controversy, confusion, and lack of detailed knowledge about virtually all aspects

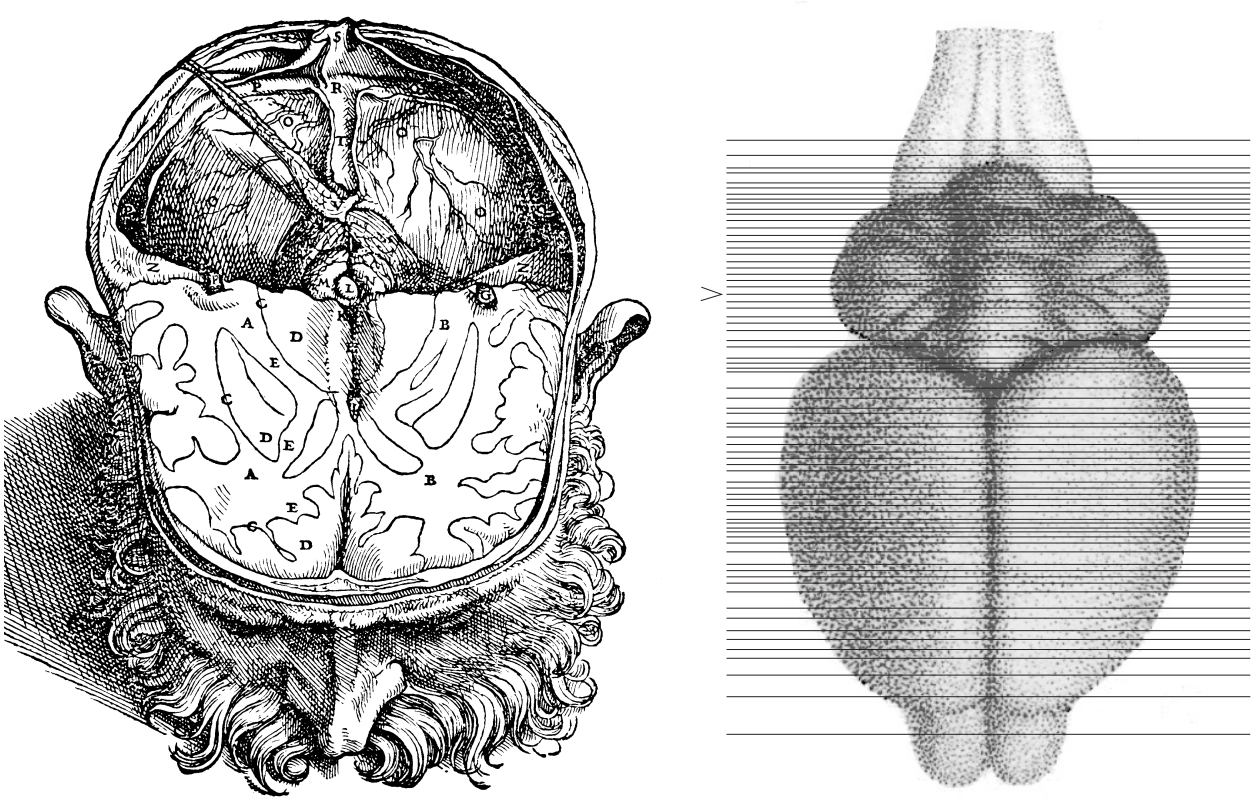


Figure 1 **(Left)** A drawing of the partly dissected human head from Vesalius's 1543 book, *The Fabric of the Human Body*. It shows a horizontal section through the rostral half of the cerebral hemispheres (indicated by A–E) after removal of the skull cap, with the caudal half of the hemispheres cut away to show the brainstem (M indicates the tectum) and cerebellum (indicated by O). **(Right)** A dorsal view of the rat brain (the drawing is from Leuret and Gratiolet, 1857) with a superimposed set of lines indicating the 73 transverse atlas levels of *Brain Maps* (Swanson, 1992, 1998–1999). The arrowhead along the left margin of atlas level lines indicates level 51, which is shown in Fig. 2. (From Swanson, L. W. (1998–1999). *Brain Maps: Structure of the Rat Brain*. Second rev. ed., Elsevier, Amsterdam. With permission. From Swanson, L. W. (1992). *Brain Maps: Structure of the Rat Brain*, Elsevier, Amsterdam. With permission.)

of brain morphology, and at a very basic level, as far as databases are concerned, one result is an unsystematic, incomplete, and contradictory nomenclature. Because of all this, a good case can be made for avoiding attempts to force the use of standard interpretations (e.g., nomenclature) of brain structure—they can only reinforce current misconceptions and retard work designed to understand the true structure of the brain (Swanson, 1992).

Having said this, it is nevertheless essential to have a standard (or perhaps better "reference") brain(s) with accompanying graphical atlas interpretations that can be used for *indexing* any and all results in a particular species (with a particular age and sex). That is, it should be possible, or results should be presented in such a way that it is possible, to say precisely how (or actually to illustrate graphically how) a given interpretation of brain structure is related to the interpretation of brain structure in a standard or reference brain and atlas. This is very easy to do when true synonyms for structures are involved (over 800 are provided in the second edition of our atlas, *Brain Maps*; Swanson 1998–1999) and progressively more difficult when there are differing opinions about the placement of borders or even about the existence of particular structures. Nevertheless, it should be obvious that when anatomical descriptors are used, their precise meaning should be made clear—which all too often has not been the case. The neuroanatomical literature is replete with ambiguities about location and structural details, which led Cajal (see Swanson and Swanson, 1995) a number of years ago to point out that "... there can never be enough [drawings], particularly in anatomy, where one could argue that drawings are more important than text ... they are documents of inestimable value that future generations may refer to with advantage in the never-ending battle of opinion and theory."

This of course raises the question as to the best way to present graphically a standard or reference atlas of the brain. Basically, 500 years of experience has led to the current standard of representing the outlines of cell groups and major fiber tracts on atlas drawings of the brain. This is somewhat equivalent to drawing the outlines of the continents, as well as of the various countries, on maps of the world. Once these basic templates have been prepared, they can be used to plot an infinite variety of other data, such as transportation systems, population

distributions, weather patterns, and so on. And now that it is obvious that electronic databases (both graphics and text) will be established, it will be necessary to develop a thesaurus of neuroanatomical nomenclature. The same "search word" can have very different meanings to different authors, and the same structure can have many different names. The amount of scholarship required to do a thorough retrospective analysis of neuroanatomical nomenclature usage is probably not feasible—there are hundreds of thousands, if not millions, of references in many different languages spanning about 2500 years. In the long run, the simplest solution is to insist from now on that anyone using neuroanatomical nomenclature define precisely what the terms mean (surprisingly, this is very rare at the moment—the dawn of the 21st century).

Normal Brain Structure (Cell Groups and Fiber Tracts)

As just mentioned, the bare essentials for a good traditional brain atlas include clear indications of how the major cell groups and fiber tracts are distributed within a series of histological sections. At the gross anatomical level, this amounts to showing the spatial distribution of the main centers or nodes in brain circuitry (e.g., cell groups are analogous to major cities on a continent map), and the main fiber tracts (bundles of conducting axons) between them (e.g., fiber tracts are analogous to major highways on a continent map).

The traditional, best, and most convenient way to display the organization of cell groups in a histological section of the CNS is with a Nissl stain, which relies on basic aniline dyes interacting with nucleic acids in the section. The result is a very clear picture of the distribution pattern, size, orientation, shape, and staining intensity of neurons (as well as glial, endothelial, and mast cells) in the brain; the creation of such pictures is known as cytoarchitectonics. In contrast, fiber tracts in the brain are typically revealed with a myelin stain, and the formal study of their spatial distribution is known as myeloarchitectonics. Interestingly, a good indication of major fiber tract distribution in frozen sections can often be gained simply by utilizing dark-field illumination. For an introduction to the literature on these approaches see Swanson (1998–1999, 1999).

A Typical Atlas Level (*Interactive Brain Maps*)

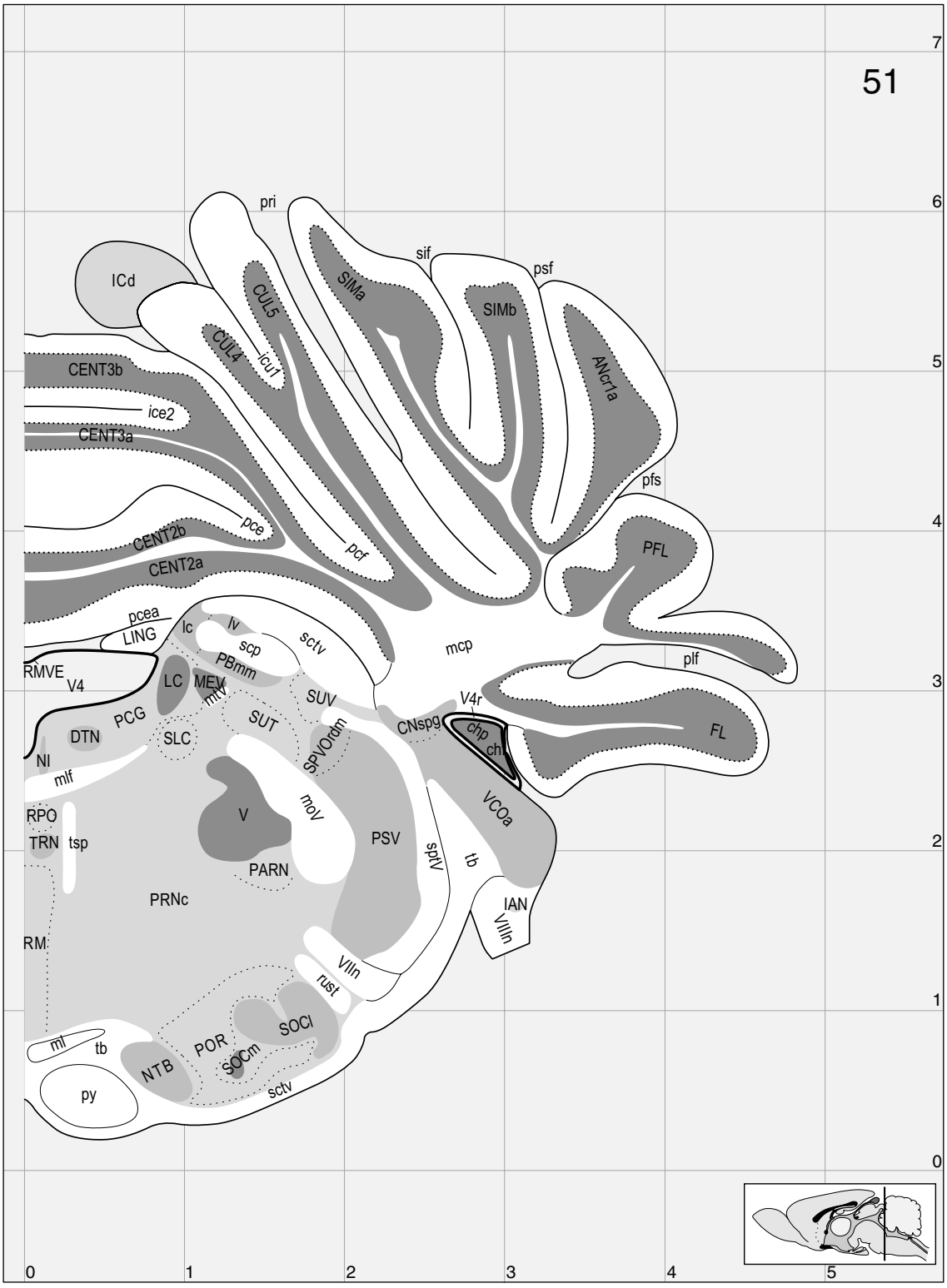
The traditional approach just described for illustrating the disposition of major cell groups and fiber tracts was used for our atlas of the adult male rat brain (Swanson, 1992), which was prepared in the transverse (frontal) plane because experience has shown that in this species a series of transverse sections is most commonly useful for mapping datasets that extend through much of the brain (instead of being confined to one cell group or another). Of the 556 serial sections through the brain, 73 were illustrated in detail; virtually every known cell group is represented on at least two of these levels.

One unusual feature of this atlas at the time of publication in 1992 was that the brain maps were drawn with a computer graphics application (Adobe Illustrator) rather than with pen and ink (Fig. 2); traditional photographs of histological sections were scanned and used as templates for tracing on the computer monitor, aided by a microscope (with the corresponding histological sections) placed next to the monitor. In retrospect, this was a fortunate choice of methods because: (1) the vector-based drawings are much smoother than pen-and-ink drawings, and they can be modified much more conveniently; (2) the vector graphics files can be scaled virtually infinitely without loss of resolution; (3) as we shall return to later in this chapter, the electronic format of the maps lends them immediately to use on the World Wide Web, especially as templates in a standardized atlas for databases of graphical neuroanatomical information (Dashti *et al.*, 1997); and (4) it has become clear that the electronic format allows one to develop a new generation of atlases that are interactive rather than static (printed).

The atlas drawings from the first edition of *Brain Maps: Structure of the Rat Brain* (Swanson, 1992) were soon made available on floppy discs (Swanson, 1993), and the files simply consisted of the brain-section drawings (which are of the right side of the brain and include a gross outline of the brain and ventricles, cell group outlines, fiber tract outlines, abbreviations, and a mask so that overlapping stacks of sections can be used). The second edition of *Brain Maps* (Swanson 1998–1999) included a double CD-ROM with a much more advanced version of the 73 atlas-level templates. The major technical advance that led to the new electronic atlas format was the introduction of a layer manager palette to computer graphics illustration applications, and its use prompted us to refer to the new atlas as *Interactive Brain Maps*. In essence, contemporary illustration applications (based on vector graphics) allow a great deal of flexibility in modifying, viewing or hiding, and printing or not printing various components of a file containing an atlas level, and one can do so essentially in real time.

The layer manager palette allows one to create an essentially infinite set of transparent (or translucent), perfectly aligned overlays for a map template and to arrange and view them in any order. In other words, a layer manager is simply a list of overlays. The stacking order can be changed in any way desired, and individual layers can be named, hidden or shown, and printed or not printed.

In *Interactive Brain Maps*, different layers are used to display the following features of each atlas level: (1) a bilateral drawing of the brain, (2) a unilateral photograph of the Nissl-stained histological section used to prepare the drawing, (3) a grid of physical coordinates,



15.85 (-9.80)

Figure 2 A map of atlas level 51 from the first edition of *Brain Maps* (Swanson, 1992). The drawing was made by tracing a photomicrograph of the corresponding Nissl-stained histological section using a computer graphics application and checking all details by viewing the section under a microscope at the side of the monitor. The position of the section/level is indicated in the schematic sagittal section in the lower right corner of the figure and by the arrowhead in Fig. 1 (right). The grid behind the map is a scale in millimeters; the number in the lower left is the distance along the rostrocaudal (z) axis. Thus, the brain is placed in a Cartesian coordinate system, and every location has an x, y, and z coordinate (in addition to being in a named structure). All structures have been arranged in a hierarchical nomenclature table, with references to the primary literature. (From Swanson, L. W. (1992). *Brain Maps: Structure of the Rat Brain*, Elsevier, Amsterdam. With permission from Elsevier Science.)

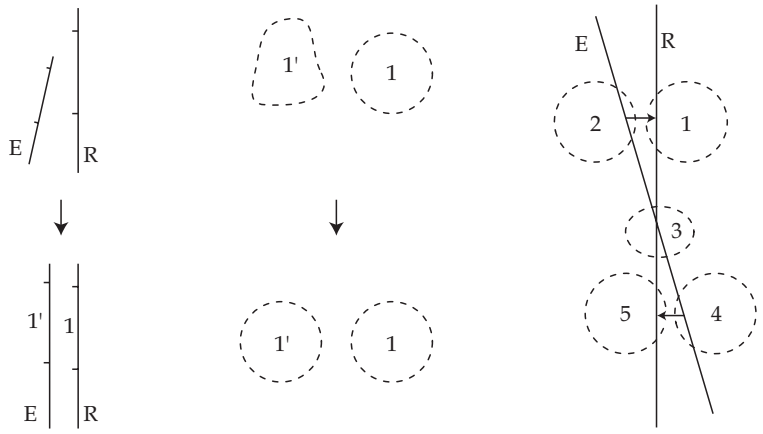
(4) a grid of stereotaxic coordinates and a database fiducial (see below), (5) a list of abbreviations, and (6) a mask for stacking levels. A Web site for the second edition of *Brain Maps*, including *Interactive Brain Maps*, may be found at http://www.elsevier.com:80/homepage/sah/brainmaps/. It contains sample files that can be downloaded for manipulation and printing. Use of these interactive template files on a computer highlights immediately the advantages over static printed maps.

4.1.5 Transferring Data from Experimental Brain to Standard (Atlas Reference) Brain

The time-honored method of mapping neuroanatomical data essentially involves drawing the cell bodies and fiber tracts as they appear on an individual histological section and then drawing the data (axonal or histochemical labeling, for example) on that map—using a camera lucida or equivalent approach. These drawings or maps are an abstraction of data, and the data are represented in a drawing of the histological section that contains them. However, when histological analysis is involved, no two brains are cut in exactly the same plane, and each section from every brain is distorted in a different way. These problems can be approached more or less successfully in the following ways, with the goal in mind of comparing the results of different experiments as plotted on a standard or reference series of templates. The results of such comparisons are, of course, qualitative rather than quantitative, but they are very useful for comparing general distribution patterns. The only way of comparing distribution patterns quantitatively is to carry out multiple staining methods on individual sections so that the patterns are compared directly in the same section.

Linear Rescaling

Different histological procedures result in more or less shrinkage or expansion of the brain and/or tissue sections. For example, our atlas brain was embedded in celloidin for sectioning, and as a result underwent considerable shrinkage (on the average, about 38% dorsoventrally, 21% rostrocaudally, and 28% mediolaterally). To a first approximation it seems reasonable to assume that a great deal of this distortion may be corrected for by linear scaling along each of the three cardinal axes (which can be accomplished trivially in computer graphics applications; Fig. 3a). However, it is not possible to be sure how much nonlinear distortion is present, due, for example, to mechanical factors such as the presence of fiber tracts running through gray matter (the physical texture of white and gray matter is quite different). In *Brain Maps*, such linear rescaling was used to produce a stereotaxic coordinate system from the physical coordinate system. This approximation was based on a com-



a. Align, linear rescale *b. nonlinear warping* *c. data transfer, different plane*

Figure 3 Key factors related to comparing spatial features in a histological section from an atlas or reference brain (*R*) to those in an experimental brain (*E*). **(a)** Assuming the two brains are cut in the same plane, the simplest first step would involve correcting for shrinkage or expansion by linear rescaling and then aligning the two sections. **(b)** The second step would involve removing as much nonlinear warping of the experimental section as possible. Here structure 1 is distorted in the experimental section (it has shape 1′). The location of structure 1 (and 1′) is indicated in (a). **(c)** If, or really because, the experimental brain section (*E*) is cut in a different plane than the reference or atlas brain section (*R*), errors in the assignment of spatial location to data occur. For example, data in structure 2 of the experimental brain section will be mapped onto structure 1 of the atlas or reference brain level, and data in structure 4 of the experimental section will be mapped onto structure 5. Accurate data transfer occurs only at one point in structure 3, and transfer errors increase as the distance from this point increases (and as the angle between the two sections increases).

parison with the atlas of Paxinos and Watson (1986), where frozen sections were used, and there was relatively little shrinkage distortion. In the case of the brain used for our atlas, nonlinear distortions are at least an order of magnitude less than the linear shrinkage.

Nonlinear Warping

Because histological sections are so thin (e.g., 30 μm) relative to the dimensions of the section itself (about 5000×6000 μm for a typical rat brain section) and because brain tissue is so fragile to begin with, these sections undergo considerable nonlinear, uncontrollable distortion or warping when mounted on glass slides for observation under the microscope (Fig. 3b). Mounting such a tissue section is a little like trying to lay a giant crêpe down flat on a plate—assuming one could lay the same crêpe down over and over, its exact shape would be different each time because it is so thin and pliable. If an experimental brain could be cut in exactly the same plane of section as a reference brain, then a wide variety of warping algorithms (see Chapter 4.6 and Toga, 1999) could be applied to remove distortions in sections of the experimental brain, relative to those of the reference brain (after the application of linear rescaling, if necessary). However, it is incumbent upon the user to quantitate the extent of distortion correction, and no one has remotely approached the highly accurate removal of warping from tissue sections relative to atlas levels (in terms of cell group and fiber tract borders). And, of course, warping cannot deal with common defects in tissue sections such as folds, tears, bubbles, and holes.

Correcting for Plane of Section Differences

Another very serious problem is that every brain processed for histology is cut in (at least a slightly) different plane of section because of technical factors involved in mounting the brain on a microtome stage for cutting. The results of this difference in plane of section for direct mapping of experimental data onto standard atlas levels is illustrated in Fig. 3c: data are not placed in the spatially correct location, and errors involved become greater (1) the greater the difference in plane of section, and (2) the farther away one is from the point of intersection of the two sections (Swanson, 1998–1999).

Conceptually at least, there are two obvious solutions to this problem. First, the neuroanatomist can sit at the microscope for many hours correcting the plane of section difference mentally, using a method that has been described in some detail (Swanson, 1998–1999). This method requires a great deal of patience and knowledge, is exceptionally time consuming, and obviously is qualitative in nature; however, it is the only method that has been shown empirically to work satisfactorily at the present time for large-scale brain mapping of data onto standard atlas levels.

The second approach would involve resectioning a three-dimensional computer graphics model of the brain in the plane of the experimental brain, subjecting the experimental section to linear scaling and warping, and then transferring the data to the template from the three-dimensional model, ideally using image analysis methods. However, to be maximally useful for comparison and databasing purposes, a continuous, three-dimensional model of the data itself would have to be constructed, and then the data model would have to be resliced in a standard or reference plane. It does not seem likely that this goal will be accomplished fully in the foreseeable future (see below), although a very good start at laying the groundwork for this approach has been made (Chapter 4.6).

4.1.6 Toward Textual and Graphical Databases on the Web

Because of the explosion in neuroanatomical data beginning around 1970, there is no doubt that electronic databases available over the World Wide Web would be of great value to experimental and computational scientists alike. Obviously, there are two broad classes of relevant databases: textual and graphical. Approaches to textual databases (and knowledge bases) of neuroanatomical information are dealt with in Chapter 6.2, where NeuroScholar™ is considered in detail (also see http://neuroscholar.usc.edu/). The development of our database and query manager for atlas-based neuroanatomical data, NeuARt, is described in Chapter 4.3, where the need for both textual and spatial query managers (Dashti *et al.*, 1997; Shahabi *et al.*, 1999) is emphasized. The goal is to integrate seamlessly these textual and graphical databases of neuroanatomical information. At the simplest level of integration, the *names* of structures in the atlas ("places") templates of the graphics database can be used as *keywords* for querying the textual database.

4.1.7 Three-Dimensional Computer Graphics Models of the Brain

Excellent three-dimensional drawings of brain structure also date back to the sixteenth-century work of Vesalius (and the long-unpublished drawings of Leonardo). Particularly good modern examples can be found in books by Krieg (1955, 1966), who used a systematic method based on reconstructing series of histological sections from rat and human brains, and by Nieuwenhuys and colleagues (1988, 1997), who by and large used more traditional artistic methods. In addition, many histological atlases of the brain have used sections cut in the three standard planes (for the rat, see Paxinos and Watson, 1986, 1998; Kruger *et al.*, 1995).

Today, sophisticated computer graphics methods can be used to design, construct, and display digital three-dimensional models of the brain. There are two basic approaches to three-dimensional computer graphics modeling: voxel-based and vector-based. "Voxels" are "volume elements" (rather than "pixels" or "picture elements"), and their use was spurred by the development of computerized tomography (e.g., CAT, PET, and fMRI scans). The great advantages of this approach are that a "solid" three-dimensional image of the living brain (or other organ) can be obtained, and when this image is resectioned electronically in any plane the slices are virtually perfectly aligned (see Toga and Mazziota, 1996). The major disadvantages of this approach are low resolution and contrast relative to histological sections prepared for microscopic examination (see above and Fig. 4).

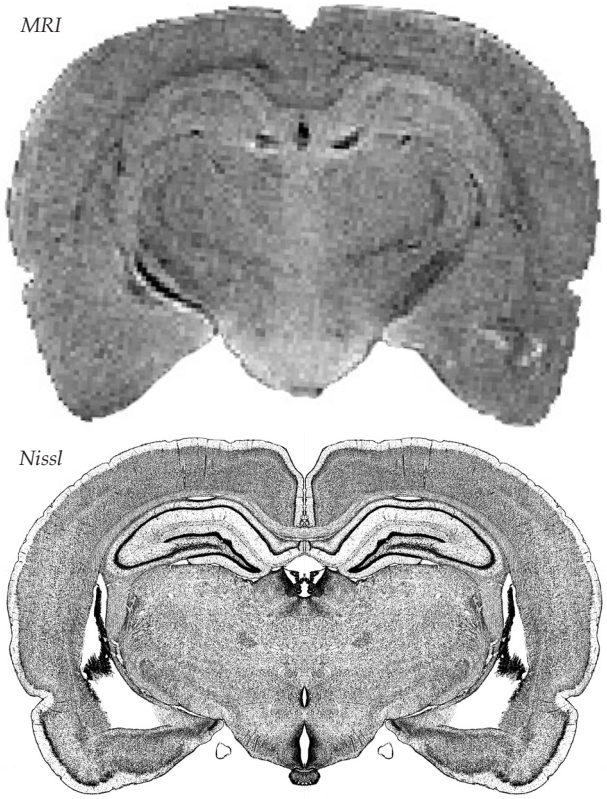


Figure 4 A comparison of the resolution obtained in photos of rat brain sections from MRI **(top)** and Nissl-stained histological sections (bottom). The MRI voxels were 100 μm^3 and data for the whole brain took about 24 hours to collect. The dataset was obtained by Russell Jacobs and Eric Ahrens at Caltech. The Nissl-stained section is from *Brain Maps* (Swanson, 1998–1999) and was used to prepare atlas level 32. Needless to say, the histological section can be viewed under the light microscope, which has a resolution on the order of 1 μm. The MRI image is from a male rat that was the same size as the rat used to prepare *Brain Maps*, and the section shown here is approximately the same as level 32 in *Brain Maps*. In comparing the two images, the most obvious difference is that the MRI does not have cellular resolution; cells in the rat brain range between 5 and 25 μm in diameter. (Both photos from Swanson, L. W. (1998–1999). *Brain Maps: Structure of the Rat Brain*. Second rev. ed. Elsevier, Amsterdam. With permission from Elsevier Science.)

The vector-based approach depends on reconstructing surfaces from series of cross-sections with vector graphics—that is, building computer graphics models of the brain from drawings such as those prepared for our atlas, *Brain Maps* (Swanson, 1993, 1998–1999). These highly simplified models have the advantages of relatively small file sizes and essentially infinite scalability (see Chapter 4.6). One of their major disadvantages is that they are reconstructed from histological sections. This is a problem for two major reasons. First, it is not possible to align a series of histological sections of the brain absolutely correctly because there are no invariant fiducial structures (Weninger *et al.*, 1998), although accuracy may be increased significantly by comparing section alignment with an MRI scan of the head from which the brain was removed. And, second, as mentioned above, each histological section undergoes unique nonlinear distortion when mounted on glass; therefore, the outlines (or "surface") of a brain structure reconstructed from a series of histological sections will have more or less "noise" (deviation from true position and shape) based on a number of factors, including the skill of the histologist who mounted the sections on glass. These considerations have led to the conclusion that the templates or maps generated for *Brain Maps* (Swanson, 1993, 1998–1999) must be redrawn and redesigned for use in constructing a three-dimensional model of the rat brain. In addition to smoothing outlines in the maps to eliminate warping, many more sections of the brain used to prepare *Brain Maps* must be drawn (only 73 of 556 have thus far been drawn completely), and complete outlines of all individual structures (blobs or paths) must be provided.

At least four major uses of three-dimensional computer graphics models of the brain come readily to mind. First, as mentioned above, they could be sliced in the same plane of section as any experimental brain, for easier mapping of data onto computer graphics templates. Obviously, once a brain cut in a particular plane of section (say transverse) is rendered as a three-dimensional model, the latter can then be resliced in the other two cardinal planes of section (say horizontal and sagittal). Second, the delineation of surface features required for the construction of three-dimensional models lends itself immediately to quantitative morphology (for example, measurements of volume, surface area, shape, and distance). In principle, vector graphics surfaces can be analyzed mathematically, in terms of both their geometry and topology. Third, three-dimensional models of the brain can be used to illustrate clearly the physical location and shape of brain structures and pathways (as is so helpful in textbooks). And, fourth, it will be possible to animate three-dimensional models of the brain and nervous system as a whole. For example, "physical models" of brain circuitry could be animated in terms of

dynamic patterns of action potentials or information flow within specific pathways between specific cell groups, or more accurately, between specific cell types. It remains to be determined how far this approach must be refined before it can escape the realm of a gross cartoon that ignores the true subtleties of neuronal information processing.

4.1.8 Two-Dimensional Flatmaps: Schematic Circuit Diagrams and Distribution Patterns

Although they contain very significant distortions, maps are used much more widely than globes because they are so convenient. There has been relatively little work toward a systematic flatmap of the brain because this would involve flattening a highly compartmentalized solid object rather than just the surface of a sphere. The best examples so far have been unilateral flatmaps of the amphibian brain (Herrick, 1948) and mammalian brain (Nauta and Karten, 1970), and a bilateral flatmap of the rat (Swanson, 1992) and human (Swanson, 1995) CNS (Fig. 5) based on a fatemap of the embryonic neural plate, which is a flat sheet topologically (see above).

Our flatmap has a number of obvious uses, especially for comparing patterns of gene expression and neurochemical distribution, and for illustrating schematically the organization of various circuits. These applications are facilitated greatly by use of the flatmap as a template in an electronic database. For example, different pathways or sets of pathways can be stored in transparent overlays (layers) and can then be displayed in any desired combination, just as for the data layers over atlas levels considered above. In fact, to aid in the design of rat brain circuits, all of the major pathways and cranial nerves have been placed in a standard way over the flatmap, with different functional systems in different layers (Swanson, 1998–1999). Obviously, flatmap layers containing various expression patterns, circuit elements, and other information could be stored in a database for retrieval when needed.

4.1.9 The Future: Atlases as Expandable Databases and Models

It is becoming obvious very quickly that the traditional role of brain maps and atlases is changing in a fundamental way. Instead of being static images of the

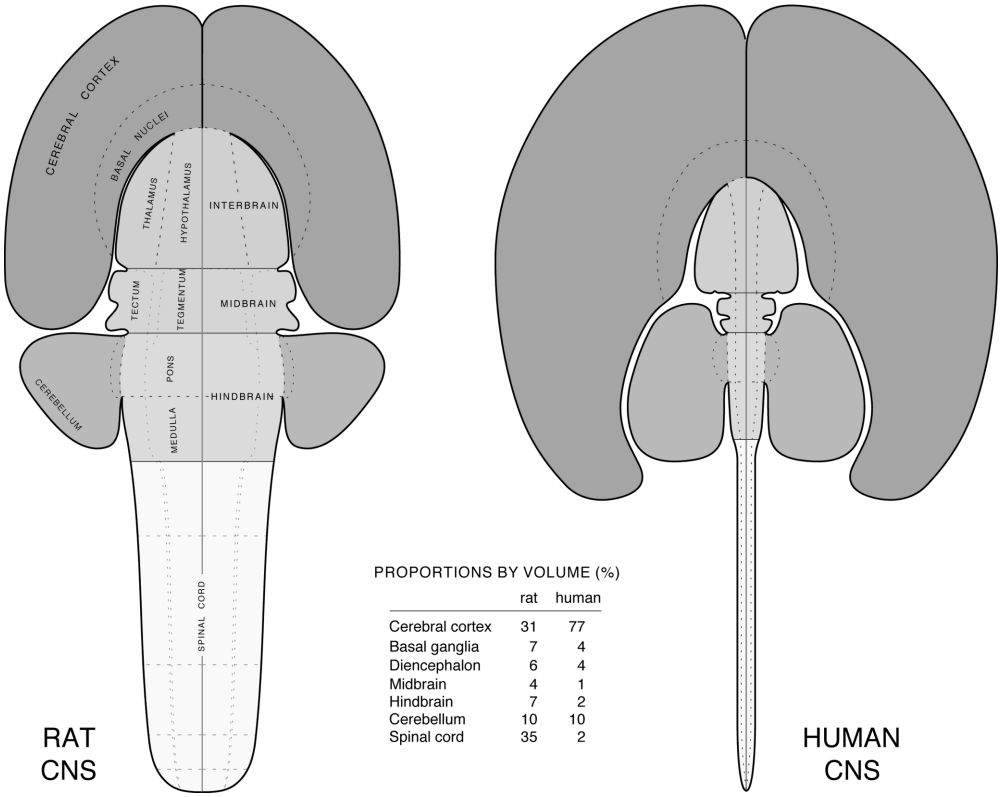


Figure 5 Flatmaps of the rat (left) and human (right) central nervous system. For simplicity, the volume of structures in the actual brain is proportional to their area in the schematic flatmap. The table in the center of the figure compares the size of major central nervous system divisions between rat and human. See text for further details. (From Swanson, L. W. (1995). *Trends Neurosci.*, **18**, 471–474. with permission from Elsevier Science.) (See color plates.)

brain—whether slices or volumes—they will be dynamic computer graphics models that serve multiple, expandable purposes, including the framework for databases. This approach is already practical for much simpler applications such as Geographical Information Systems (Chapter 4.2), and the computer-aided design of buildings, cars, and airplanes. Functioning, useful applications to biology, including neuroscience, will be next!

The development of optimal digital brain models and databases will utilize all of the topics covered in this book. First, there is the construction of an interactive "physical" model of the brain using three-dimensional computer graphics software. Because of the brain's structural complexity, these models (say, for different species, sexes, and ages) will probably never be completed, but instead will become progressively more detailed. As more is learned about the brains of various species, controversies about nomenclature, connections, and so on will gradually be resolved. This has already happened for most of the rest of the body—there is very little controversy about the structural organization and nomenclature of the skeletal, muscular, cardiovascular, and digestive systems, for example—and the same will inevitably apply to the nervous system in due time.

A second step will involve building a whole variety of neuroscience databases, implementing ways to federate them seamlessly, designing powerful ways to search for information within the federation, and then tying the database federation to the three-dimensional computer graphics models of the brain just mentioned. And, as a third phase, one might envision creating dynamic computer graphics models of brain structure and function based on knowledge extracted from the databases. In essence then, the computer graphics models could become knowledge bases of brain structure and function. As such, they could be used to test hypotheses generated from existing knowledge and to suggest new hypotheses that could be tested experimentally. How far will it be possible to develop the idea of a computer graphics virtual brain whose parts are fully documented by links to databases, knowledge bases, and modeling/simulation tools?

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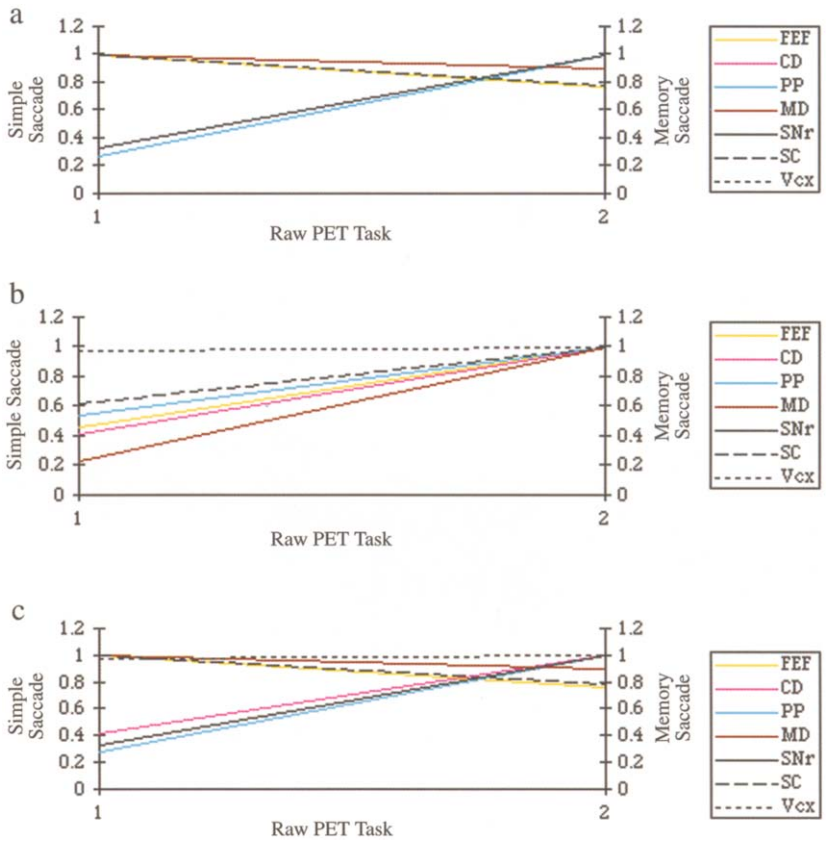
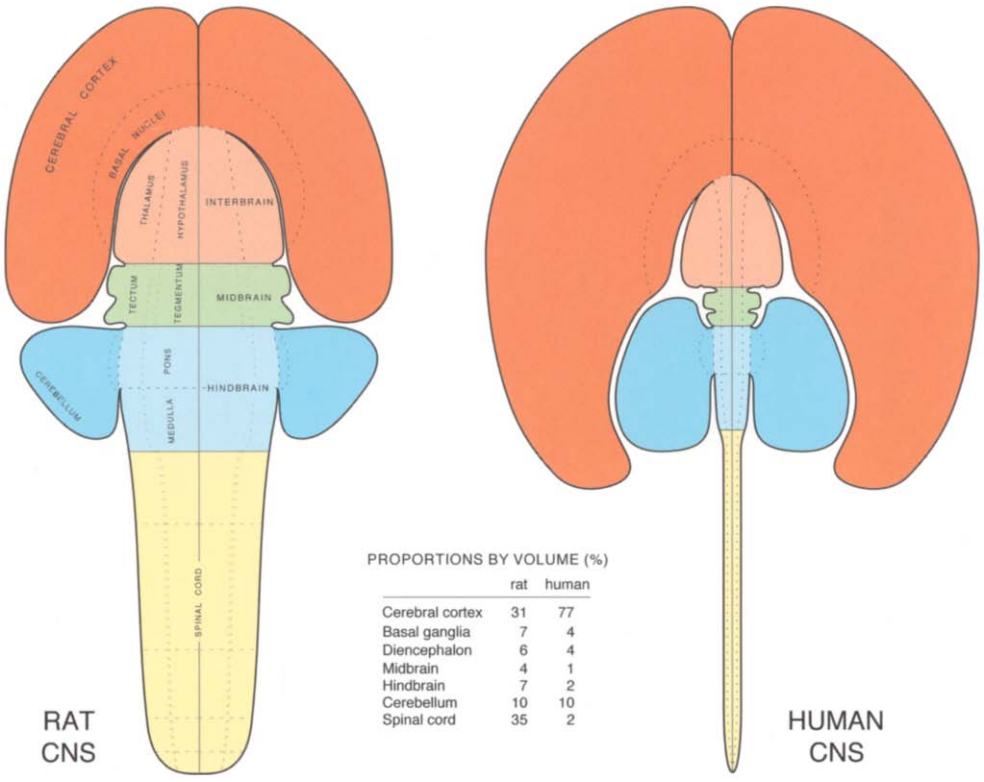


CHAPTER 2.4, FIGURE 6 Simple vs. memory saccade-related raw activity $rPET_A$ associated with each cell group A in the neural network model for saccade generation obtained by integrating: (a) over inhibitory connections; (b) over excitatory connections; and (c) over all connections. Left column: $rPET_A$ values for the simple saccade task. Right column: values for the memory saccade task. Note that in B, CD and Vcx coincide, as do SC and FEF. Similarly, FEF and SC coincide in C. CD, caudate; FEF, frontal eye fields; PP, posterior parietal cortex; SC, superior colliculus; SNr, substantia nigra pars reticulata; MD, mediodorsal thalamus; and Vcx, visual cortex.



CHAPTER 4.1, FIGURE 5 Flatmaps of the rat (left) and human (right) central nervous system. For simplicity, the *volume* of structures in the actual brain are proportional to their *area* in the schematic flatmap. The table in the center of the figure compares the size of major central nervous system divisions between rat and human. See text for further details. (From Swanson, L.W. (1995) *Trends Neurosci.* **18**, 471–474. With permission from Elsevier Science.)