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Review

Data integration through brain atlasing: Human Brain Project tools and strategies

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ABSTRACT

The Human Brain Project (HBP), an EU Flagship Initiative, is currently building an infrastructure that will allow integration of large amounts of heterogeneous neuroscience data. The ultimate goal of the project is to develop a unified multi-level understanding of the brain and its diseases, and beyond this to emulate the computational capabilities of the brain. Reference atlases of the brain are one of the key components in this infrastructure. Based on a new generation of three-dimensional (3D) reference atlases, new solutions for analyzing and integrating brain data are being developed. HBP will build services for spatial query and analysis of brain data comparable to current online services for geospatial data. The services will provide interactive access to a wide range of data types that have information about anatomical location tied to them. The 3D volumetric nature of the brain, however, introduces a new level of complexity that requires a range of tools for making use of and interacting with the atlases. With such new tools, neuroscience research groups will be able to connect their data to atlas space, share their data through online data systems, and search and find other relevant data through the same systems. This new approach partly replaces earlier attempts to organize research data based only on a set of semantic terminologies describing the brain and its subdivisions.

1. Introduction

Knowledge about brain functions is needed not only to help alleviate mental illness, neurological diseases, memory loss and aging, but also to learn more about the normal organization of the brain and the massive information arrays that are handled by natural neural networks. Converting data from the brain to knowledge about the healthy and diseased brain requires comprehensive data integration, since the brain can be fully characterized and understood only by combining a wide range of data acquired at different spatial and temporal scales and with manifold techniques. As in many other fields of science, however, the capacity to generate massive amounts of new data has by far surpassed the ability to integrate and make sense of the data collected. The challenge of combining and unifying disparate multimodal and multilevel data collected from the brain into meaningful and valuable information, has triggered developments in the field of neuroinformatics, which combines neuroscience with information technology and deals with the creation of data systems that are required to achieve advanced integration of data needed to understand the nervous system [1–3].

The Human Brain Project (HBP), a multinational European brain research initiative, was formed to advance neuroscience and medicine and to create brain-inspired information technology [4]. The project comprises multiple subprojects, including experimental neuroscience research and infrastructure platforms contributing tools and workflows for data analysis, modeling and simulation, robotics, and ethics frameworks. A key concept is the integration of heterogeneous data from human and rodent brain in a common data system, and the use of such data for analysis and computational modeling and simulation of brain function. The project's Neuroinformatics Platform, in close interaction with other parts of the project, covers the preparatory steps for data integration: making data discoverable, accessible, interpretable, and reusable, as captured in the recently introduced FAIR Guiding Principles (Findability, Accessibility, Interoperability, and Reusability; [5]). A prerequisite for data integration is that the nature and relationships of data parameters are well defined, and possible to

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compare. As a start, basic features of data to be used in data integration efforts must be consistently and reliably described. Metadata is the term used to describe and characterize features of data ("data about data"), and the use of controlled vocabularies and ontologies is key to making metadata consistent [6–9]. A special category of metadata related to the brain is spatial metadata, describing the anatomical location from which the data originates. Location is a critical descriptor for brain data, since the brain is organized into numerous structures with different subparts, cell groups, or layers, and with function closely coupled to location. Location thus provides a natural basis for organizing data across spatial scales, and reference atlases of the brain and neuroinformatics tools have emerged as relevant technologies in support of such efforts [10–12].

In this paper, we illustrate key principles of the HBP workflows used for registration of a range of data categories to reference atlases of the brain. Neuroscientists upload experimental data and associated metadata to the HBP data systems. A curation service delivered by the Neuroinformatics platform organizes the data and helps standardize the metadata. The curation process includes registration of experimental data to common frameworks represented by the reference atlases. We exemplify the workflows using rodent brain data and demonstrate how data from different experimental modalities, registered to reference atlases, can be combined and unified with other data categories. Finally, we discuss the application of these approaches for characterization and analysis of rodent models of neurological diseases.

2. Assigning location to data from the brain: reference atlases for spatial data integration

Assigning anatomical location to data acquired from the brain can be done at the level of structures of the brain, or through the use of coordinate systems. Reference atlases offer a standardized representation of anatomical location and are commonly used tools to assign location to data. They are thus highly relevant tools for spatial data integration.

Traditional atlases of the brain are books or articles containing series of two-dimensional (2D) diagrams of cross-sections through a brain, showing delineations and names of the structures present in each section (see, *e.g.* [13,14]). The structural delineations are typically derived from interpretations of features observed in histological sections. The limitations of such 2D reference atlases are primarily the missing information between each diagram (due to use of incomplete histological material) and the single plane of orientation of the diagrams. For future data integration efforts, a new generation of three-dimensional (3D) reference atlases is used ([15–19]; see also www.brain-map.org; www.nitrc.org; http://scalablebrainatlas.incf.org). These atlases are based on either 3D reconstruction of images taken from complete series of histological sections, or on tomographic imaging data acquired with, *e.g.*, magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI). The volumetric data in these reference atlases allows the image volumes to be re-sliced and viewed in arbitrary angles with minimal loss of image quality due to the isotropic acquisition of the images. For rodent experimental data, the Human Brain Project uses two volumetric atlases (Fig. 1): the Allen Mouse Brain Atlas [20] and the Waxholm Space rat brain atlas [16,21].

The first version of the Allen Mouse Brain Atlas was reconstructed from multiple series of Nissl stained histological sections [22]. Building on the high level of architectonical details available in the histological material, more than a thousand anatomical regions were delineated. The latest version of the atlas (v3) contains a high resolution population average image volume from serial two-photon tomography, integrating shape and signal intensity over 1675 specimens (mouse.brain-map.org). The Allen Mouse Brain Atlas employs a Cartesian coordinate system, referred

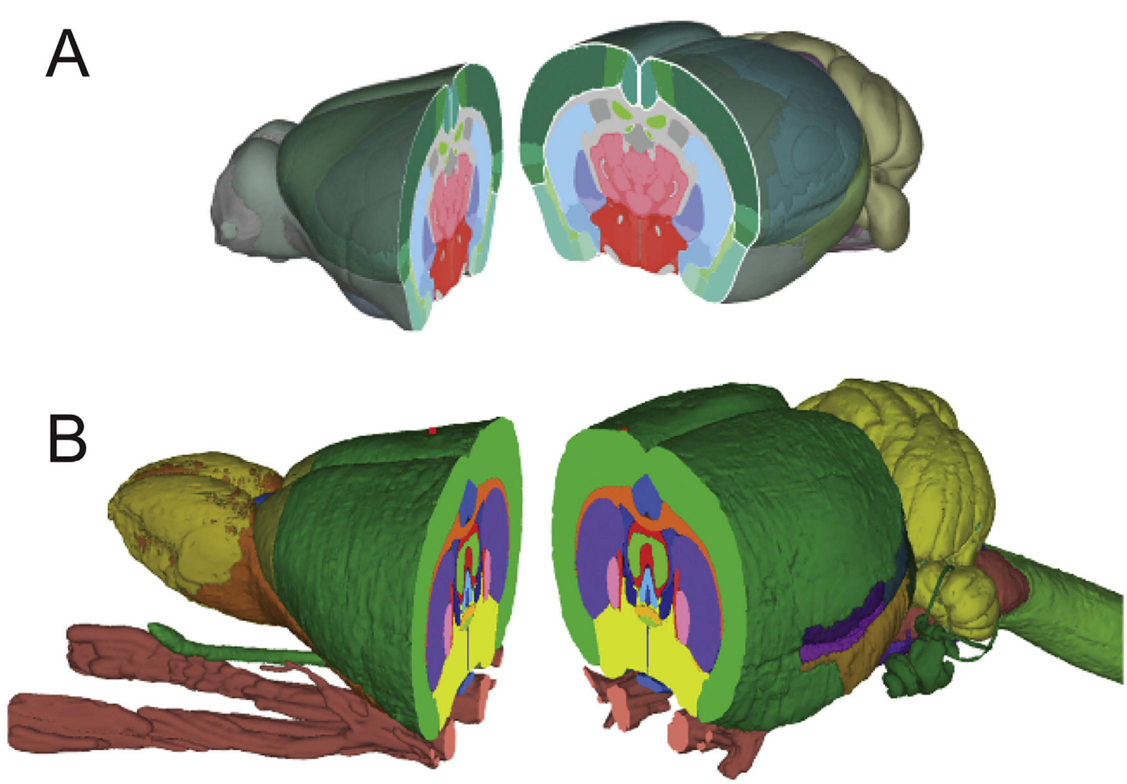

Fig. 1. Three-dimensional rodent brain reference atlases used by the HBP.
(A) The Allen Mouse Brain Atlas (v.3; 13; see also [22] and (B) the Waxholm Space atlas of the Sprague Dawley rat brain [16,21]. The atlases have been sliced coronally, giving a view of deep brain structures. The volumetric reference atlas delineations have isotropic voxels and can be arbitrarily sliced in any angle of orientation.

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