Windows on the brain: the emerging role of atlases and databases in neuroscience

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Brain atlases and associated databases have great potential as gateways for navigating, accessing, and visualizing a wide range of neuroscientific data. Recent progress towards realizing this potential includes the establishment of probabilistic atlases, surface-based atlases and associated databases, combined with improvements in visualization capabilities and internet access.

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Abbreviations

3D	three-dimensional
fMRI	functional MRI
MRI	magnetic resonance imaging

Introduction

As in several other areas of modern biology, neuroscientists are faced with an embarrassment of riches: an explosion of experimental data that overwhelms the information-carrying capacity of traditional publication mechanisms. One general solution to this problem involves the creation of a parallel information infrastructure, centered around databases that allow rapid, user-friendly access to vast amounts of data at many levels of abstraction [1–4]. The power and utility of this approach has been compellingly demonstrated in genomics and proteomics, where countless investigators rely heavily on sequence databases for genes and proteins and on protein structure databases.

In the neuroscience arena, the need for an analogous infrastructure is equally great, but a combination of factors makes the challenge uniquely daunting. First and foremost, the brain is enormously complex in its spatial organization, with thousands of anatomically distinct subdivisions, and is even more complex in terms of its intricate patterns of connectivity. This spatial complexity is exacerbated by individual variability in structure and function. Individual variability arises from many factors, including developmental age, experience, and genetic background; it is especially pronounced in cerebral and cerebellar cortex, the dominant structures of the mammalian brain. Finally, the brain is studied using an impressive variety of experimental methods, collectively spanning many levels of spatial resolution, with great diversity in data formats and enormous amounts of image- and time-dependent data.

Given the central importance of spatial location, brain atlases are natural gateways for navigating and visualizing a wide range of neuroscientific data. Atlases provide a common spatial framework that compensates for individual differences in brain structure [5–8]. When linked to suitable databases, atlases can mediate access to what is known about the brain and can lead to new insights through meta-analyses carried out on diverse datasets. Because conventional print-based brain atlases are inadequate in many respects, much effort has gone into generating electronically accessible atlases that are better suited for these purposes.

Ideally, brain atlases having several basic characteristics should be available for each widely studied experimental species. First, they should provide accurate three-dimensional (3D) representations of brain structure, how this varies across individuals, and how it changes during development. Second, atlases within a species and across species should be linked to one another and to an emerging federation of databases. Third, options for searching, selecting, and visualizing data should be powerful and flexible. Fourth, high-speed internet connectivity and well-designed user interfaces should promote universal access and easy use.

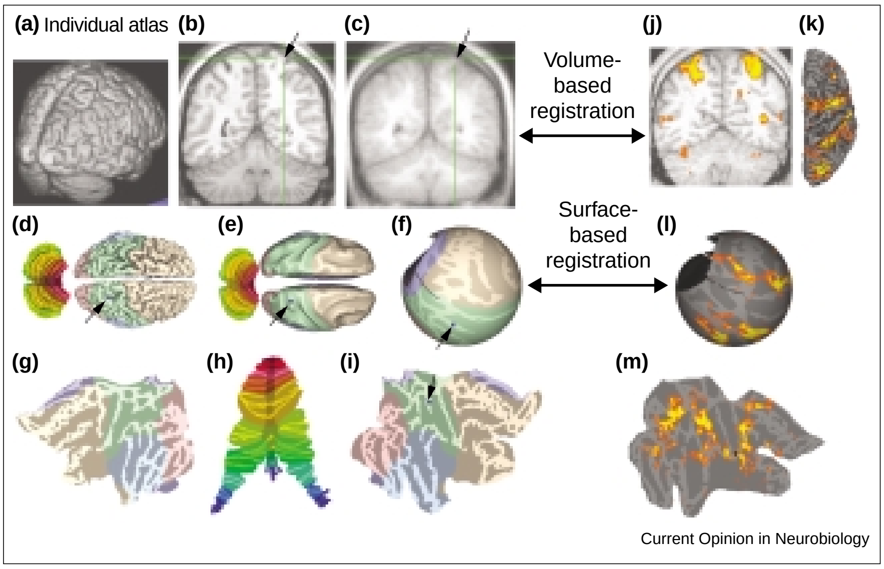
Although no currently available atlas meets all of these criteria, progress has occurred on many fronts. In this review, I highlight recent progress on atlases and spatially organized databases pertaining to the mammalian brain. A major emphasis is on the human brain and on cerebral and cerebellar cortex, because they are dominant structures that pose a special set of challenges.

A multiformat human brain atlas

Atlases can represent brain structure using a variety of imaging methods and visualization options. Many recent atlases are based on structural magnetic resonance imaging (MRI), which provides good resolution in all three spatial dimensions. Some are derived from an individual brain [9,10,11•]. Others represent an average of many individuals registered to the same stereotaxic space, resulting in images that are blurred but avoid biases associated with the idiosyncratic shape of even the most ‘typical’ brain [12,13]. For the cerebral cortex, a complementary strategy is to generate a surface-based atlas that explicitly represents the highly convoluted cortical sheet [7].

Each of these approaches has inherent limitations that can be minimized by generating a multiformat atlas [14–16], as shown in Figure 1. This atlas includes an individual brain [17] (Figure 1a,b) and a population-averaged brain registered

Figure 1



A multiformat human brain atlas that illustrates the complementarity of volume and surface representations and of an individual versus a population-averaged brain. **(a,b)** Volume representations of the individual human 'Colin' atlas [14–17] generated from high-resolution structural MRI and shown as (a) a volume rendering and (b) in a coronal slice. **(c)** Volume representation of the 711-2B population average atlas [18], generated by scanning a population of subjects and registering them to Talairach stereotaxic space, using a volumetric registration method that compensates for some but not all aspects of individual variability. **(d–i)** Surface-based atlas of the human 'Colin' cerebral and cerebellar cortex. The surfaces were generated from segmentations made using the SureFit method and are shown in (d) their fiducial configuration, (e) inflated to smooth out folds, (f) projected to a sphere (right hemisphere only) for delineating latitude and longitude, and (g-i) converted to flat maps that allow each surface to be seen in its entirety in a single view. The individual brain allows fine structural details to be seen and is essential for generating cortical surface reconstructions. The population-averaged brain is blurred but circumvents the idiosyncratic shape of any single brain. Corresponding locations in the volume and surface representations can be identified interactively (arrows) using freely available software [16,19,20] The atlas data set can be downloaded at http://brainmap.wustl.edu/caret/#DownloadAtlas. **(j–m)** Volume and surface representations of (j) an individual brain and (k–m) right cerebral hemisphere, showing attention-related fMRI activations [21], as an illustration of one type of experimental data that is desirable to bring into register with the atlas. Data from the entire brain can be registered using volumetric methods. For data related to cerebral cortex, surface-based registration to the atlas has inherent advantages because it respects the topology of the cortical surface.

to the same space [18] (Figure 1c). It also includes volumetric representations of the whole brain plus surface reconstructions of both cerebral hemispheres and the entire cerebellar cortex for the individual brain. The surfaces are shown in their fiducial (native) configuration (Figure 1d), after inflation to smooth out major folds (Figure 1e), as a spherical map (right hemisphere only; Figure 1f), and as cortical flat maps (Figure 1g–i). In each configuration, cerebral lobes and cerebellar lobules are painted various colors, and buried cortex is shaded more darkly. Using appropriate visualization software (e.g. Caret for surfaces [16,19] http://brainmap.wustl.edu/caret/, AFNI for volumes [20] http://afni.nimh.nih.gov/afni/edu), the relationship between volume and surface representations can be viewed interactively; identifying any location on the surface (blue marks, arrows in Figure 1d–f,i) highlights the corresponding volume location (cross-hairs, arrows in Figure 1a,c) and vice versa.

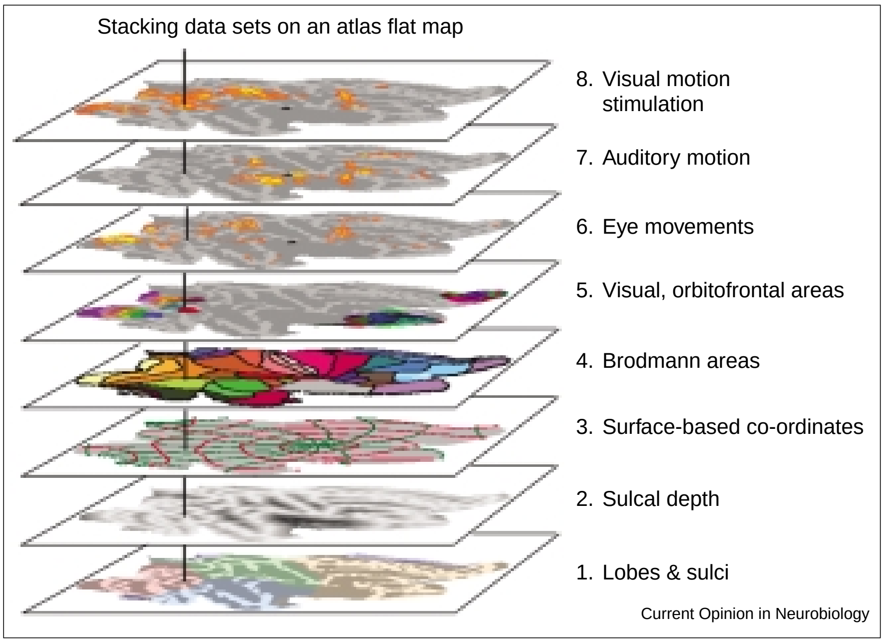
Mapping data onto an atlas generally entails deforming an individual brain (Figure 1j–m) to match the shape of the target atlas, then carrying experimental data, such as a functional MRI (fMRI) activation pattern [21], passively along with the deformation. Of the many registration methods available [22–24], a primary distinction is between volume-based and surface-based approaches. Because surface-based registration respects the topology of the cortical sheet, it has the potential for inherently greater fidelity, especially when it is applied to spherical maps to circumvent the artificial cuts needed when making flat maps [25–27,28•,29].

Stacking up the data

Atlases provide invaluable substrates for analyzing complex spatial patterns and comparing among many types of data. The preferred visualization format depends on the nature of the data and on the specific questions to be addressed. For cortical analyses, it is often most efficient to use surface maps, especially flat maps, as illustrated schematically by the stack of flat maps in Figure 2. This stack includes a variety of data types that can be compared by rapid switching and/or overlaying of different maps [28•]. For example, an fMRI activation pattern from one paradigm (e.g. visual motion stimulation, level 8) [30] can be compared with the pattern for other paradigms (e.g. auditory motion on level 7; eye movements on level 6) [21,30]. The location of any particular activation focus (e.g. arrow, level 8) can be specified in several ways: first, by the cortical area(s) it intersects with according to various partitioning schemes (levels 4,5); second, by its sulcal or gyral identity (level 1); third, by its latitude and longitude (level 3), based on spherical coordinates projected to the flat map, just as is routinely done with earth maps [28•,31].

The data illustrated in Figure 2 are available via the internet-accessible Surface Management System (SuMS)

Figure 2



Comparisons across data sets using a stack of flat maps. Large amounts and diverse types of data can be displayed compactly and in register, by treating each dataset as a separate layer for viewing on an atlas cortical flat map [15,16]. In this example, layers 1–3 show structural information about the atlas right cerebral hemisphere, to provide a suitable spatial framework. Layers 4 and 5 show two different partitioning schemes for cerebral cortex. Layers 6–8 show complex fMRI activation patterns from three different behavioral paradigms that were mapped from Talairach stereotaxic space to the atlas surface. This data set, and any number of analogous ones, can be loaded concurrently in Caret software and viewed in different combinations and overlays, in order to make a wide variety of comparisons and analyses. This includes assessment of similarities and differences between any of the currently loaded fMRI activation patterns and assessment of whether any given activation focus is in one or another cortical area by any of the partitioning schemes represented in the atlas. In making such comparisons, surface-based coordinates of latitude and longitude provide a concise and objective way to identify precise locations on the atlas map. The experimental data set is available at http://brainmap.wustl.edu/sums/sums.cgi?specfile=human.colin_avg20.R.Cerebral.ATLAS.

database [32] (http://brainmap.wustl.edu/sums/sums.cgi). SuMS is designed as an open-ended repository of surface-related data, with flexible search options for selecting diverse combinations of data that can be efficiently downloaded and analyzed.

Probabilistic atlases in health and disease

Registering an individual brain to an atlas cannot compensate perfectly for individual variability. Hence, any given location in an atlas may correspond to different anatomical or functional subdivisions within a population of brains mapped to the atlas. Probabilistic atlases are a natural way to systematically represent whatever variability persists after the registration process, plus any other uncertainties associated with categorizing brain structures. Besides representing variability in a normal population, probabilistic atlases are well suited for analyzing how brain structure and function is affected in a variety of psychiatric and neurological disorders.

Several recent studies have demonstrated the power of this approach. Fischl *et al.* [33••] used automated segmentation and registration to generate a probabilistic MRI-based atlas of major subcortical structures. Comparisons of Alzheimer's versus normal brains revealed significant disease-related changes in several subcortical structures. Geyer *et al.* [11•] mapped cytoarchitectonic subdivisions of somatosensory cortex from individual postmortem brains onto a probabilistic atlas. A larger-scale multi-institutional endeavor [34•] involves a probabilistic human brain atlas based on thousands of normal subjects, each accompanied by extensive ancillary data. Preliminary comparisons of subjects from disease groups (Alzheimer's, schizophrenia) have revealed significant structural abnormalities [35,36].

For the cerebral cortex, individual variability involves several factors. Besides the aforementioned individual differences in folding patterns, individual areas can vary two-fold or more in their absolute size and in their location relative to gyral/sulcal landmarks [11•,29]. Consequently, registration of cortical maps can benefit from explicit surface representations, as noted above, and from functional landmarks that can be consistently identified across individuals using fMRI or other methods. Probabilistic surface-based atlases (e.g. [25,27,29]) that make increasing use of these constraints are likely to proliferate.

As visualization and analysis methods for neuroimaging data continue to improve, insights will increasingly be gained from post-hoc analysis of data from individual studies or from meta-analyses across studies. Such efforts can benefit greatly from large-scale publicly accessible neuroimaging databases, such as that underway at the fMRI Data Center [37•,38]. There are, however, many challenges involved in such endeavors, including making data entry and retrieval easy and fast, ensuring confidentiality for human subjects data, and promoting the willingness of investigators to share hard-won primary data [3,39,40].

Atlases of other species

Brain atlases and spatially organized databases are just as important for studies of laboratory animals as they are for the human brain. The conceptual and methodological issues in both situations are similar in many respects, despite the large differences in spatial scale and in the predominant types of experimental data available. Atlases are becoming available for invertebrates such as *Drosophila melanogaster* [41] and a variety of vertebrates, but the focus here remains on mammalian species.

Non-human primates

Recent electronically accessible atlases of non-human primates include a macaque atlas based on histological sections [42,43] and an MRI-based baboon atlas [44]. A multiformat volumetric and surface-based macaque atlas [14,16], analogous to the human atlas in Figure 1, includes many different partitioning schemes for cerebral cortex and some connectivity data. Complementary approaches to the representation of connectivity data include CoCoMac, a textual database of connectivity data in the macaque [45•], and XANAT, a graphical database [46].

Comparisons between macaque and human are especially challenging for cerebral cortex, because of the dramatic differences in convolutions and in the relative location of major functional domains (e.g. visual cortex). Nonetheless, potential homologies can be examined systematically using surface-based registration, constrained by functional landmarks common to both species [14,16,29].

Rodents

The rat has been a major neurobiological model system for many decades; the mouse is becoming increasingly important owing to the wealth of genetic mutations, powerful transgenic mouse capabilities, and availability of its genome sequence. Recent atlases of adult rodents include CD-based atlases for the rat [47] and the mouse [48], plus a multiformat volume- and surface-based atlas for the mouse [14,16].

The mouse is increasingly popular as a model system for neural development. Enormous amounts of information are becoming available regarding spatial patterns of expression for large numbers of genes and proteins at different developmental ages [49•,50]. It is obviously desirable to register such data to atlases, such as those now available for several developmental stages in the mouse [51,52,53•]. Taking full advantage of such an opportunity will require improved methods for accurately and automatically registering data from histological sections of individual brains onto atlases [49•]. Moreover, registering atlases across different developmental ages entails another set of challenges, analogous to those discussed above for registering between species.

Conclusions

A decade's effort, inspired directly and indirectly by the Human Brain Project [54], has now generated a solid foundation for electronically accessible brain atlases and spatial databases. The examples reviewed here represent important steps towards the capabilities needed for easy and orderly navigation through vast collections of data derived from laboratories around the world. Much of this information will be incorporated into probabilistic representations of the structure, function, connectivity, molecular expression profiles, transmitter and receptor characteristics for any brain region of interest, and will be mapped across species, developmental ages, and disease states. It should also be viewable on atlases or after mapping back to individual brains, using a host of visualization tools at fingertip access.

Rapid progress towards these objectives will require increasing contributions from the arena of neuroinformatics, akin to the growing role of bioinformatics in other areas of biology. It will also require major sociological shifts in attitudes towards data sharing. Success in this endeavor will provide enormous benefits to the basic and clinical neuroscience communities and to a pipeline of students who will be fascinated and captivated by a new discovery era in neuroscience.

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