

EBRAINS Brain Atlas Services (SC2) - status at M42 (D4.15 - SGA3)

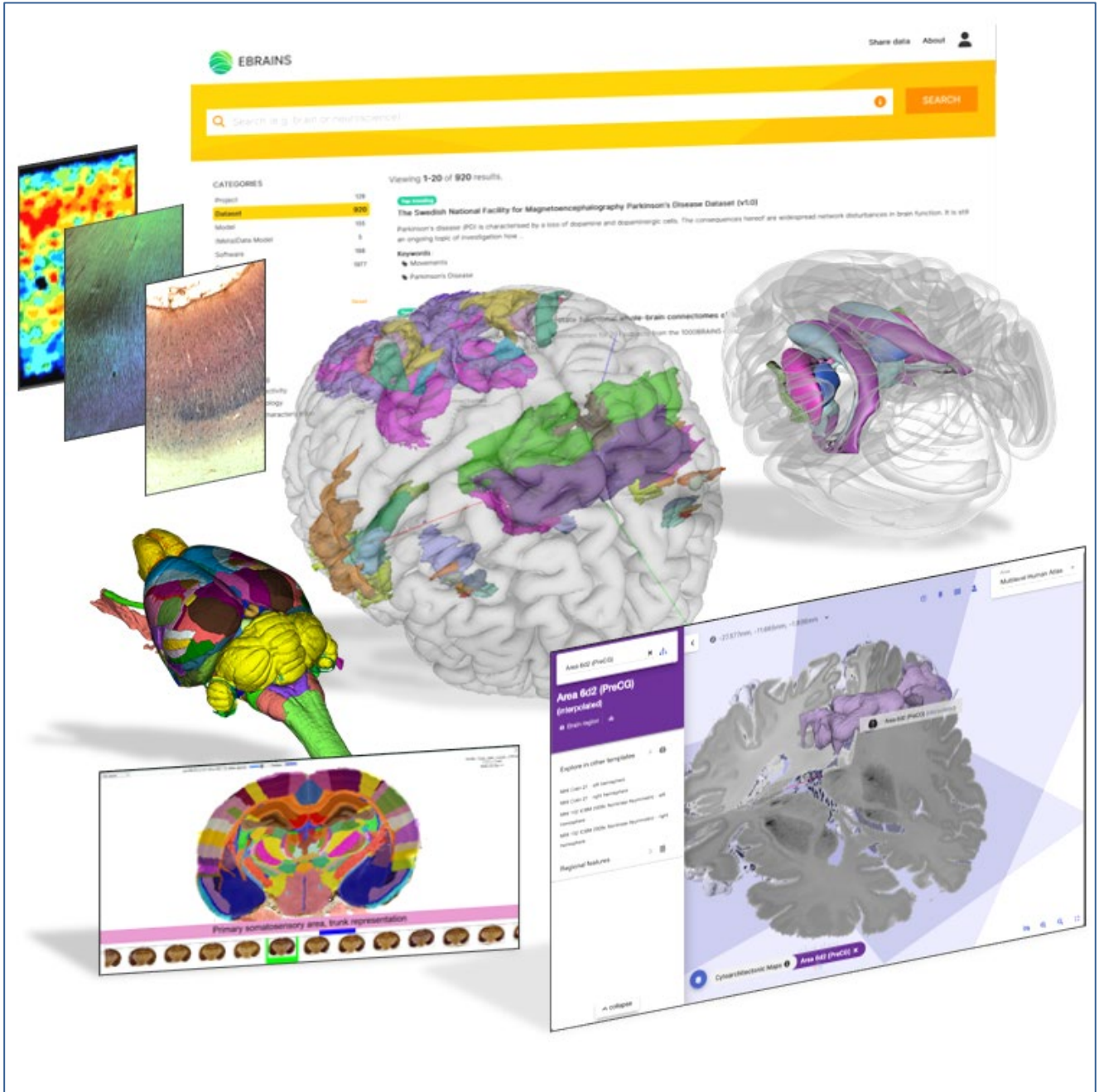


Figure 1: EBRAINS atlas services allow exploration and analysis of the brain in its different facets

Project Number:	945539	Project Title:	HBP SGA3
Document Title:	EBRAINS Brain Atlas Services (SC2) - status at M42		
Document Filename:	D4.15 (D16) SGA3 M42 SUBMITTED 230925.docx		
Deliverable Number:	SGA3 D4.15 (D16)		
Deliverable Type:	Other		
Dissemination Level:	PU = Public		
Planned Delivery Date:	SGA3 M42 / 30 SEP 2023		
Actual Delivery Date:	SGA3 M42 / 25 SEP 2023		
Author(s):	Timo DICKSCHEID, JUELICH (P20)		
Compiled by:	Susanne WENZEL, JUELICH (P20)		
Contributor(s):	<p>Trygve LEERGAARD, UIO (P81), contributed Section 2.2</p> <p>Maja Puchades, UIO (P81), contributed Sections 4.1 and 5.2</p> <p>Wim VANDUFFEL, KUL (P111), contributed to Section 2.3</p> <p>Nicola PALOMERO-GALLAGHER, JUELICH (P20), contributed to Section 2.3</p> <p>Anna KRESHUK, EMBL (P123), contributed Section 5.1</p> <p>Nicolas BERNAOLA, UPM (P68), contributed Section 5.3</p> <p>Michael HANKE, JUELICH (P20), contributed Section 3.2.4</p> <p>Julia THOENNISSSEN JUELICH (P20), contributed to Sections 4.2 and 4.3</p> <p>Xiaoyun GUI, JUELICH (P20), contributed to Sections 3.1 and 3.2</p> <p>Jean-François MANGIN, CEA (P11), contributed to Section 2.1 and 3.2.3</p> <p>Bertrand THIRION, INRIA (P33), contributed to Section 5.4</p> <p>Yasmin MZAYEK, INRIA (P33), contributed to Section 5.4</p>		
WP QC Review:	Martha Elisabeth BRIGG, UIO (P81)		
WP Leader / Deputy Leader Sign Off:	Jan BJAALIE, UIO (P81)		
T7.4 QC Review:	Formatted by Annemieke MICHELS, EBRAINS (P1)		
Description in GA:	Updated, high-coverage brain atlases including several ultrahigh-resolution 3D regions of interest from different modalities computed on FENIX HPC facilities, along with a software development kit for atlas services, and an inventory of well-integrated web-based registration and analysis tools.		
Abstract:	EBRAINS offers detailed atlases for the human, macaque monkey, rat, and mouse brain. These atlases provide comprehensive maps of brain regions defined based on structure, function, and neural connections. As spatial reference systems for neuroscience, they are essential for understanding the complexity of the healthy brain, studying brain disorders, and seeking to develop new treatments. EBRAINS atlases give access to a broad range of multimodal data features describing molecular, cellular, and functional characteristics of brain regions and locations, including connectivity, and covering regional and population variance. All atlases		



	can be explored visually in the 3D interactive online viewer and used in scripts and software environments through a REST API and a Python client. Atlas contents are stored as datasets with rich metadata in the EBRAINS Knowledge Graph and complemented with interfaces to selected external repositories. To facilitate the continuous integration of data into the atlases, online tools for the spatial registration of common data types are available and accessible via the EBRAINS web portal. A range of analysis tools allows data to be processed and investigated in the anatomical context provided by the reference atlases. The present report summarises the status of EBRAINS Brain Atlas Services as of September 2023.
Keywords:	Reference atlases, WHS, Julich-Brain, macaque brain, atlas ontology, spatial registration, coordinate transformation, siibra toolsuite, python client, python library, DOPAMAP, BRAINSPACE, multimodal data, interactive analysis, QUINT, imaging data, community, Nilearn, image segmentation
Target Users/Readers:	computational neuroscience community, computer scientists, consortium members, funders, general public, neuroimaging community, neuroinformaticians, neuroscientific community, neuroscientists, platform users, researchers, scientific community, students.

Table of Contents

1. Introduction	5
2. Reference brain atlases	6
2.1 Human brain atlas	6
2.2 Waxholm Space Rat Brain Atlas.....	8
2.3 Macaque brain atlas	9
2.4 Atlas Ontology Model.....	10
3. Software interfaces to atlases	11
3.1 Visually guided 3D exploration (siibra-explorer)	11
3.2 Integration into reproducible workflows	14
3.2.1 Python interface (siibra-python).....	14
3.2.2 HTTP interface (siibra-api)	16
3.2.3 Coordinate transformation service for human reference spaces.....	17
3.2.4 Distributed dataset management.....	18
4. Data integration to reference atlases	18
4.1 Rodent brain sections	18
4.2 High-resolution volumes of interest	20
4.3 Anchoring MRI volumes (voluba-mriwarp).....	22
4.4 Anchoring neuron morphologies	23
5. Atlas-driven data analysis	24
5.1 Feature extraction from images (web-ilastik).....	24
5.2 Atlas-guided quantification of labelled features.....	25
5.2.1 Workflow for image annotation and extraction of point clouds.....	25
5.2.2 Cellular quantification and distribution with the QUINT workflow	26
5.3 Atlas guided analysis of cellular networks	28
5.4 Atlas-guided analysis of fMRI data (nilearn/nibabel).....	29
Appendix	31
References	31

Table of Tables

Table 1: Separation of semantic atlas concepts from their spatial representations in siibra	14
---	----

Table of Figures

Figure 1: EBRAINS atlas services allow exploration and analysis of the brain in its different facets	1
Figure 2: EBRAINS reference atlases of the human, macaque, rat, and mouse brain	5
Figure 3: Reduced GapMaps in Version 3 of the Julich-Brain cytoarchitectonic maps	7
Figure 4: siibra-explorer displaying a 1 micron resolution coronal section in BigBrain space	8
Figure 5: Waxholm Space Rat Brain atlas version 4	8
Figure 6: Anatomical template of the macaque monkey 'MEBRAINS'	9
Figure 7: Folded and inflated surface representations of the MEBRAINS template	10
Figure 8: Basic elements of a reference atlas (a) defined in the Atlas Ontology Model (b)	10
Figure 9: Selected features of the interactive viewer siibra-explorer	12
Figure 10: Interactive exploration of a border region in siibra-explorer	13
Figure 11: <i>siibra-explorer</i> running on mobile devices	13
Figure 12: A typical workflow in siibra-python	15
Figure 13: The spatial transformation service employed by the <i>siibra</i> toolsuite	17
Figure 14: User interface of WebAlign for 2D rodent section image registration.	19
Figure 15: Possibility to work on curated Knowledge graph datasets	20
Figure 16: Graphical user interface of voluba	21
Figure 17: Atlas-based analysis of a location in an MRI scan	22
Figure 18: Web-based slice aligner interface.	24
Figure 19: Cortical projections of a thalamocortical neuron	24
Figure 20: Screenshot of web-ilastik front end on top of Neuroglancer	25
Figure 21: Annotation of amyloid plaques using LocaliZoom and visualisation in MeshView	26
Figure 22: Updated QUINT workflow	27
Figure 23: Workbench for online QUINT workflow	27
Figure 24: User interface of Bayessuites	28
Figure 25: Parcellation map fetched with siibra and plotted with nilearn's plotting module	29
Figure 26: Comparing structural with functional connectivity using siibra and nilearn	30

1. Introduction

Brain atlases provide spatial reference systems for neuroscience, enabling the navigation, characterisation and analysis of information based on anatomical location. They define the shape, location, and variability of brain regions in common coordinate spaces, and allow the interpretation, integration and comparison of observations and measurements collected from various sources and brains. As spatial reference systems for neuroscience, they are essential for understanding the complexity of the healthy brain, studying brain disorders, and seeking to develop new treatments. EBRAINS offers detailed atlases for the human, macaque monkey, rat, and mouse brain. These atlases provide maps of brain regions defined based on structure, function, and neural connections. They give access to a broad range of multimodal data features describing molecular, cellular, and functional characteristics of brain regions and locations, including connectivity and covering regional and population variance.

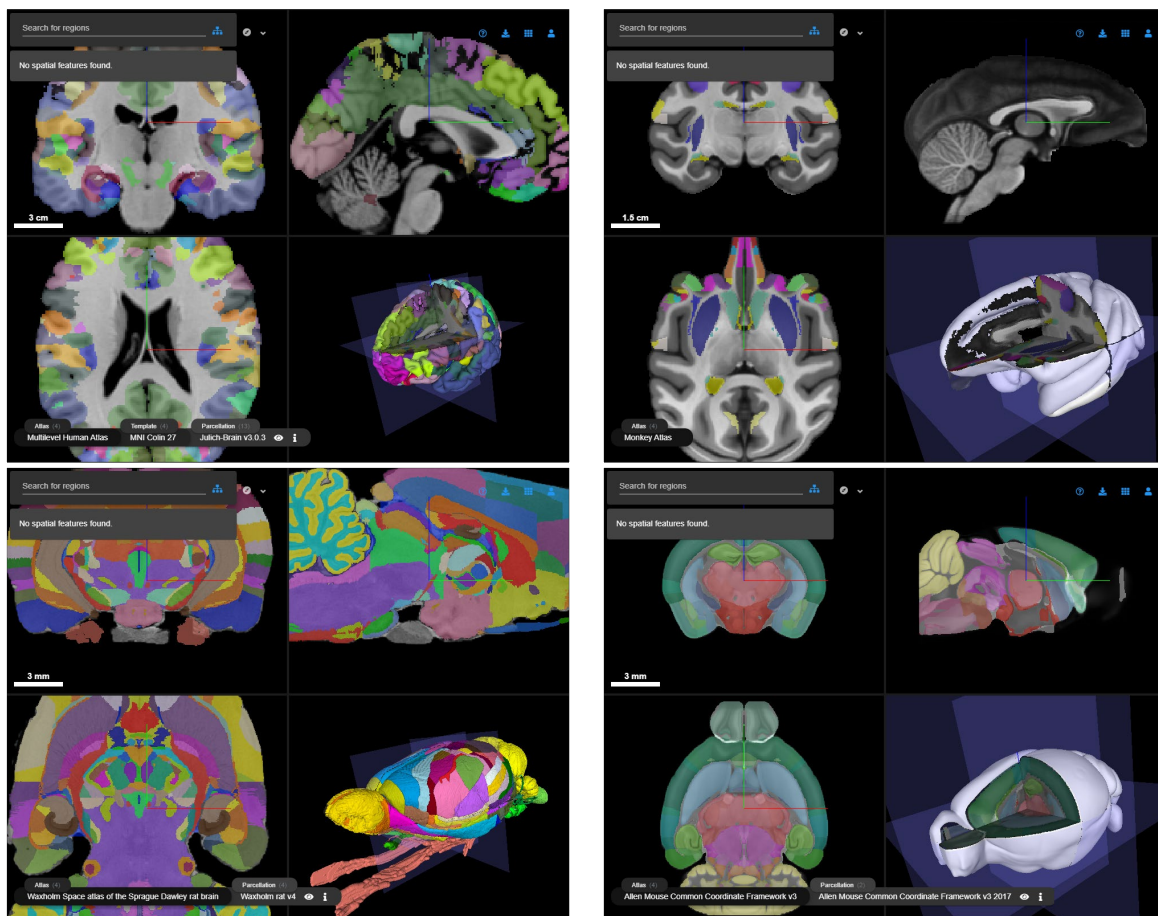


Figure 2: EBRAINS reference atlases of the human, macaque, rat, and mouse brain

All reference atlases can be explored using the interactive atlas viewer [siibra-explorer](https://atlasses.ebrains.eu/viewer)¹ and are documented at ebains.eu².

The primary point of access to the reference atlases is the [EBRAINS portal](https://ebains.eu)³. All atlases can be explored visually in the 3D interactive atlas viewer (Figure 2; Section 3.1), and used in scripts and software environments through a REST API (Section 3.2.2) and a Python client (Section 3.2.1). Atlas contents are stored as datasets with rich metadata in the EBRAINS Knowledge Graph and complemented with interfaces to selected external repositories. To facilitate continuous integration of data to the atlases, online tools for spatial registration of common data types are available via

¹ <https://atlasses.ebrains.eu/viewer>

² <https://ebains.eu/brain-atlasses/reference-atlasses>

³ <https://ebains.eu/services/atlasses>

the [EBRAINS web portal](#)⁴. A range of analysis tools allows data to be processed and investigated in the anatomical context provided by the reference atlases (Section 5).

EBRAINS atlas services offer key functionalities for enabling research workflows in different fields of neuroscience. Some exemplary use cases are the following:

- **experimental neuroscience:** Co-displaying experimental data in a 3D high resolution reference brain space; determining anatomical location and finding spatially relevant features to interpret data and confirm or support user studies.
- **computational neuroscience:** Constructing models of brain simulations with plausible anatomical constraints and comprehensive regional characterisations of brain organisation, including cellular, molecular and connectivity features.
- **neuroanatomy:** Exploring brain architecture in 3D at different spatial resolutions, without installing additional software, and studying the shape and spatial relationships of brain regions, functional modules, and their connections.
- **neuroimaging:** Performing anatomical assignment of signal patterns, e.g. fMRI activations. Combining whole brain imaging data with multimodal features at the cellular scale from the meso- and microscopic scales.
- **brain-inspired AI:** For biologically plausible AI models, extracting quantitative aspects of the structure of the biological networks in the brain, resolved with a spatial specificity of individual cortical layers.
- **neurosurgery and medicine:** Understanding the multilevel brain architecture in the vicinity of surgical target regions, identifying paths to regions of interest, and understanding the cellular composition of regions of interest, e.g. in Parkinson's and epilepsy.

EBRAINS atlas services can be grouped into three main categories:

- 1) Services providing interactive and programmatic access to reference atlases (<https://ebrains.eu/brain-atlases/reference-atlases>; <https://ebrains.eu/brain-atlases/apis>)
- 2) Services for anatomical anchoring of datasets and models (<https://ebrains.eu/brain-atlases/data-integration>)
- 3) Services for atlas-driven data analysis (<https://ebrains.eu/brain-atlases/analysis>)

These services are built on top of the EBRAINS base infrastructure, in particular by managing its main contents in the [EBRAINS Knowledge Graph](#)⁵ and the storage infrastructure provided by [FENIX](#)⁶ by hosting their online services on EBRAINS virtual machines, and by working closely with EBRAINS curation services.

2. Reference brain atlases

2.1 Human brain atlas

The human brain atlas includes the most recent version 3.1 of the Julich-Brain probabilistic cytoarchitectonic maps ([Amunts et al. 2020](#)), which is for the first time released in two different granularities. The default granularity defines 199 structures per hemisphere, while the higher granularity includes finer structures totalling to 214 brain regions per hemisphere. All brain region maps are distributed as individual probabilistic maps which encode the variation of each area observed in ten different post-mortem brain. The default granularity is additionally distributed in the form of a simplified maximum probability map, a single volume which labels each voxel by the

⁴ <https://ebrains.eu/brain-atlases/data-integration>

⁵ <https://kg.ebrains.eu>

⁶ <https://fenix-ri.eu/>

most probable brain region. To serve a wide range of neuroscience workflows, all probabilistic and maximum probability maps are distributed in the MNI Colin 27 single subject space, the ICBM152 2009c nonlinear asymmetric space, and the Freesurfer surface space.

The probabilistic cytoarchitectonic maps are linked with a growing set of ultrahigh-resolution 3D maps delineated natively in the BigBrain reference template. Here we follow a continuous release process, which starts with early versions of each map based on a 3D interpolation of a sparse set of reference delineations in some sections. These interpolated versions are then upgraded to a detailed map where each tissue section is segmented in detail by a deep learning workflow (Schiffer et al. 2021) and validated by an expert. The set of available maps includes different visual areas (e.g. hOc1, hOc2, hOc3v, hOc5), auditory areas (e.g. STS1/2, Heschl (TE1.0/1.1/1.2)), somatosensory areas (e.g. preSMA, SMA) but also subcortical areas (e.g. amygdala, CGM, CGL)(Kiwitz et al. 2022; Brandstetter et al. 2021; Behuet et al. 2021). Including their subdivisions across both hemispheres, these amount to ~120 maps which can be explored in 3D at full resolution using the 3D atlas viewer *siibra-explorer*⁷.

Since all cytoarchitectonic maps are derived using the same delineation criteria and nomenclature, they provide a well-defined anatomical link from the millimetre (probability maps) to the micrometre (detailed BigBrain maps) scale. The cellular resolution level has been further expanded by a selection of ~150 microscopic scans at 1 micrometre resolution, picked in a careful review process to cover the whole brain in approximately equal intervals while providing good tissue and image quality (Figure 4). These scans have been non-linearly registered to the 20 micrometre template, released on EBRAINS (Schiffer et al. 2022), and directly accessible via the *siibra-toolsuite* using the new spatial search functionality (Figure 9D).

All maps and data are released as curated datasets in the knowledge graph, making up several 100 datasets (search.kg.ebrains.eu⁸), and are listed on the EBRAINS portal with documentation and support resources.

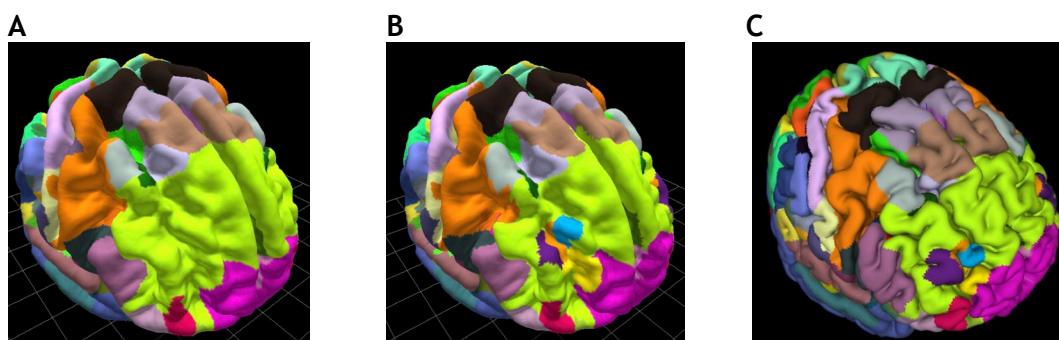


Figure 3: Reduced GapMaps in Version 3 of the Julich-Brain cytoarchitectonic maps

Surface view in fsaverage space of maximum probability map at version 2.9 (A) and [version 3.0.2](#)⁹ (B). Amongst other regions, the Frontal GapMap has been reduced by the introduction of new areas. C: Corresponding view of version 3.0.2 on the MNI Colin 27 surface.

The Julich-Brain cytoarchitectonic maps are already employed for a variety of neuroscience studies. Their use for simulation revealed a specific challenge related to remaining GapMaps, which represent areas where mapping is still in progress. Despite being incrementally reduced with each release (cf. Figure 3), the size of some GapMaps is still significant as these last regions are the most difficult to decipher. The difficulty regarding simulations of the brain dynamics is that large gap maps summarise different areas that shall ultimately be represented by several nodes. To overcome this difficulty, we have adapted an algorithmic technology developed in earlier project phases to parcel out grey matter based on connectivity profiles estimated from diffusion MRI, and applied it to the connectivity maps computed from the 1,000 subjects of the Human Connectome Project (Langlet et al. 2023). Each GapMap has been subdivided into homogeneous regions in terms of these profiles, a credible proxy for architectural subdivisions. This approach, complementing the already available

⁷ <https://atlases.ebrains.eu/viewer/go/bigbrain>

⁸ <https://search.kg.ebrains.eu/instances/f5a9e274-b291-4f79-9c19-f3467ee753d5>

⁹ <https://atlases.ebrains.eu/viewer/go/julich302fsavg>

Julich-Brain maps, allows modellers a complete parcellation of the cortex homogeneous from the point of view of the size of the nodes.

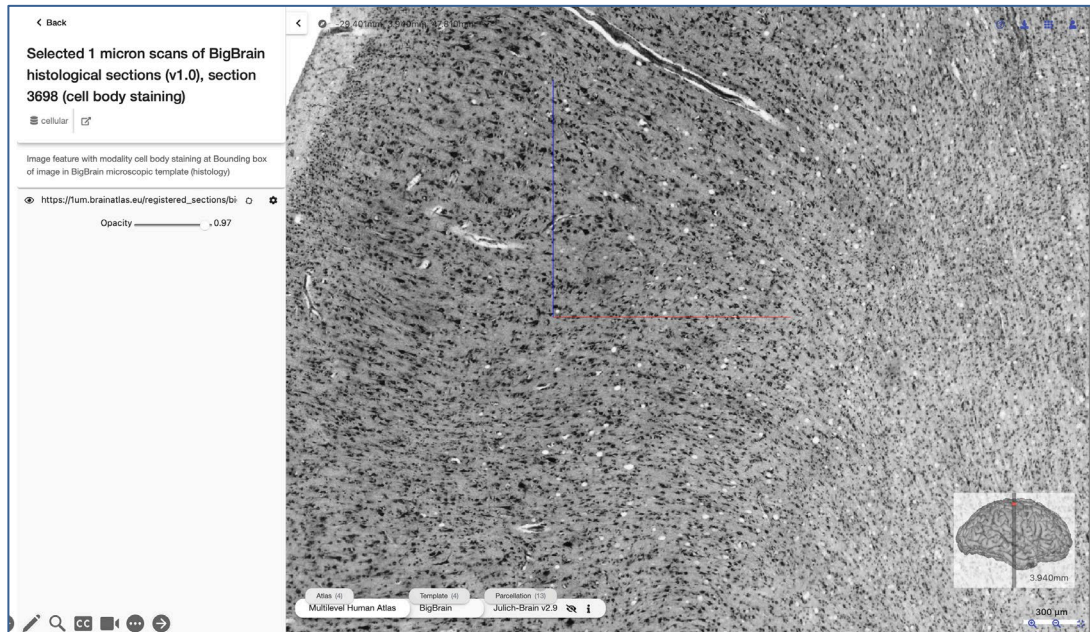


Figure 4: siibra-explorer displaying a 1 micron resolution coronal section in BigBrain space

High-resolution sections and volumes of interest add more detail and specificity to the atlas. A set of several hundred 1 micron resolution sections in BigBrain space can be explored using the new spatial search capability of the atlas viewer *siibra-explorer*, and also accessed using the *siibra-python* library.

2.2 Waxholm Space Rat Brain Atlas

The Waxholm Space (WHS) rat brain atlas is defined in a high-resolution volumetric magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) template of an adult Sprague Dawley rat brain (Papp et al. 2014; Kjonigsen et al. 2015; Osen et al. 2019). The most recent version 4.01 of the atlas (released April 2023) features 224 delineated brain regions, including 112 new structures and 58 revised delineations. The main new features of the atlas are detailed expert defined subdivisions of the cerebral cortex (35 new, 4 revised structures), basal ganglia (11 new, 2 revised structures), and thalamus (60 new, 10 revised structures) (Figure 5). The atlas has been released with a hierarchical organisation of structures under a CC-BY license (Kleven, Bjerke, et al., now in press in Nature Methods) The atlas has been downloaded >30.000 times and is already utilized commercially.

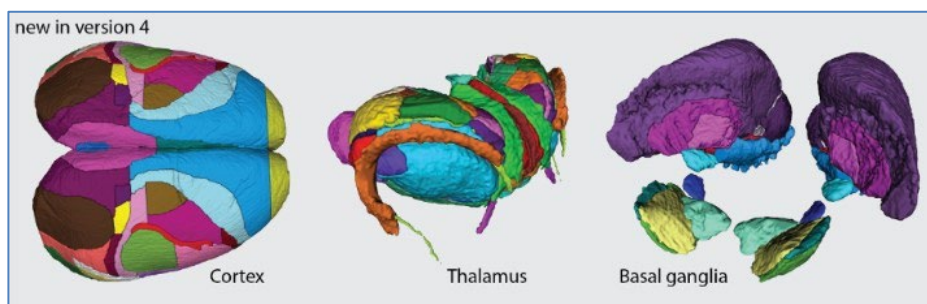


Figure 5: Waxholm Space Rat Brain atlas version 4

The fourth version of the WHS rat brain atlas includes 112 new subdivisions for the cerebral cortex, thalamus and basal ganglia, together with 56 revised adjacent structures (atlases.ebrains.eu¹⁰).

The atlas has been integrated with the siibra toolsuite and can thus be explored in the interactive viewer (siibra-explorer; Section 3.1). It is also integrated with tools for registering, visualising, and analysing data, all shared via E BRAINS with documentation and support resources. A supplementary

¹⁰ <https://atlases.ebrains.eu/viewer/saneurl/whs4>

derived dataset released via EBRAINS allows interactive inspection of the WHS reference MRI image data together with corresponding atlas delineations, as a guide for stereotaxic procedures with possibility to read out WHS and stereotaxic coordinates for user-defined points of interest.

2.3 Macaque brain atlas

The “MEBRAINS Multilevel Macaque Brain Atlas” has been integrated into the [atlas services](#)¹¹. As a first important result towards the implementation of this atlas, a new reference template - MEBRAINS - was developed and released for public use ([Balan, Zhu, Li, Bakker, et al. 2023](#); [Balan, Zhu, Li, Niu, et al. 2023](#)). The template represents a population average of structural (T₁, T₂) from 10 macaque brains and CT scans of 9 subjects (Figure 6) and was constructed from co-registered structural MRI images by combined voxel intensity information using the multi-brain toolbox for SPM12¹².

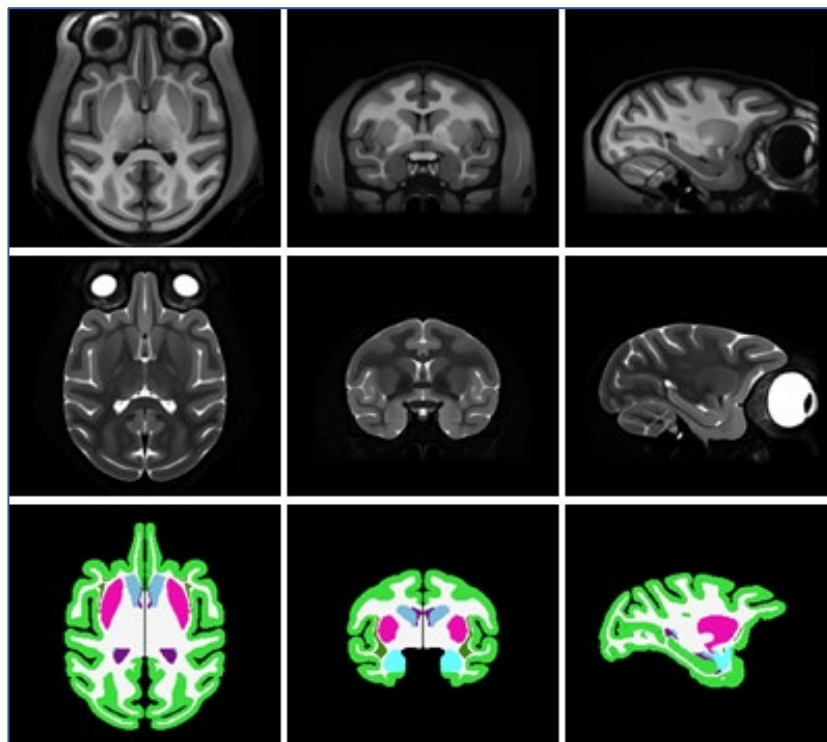


Figure 6: Anatomical template of the macaque monkey ‘MEBRAINS’

Anatomical template of the macaque monkey ‘MEBRAINS’ whole brain T1 (first row), T2 (second row) and segmentation (pial surface, white/grey matter interface, ventricles, amygdala, caudate, claustrum, putamen) images.

The atlas has been populated with the “Julich Brain Macaque Maps” a parcellation scheme encompassing a total of 88 areas located throughout the macaque monkey occipital l ([Rapan et al. 2022](#)), parietal ([Impieri et al. 2019](#); [Niu et al. 2020](#); [Niu et al, 2021](#)), (pre)motor ([Rapan et al. 2021](#)) and prefrontal ([Rapan et al. 2022](#)) cortex (Figure 7). The borders between these areas were identified using a quantifiable cyto- and multireceptor architectonic analysis. The maps and the densities of 14 different receptors measured in each area are made available to the community via the “MEBRAINS Multilevel Macaque Brain Atlas” and the EBRAINS Knowledge Graph¹³. Furthermore, the atlas facilitated a comparative analysis of receptor densities in the macaque brain with those in the human and rat brains ([Froudish-Walsh et al. 2023](#); [Haghir et al. 2023](#)).

Traditional neuroimage analysis pipelines involve computationally intensive, time-consuming optimisation steps, often requiring additional manual interventions. We adapted FastSurfer for

¹¹ <https://atlases.ebrains.eu/viewer/monkey>

¹² <https://github.com/WTCN-computational-anatomy-group/diffeo-segment>

¹³ <https://search.kg.ebrains.eu/instances/e39a0407-a98a-480e-9c63-4a2225ddfbe4>

human subjects¹⁴ to the macaque (Balan, Zhu, Li, Niu, et al. 2023). FastSurfer is a fast and accurate deep learning-based neuroimaging pipeline for the automated processing of structural human brain MRI scans, replicating freesurfer’s anatomical segmentation including surface reconstruction and cortical parcellation (Balan, Zhu, Li, Niu, et al. 2023)(Figure 7).

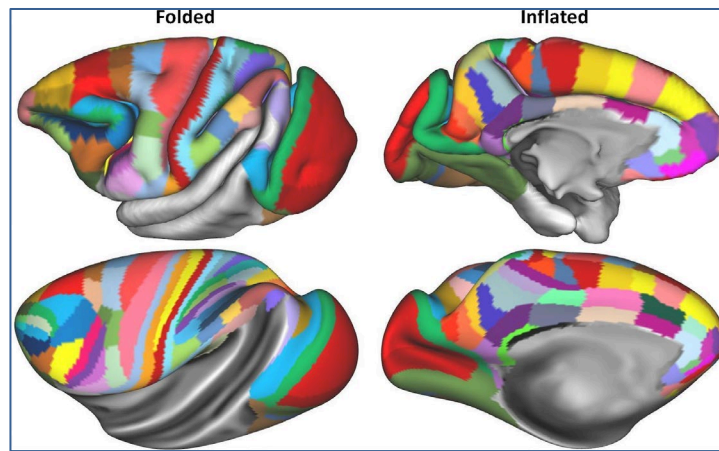


Figure 7: Folded and inflated surface representations of the MEBRAINS template

Folded and inflated surface representations of the MEBRAINS template, onto which areas of “Julich Brain Macaque Maps” (Rapan et al. 2021, 2022; Impieri et al. 2019; Niu et al. 2020, 2021) have been warped.

2.4 Atlas Ontology Model

An ontology model for the reference atlases ‘AtOM’ has been developed in a collaboration between researchers at University of Oslo, KnowledgeSpace¹⁵, and INCF (International Neuroinformatics Coordinating Facility). This Atlas Ontology Model provides a theoretical basis for specifying four fundamental elements: 1) a reference data set, 2) a coordinate system, 3) a set of annotations and 4) a specific terminology. Each of the elements and their parts have detailed metadata, providing the parameters needed to identify, understand, and utilise the different elements and thus the unique configurations of atlases (Figure 8). The AtOM elements allow specification of the different elements that constitute unique atlas versions. The specific relations among the atlas elements provide a framework for translating information across data that have been spatially registered to an atlas or specified semantically using anatomical terms. A detailed description of the model and its application to the mouse, rat, and human brain atlases used for integration of data in EBRAINS are provided in an original article by (Kleven, Gillespie, et al. 2023).

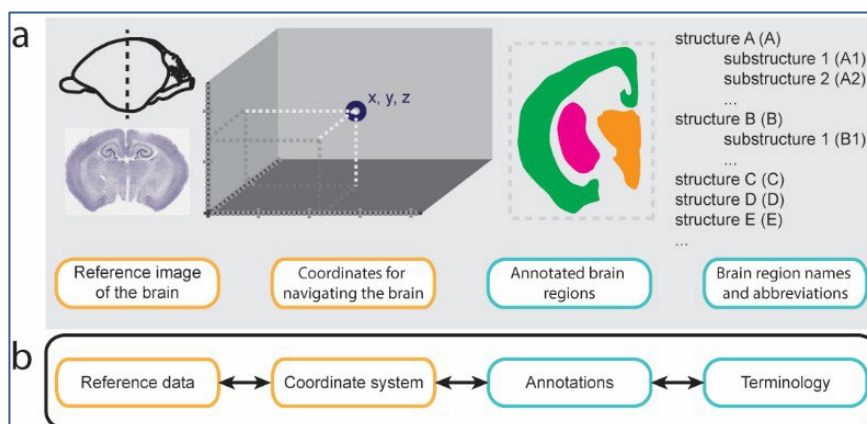


Figure 8: Basic elements of a reference atlas (a) defined in the Atlas Ontology Model (b)

¹⁴ <https://github.com/Deep-ML/FastSurfer.git>

¹⁵ <https://knowledge-space.org/>

The third version of the [openMINDS](#)¹⁶ model hosts the SANDS extension which includes the AtOM schema definitions and metadata implementations for selected brain atlases (Waxholm Space rat brain atlas, Allen Mouse Brain Atlas, Julich-Brain Cytoarchitectonic Atlas).

3. Software interfaces to atlases

To enable sustainable support and detailed documentation, atlas content is hosted in the form of curated and publicly shared datasets in the [EBRAINS Knowledge Graph](#)¹⁷, with the exception of data linked from external resources such as the Allen Brain atlas¹⁸ and rare cases of pre-released data. All parcellation maps, templates, and linked data can thus be found and downloaded in the search user interface of the Knowledge Graph together with comprehensive metadata.

Siibra is a software tool suite that implements a multiscale atlas ecosystem on top of these datasets, by offering 3D exploration of the reference maps and templates at full spatial resolution, region- and coordinate-based queries of multimodal features of brain organisation, and direct integration of parcellations maps and regional data features into scripts and computational workflows. It supports both discretely labelled and statistical (probabilistic) parcellation maps, which can be used to assign brain regions to spatial locations and image signals, to retrieve region-specific neuroscience datasets from multiple online repositories, and to sample information from high-resolution image data. The datasets anchored to brain regions address features of molecular, cellular and architecture, as well as connectivity, and are complemented with live queries to external repositories, as well as dynamic extraction from “big” image volumes such as the 20 micrometre BigBrain model. The tool suite includes a web-based 3D viewer (*siibra-explorer*; Section 3.1), a comprehensive Python library (*siibra python*; Section 3.2.1), and an HTTP API (*siibra-api*; Section 3.2.2). These support a broad range of use cases, range from interactive exploration to analytical workflows and professional software development.

3.1 Visually guided 3D exploration (*siibra-explorer*)

The interactive 3D viewer *siibra-explorer* can be accessed using any recent web browser by following the links in the [EBRAINS portal](#)¹⁹ or using the direct link <https://atlases.ebrains.eu/viewer>. It embeds both a volumetric and a pure surface view into a rich web application with functionalities for navigating different template spaces, selecting parcellation maps, exploring brain region hierarchies, selecting regions, and discovering regional data features and connectivity data.

The volumetric view is based on Google’s [neuroglancer](#)²⁰ ([Maitin-Shepard et al. 2021](#)) technology, which is capable to display image volumes at Terabyte scale from cloud storage. This allows to zoom to the full resolution of the BigBrain model where detailed structures like cortical laminae and larger cells can be identified. It provides four panels, with three planar views that allow to zoom into full detail, as well as a rotatable 3D overview of the whole brain for orientation. Each panel can be maximised to occupy the complete window, which effectively allows for dedicated 2D and surface viewing modes. The planar views can be adjusted in real-time to display arbitrary oblique cutting planes, which is important to selecting orthogonal views of laminar structures instead of being restricted to the original axis-aligned planes. The dedicated surface view is automatically activated when selecting the popular Freesurfer surface space, and supports the white matter, pial and inflated surface representations. The viewer supports multiple image layers to co-display brain region maps with additional image data.

A recently added feature is a spatial search functionality. Based on the currently selected view of and reference space, *siibra* displays a set of spatially anchored features, typically 2D images and

¹⁶ https://github.com/HumanBrainProject/openMINDS_SANDS/tree/v3

¹⁷ <https://kg.ebrains.eu>

¹⁸ © 2015 Allen Institute for Brain Science. Allen Brain Atlas API

¹⁹ <http://ebrains.eu/services/atlases/>

²⁰ <https://github.com/google/neuroglancer>

partial volumes integrated using the corresponding anchoring tools (Section 4). The availability of anchored features is shown by visual indicator, which can be clicked to open a side panel showing the list of spatially anchored features, as well as displaying their bounding boxes as wireframes (Figure 9D, Figure 10). The list of features is continuously updated while browsing the reference template. By selecting a feature, it will be displayed as a visual overlay with basic controls, as shown in Figure 4.

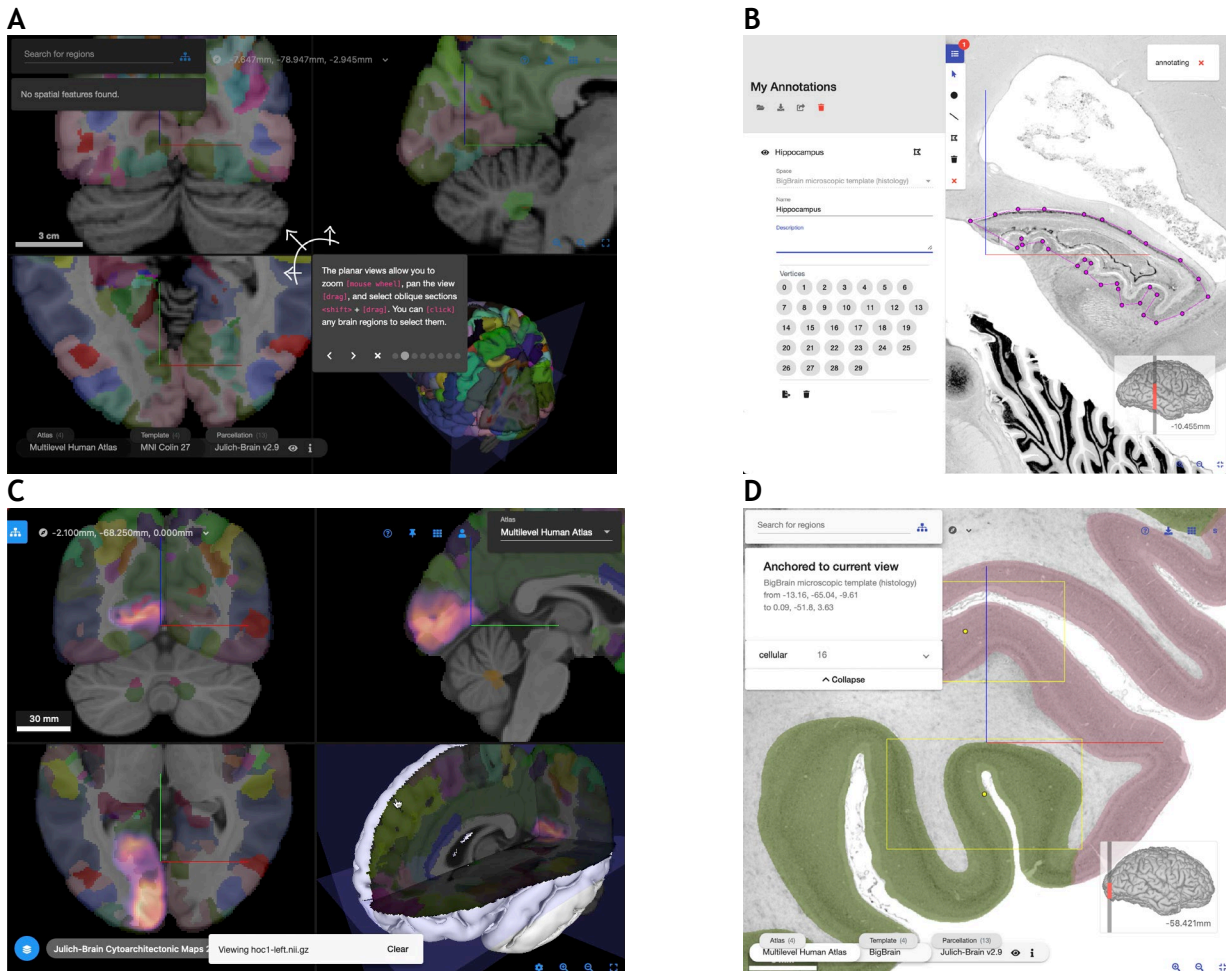


Figure 9: Selected features of the interactive viewer siibra-explorer

A: Quick tour, interactively guiding new users through basic navigational elements. **B:** Interactive annotation mode. **C:** Superimposition of image volumes stored locally on the user’s computer by simple drag and drop of a NifTI file. **D:** Spatial search for finding images that were spatially anchored to the currently shown view of the reference space.

The siibra-explorer also provides a basic annotation mode for entering 3D points and polylines as landmarks, which can be stored, shared with other users, and exported. Exported annotations can be directly imported in siibra-python for scripting.

A notable feature is the ability to superimpose an image volume with the atlas by simple drag-and-drop of a local image file onto the browser window. The volumes need to be in a compatible NifTI format with a valid affine matrix pointing to the physical reference space. This allows a visually guided anatomical assessment of a spatial distributions, such as an fMRI activation map or PET image, without the need of uploading the image (Figure 9C). This is particularly suitable for sensitive data, as the data stays fully on the local computer while being visually combined with the online information from the atlas. The volume can be flexibly adjusted in terms of colour, contrast, brightness, and transparency; and background signal can be removed by applying a custom threshold.

The basic functionalities of siibra-explorer can be explored using the interactive “quick tour” offered directly in the application, which is launched on first use or via the help panel. Several video tutorials

are available that explain features in more depth (D6843). An online documentation is maintained through continuous integration with the software at [readthedocs](https://readthedocs.org/projects/siibra-explorer)²¹.

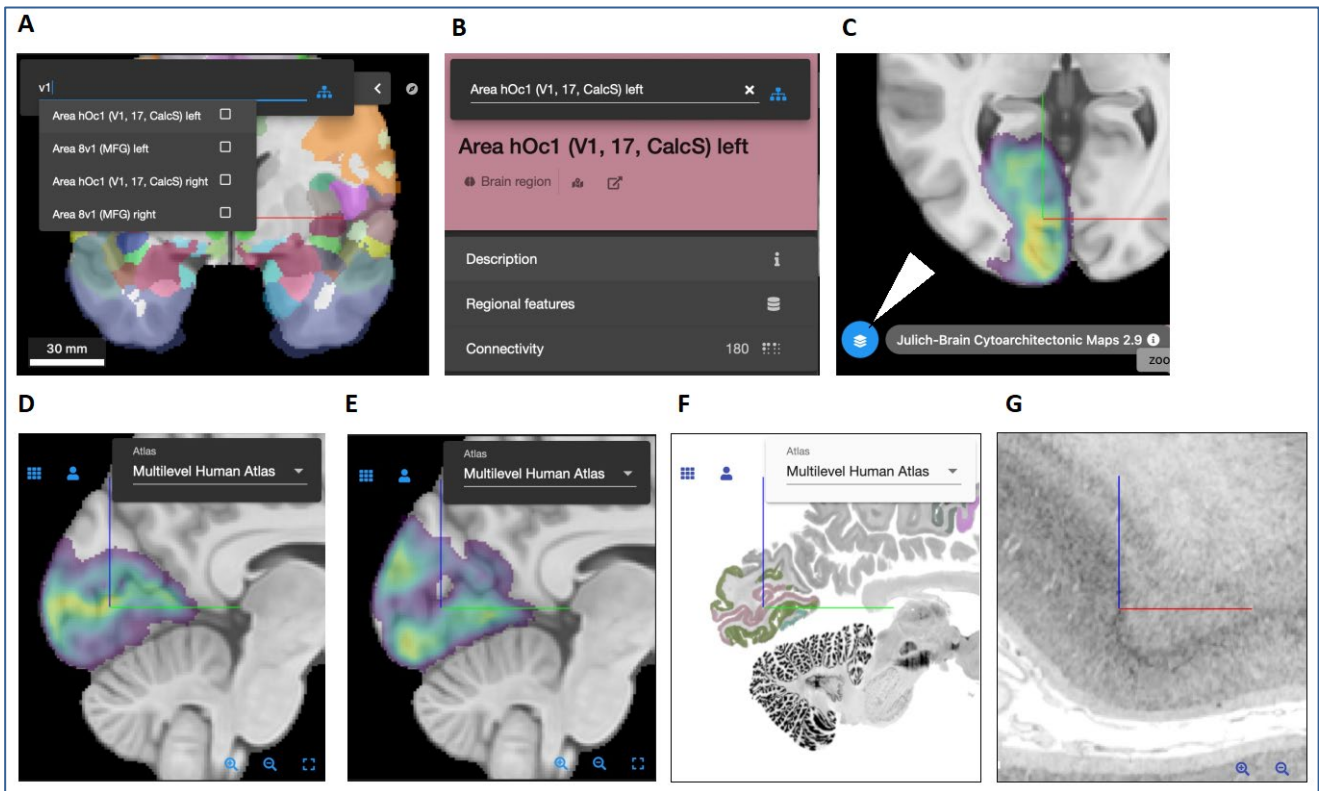


Figure 10: Interactive exploration of a border region in siibra-explorer

A: Using region search to find the primary visual cortex by name. B: Side panel for the resulting region with regional information and functionalities. C: Layer selector to switch between different templates and parcellations. D: Probability map of area hOc1 left (V1). E: Probability map of neighbouring area hOc2 left (V2). F: Corresponding view obtained when switching from the MNI reference space (D, E) to BigBrain space. G: Zoomed in detail of a border region between hOc1 and hOc2 in the left hemisphere in BigBrain, showing the change in laminar structure.

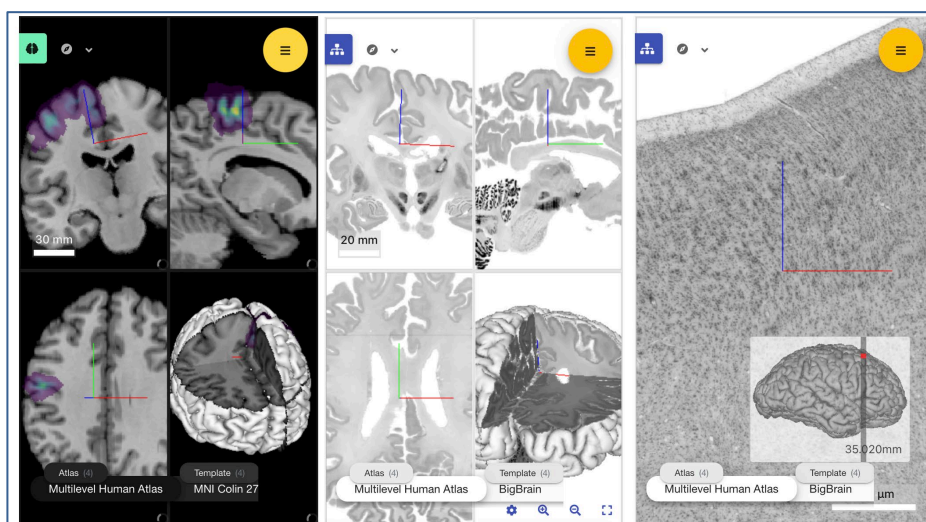


Figure 11: siibra-explorer running on mobile devices

The interactive 3D atlas viewer siibra-explorer is now compatible with browsers on most mobile devices, allowing to browse EBRAINS reference atlases at full resolution using touch navigation even on a smartphone.

The most recent version of siibra-explorer is compatible with most mobile devices, allowing to browse all reference atlases even with a smartphone and touch navigation (Figure 11).

²¹ <https://siibra-explorer.readthedocs.io/en/latest/>

The code of *siibra-explorer* is shared under an open source license and maintained at [github](#)²². Besides many internal software improvements, there are several new features visible to users.

3.2 Integration into reproducible workflows

Besides interactive exploration (Section 3.1) and predefined analysis workflows (Section 5), EBRAINS atlases can be used to build fully customized scripts, workflows, and pipelines. For this purpose, programming interfaces are available in the form of a comprehensive Python client (Section 3.2.1) and an HTTP interface (Section 3.2.2), which together with the interactive 3D viewer described in Section 3.1 form the *siibra toolsuite*. In addition, first implementations of a command line interface (*siibra-cli*²³) and Matlab® toolbox (*siibralab*²⁴) are available which will be maintained together with the toolsuite. Together with a new EBRAINS interface for datalad (Section 3.2.4), these tools allow to build fully reproducible neuroscience workflows based on EBRAINS atlases.

3.2.1 Python interface (*siibra-python*)

The Python library, *siibra-python*, is designed for integrating the multilevel atlas framework into scripts and computational workflows. It covers all functionalities in *siibra-explorer* and enables more advanced utilization of atlas information.

siibra-python implements semantic concepts for parcellations and reference spaces and separates them from their various spatial representations in image and surface form (Table 1), this way realizing central ideas of the AtOM model (Section 2.4). The framework is designed to allow safe interaction with brain regions defined in different parcellations, to provide streamlined access to multimodal data features linked to brain regions, and to access data from different spatial scales, such as MRI-scale image volumes in MNI space and full resolution microscopic data anchored to BigBrain space.

Table 1: Separation of semantic atlas concepts from their spatial representations in *siibra*

Concept	Spatial Representation	Exemplary linked data features
Parcellation	Parcellation map	Connectivity matrix of streamline counts averaged by Julich-Brain 2.9
Brain region	Region map (e.g. probability map)	Distributions of receptor GABAA in FrontalPole (FP1) of left hemisphere
Reference space	Reference template	Gene expression for TAC1 measured at position X/Y/Z in MNI space

To provide modular handling of the different template spaces, *siibra-python* implements locations as an object class hierarchy, which includes structures for points, point distributions and bounding boxes. Each location object is strictly associated with a reference space but can be warped to other spaces on the fly using the coordinate translation service (Section 3.2.3). To reflect the highly different reliability of coordinate specifications, such as the highly different precision of locations of EEG electrodes in comparison to the centroid of a segmented cell, *siibra*'s location objects explicitly support location uncertainty.

Regions and locations are linked with a broad range of multimodal data features. *Siibra* currently supports features of cellular architecture (layer wise neuron densities; staining profiles), molecular architecture (receptor densities; gene expressions), and connectivity (streamlines and functional connectivity from different cohorts) and allows to extract custom regions of interest from the BigBrain model and a growing set of histological sections and volumes at their full resolutions. The

²² <https://github.com/FZJ-INM1-BDA/siibra-explorer>

²³ <https://pypi.org/project/siibra-cli>

²⁴ <https://www.mathworks.com/matlabcentral/fileexchange/121148-siibralab>

features are compatible with common data structures in [pandas](https://pandas.pydata.org)²⁵ and [nibabel](https://nipy.org/nibabel)²⁶, and tagged with metadata, spatial anchoring, and links to their original online resources.

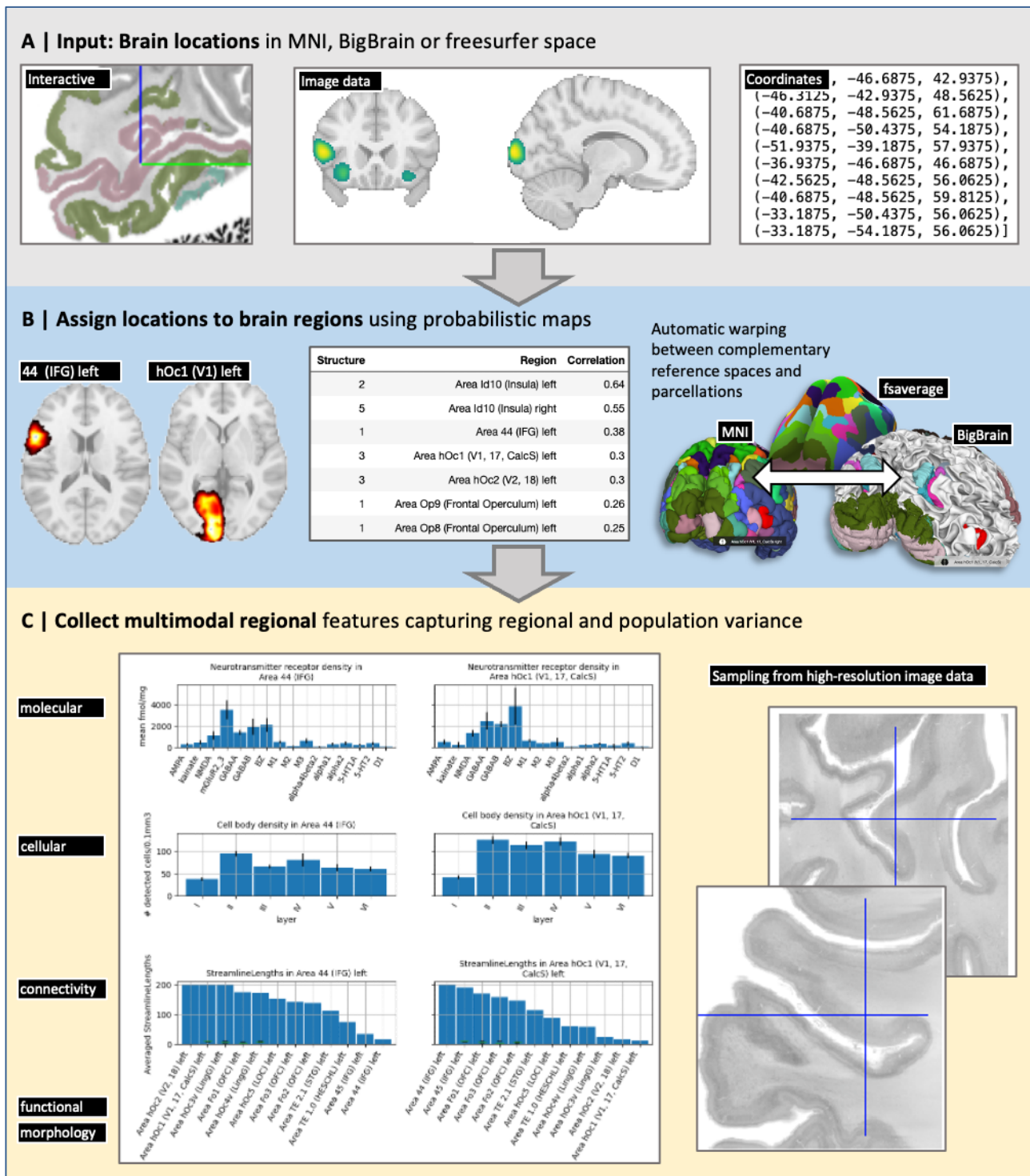


Figure 12: A typical workflow in siibra-python

Typical workflows in siibra-python start by specifying a brain location of interest in the form of images or coordinates (A), then assigns them to brain regions from complementary parcellations (B) and collects multimodal data features for the identified regions of interest (C), which characterize the involved regions with respect to various aspects of brain organization, regarding intra-region variability as well as population invariance. A Jupyter notebook reproducing the main parts of this figure is provided at [github](https://github.com/FZJ-INM1-BDA/siibra-tutorials)²⁷.

²⁵ <https://pandas.pydata.org>

²⁶ <https://nipy.org/nibabel>

²⁷ <https://github.com/FZJ-INM1-BDA/siibra-tutorials>

The hierarchical structure of regions, locations and data features allows to perform semantic and spatial queries through a single unified interface. Siibra provides a common interface to access a heterogeneous pool of potentially Terabyte-sized 3D volumes in various mesh and voxel representations, including locally and remotely stored NIfTI images, GlTF meshes, cloud-hosted neuroglancer multiresolution data, and efficient sparse representations of statistical maps.

Typical workflows in siibra-python start by specifying brain locations in a reference space, e.g., by loading a list of 3D coordinates, or providing a NIfTI file with a spatial map (Figure 12A). Siibra then assigns brain regions from different parcellations to points, signal peaks or imaged 3D structures (Figure 12B). The assignment utilizes probabilistic maps if available, and distinguishes clearly between incidence, correlation and overlap of 3D structures. siibra-python also allows to include custom parcellation maps into this workflow. To evaluate structures in different template spaces and resolutions, siibra warps locations between the MNI Colin 27, ICBM 2009c asym and BigBrain spaces using diffeomorphic transformations. The resulting matched brain regions and coordinates can then be used to query multimodal data features describing various aspects of brain organization for the identified structures (Figure 12C).

In line with the FAIR principles all content used by siibra-python is stored as public datasets on the [FENIX](#)²⁸ infrastructure with comprehensive metadata curated in [EBRAINS KG](#)²⁹. Multimodal features are complemented by live queries to established repositories such as the Allen human brain atlas³⁰.

Siibra-python is developed in the public domain under Apache2 licence and maintained at [github](#)³¹, with regular releases of development snapshots on [pypi.org](#)³², and a documentation with downloadable code examples at [readthedocs](#)³³. A range of tutorial videos³⁴ and a set of interactive tutorials³⁵ are also available.

The siibra toolsuite has been used successfully for a range of recently published studies, such as an investigation into the biological correlates of function and connectivity in the context of psychiatric disorders ([Zachlod et al. 2023](#)) and parameter inference in neural mass models ([Sip et al. 2023](#)).

3.2.2 HTTP interface (siibra-api)

siibra-python is the main codebase for the multilevel atlas framework. To expose the implemented functions to external applications, we provide the RESTful http interface *siibra-api*, which provides remarkably similar functionality to the Python client. The recent version of the API is available and documented at [swagger](#)³⁶ and [redoc](#)³⁷. Additional documentation is maintained at [readthedocs](#)³⁸.

siibra-api is used to serve the interactive viewer siibra-explorer (Section 3.1), providing a clear modularization and separation of user interface and core. Furthermore, siibra-api has been used for implementing a first basic version of a Matlab© toolbox ([siibralab](#)³⁹) in cooperation with Mathworks⁴⁰. This toolbox showcases how siibra-api can be used to connect EBRAINS atlases to external applications in a well-defined way.

²⁸ <https://fenix-ri.eu>

²⁹ <https://kg.ebrains.eu>

³⁰ © 2015 Allen Institute for Brain Science. Allen Brain Atlas API

³¹ <https://github.com/FZJ-INM1-BDA/siibra-python>

³² <https://pypi.org/project/siibra/>

³³ <https://siibra-python.readthedocs.io/>

³⁴ e.g. https://youtu.be/H_6-RPLZkYM

³⁵ <https://github.com/FZJ-INM1-BDA/siibra-tutorials>

³⁶ https://siibra-api-stable.apps.hbp.eu/v3_0/docs#/

³⁷ https://siibra-api-stable.apps.hbp.eu/v3_0/redoc

³⁸ <https://siibra-api.readthedocs.io/en/latest>

³⁹ <https://www.mathworks.com/matlabcentral/fileexchange/121148-siibralab>

⁴⁰ <https://mathworks.com>

3.2.3 Coordinate transformation service for human reference spaces

We developed a method for robust spatial alignment of different human brains using sulcal constraints to drive a diffeomorphic alignment (Lebenberg et al. 2018). The algorithm is part of the [brainvisa](https://brainvisa.info/)⁴¹ software determines accurate deformation fields between the different human reference template spaces. These deformation fields establish spatial relationships across these spaces, implementing cross-template queries for spatial coordinates, simplifying cross-template navigation, and enabling the warping of imaging data from one space to another.

At its core, the spatial transformation service is hosting a containerised installation of a software stack including the brainvisa library, together with a static set of precomputed cross-template transformations. These transformations are 3D diffeomorphisms, computed based on aligning the folding patterns in the different brains using the DISCO method (Auzias et al. 2011; Glaunes, Trouve, and Younes 2004; Lebenberg et al. 2018), and maximising the overlap of grey- and white matter segmentations, using the established method DARTEL (Ashburner 2007). Coordinates can be transferred between those spaces using a simple REST API, documented at [redoc](https://redoc.hbp.eu/)⁴². The source code of the back end is available at [github](https://github.com/HumanBrainProject/hbp-spatial-backend)⁴³.

Using this service, the atlas viewer *siibra-explorer* (Section 3.1) will approximately preserve the current viewport (orientation, position, zoom level) selected by the user when switching between human template spaces. For example, if a user is browsing brain area hOc1 (V1, 17, CalcS) in the MNI 152 template space and switches to the BigBrain template space, the viewport will be "approximately" centred on brain area hOc1 (V1, 17, CalcS) in BigBrain (Figure 13A, B). In *siibra-python* the service is employed to warp coordinates across spaces, and realise, for example, automatic cross-space feature queries (Section 3.2.1).

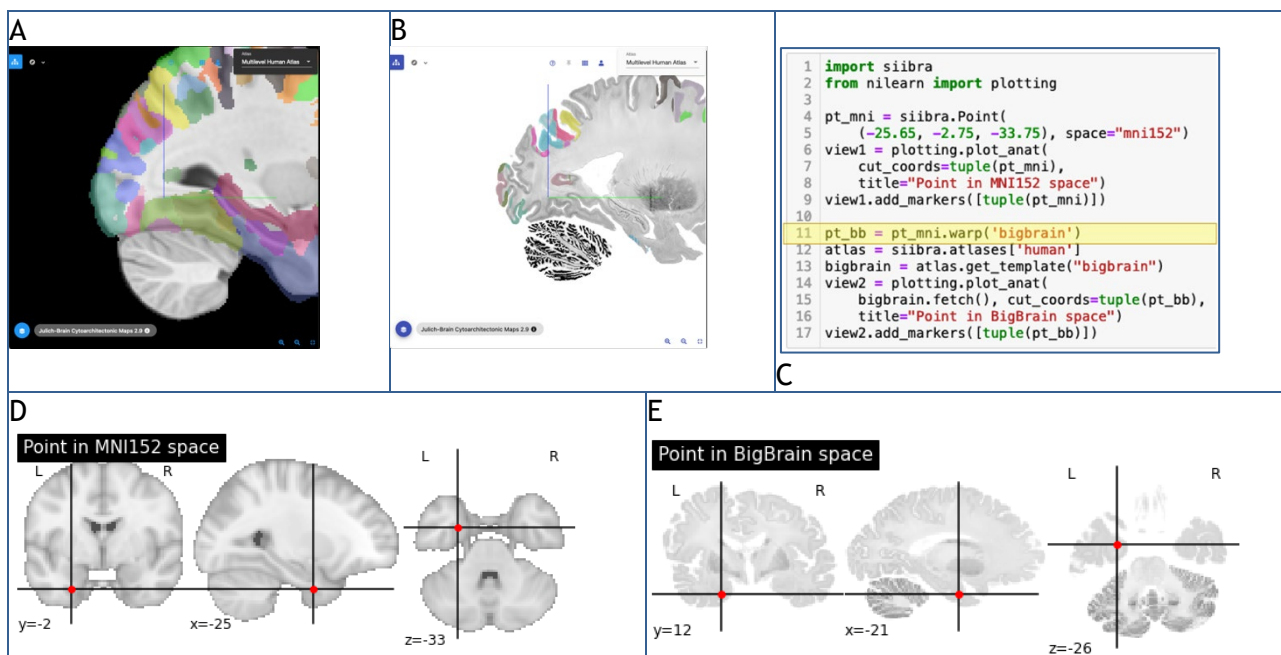


Figure 13: The spatial transformation service employed by the *siibra* toolsuite

A: View selected by the user in MNI152 space; B: Corresponding view in BigBrain space, automatically selected by *siibra-explorer* using the spatial transformation service; C: Code snippet in *siibra-python* which warps a point from MNI152 to BigBrain space; D, E: Output of the code in C.

⁴¹ <https://brainvisa.info/web/>

⁴² <https://hbp-spatial-backend.apps.hbp.eu/redoc>

⁴³ <https://github.com/HumanBrainProject/hbp-spatial-backend>

3.2.4 *Distributed dataset management*

An extension package has been implemented for the [DataLad](#)⁴⁴ software, which enables DataLad users to obtain any publicly accessible dataset hosted on the EBRAINS platform in the form of a DataLad dataset. DataLad datasets are technically Git repositories that utilize the software [git-annex](#)⁴⁵ to efficiently handle arbitrarily large files by only tracking file identity and availability metadata, instead of a file's actual content.

The [datalad-ebbrains extension package](#)⁴⁶ queries the EBRAINS knowledge graph to retrieve a complete version history of any public EBRAINS dataset. Within the resulting Git repository, all files of each dataset version are represented with the exact same layout with which the data were originally ingested to EBRAINS. Users can switch between versions, utilize Git branches to consume data, capture computed data derivatives, or apply any Git-compatible software or workflow. DataLad datasets generated from a knowledge graph query are bit-identically reproducible. This means that when no information in the knowledge graph changes, the complete state of datasets resulting from two independent queries will be identical.

Consequently, users need not maintain persistent copies of such datasets, but can rely on the EBRAINS platform to provide enough information to enable their on-demand recreation. This is the precondition for using such DataLad dataset as input (i.e., data dependencies) for further processing within the framework of DataLad's facilities to capture computational provenance. This provenance metadata can be verified (by automated recomputation, for example when using a containerized pipeline). Taken together, this provides a viable paradigm for enabling off-site processing of EBRAINS data for the purpose of ingesting the computational outcomes back onto the EBRAINS platform without compromising on the trust in computational outcomes, because the critical information submitted to EBRAINS are the computational instructions, not the computed outcomes.

datalad-ebbrains presently supports direct knowledge graph queries, and file repository queries via the EBRAINS data-proxy API. Within the DataLad project this effort yielded the first metadata-driven tool to "deserialize" a dataset representation in an independent database into a fully functional Git-based dataset. Based on this development a generalized implementation can be developed that supports additional terminologies and APIs, beyond the EBRAINS knowledge graph and the OpenMINDS metadata standard.

4. Data integration to reference atlases

A core concept of EBRAINS atlases is their role as an anatomical reference framework for models and data features from different spatial scales and modalities, resulting in a continuously growing knowledge base of the multi-faceted characteristics of brain regions and their connections. To link new datasets to anatomical structures in the brain, EBRAINS atlas services include several tools for spatial anchoring of data.

4.1 Rodent brain sections

The stand-alone image registration tools [QuickNII](#)⁴⁷ and [VisuAlign](#)⁴⁸ have been endorsed by the neuroscientific community with more than 10.000 downloads (8000 times for QuickNII), over 60 citations in scientific papers and are listed in the Brain Initiative data ecosystem resources

⁴⁴ <https://datalad.org>

⁴⁵ <https://git-annex.branchable.com>

⁴⁶ <https://github.com/datalad/datalad-ebbrains>

⁴⁷ <https://ebbrains.eu/tools/quicknii>

⁴⁸ <https://ebbrains.eu/tools/visualign>

([Hawrylycz et al. 2023](#)). All documentation is accessible through the EBRAINS portal⁴⁹ and online manuals⁵⁰.

Several atlases are available in the tools, i.e., the Allen Mouse atlas common coordinate framework version 3 and the Waxholm Space Atlas of the Sprague Dawley rat brain version 4. A new version of QuickNII with the Unified Mouse atlas from the Kim lab has been released⁵¹, adding a new atlas to the repertoire of reference atlases provided to EBRAINS users.

QuickNII and VisuAlign have been used to register many large datasets shared via EBRAINS to mouse or rat brain atlases allowing researchers to interactively investigate brain-wide distributions of e.g. calcium-binding proteins (Bjerke et al., 2020), dopamine receptor distributions (Bjerke et al., 2022) zincergic terminal fields and metal containing glia (Blixhavn et al., 2023), efferent connections of cortical association areas (Reiten et al., 2023), or Alzheimer related neuropathologies (Gurdon et al., 2023), by inspecting high-resolution microscope images with custom atlas overlays in an online viewer tool, directly accessible via links in the EBRAINS data cards. The atlas registration (QuickNII) and viewer tools (LocalZoom, MeshView) also allow efficient visualization and analysis of spatial distribution patterns in normal and transgenic mice using point coordinate data derived from microscopic imaging data (see, e.g. Tocco et al., 2022; Leergaard and Bjaalie, 2022).

In the BRAINSPACE project, we developed the new [QCAIAlign](#)⁵² ([Gurdon et al. 2023](#)) tool for assessment of precision of the atlas registrations with statistical analysis of confidence levels in the different atlas regions. This standalone tool supports users when preparing their data for high-throughput studies with the QUINT analysis workflow.

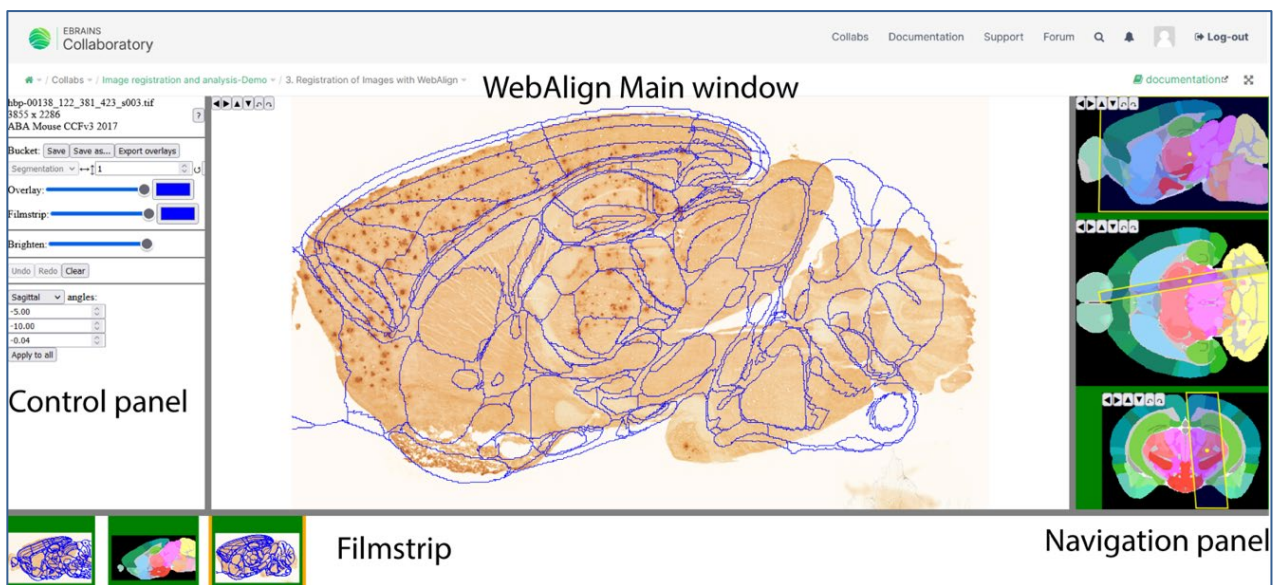


Figure 14: User interface of WebAlign for 2D rodent section image registration.

The main window is showing the experimental data with the atlas overlay. The navigation panel is used for changing the position of the atlas plane matching the data. Transformation of the atlas, like rotation, panning and stretching is achieved with dedicated short keys (space, esc, arrow keys). The control panel gives an overview of the defined angles, allows to save results, change overlay colour, and export descriptor files for the QUINT workflow.

In addition to the desktop registration tools QuickNII and VisuAlign, EBRAINS users now have access to the registration webservice [WebAlign](#)⁵³ (Figure 14) and [WebWarp](#)⁵⁴ for linear and non-linear image registration. They can upload their own datasets into a private working space after logging in via EBRAINS and use entire analytical pipelines, where image registration to reference atlases of

⁴⁹ <https://ebrains.eu/brain-atlases/data-integration/2d-sections>

⁵⁰ <https://quicknii.readthedocs.io/en/latest/>; <https://visualign.readthedocs.io/en/latest/>.

⁵¹ <https://www.ebrains.eu/news-and-events/new-unified-mouse-atlas-from-the-kim-lab-is-now-available-in-the-ebrains-quicknii-image-registration-tool>

⁵² <https://ebrains.eu/tools/qcalign>

⁵³ <https://ebrains.eu/tools/webalign>

⁵⁴ <https://ebrains.eu/tools/webwarp>

mouse and rat brain is the first step. We have set up a public [demonstration collab](#)⁵⁵ to guide our users. After a short introduction on how to setup all the webapps and convert the image files to pyramid files (DZI format), the online registration is done interactively in the web browser.

All the results are saved in the collaboratory bucket storage and can be opened in the WebWrap tool for refinement with non-linear registration. WebWarp is also using the DZI file format, which allow users to zoom in the high-resolution image, better decipher region boundaries and achieve a more precise registration. EBRAINS users have also the possibility to open curated and ingested datasets by fetching a link on the dataset card (Figure 15). All the resulting registration files are compatible with online analytical pipelines (Section 5.2).

We also developed an automatic, deep learning based, registration app, DeepSlice ([Carey et al.2022](#)) for coronal mouse brain sections, motivated by the need to increase efficiency in the workflow.

The DeepSlice model is based on convolutional neuronal network trained on thousands of histological section images. Users will also have access to a beta rat version on the [DeepSlice website](#)⁵⁶.

Overview

DOI: 10.25493/T686-7BX

License: Creative Commons Attribution 4.0 International

Custodians: Leergaard, T. B.

The dataset comprises high-resolution bright-field microscopy images of coronal, horizontal and sagittal serial rat brain sections in which zincergic terminal fields and metal-containing glia are visualised. historical histological material was originally prepared to map the presence of zinc and heavy metals in the adult Wistar rat brain, especially in the hippocampal formation. Alternating sections were stained with the Timm-Haug73 modification of the Timm's sulphid silver method or Nissl staining for cytoarchitecture. The images are suitable as a microscopic reference resource for studies of terminal fields of zincergic fibre systems, and sulphide silver stained neuro perikarya and glial cells, and as a general histological reference for researchers interested in normal rat brain architecture.

Version specification: This is the first version of this dataset

View data in LocalZoom:

- subject H108
- subject H108a_Timm_light
- subject H108b_Timm_dark

WebAlign

Last modified by Maps P. on 2023/07/05 16:38

New series from url
[\[New series from url\]](#)

Enter name of image-chunk collab: [img-362265a-e645-11e] |
 Target atlas: [H108_S0 Rat v4 39um] |
 [Create] [Cancel]

Ready:

name	format	width	height	tilesize	overlap
H108a_Timm_light_coronal_s004.tif.png		17100	18675	254	1
H108a_Timm_light_coronal_s005.tif.png		17431	18973	254	1
H108a_Timm_light_coronal_s010.tif.png		16168	17289	254	1
H108a_Timm_light_coronal_s013.tif.png		14557	14160	254	1
H108a_Timm_light_coronal_s016.tif.png		18246	19058	254	1
H108a_Timm_light_coronal_s019.tif.png		17916	18035	254	1
H108a_Timm_light_coronal_s022.tif.png		18557	19902	254	1
H108a_Timm_light_coronal_s025.tif.png		18578	18150	254	1
H108a_Timm_light_coronal_s028.tif.png		19467	19783	254	1
H108a_Timm_light_coronal_s031.tif.png		18863	18468	254	1
H108a_Timm_light_coronal_s034.tif.png		22128	27645	254	1

Figure 15: Possibility to work on curated Knowledge graph datasets.

New WebAlign series can be created by fetching the URL of a curated knowledge graph dataset found on the dataset card. The image series is automatically created and saved as a WebAlign file (.waln) in the storage bucket. Users can then modify the registration or apply non-linear corrections using WebWarp

4.2 High-resolution volumes of interest

Spatial anchoring of high-resolution volumes of interest (VOIs) from different imaging experiments into the detailed anatomical context of a high-resolution reference model such as the BigBrain (Amunts et al. 2013) became an important practical problem with increasingly available datasets during recent years. Typical examples include the integration of high-resolution MRI, 3D Polarized Light Imaging, or X-ray computed tomography measurements of brain tissues, which would be appropriately organised in the detailed anatomical context of the BigBrain model. However, working on a proper anchoring of such imaging data to the full-resolution reference template is out of reach for many neuroscientists due to the sheer size of the datasets, the lack of available tools, but also

⁵⁵ <https://wiki.ebrains.eu/bin/view/Collabs/image-registration-and-analysis-demo>

⁵⁶ <https://deepslice.org>

the problem to identify correspondences between the datasets in a reliable and reproducible way. Here we present a new release of the interactive volumetric alignment tool voluba, which allows anchoring of volumetric image data to reference volumes at microscopical spatial resolutions. Voluba is implemented as an online web service and enables interactive manipulation of image position, scale, and orientation, flipping of coordinate axes and entering of anatomical point landmarks in 3D. The resulting transformation parameters can be downloaded in JSON format or used to view the anchored image volume in the interactive atlas viewer siibra-explorer.

voluba offers a highly interactive workflow. Users can log in with their ORCID or EBRAINS account to upload a dataset into a private working space to perform the anchoring process. The BigBrain model serves as the default reference volume. The input volume is presented as a graphical overlay in a 3D view with orthogonal cross sections, which utilizes Google’s neuroglancer engine (Maitin-Shepard et al. 2021) (Figure 16 left). The latest voluba release provides options to fine tune the overlay by customizing contrast, brightness, colourmaps, and intensity thresholds. The 3D view can be used to directly manipulate the relative position and orientation of the input volume. A dialogue window further enables adjustment of its voxel scaling and axis orientations. These settings determine a rigid transformation between the two volumes, which is modelled as a 3D affine matrix. A 3D landmark editor can then refine the transformation by specifying pairs of corresponding anatomical points between the volumes. This is further facilitated by an optional side-by-side navigation mode, where the incoming and reference volume are shown in two separate views. From a set of landmarks, the affine transformation matrix can be recalculated with additional degrees of freedom, including shearing. Alignment actions can be performed and repeated in arbitrary order, supported through a history browser which allows to undo individual anchoring steps.

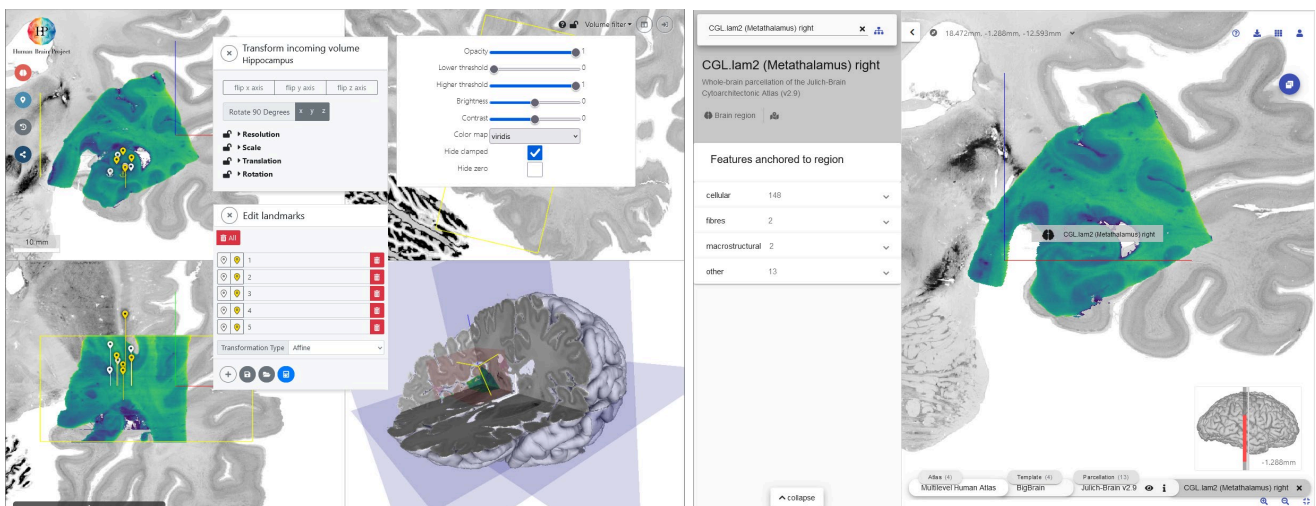


Figure 16: Graphical user interface of voluba.

Left: After uploading a volumetric dataset, various filters like contrast or colour maps allow to configure the presentation of the data. The user can position the volume on top of a reference brain (here: the BigBrain model) by shifting and rotating the input in any of the 3 planar views. Further linear geometric alignments can be adjusted in a parameter window. For more detailed affine adjustment, corresponding point landmarks can be entered. Right: Users can view the anchoring result as an overlay in the interactive atlas viewer siibra-explorer. Thus, the user can directly inspect the aligned data superimposed with the full atlas context and compare it to atlas regions as well as other data linked to the same reference space

Anchoring results from voluba can be used in several ways. First, users can download the parameters of the affine transformation matrix as a JSON file for reference. The stored transformation file can be re-imported in voluba, and due to its simple structure be utilized in other tools and workflows. Alternatively, the uploaded NIfTI image can be re-downloaded with an updated affine, that includes all applied transformations. Moreover, voluba is connected to the EBRAINS Knowledge Graph which allows the user to store the transformation parameters and link them to an EBRAINS dataset. Furthermore, voluba can generate a private URL to view and share the anchored volume as a remote dataset in neuroglancer-based image viewers. Most importantly, voluba offers a direct link to open the anchored volume as a semi-transparent layer in the interactive atlas viewer siibra-explorer (Figure 16 right). voluba has been used successfully by EBRAINS curation teams and different research labs to anchor volumes of interest to BigBrain reference space. Examples include a

hippocampus sample imaged with MRI and 3D Polarized Light Imaging (Ayer, Poupon, and Costantini 2020), a hippocampus sample imaged with phase-contrast computed tomography (Eckermann et al. 2021), and a 3D model of the human brain stem (Lechanoine et al. 2021). voluba is openly accessible in its most recent version at <https://voluba.apps.hbp.eu>. Detailed documentation is available at [readthedocs](#)⁵⁷.

4.3 Anchoring MRI volumes (voluba-mriwarp)

Warping whole brain human MRI scans to a standardized space such as the ICBM MNI152 2009c nonlinear asymmetric template enables spatial integration to the human brain atlas. However, while tools for skull stripping and nonlinear registration are available, their proper configuration and use often requires significant expertise. voluba-mriwarp is a tool that aims to simplify both nonlinear anchoring of MRI volumes to MNI reference space, as well as interaction with the EBRAINS human brain atlas on the basis of the MNI volume, in order to assign brain regions and browse related data. voluba-mriwarp incorporates these components by automatically applying a set of predefined parameters to perform skull stripping and nonlinear registration to MNI152 space. The resulting deformation field can then be easily utilized to perform an atlas-based analysis of brain regions and linked data features in the input scan via the siibra toolsuite . These core functionalities are based on a selection of established community tools, such as HD-BET, ANTs, and siibra-python (Section 3.2.1).

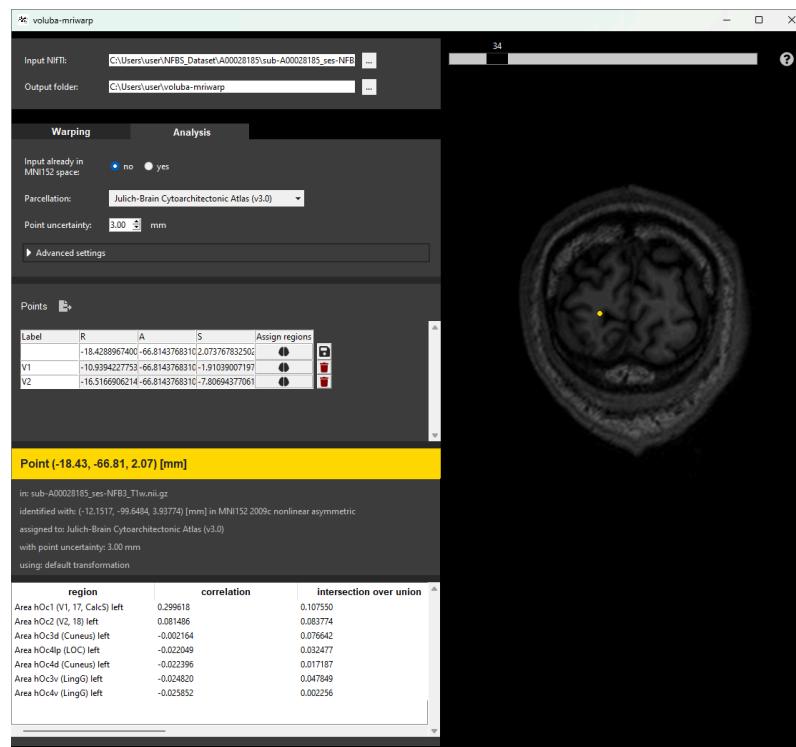


Figure 17: Atlas-based analysis of a location in an MRI scan

After warping the input MRI scan to MNI152 space, users can select locations in the input space and perform an atlas-based analysis. This includes different measures like the probability values of regions in the chosen parcellation. For further analysis assigned regions as well as linked data can be exported to a PDF report.

voluba-mriwarp is implemented as a desktop application that is primarily designed for Windows 10 but can also be executed on Linux. Therefore, MRI data will not be uploaded to any online services but remain on the user’s local computer. Installation instructions as well as detailed documentation is available at [readthedocs](#)⁵⁸.

⁵⁷ <https://voluba.readthedocs.io/en/latest/>

⁵⁸ <https://voluba-mriwarp.readthedocs.io/en/latest/>

To perform a detailed analysis of an MRI volume in the atlas context the input scan needs to be warped to MNI152 space. In `voluba-mriwarp` the user can choose between different parameters for registration. The default parameters yield fast and reasonable results, whereas the advanced set of parameters achieves a higher registration accuracy. Users familiar with ANTs can also define and apply their own registration parameters in a JSON file. Based on the resulting nonlinear transformation, locations in the MRI scan can be analysed in the anatomical context of the EBRAINS Multilevel Human Atlas. The core functionality of the analysis is the probabilistic assignment of exact or imprecise coordinates in the input space to brain regions of the atlas. For this, the user can opt for different atlas parcellations representing cytoarchitecture, fibre architecture or function. Locations can be selected via double click in the viewer or manually entered into a table (Figure 17). After passing the given information to `siibra-python` (Section 3.2.1) `voluba-mriwarp` presents different measures for the selected coordinate such as a correlation coefficient or the probability values of regions in the chosen parcellation. Furthermore, each region listed can be viewed in `siibra-explorer` (Section 3.1). For retaining and extending the atlas-based analysis, points can be saved for PDF export. The export functionality will save the anatomical assignments together with linked data features (e.g. cell density, receptor density or connectivity) for each assigned region to a PDF report.

4.4 Anchoring neuron morphologies

Recently large quantities of fully reconstructed long range projection neurons have been released in public databases ([Peng et al. 2021](#); [Winnubst et al. 2019](#)). The neurons are reconstructed from digital volumes of 3d scanned brain tissue. In smaller scale, hypothesis driven projects morphologies are reconstructed from brain slices, using microscope-attached software such as NeuroLucida (MBF Bioscience). For this use case it is particularly challenging to register neurons to a reference brain, since no intact 3d volume is available to drive the registration. We have created a collection of tools aid in this process, described in a [collab wiki](#)⁵⁹. The toolbox consists of

- 1) a python library for pre-processing of experimental brain sections, including background removal and contrast enhancement.
- 2) a web-based [neuron morphology viewer](#)⁶⁰, started in SGA1, that supports 3d viewing of neurons, can load/save various formats including SWC and NeuroLucida XML, and allows for saving subsets of the neuron.
- 3) a web-based tool (`slice-aligner`⁶¹) to manually align a stack of brain sections, which allows to interactively align adjacent sections based on either tissue features or traced neuron segments (Figure 18).
- 4) a pipeline for registering reconstructed neurons to a reference brain, for the use case of having a sliced brain with a NeuroLucida-reconstructed morphology, implemented as a Jupyter notebook (`morphology-atlas-registration-v2`⁶²).
- 5) a tool to visualize the registered neuron on a cortical flatmap of the Allen Mouse Atlas, implemented as a python library and accompanying web viewer (`allen-flatmap`⁶³) (Figure 19).
- 6) a website created in the context of partnering project NeuronsReunited in which large databases of fully traced neurons in mouse (currently more than 10000) can be consulted and searched by brain region (`neuronsreunited-viewer`⁶⁴).

⁵⁹ <https://wiki.ebrains.eu/bin/view/Collabs/morphology-alignment-tool>

⁶⁰ <https://neuroinformatics.nl/HBP/morphology-viewer>

⁶¹ <https://slice-aligner.apps.hbp.eu/>

⁶² <https://wiki.ebrains.eu/bin/view/Collabs/morphology-atlas-registration-v2>

⁶³ <https://neuroinformatics.nl/HBP/allen-flatmap/>

⁶⁴ <https://neuroinformatics.nl/HBP/neuronsreunited-viewer/>

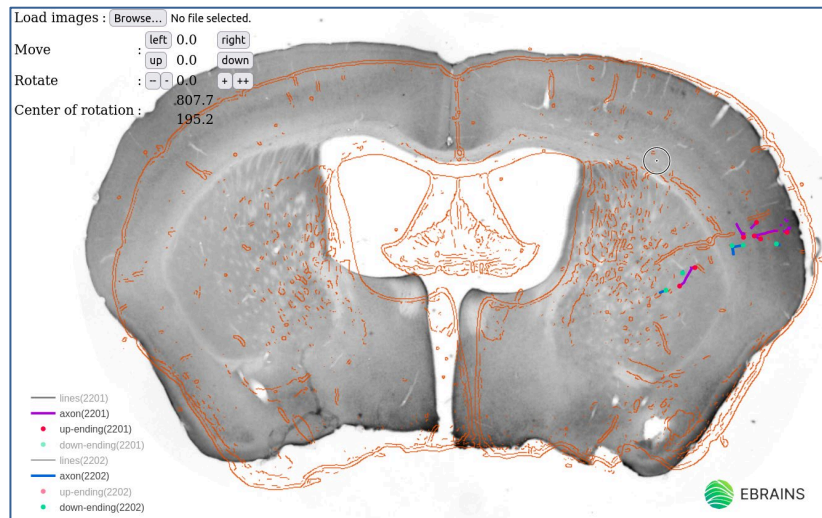


Figure 18: Web-based slice aligner interface.

The interface shows the edge features of one section on top of the grayscale tissue of the adjacent section. In addition, traced neuron segments in the two sections are displayed.

The tools have been extensively used by partner labs and directly applied to experimental data. A [poster](#)⁶⁵ depicting the workflow was presented at the EBRAINS Summit 2023.

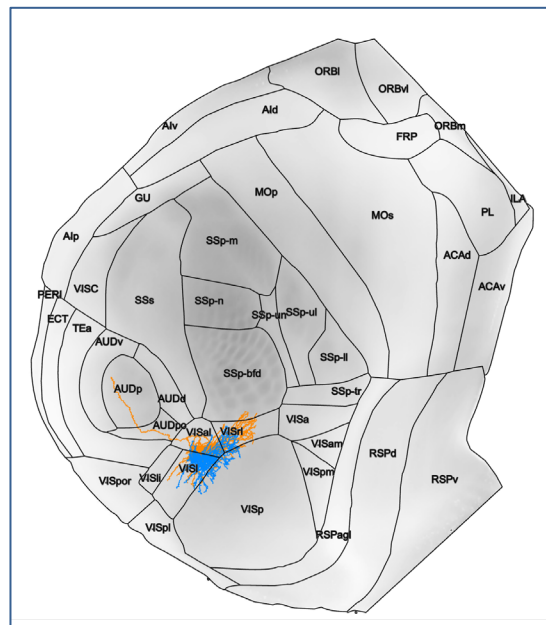


Figure 19: Cortical projections of a thalamocortical neuron

The projections were registered to the Allen CCF3 reference brain with two methods, manual placement in 3d (blue) and using the slice-based alignment pipeline (orange).

5. Atlas-driven data analysis

5.1 Feature extraction from images (web-ilastik)

The online image segmentation tool, web-ilastik, provides users of the EBRAINS platform with the ability to analyse their images directly in the web browser (Figure 20). The project leverages EBRAINS

⁶⁵ <https://www.scienceopen.com/document/read?vid=6fa9ee94-4ad7-484e-a321-3b46c5f64f15>

and FENIX resources to authenticate users, provide storage for reading datasets and writing results, and allocate compute sessions.

From the Graphical User Interface, users can request and manage compute sessions from different High Performance Computing sites (CSCS and JUSUF), check the status of any currently running sessions or leave and rejoin them later as necessary. The compute resources are charged from webilastik’s own service account in the HPCs, which gives authenticated users immediate access to compute without having to be personally granted resources by any of the HPCs.

Users can open “Precomputed Chunks” or “Deep Zoom” datasets from their Data Proxy buckets using the built-in filepicker, interactively train a pixel classifier by annotating their datasets with the brushing tools, then export the segmentation results back to the Data Proxy buckets (in “Precomputed Chunks,” “Zipped DZI” or “N5” formats). The same classifier can also be used to process other datasets in asynchronous jobs and the entire project can be saved to the Data Proxy or directly downloaded to the users’ own computer.

Webilastik can be accessed directly at <https://app.ilastik.org> and its source code is hosted at [github](https://github.com)⁶⁶. It also implements custom integration logic to be used as part of the QUINT workflow at <https://neural-systems-at-uio.github.io/>

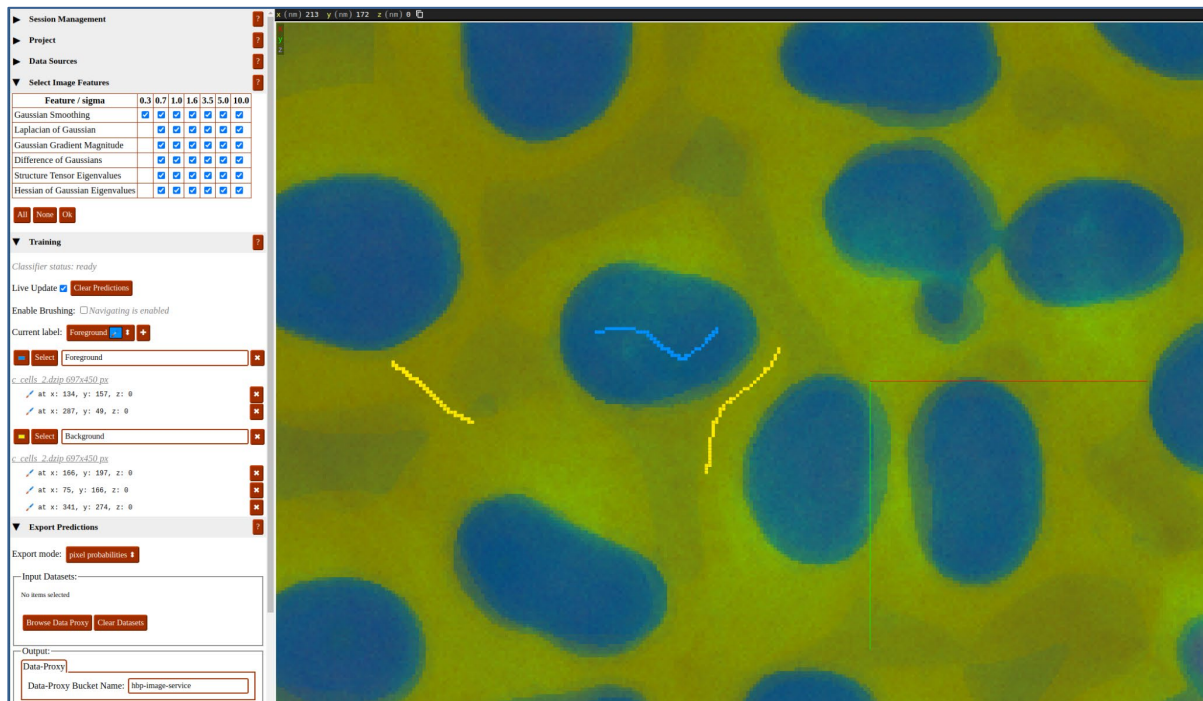


Figure 20: Screenshot of web-ilastik front end on top of Neuroglancer

Predictions from the back end overlaid in colours: yellow for background and blue for foreground (nuclei). Classifier trained on the annotations visible in the screenshot. The sidebar to the left shows the control widgets for session management, feature selection, creation, and deletion of annotations, as well as exporting of results.

5.2 Atlas-guided quantification of labelled features

5.2.1 Workflow for image annotation and extraction of point clouds

This online workflow allows users to upload their 2D experimental rodent brain section images to their collab working space and extract quantitative information from the data. Example of relevant dataset are analysis of implanted electrode positions, tract-tracing connectivity analysis, or mapping

⁶⁶ <https://github.com/ilastik/webilastik/>

of dense cellular features. The workflow consists of the online services [WebAlign](#)⁶⁷ and [WebWarp](#)⁶⁸ for image registration, [LocaliZoom](#)⁶⁹ for image annotation and extraction of object coordinates and [MeshView](#)⁷⁰ for visualisation of the objects in 3D as point clouds. Instructions and workspace setup are found in a public [collab](#)⁷¹.

Briefly, users upload their images to the private storage bucket using the data proxy, the images are converted to pyramid files (DZI format) using an ingestion app. They can also choose a curated KG dataset. The images are then registered to a reference atlas with WebAlign, non-linear refinement of this registration is obtained with WebWarp. All webapps are running on OKD Openshift. New file formats ensure a seamless flow between apps in the pipeline. In LocaliZoom, users can zoom into the experimental images and place markers. The coordinates of these markers are stored in a .lz file and can be exported as an Excel workbook. The LocaliZoom file (.lz) can be opened in the 3D viewer MeshView (Figure 21).

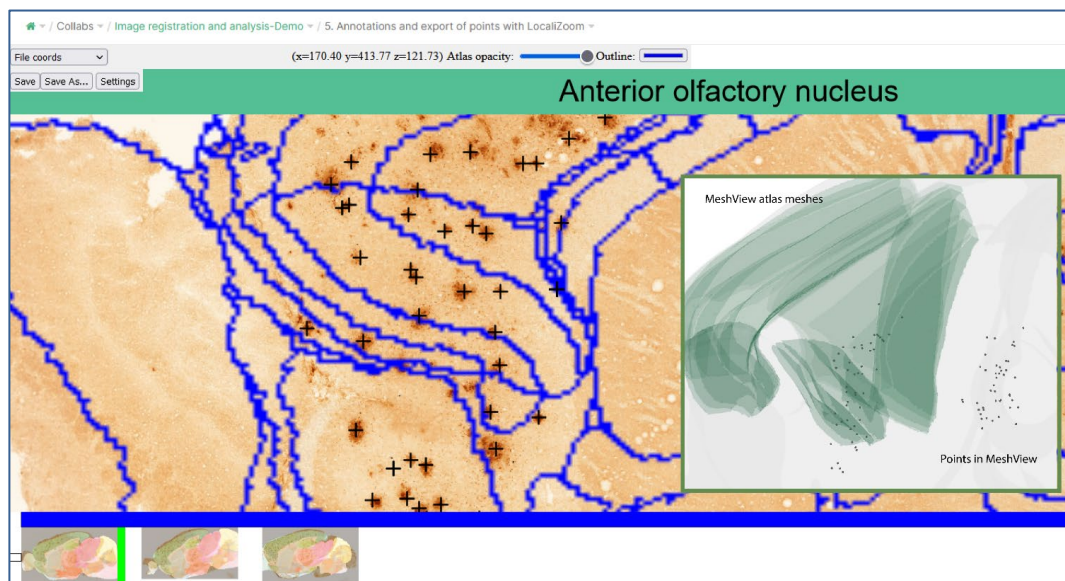


Figure 21: Annotation of amyloid plaques using LocaliZoom and visualisation in MeshView

The Dataset shared on EBRAINS illustrated here is “[Brain-wide distribution of amyloid deposits in adult tg-ArcSwe mice](#)”⁷². As a result of using pyramid file format, users can zoom in their high-resolution images for marking the objects they want to extract. Coordinates are stored in a specific file format compatible with MeshView. Users can also export the coordinates to an Excel workbook.

5.2.2 Cellular quantification and distribution with the QUINT workflow

The QUINT workflow⁷³ ([Gurdon et al. 2023](#); [Yates et al. 2019](#)) comprises a flexible suite of software designed to support atlas-based quantification of labelled features in series of histological images from mouse or rat brain. It supports the latest versions of the Allen mouse atlas, CCFv3 and Waxholm rat atlas version 2, 3 and 4. New features in Nutil now support nonlinear registrations from VisuAlign with updated object reports and point cloud files as well as support for defining custom regions for the [QCalign](#)⁷⁴ ([Gurdon et al. 2023](#)) software (Figure 22). Error messages in the GUI have been improved and the user documentation is considerably improved. The user community is very active,

⁶⁷ <https://ebrains.eu/tools/webalign>

⁶⁸ <https://ebrains.eu/tools/webwarp>

⁶⁹ <https://ebrains.eu/tools/localizoom>

⁷⁰ <https://ebrains.eu/tools/meshview>

⁷¹ <https://wiki.ebrains.eu/bin/view/collabs/image-registration-and-analysis-demo>

⁷² <https://doi.org/10.25493/G6CQ-D4D>

⁷³ <https://quint-workflow.readthedocs.io>

⁷⁴ <https://ebrains.eu/tools/qcalign>

which is seen by increasing support requests and citing publications (67 citation for QuickNII (Puchades et al. 2019) and 27 for the QUINT workflow (Yates et al. 2019)). A collection of use cases is published in a recent review article in Science (Leergaard and Bjaalie, 2022).

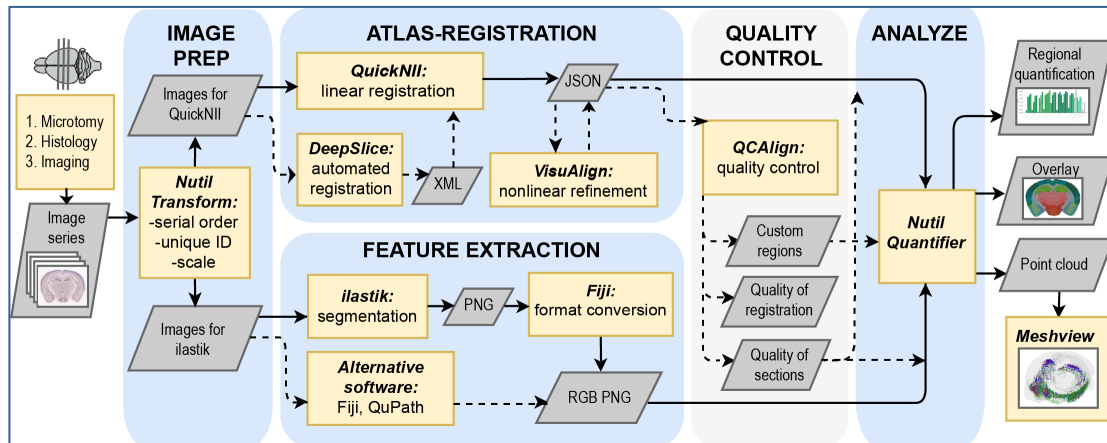


Figure 22: Updated QUINT workflow

Atlas based quantification of labelled features in experimental rodent brain sections images. The main steps are image registration to the atlas, object segmentation and quantification per atlas region. The outputs are quantitative reports (CSV format) and point cloud files (JSON format).

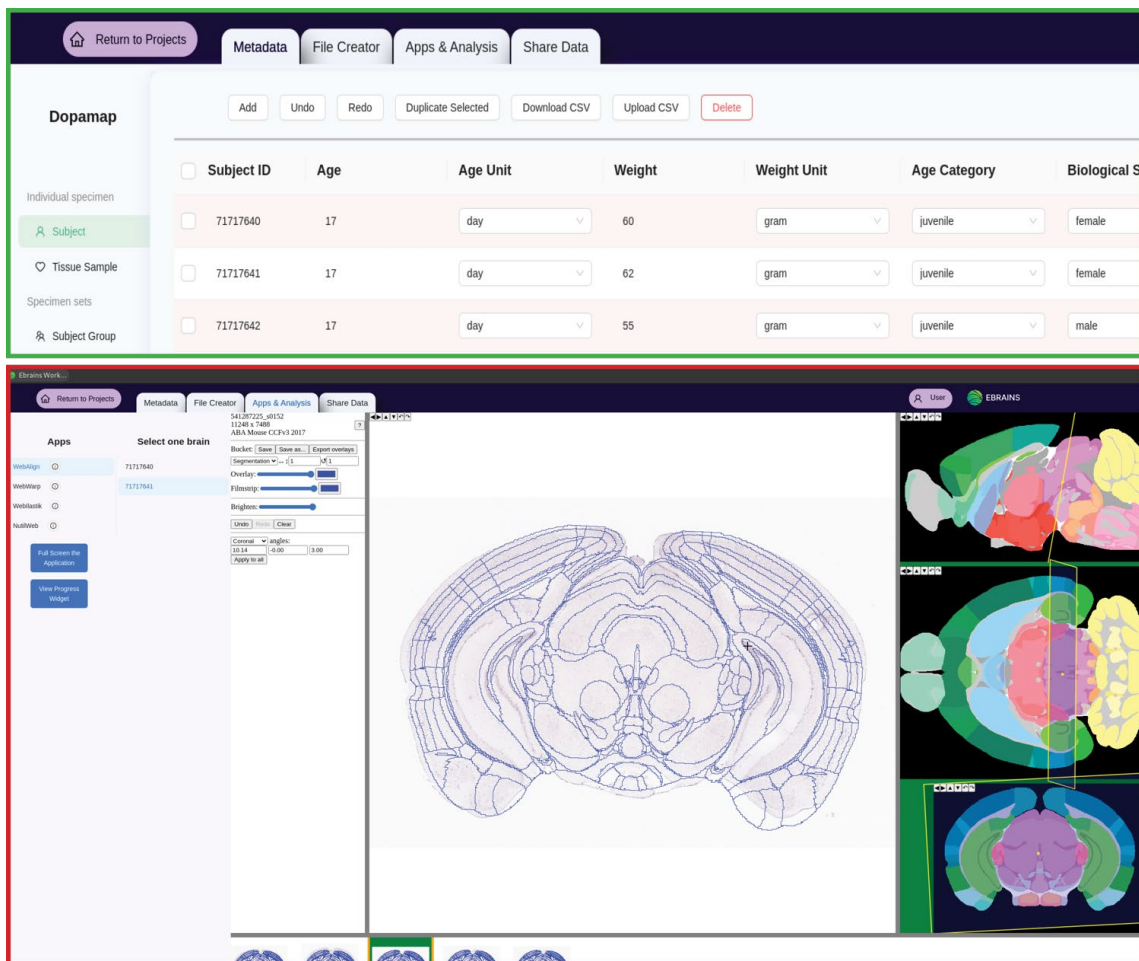


Figure 23: Workbench for online QUINT workflow

In the workbench, EBRAINS users can upload their brain section images and collect metadata about their experiment. The second tab, “File creator” enables creation of pyramid files (DZI format) directly compatible with all apps. In the third tab, users can perform the different steps of the QUINT workflow: registration, segmentation, and quantification. The results and metadata are pre-formatted to be easily shared on the EBRAINS platform with the “share” tab.

As mentioned in the atlas registration tools paragraph, we have developed webapps and we can now propose to EBRAINS users a complete online [QUINT workflow](#)⁷⁵. All the webapps have been integrated in a workbench available here: <https://rodent-brain-workbench.apps.hbp.eu> (Figure 23). A user manual is provided as [readthedocs](#)⁷⁶.

After logging in, EBRAINS users will be able to 1) create a project; 2) upload images; 3) create a brain series; 4) register the images to a reference atlas with WebAlign; 5) adjust the registration non-linearly with WebWarp (if desired); 6) segment the images with web-ilastik; 7) perform quantification analyses with the Nutil Quantifier module and 8) visualise the generated results as point clouds in MeshView (see Section 5.2.1).

The online QUINT workflow is currently deployed at CSCS and is accessed via an EBRAINS account. It will be accessible from other sites as well. The output of the workflow is both point cloud jsons, and statistical information available as a csv file. All output files are available as both direct downloads through the application and are deposited into a linked EBRAINS collaboratory bucket, enabling seamless integration with the collaboratory notebooks.

5.3 Atlas guided analysis of cellular networks

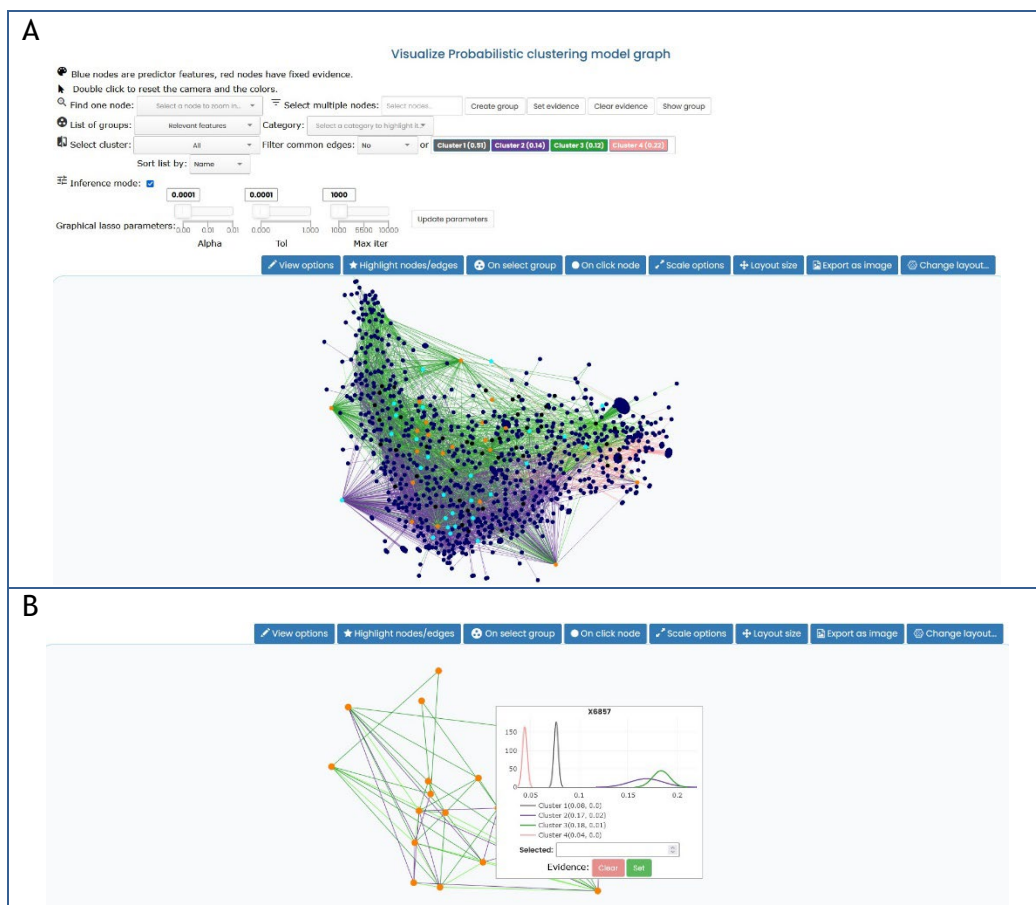


Figure 24: User interface of Bayessuites

A: Visual representation of the probabilistic clustering of the example data set Allen model⁷⁷. B: Selection of a group with the 20 most relevant nodes according to the uploaded metadata of the data set in A.

[NeuroSuites](#)⁷⁸ is a collection of online services for interactive neuroscience data analysis, with a focus on machine learning algorithms for morphological analyses of neurons and cellular networks

⁷⁵ <https://neural-systems-at-uoio.github.io/>

⁷⁶ <https://quint-webtools.readthedocs.io/en/latest/>

⁷⁷ https://neurosuites.com/morpho/ml_probabilistic_clustering

⁷⁸ <https://neurosuites.com/>

(Bernaola et al. 2020; Moreno-Rodríguez et al., 2023). The services are designed as interactive tools to be employed directly in the web browser, with intuitive controls that can also be used by non-specialists. The recent version of the web interface has undergone a redesign that provides a significantly improved user experience. A particular focus in the context of EBRAINS atlas services is a selection of algorithms for analysing gene expression data and the estimation of gene regulatory networks. These algorithms have now been modularised into a dedicated python library, *neurogenpy*, which is used to connect this functionality to the EBRAINS atlas services for convenient computation and visualisation of such networks for specific brain regions. This exploits the already existing capabilities of *siibra-python* (cf. Section 3.2.1) to extract gene expression levels, and the capability of *siibra-explorer* (cf. Section 3.1) to allow the implementation of plugins. The latest version relaxes the Gaussianity assumption of the node distributions to allow them to coexist with kernel density-based distributions (shaping semiparametric Bayesian networks) (Figure 24).

5.4 Atlas-guided analysis of fMRI data (nilearn/nibabel)

*Nilearn*⁷⁹ enables approachable and versatile analyses of brain volumes. It provides statistical and machine-learning tools, with instructive documentation and an open community. It supports general linear model (GLM) based analysis and leverages the scikit-learn Python toolbox for multivariate statistics with applications such as predictive modelling, classification, decoding, and connectivity analysis. Ongoing development has resulted in 2 releases this year: v0.10.0 in January and v0.10.1 in April 2023. An associated python package that provides read and write access to some common medical and neuroimaging file formats, *Nibabel*⁸⁰, has been released in April 2023 (v5.1.0). This tool is part of the *nipy*⁸¹ community. In March 2023, several workshops were held, including at the HBP summit in Marseille, demonstrating *nilearn* functionality.

Integration of *Nilearn* with the EBRAINS Knowledge Graph and the *siibra-python* client based on an *interactive notebook*⁸² is now completed (Figure 25; Figure 26). The integration demonstrates how the combination of EBRAINS atlases and data with *Nilearn* and *Nibabel* make it easy to run a functional connectivity analysis to study brain architecture or compare groups of individuals. Current efforts include a better handling of surface, further development on BIDS interfacing, and active community outreach to facilitate interactions with relevant community tools.

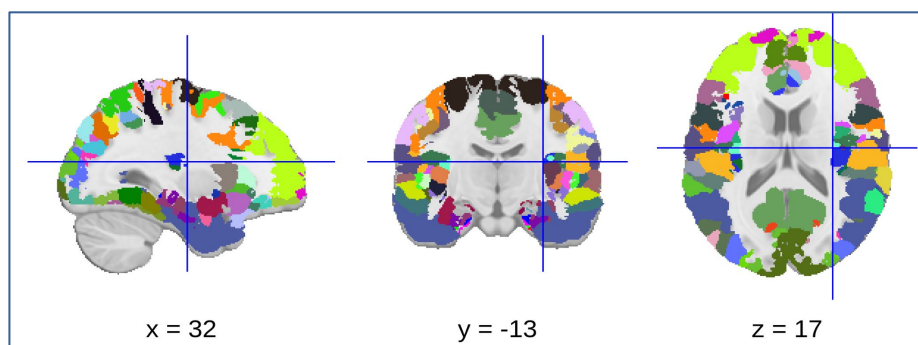


Figure 25: Parcellation map fetched with *siibra* and plotted with *nilearn*'s plotting module

⁷⁹ <https://nilearn.github.io/>

⁸⁰ <https://nipy.org/nibabel/>

⁸¹ <https://nipy.org>

⁸² <https://github.com/ymzayek/EBRAINS-Connectivity-Analysis>

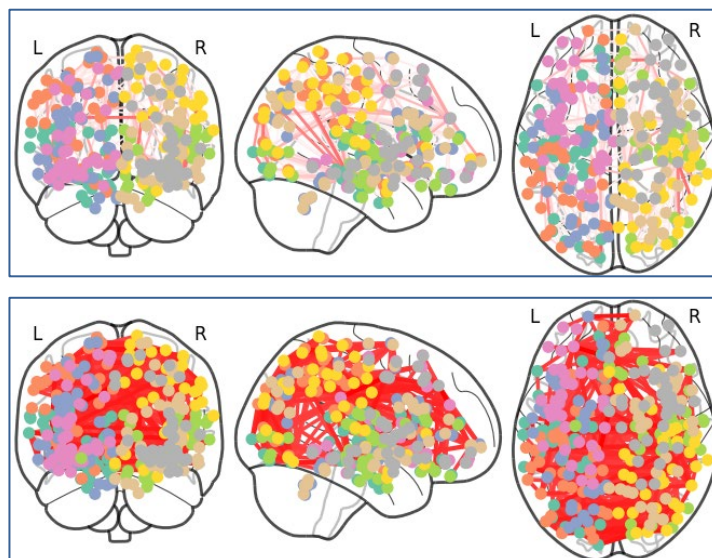


Figure 26: Comparing structural with functional connectivity using siibra and Nilearn

Comparison of structural connectivity results (top) fetched from EBRAINS Knowledge Graph using siibra and functional connectivity results (bottom) from analysis with Nilearn

Appendix

References

- Amunts, Katrin, Claude Lepage, Louis Borgeat, Hartmut Mohlberg, Timo Dickscheid, Marc-Etienne Rousseau, Sebastian Bludau, et al. 2013. "BigBrain: An Ultrahigh-Resolution 3D Human Brain Model." *Science* 340 (6139): 1472-75. <https://doi.org/10.1126/science.1235381>.
- Amunts, Katrin, Hartmut Mohlberg, Sebastian Bludau, and Karl Zilles. 2020. "Julich-Brain: A 3D Probabilistic Atlas of the Human Brain's Cytoarchitecture." *Science* 369 (6506): 988. <https://doi.org/10.1126/science.abb4588>. P2583
- Ashburner, John. 2007. "A Fast Diffeomorphic Image Registration Algorithm." *NeuroImage* 38 (1): 95-113. <https://doi.org/10.1016/j.neuroimage.2007.07.007>.
- Auzias, Guillaume, Olivier Colliot, Joan Alexis Glaunes, Matthieu Perrot, Jean-François Mangin, Alain Troune, and Sylvain Baillet. 2011. "Diffeomorphic Brain Registration Under Exhaustive Sulcal Constraints." *IEEE Transactions on Medical Imaging* 30 (6): 1214-27. <https://doi.org/10.1109/TMI.2011.2108665>.
- Axer, M., C. Poupon, and I. Costantini. 2020. "Fiber Structures of a Human Hippocampus Based on Joint DMRI, 3D-PLI, and TPFM Acquisitions." Human Brain Project Neuroinformatics Platform. <https://doi.org/10.25493/JQ30-E08>.
- Balan, Puiu F., Qi Zhu, Xiaolian Li, Rembrandt Bakker, Nicola Palomero-Gallagher, and Wim Vanduffel. 2023. "MEBRAINS: A New Population-Based Monkey Template (v1.0)." EBRAINS. <https://doi.org/10.25493/5454-ZEA>.
- Balan, Puiu F., Qi Zhu, Xiaolian Li, Meiqi Niu, Lucija Rapan, Thomas Funck, Rembrandt Bakker, Nicola Palomero-Gallagher, and Wim Vanduffel. 2023. "MEBRAINS 1.0: A New Population-Based Macaque Atlas." Preprint. Neuroscience. <https://doi.org/10.1101/2023.06.21.545953>. P4128
- Behuet, Sabrina, Sebastian Bludau, Olga Kedo, Christian Schiffer, Timo Dickscheid, Andrea Brandstetter, Philippe Massicotte, Mona Omidyeganeh, Alan Evans, and Katrin Amunts. 2021. "A High-Resolution Model of the Human Entorhinal Cortex in the 'BigBrain' - Use Case for Machine Learning and 3D Analyses." In Brain-Inspired Computing (BrainComp), edited by Katrin Amunts, Lucio Grandinetti, Thomas Lippert, and Nicolai Petkov, 3-21. Lecture Notes in Computer Science. Cham: Springer International Publishing. https://doi.org/10.1007/978-3-030-82427-3_1. P2962
- Bernaola, Nikolas, Mario Michiels, Pedro Larrañaga, and Concha Bielza. 2020. CLearning Massive Interpretable Gene Regulatory Networks of the Human Brain by Merging Bayesian Networks." bioRxiv. <https://doi.org/10.1101/2020.02.05.935007>. P2329
- Bjerke, Ingvild, Sharon C. Yates, Arthur Laja, Menno P. Witter, Maja A. Puchades, Jan G. Bjaalie, and Trygve B. Leergaard. 2020. "Densities and numbers of calbindin and parvalbumin positive neurons across the rat and mouse brain." *iScience*. <https://doi.org/10.1016/j.isci.2020.101906>. P2682
- Bjerke, Ingvild, E.R Cullity, K. Kjelsberg, K. M. Charan, T. B. Leergaard, and J. H. Kim. 2022. "DOPAMAP, high-resolution images of dopamine 1 and 2 receptor expression in developing and adult mouse brains." *Sci Data*. <https://doi.org/10.1038/s41597-022-01268-8>. P4185
- Blixhavn, Camilla, Finn-Mogens Š. Haug, Heidi Kleven, Maja A. Puchades, Jan G. Bjaalie and Trygve B. Leergaard. 2023. "A Timm-Nissl multiplane microscopic atlas of rat brain zincergic terminal fields and metal-containing glia." *Sci Data*. <http://dx.doi.org/10.1038/s41597-023-02012-6>
- Brandstetter, Andrea, Najoua Bolakhrif, Christian Schiffer, Timo Dickscheid, Hartmut Mohlberg, and Katrin Amunts. 2021. "Deep Learning-Supported Cytoarchitectonic Mapping of the Human Lateral Geniculate Body in the BigBrain." In Brain-Inspired Computing (BrainComp), edited by Katrin Amunts, Lucio Grandinetti, Thomas Lippert, and Nicolai Petkov, 22-32. Lecture Notes in Computer Science. Cham: Springer International Publishing. https://doi.org/10.1007/978-3-030-82427-3_2. P2961
- Carey, Harry, Michael Pegios, Lewis Martin, Christine Saleeba, Anita Turner, Nicholas Everett, Maja Puchades, Jan Bjaalie, and Simon McMullan. 2022. "DeepSlice: Rapid Fully Automatic

- Registration of Mouse Brain Imaging to a Volumetric Atlas.” *Nature Communications* <https://doi.org/10.1038/s41467-023-41645-4>. P4181
- Eckermann, Marina, Bernhard Schmitzer, Franziska van der Meer, Jonas Franz, Ove Hansen, Christine Stadelmann, and Tim Salditt. 2021. “Three-Dimensional Virtual Histology of the Human Hippocampus Based on Phase-Contrast Computed Tomography.” *Proceedings of the National Academy of Sciences* 118 (48): e2113835118. <https://doi.org/10.1073/pnas.2113835118>.
- Froudust-Walsh, Sean, Ting Xu, Meiqi Niu, Lucija Rapan, Ling Zhao, Daniel S. Margulies, Karl Zilles, Xiao-Jing Wang, and Nicola Palomero-Gallagher. 2023. “Gradients of Neurotransmitter Receptor Expression in the Macaque Cortex.” *Nature Neuroscience* 26 (7): 1281-94. <https://doi.org/10.1038/s41593-023-01351-2>. P4115
- Glaunes, J., A. Trouve, and L. Younes. 2004. “Diffeomorphic Matching of Distributions: A New Approach for Unlabelled Point-Sets and Sub-Manifolds Matching.” In *Proceedings of the 2004 IEEE Computer Society Conference on Computer Vision and Pattern Recognition, 2004. CVPR 2004.*, 2:II-II. <https://doi.org/10.1109/CVPR.2004.1315234>.
- Gurdon, Brianna, Sharon C. Yates, Gergely Csucs, Nicolaas E. Groeneboom, Niran Hadad, Maria Telpoukhovskaia, Andrew Ouellette, et al. 2023. “Detecting the Effect of Genetic Diversity on Brain Composition in an Alzheimer’s Disease Mouse Model.” Preprint. *Neuroscience*. <https://doi.org/10.1101/2023.02.27.530226>. P3880
- Haghir, Hossein, Anika Kuckertz, Ling Zhao, Javad Hami, and Nicola Palomero-Gallagher. 2023. “A New Map of the Rat Isocortex and Proisocortex: Cytoarchitecture and M2 Receptor Distribution Patterns.” *Brain Structure and Function*, June. <https://doi.org/10.1007/s00429-023-02654-7>. P4111
- Hawrylycz, Michael, Maryann E. Martone, Giorgio A. Ascoli, Jan G. Bjaalie, Hong-Wei Dong, Satrajit S. Ghosh, Jesse Gillis, et al. 2023. “A Guide to the BRAIN Initiative Cell Census Network Data Ecosystem.” *PLOS Biology* 21 (6): e3002133. <https://doi.org/10.1371/journal.pbio.3002133>. P4130
- Impieri, Daniele, Karl Zilles, Meiqi Niu, Lucija Rapan, Nicole Schubert, Claudio Galletti, and Nicola Palomero-Gallagher. 2019. “Receptor Density Pattern Confirms and Enhances the Anatomic-Functional Features of the Macaque Superior Parietal Lobule Areas.” *Brain Structure and Function* 224 (8): 2733-56. <https://doi.org/10.1007/s00429-019-01930-9>. P2063
- Kiwitz, Kai, Andrea Brandstetter, Christian Schiffer, Sebastian Bludau, Hartmut Mohlberg, Mona Omidyeganeh, Philippe Massicotte, and Katrin Amunts. 2022. “Cytoarchitectonic Maps of the Human Metathalamus in 3D Space.” *Frontiers in Neuroanatomy* 16 (March). <https://doi.org/10.3389/fnana.2022.837485>. P3263
- Kjonigsen, Lisa J., Sveinung Lillehaug, Jan G. Bjaalie, Menno P. Witter, and Trygve B. Leergaard. 2015. “Waxholm Space Atlas of the Rat Brain Hippocampal Region: Three-Dimensional Delineations Based on Magnetic Resonance and Diffusion Tensor Imaging.” *NeuroImage* 108 (March): 441-49. <https://doi.org/10.1016/j.neuroimage.2014.12.080>. P3304
- Kleven, Heidi, Ingvild Bjerke, Francisco Clascá, Hendrik Groenewegen, Jan Bjaalie, and Trygve Leergaard. 2023. “Waxholm Space Atlas of the Rat Brain: A 3D Atlas Supporting Data Analysis and Integration.” Preprint. In Review. <https://doi.org/10.21203/rs.3.rs-2466303/v1>. P3851
- Kleven H, Gillespie TH, Zehl L, Dickscheid T, Bjaalie JG, Martone ME, Leergaard TB. AtOM, an ontology model to standardize use of brain atlases in tools, workflows, and data infrastructures. *Sci Data*. 2023 Jul 26;10(1):486. <https://doi.org/10.1038/s41597-023-02389-4>. P4132
- Langlet, C., D. Rivière, A. Grigis, V. Frouin, and J.-F. Mangin. 2023. “Nested Parcellations Connectome Delivered for One Large Dataset Using Constellation Algorithm v1.2.” *EBRAINS KG*. <https://doi.org/10.25493/1CFB-ZF8>.
- Lebenberg, Jessica, Mickael Labit, G. Auzias, Hartmut Mohlberg, C. Fischer, D. Rivière, Edouard Duchesnay, et al. 2018. “A Framework Based on Sulcal Constraints to Align Preterm, Infant and Adult Human Brain Images Acquired in Vivo and Post Mortem.” *Brain Structure and Function* 223 (9): 4153-68. <https://doi.org/10.1007/s00429-018-1735-9>. P1391
- Lechanoine, François, Timothée Jacquesson, Justine Beaujoin, Barthélemy Serres, Mohammad Mohammadi, Alexia Planty-Bonjour, Frédéric Andersson, Fabrice Poupon, Cyril Poupon, and Christophe Destrieux. 2021. “WIKIBrainStem: An Online Atlas to Manually Segment the

- Human Brainstem at the Mesoscopic Scale from Ultrahigh Field MRI.” *NeuroImage* 236 (August): 118080. <https://doi.org/10.1016/j.neuroimage.2021.118080>.
- Leergaard TB, Bjaalie JG. Atlas-based data integration for mapping the connections and architecture of the brain. *Science*. 2022 Nov 4;378(6619):488-492. <https://doi.org/10.1126/science.abq2594>. Epub 2022 Nov 3. P3717
- Maitin-Shepard, Jeremy, Alex Baden, William Silversmith, Eric Perlman, Forrest Collman, Tim Blakely, Jan Funke, et al. 2021. “Google/Neuroglancer.” Zenodo. <https://doi.org/10.5281/zenodo.5573294>.
- Moreno-Rodríguez, José Luis, Pedro Larrañaga, and Concha Bielza. 2023. “NeuroSuites: An Online Platform for Running Neuroscience, Statistical, and Machine Learning Tools.” *Frontiers in Neuroinformatics* 17. <https://www.frontiersin.org/articles/10.3389/fninf.2023.1092967>.
- Niu, Meiqi, Daniele Impieri, Lucija Rapan, Thomas Funck, Nicola Palomero-Gallagher, and Karl Zilles. 2020. “Receptor-Driven, Multimodal Mapping of Cortical Areas in the Macaque Monkey Intraparietal Sulcus.” *ELife* 9 (July): e55979. <https://doi.org/10.7554/eLife.55979>. P2651
- Niu, Meiqi, Lucija Rapan, Thomas Funck, Seán Froudish-Walsh, Ling Zhao, Karl Zilles, and Nicola Palomero-Gallagher. 2021. “Organization of the Macaque Monkey Inferior Parietal Lobule Based on Multimodal Receptor Architectonics.” *NeuroImage* 231: 117843. <https://doi.org/10.1016/j.neuroimage.2021.117843>. P2801
- Osen, Kirsten K., Jala Imad, Arvind E. Wennberg, Eszter A. Papp, and Trygve B. Leergaard. 2019. “Waxholm Space Atlas of the Rat Brain Auditory System: Three-Dimensional Delineations Based on Structural and Diffusion Tensor Magnetic Resonance Imaging.” *NeuroImage* 199 (October): 38-56. <https://doi.org/10.1016/j.neuroimage.2019.05.016>. P1879
- Papp, Eszter Agnes, Trygve Brauns Leergaard, Evan Calabrese, G. Allan Johnson, and Jan G. Bjaalie. 2014. “Waxholm Space Atlas of the Sprague Dawley Rat Brain.” *NeuroImage* 97 (August): 374-86. <https://doi.org/10.1016/j.neuroimage.2014.04.001>. P3302
- Peng, Hanchuan, Peng Xie, Lijuan Liu, Xiuli Kuang, Yimin Wang, Lei Qu, Hui Gong, et al. 2021. “Morphological Diversity of Single Neurons in Molecularly Defined Cell Types.” *Nature* 598 (7879): 174-81. <https://doi.org/10.1038/s41586-021-03941-1>.
- Puchades, Maja A., Gergely Csucs, Debora Ledergerber, Trygve B. Leergaard, and Jan G. Bjaalie. 2019. “Spatial Registration of Serial Microscopic Brain Images to Three-Dimensional Reference Atlases with the QuickNII Tool.” Edited by Manuel S. Malmierca. *PLOS ONE* 14 (5): e0216796. <https://doi.org/10.1371/journal.pone.0216796>. P2182
- Rapan, Lucija, Sean Froudish-Walsh, Meiqi Niu, Ting Xu, Thomas Funck, Karl Zilles, and Nicola Palomero-Gallagher. 2021. “Multimodal 3D Atlas of the Macaque Monkey Motor and Premotor Cortex.” *NeuroImage* 226 (February): 117574. <https://doi.org/10.1016/j.neuroimage.2020.117574>. P2623
- Rapan, Lucija J., Sean Froudish-Walsh, Meiqi Niu, Ting Xu, Ling Zhao, Thomas Funck, Xiao-Jing Wang, Katrin Amunts, and Nicola Palomero-Gallagher. 2022. “Cytoarchitectonic, Receptor Distribution and Functional Connectivity Analyses of the Macaque Frontal Lobe.” Preprint. *Neuroscience*. <https://doi.org/10.7554/eLife.82850>. P4117
- Rapan, Lucija, Meiqi Niu, Ling Zhao, Thomas Funck, Katrin Amunts, Karl Zilles, and Nicola Palomero-Gallagher. 2022. “Receptor Architecture of Macaque and Human Early Visual Areas: Not Equal, but Comparable.” *Brain Structure and Function* 227 (4): 1247-63. <https://doi.org/10.1007/s00429-021-02437-y>. P3167
- Reiten, Ingrid, Grethe M. Olsen, Jan G. Bjaalie, Menno P. Witter, and Trygve B. Leergaard. 2023. “The efferent connections of the orbitofrontal, posterior parietal, and insular cortex of the rat brain.” *Sci Data* <http://dx.doi.org/10.1038/s41597-023-02527-y>. P4180
- Schiffer C, Spitzer H, Kiwitz K, Unger N, Wagstyl K, Evans AC, Harmeling S, Amunts K, Dickscheid T. Convolutional neural networks for cytoarchitectonic brain mapping at large scale. *NeuroImage*. 2021;240:118327. <https://doi.org/10.1016/j.neuroimage.2021.118327>. P2872
- Schiffer, Christian, Claude Lepage, Mona Omidyeganeh, Hartmut Mohlberg, Andrea Brandstetter, Sebastian Bludau, Katja Heuer, et al. 2022. “Selected 1 Micron Scans of BigBrain Histological Sections (v1.0).” EBRAINS. <https://doi.org/10.25493/JWTF-PAB>.
- Sip, Viktor, Meysam Hashemi, Timo Dickscheid, Katrin Amunts, Spase Petkoski, and Viktor Jirsa. 2023. “Characterization of Regional Differences in Resting-State fMRI with a Data-Driven



- Network Model of Brain Dynamics.” *Science Advances* 9 (11): eabq7547.
<https://doi.org/10.1126/sciadv.abq7547>. P3924
- Tocco, Chiara, Martin Øvsthus, Jan G. Bjaalie, Trygve B. Leergaard, and Michèle Studer. 2022. “The topography of corticopontine projections is controlled by postmitotic expression of the area-mapping gene *Nr2f1*.” *Development* 149 (5). <https://doi.org/10.1242/dev.200026>. P3242
- Winnubst, Johan, Erhan Bas, Tiago A. Ferreira, Zhuhao Wu, Michael N. Economo, Patrick Edson, Ben J. Arthur, et al. 2019. “Reconstruction of 1,000 Projection Neurons Reveals New Cell Types and Organization of Long-Range Connectivity in the Mouse Brain.” *Cell* 179 (1): 268-281.e13. <https://doi.org/10.1016/j.cell.2019.07.042>.
- Yates, Sharon C., Nicolaas E. Groeneboom, Christopher Coello, Stefan F. Lichtenthaler, Peer-Hendrik Kuhn, Hans-Ulrich Demuth, Maike Hartlage-Rübsamen, et al. 2019. “QUINT: Workflow for Quantification and Spatial Analysis of Features in Histological Images From Rodent Brain.” *Frontiers in Neuroinformatics* 13 (December): 75.
<https://doi.org/10.3389/fninf.2019.00075>. P2245
- Zachlod, Daniel, Nicola Palomero-Gallagher, Timo Dickscheid, and Katrin Amunts. 2023. “Mapping Cytoarchitectonics and Receptor Architectonics to Understand Brain Function and Connectivity.” *Biological Psychiatry* 93 (5): 471-79.
<https://doi.org/10.1016/j.biopsych.2022.09.014>. P3891