New brain mapping technologies

Brain Cartography

PIOTR MAJKA
Laboratory of Neuroinformatics
Nencki Institute of Experimental Biology
Polish Academy of Sciences, Warsaw
p.majka@nencki.gov.pl
Piotr Majka is a PhD student at the Laboratory of Neuroinformatics at the PAS Institute of Experimental Biology. He designs digital maps of the brain. He is also a member of the Program on Digital Brain Atlasing as part of the International Neuroinformatics Coordinating Facility.

Brain maps are an essential tool in neurobiology. Polish researchers are making valuable contributions in their development

Most people are familiar with Google Maps. Such websites demonstrate how data from various sources and collected by different users can be made available through a single, convenient interface. Google Maps incorporates satellite maps, topographic layouts, city plans, traffic information, and so on. When we select a certain landmark, we gain instant access to photos, videos, and any other online information associated with it. This demonstrates how we can collect and combine various types of data concerning a common location defined using geographical coordinates.

All this would have been impossible just a decade or so ago. Until recently, we were mainly using printed atlases, or folding maps when out hiking on trails. Information presented on printed maps can be just as detailed as data used by Google Maps, although it is more difficult to process and share. When a person annotates their own map, the new information will only be available on that map and cannot be easily transferred to another.

But this article is about brain mapping, so why did I start by talking about Earth sciences? Neurobiology also practices its own style of cartography. Here, positioning is also key, describing the precise location of specific parts with a defined structure or function within the brain.

Unfortunately, at this point the analogy between geography and neurology breaks down. There is just one planet Earth for us to map, but a brain atlas for a given strain of laboratory mice can be prepared using just a single brain or based on a sample of several animals, and both might be taken as being representative of the entire population. The brain tissue used to generate such maps is irretrievably lost, and cannot be used in other experiments. As such, data from individual research projects must be collected in a single place to create functional brain atlases.

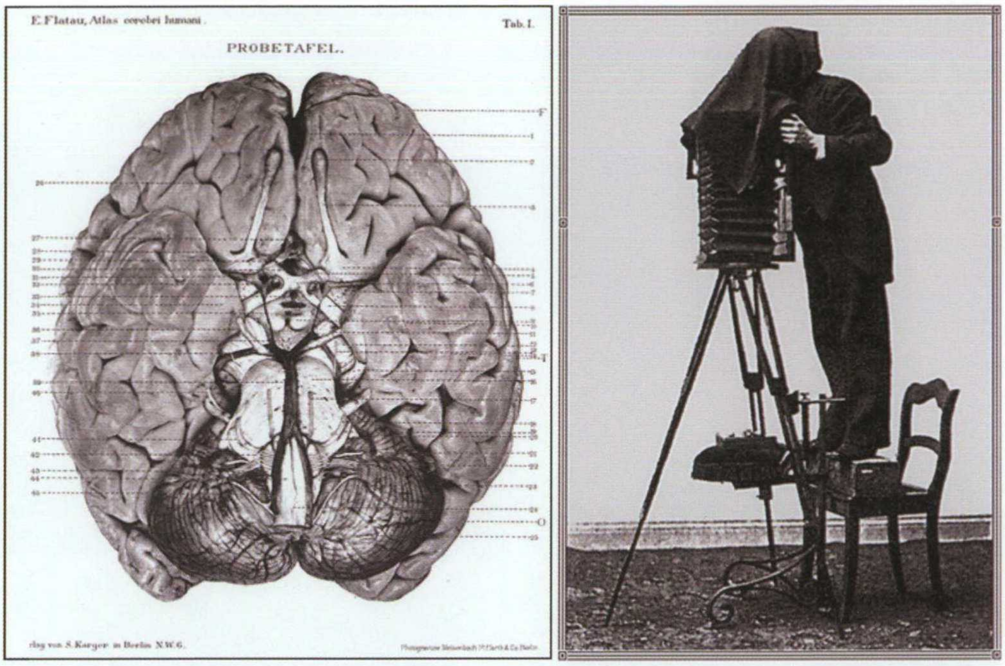
Classical brain maps

The origins of brain mapping date back to the late 19th century, coinciding with the early days of neurobiology, neuroanatomy, and behavioral sciences. One of the leaders in the field was the Polish pioneer of neuroanatomy, Edward Flatau. In 1894, he published a human brain atlas including a series of his own photographs of sections of brain tissue.

Brain maps have come a long way since then, evolving from the classical printed format similar to the familiar geographical atlases. Traditional publications include page after page of meticulous descriptions of brain section images, colored using a range of different methods. They also include exhaustive commentary written by the authors, as well as systems of coordinates making it possible to define positioning within the brain mathematically instead of using general verbal descriptions. Brain atlases are one of the key tools used in all laboratories researching brain function; in fact they are likely to be used as much as microscopes.

Techniques and calculations

In recent decades, experimental techniques, including imaging and neurophysi-



Atlas of the human brain, and the course of the nerve-fibres, Edward Flatau (1894) / Institute archives

Sample image from the Polish neurologist E. Flatau's human brain atlas (left), and Flatau demonstrating how brain images were taken (right)

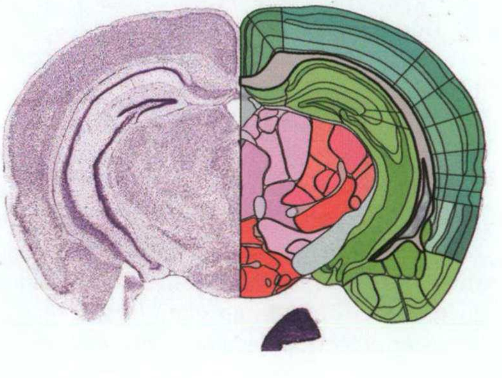
ology techniques, have made great strides in the quality and quantity of data generated. Certain techniques, such as in situ hybridization, are used as part of high-throughput regimes. Magnetic resonance (MRI and fMRI) and positron emission tomography (PET) imaging are also being used more widely, as are numerous histology and immunohistochemistry techniques. Rapid progress has been made in computational sciences, improving computer modeling of nervous systems. In certain calculations, the precise location and spatial orientation of individual stimulated cells within the brain is key.

The development of experimental and computational techniques, together with the diversity and vast amount of data, are posing new challenges for brain mapping. While having a book that one can sit and browse is extremely valuable for its sheer cognitive value, it does not meet the challenges posed by new, state-of-the-art technologies.

The traditional format of printed, two-dimensional atlases is simply not compatible with the fully 3D nature of data being generated. The human brain is a three-dimensional object, which must be taken into account while analyzing its structure and functionality. A two-dimensional atlas is significantly less accurate when trying to pinpoint locations within the brain; in turn, this makes it difficult to conduct experiments and generates numerous errors at the experimental and data analysis stages.

Into the third dimension

The next step in the development of brain maps of laboratory animals involved making the shift from two to three dimensions. What are the advantages of digital, 3D atlases over classical printed maps? Brain research commonly involves administering various injections into the brain or implanting electrodes into strictly defined locations. Navigating by means of a 2D map is difficult and requires a wealth of experience, whereas using a 3D atlas makes the process significantly easier. This translates into an ability to plan injection delivery sites



http://mouse.brain-map.org/

Example slice from a two-dimensional mouse brain atlas. Brain structures are highlighted and outlined on the right

A three-dimensional mouse brain atlas created with MRI images, showing highlighted brain structures

http://software.incf.org/software/waxholm-space/

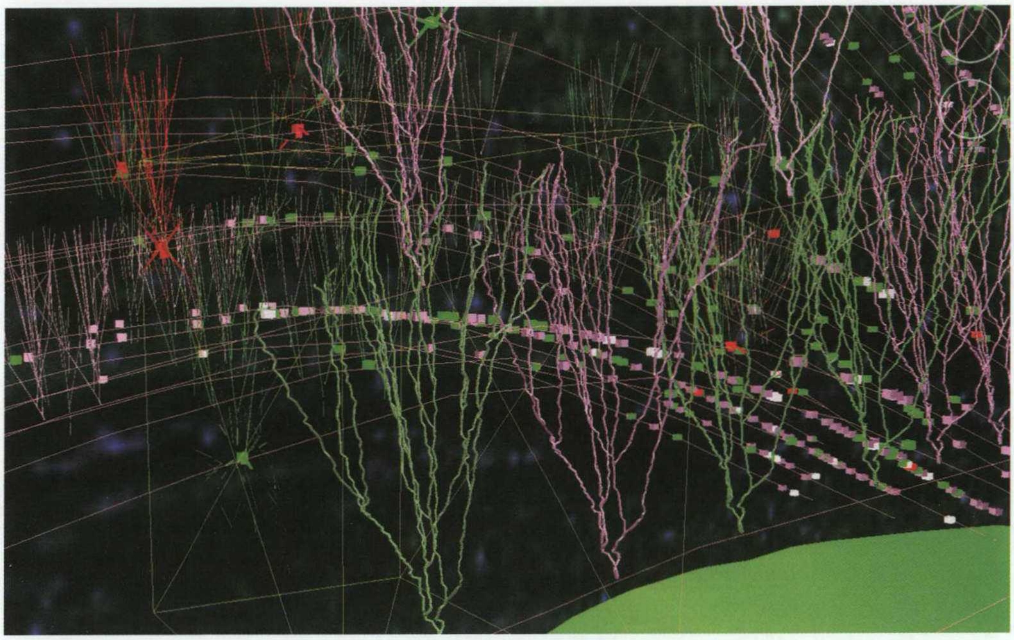
more precisely, which in turn means that fewer animals are used and the operations are performed with greater accuracy. This improves data quality and makes analyzing and interpreting results easier. A 3D map is an essential tool for both educational and research purposes. It also makes it easier to visualize the relative positions of different structures to discern ones that are adjacent, or the routes followed by bundles of nerves. Having a coherent, 3D representation of the brain also allows researchers perform virtual slicing on a computer screen, for example to design experimental cuts while preserving certain selected links between different brain structures.

Standardized brain

Three-dimensional mapping simplifies brain exploration, as well as creating a reference space (a "standard brain"). In this frame of reference, it is possible to map data collected from different individuals during separate experiments conducted by different research groups using a variety of experimental techniques, and so on. This includes histology, MRI, data on gene or protein expression, electrophysiology, and outlines of different brain structures. Additionally, digital atlases can include point data alongside continuous data such as imaging or density of gene expression. We can also include information describing the precise location of neurons in the brain. Atlases can contain references to detailed literature descriptions of each given neuron, allowing researchers to collect a complete morphology of a given cell from an associated database. As a result, by creating a reference space including our own data, we can post queries to the atlas regarding a given point within the brain or connected to a given structure within it. This simplifies the process of analyzing data from different individuals or experiments.

Global atlas infrastructure

Let us take things a step further. By creating a reference space including a defined system of coordinates and data, we are able to compare our own experimental data against results obtained by other laboratories conducting similar experiments and posting results in the same reference space (the same "standard brain"). Current efforts in the field of digital brain mapping focus on developing an infrastructure supporting collaboration



http://wholebraincatalog.org/

An example of the integration of data at different scales: detailed reconstruction of neuron morphology located in the dentate gyrus of a mouse brain

between laboratories and facilitating data exchange. The International Neuroinformatics Coordinating Facility (ICNF), an organization supporting and co-financing initiatives involved with the creation of an atlas infrastructure, also plays an important role. Poland is one of member states of the INCF.

The overall aim of this infrastructure is to make it possible to post queries regarding different types of data, such as "In which region (structure) within the brain does protein X occur in mice with induced autism versus control animals?" or "What are the directions and 'strengths' of the connections between structure Y and other structures for a given method used to mark such connections?" The openness and availability of such data reduces the need to repeat similar experiments, the number of animals used, and the amount of funding required. Such a database may even make it possible to verify certain hypotheses without the need to conduct further experiments.

The development of such a common atlas and a "standard brain," including data from numerous individuals and experiments conducted in different laboratories, brings us closer to fulfilling the dream of having everything we understand about the brains of a given species or strain focused in a single place and made available via a standardized mechanism. As such, we are drawing nearer to a point when researchers will be able to review, visualize, analyze, and use existing information and add their own data to the reference space using neuroinformatics infrastructure.

Classical atlases on their way out?

So what's to become of traditional printed atlases? Should they fade into obscurity? After all, they are the result of many years or decades of work, and their completeness is likely to continue exceeding 3D atlases for some time yet. In order to make traditional sources of neuroanatomical data available within the global neuroinformatics infrastructure, the Laboratory of Neuroinformatics of the PAS Nencki Institute has designed tools for converting classical 2D atlases into a 3D format. This provides them with most of the functionality of 3D atlases, making them a significant supplement and turning them into one element in the more general category of digital atlases. This research is being done as part of the POIG.02.03.00-00-003/09 "Biocentrum Ochota" project. ■

Further reading:

Majka P., Kublik E., Furga G., Wójcik D.K.(2012). Common Atlas Format and 3D Brain Atlas Reconstructor: Infrastructure for Constructing 3D Brain Atlases. *Neuroinformatics*, 10(2), 181-197.

3d Brain Atlas Reconstructor (http://www.3dbar.org),

The International Neuroinformatics Coordinating Facility (http://incf.org).