

**EBRAINS Brain Atlas Services (SC2) - status at M18**  
**(D4.8 - SGA3)**



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

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<b>Author(s):</b>	Timo DICKSCHEID, JUELICH (P20)		
<b>Compiled by:</b>	Anna HILVERLING, JUELICH (P20)		
<b>Contributor(s):</b>	Trygve LEERGAARD, UiO (P81), contributed to Section 2.1.2, 2.1.3, 4.1, 4.2 Maja Puchades, UiO (P81), contributed to Section 2.3.1, 2.4.5, 4.1, 4.2, 4.3, 4.4 Wim VANDUFFEL, KUL (P111), contributed to Section 2.1.4, 4.1 Puiu BALAN, KUL (P111), contributed to Section 2.1.4, 4.1 Nicola PALOMERO-GALLAGHER, JUELICH (P20), contributed to Section 2.1.4, 4.1 Anna KRESHUK, EMBL (P123), contributed to Section 2.4.1, 4.3 Dominik KUTRA, EMBL (P123), contributed to Section 2.4.1, 4.3 Tomaz VIEIRA, EMBL (P123), contributed to Section 2.4.1, 4.3 Nicolas BERNAOLA, UPM (P68), contributed to Section 2.4.2 José Luís MORENO, UPM (P68), contributed to Section 2.4.2 Michael HANKE, JUELICH (P20), contributed to Section 4.2 Hiba ASIM, JUELICH (P20), contributed to Section 3 Lyuba ZEHL, JUELICH (P20), contributed to Section 2.1.3 Xiaoyun GUI, JUELICH (P20), contributed to Section 2.2.1, 4.2 Jean-François MANGIN, CEA (P11), contributed to Section 2.2.3, 4.1 Bertrand THIRION, INRIA (P33), contributed to Section 2.4.3		
<b>WP QC Review:</b>	Stefan KOEHNEN, JUELICH (P20)		
<b>WP Leader / Deputy Leader Sign Off:</b>	Jan BJAALIE, UiO (P81)		
<b>T7.4 QC Review:</b>	Annemieke MICHELS, Martin TELEFONT, EBRAINS (P1)		
<b>Description in GA:</b>	Extended brain atlases with major update of murine and first release of basic NHP atlas, new toolboxes supporting clinical and neuroimaging usecases, as well as new releases of web-based spatial anchoring and data analysis tools.		
<b>Abstract:</b>	EBRAINS provides access to reference atlases for the human, rat and mouse brain, which are continuously refined and improved, and is now complemented with a non-human primate atlas of the macaque monkey. All atlases can be explored visually		

<p>in the 3D interactive online viewer and are connected to programmatic workflows via a REST API and a Python client. Being closely linked to the EBRAINS Knowledge Graph, the atlas services provide access to a growing number of neuroscience datasets from a broad range of modalities across different spatial and temporal scales, which are linked to anatomical entities through the atlases. 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 “Atlases” website of 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 2021, and highlights developments since November 2020.</p>	
<b>Keywords:</b>	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
<b>Target Users/Readers:</b>	computational neuroscience community, computer scientists, Consortium members, funders, general public, neuroimaging community, neuroinformaticians, neuroscientific community, neuroscientists, platform users, researchers, scientific community, students.

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# 1. Introduction

Brain atlases provide spatial reference systems for neuroscience, giving the ability to navigate, characterise and analyse information on the basis of anatomical location. They define the shape, location and variability of brain regions in common coordinate spaces, and allow interpretation, integration, and comparison of observations and measurements collected from different sources and brains. EBRAINS atlas services build on the unique reference atlases of the rodent and human brain developed by the Human Brain Project, which is now complemented by a new non-human primate atlas. The primary point of access to the reference atlases is the online viewer (Figure 2; Section 2.2.1).

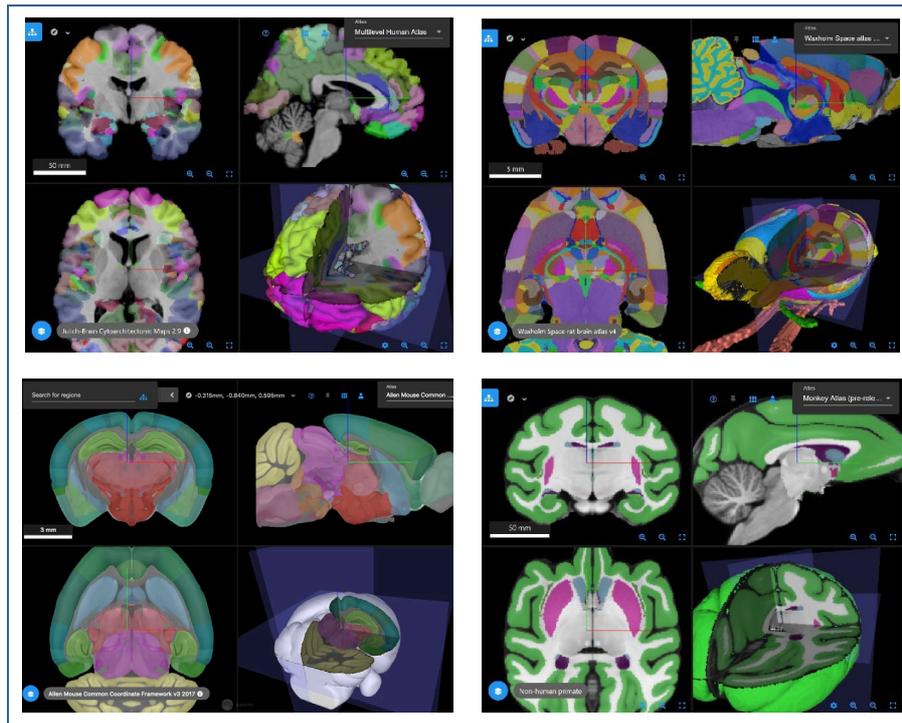


Figure 2: EBRAINS reference atlases of the human, rat, mouse and monkey brain

Atlases can be explored using *siibra-explorer*, the interactive atlas viewer hosted by EBRAINS (<https://atlases.ebrains.eu/viewer>).

As part of the Tier 2 curation process of the [EBRAINS data sharing services](#)<sup>a</sup>, these reference atlases are used to link a large fraction of the neuroscience data and models shared in the EBRAINS Knowledge Graph to anatomical locations, and thus provide an anatomically organised entry point for accessing multimodal data. In this way, highly diverse data can be spatially coupled through the anatomical delineations and terms for brain regions.

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-display experimental data in a 3D high resolution reference brain space, determine anatomical location and find spatially relevant features to interpret data and confirm or support user studies.
- **computational neuroscience:** Construct models of brain simulations with plausible anatomical constraints, and comprehensive regional characterisations of brain organisation; including cellular, molecular and connectivity features.

<sup>a</sup> <https://ebrains.eu/service/share-data>

- **neuroanatomy:** Without installing additional software, explore brain architecture in 3D at different spatial resolutions, and study the shape and spatial relationships of brain regions, functional modules and their connections.
- **neuroimaging:** Perform anatomical assignment of signal patterns, e.g. fMRI activations. Combine whole brain imaging data with multimodal features at the cellular scale from the meso- and microscopic scales.
- **brain-inspired AI research:** For biologically plausible AI models, extract quantitative aspects of the structure of the biological networks in the brain, resolved with a spatial specificity of individual cortical layers.
- **neurosurgery and medicine:** Understand the multilevel brain architecture in the vicinity of surgical target regions, identify paths to regions of interest, and understand the cellular composition of regions of interest, e.g. in Parkinson's & epilepsy.

Besides enabling such use cases for scientists, EBRAINS atlas services also constitute a key infrastructure element for other EBRAINS endeavours. For example, they offer the reference framework for enriching datasets with location metadata by EBRAINS data services (Tier 2 curation), organise the multilevel connectome that is currently being developed by HBP scientists and provide an important entry point for experimental data collection for brain simulations.

EBRAINS atlas services can be grouped into three main categories:

- 1) Services providing access to reference atlases
- 2) Services allowing to spatially integrate diverse new research data within these atlases
- 3) Services for anatomically motivated data analysis

These services are built on top of the EBRAINS base infrastructure, in particular by using the knowledge, datasets and models shared in the EBRAINS Knowledge Graph, by retrieving most of their underlying data from the storage infrastructure provided by [FENIX](#)<sup>b</sup>, by hosting their online services on FENIX virtual machines, and by working closely with EBRAINS data curation teams.

The focus of the present document is to describe new developments that have occurred within the EBRAINS atlas services in the time frame between October 2020 (M8) and September 2021 (M18). The previous status, together with a comprehensive explanation of the basic elements, is documented in [D4.2 EBRAINS Brain Atlas Services](#)<sup>c</sup>.

## 2. New developments in EBRAINS atlas services

### 2.1 Reference brain atlases

#### 2.1.1 *Julich-Brain version 2.9 with new maps and surface support*

The human brain atlas now supports the new version 2.9 of the Julich-Brain probabilistic cytoarchitectonic maps ([Amunts et al., 2020](#)<sup>1</sup>), which includes 24 new brain region maps (Table 1). In particular, it significantly expands the coverage in the frontal, temporal, and insula lobes, along with several subcortical areas, e.g. the metathalamus and the bed nucleus. The GapMaps of the cerebral cortex have been updated accordingly, and thus take a smaller fraction of the mapped volume. As a 'living atlas', Julich-Brain is constantly expanded and improved, so that future versions will further reduce the size of the GapMaps. The new Julich-Brain is openly accessible as part of the

<sup>b</sup> <https://fenix-ri.eu>

<sup>c</sup> [https://sos-ch-dk-2.exo.io/public-website-production/filer\\_public/00/b1/00b170e2-f102-4b09-ab65-030c89b2adcd/d42\\_d33\\_sga3\\_m8\\_accepted\\_210504.pdf](https://sos-ch-dk-2.exo.io/public-website-production/filer_public/00/b1/00b170e2-f102-4b09-ab65-030c89b2adcd/d42_d33_sga3_m8_accepted_210504.pdf)

multilevel atlas in the 3D interactive viewer (*siibra-explorer*, Sec. 2.2.1), as a data project in the EBRAINS Knowledge Graph, and now also via the new Python client *siibra-python* (Section 2.2.2). The new brain areas are summarised in Table 1.

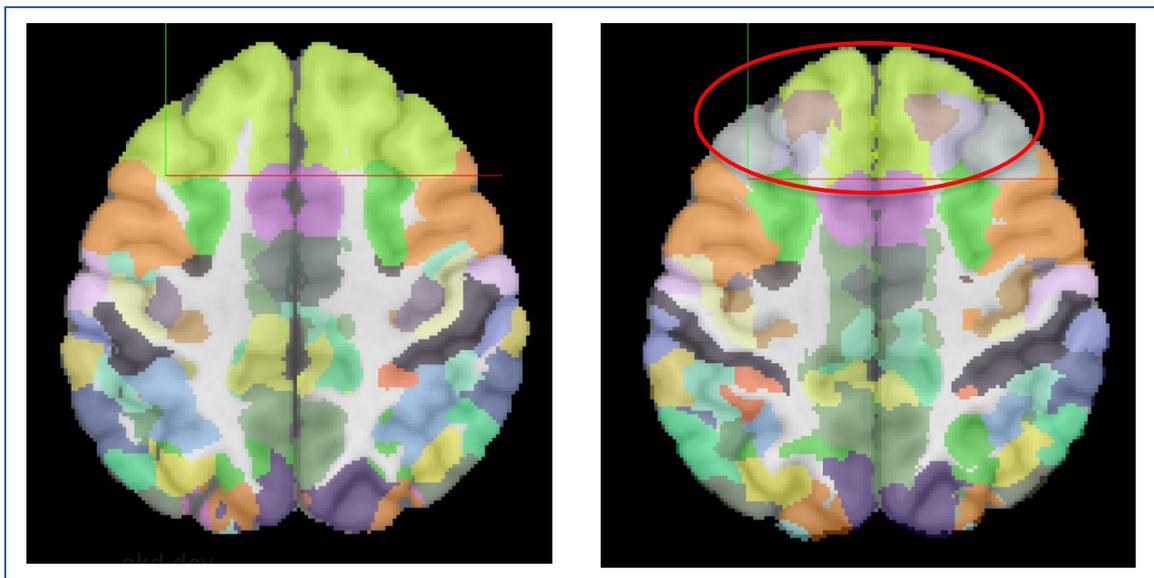


Figure 3: New version 2.9 of the Julich-Brain probabilistic cytoarchitectonic maps

New version 2.9 of the Julich-Brain probabilistic cytoarchitectonic maps (Amunts et al., 2020<sup>d</sup>). Axial view of previous Version 2.6. (left) and the newest version 2.9 (right) of the maximum probability map. Amongst other regions, the Frontal GapMap has been reduced by the introduction of three areas 8d1, 8d2, and 8v1 (grey, light purple and brown).

Table 1: List of new probabilistic cytoarchitectonic maps included in Julich-Brain version 2.9.

Lobe	Area abbreviation	Area name
Insula	Area Ia1	Agranular Insula area 1
	Area Ia2	Agranular Insula area 2
	Area Ia3	Agranular Insula area 3
	Area Id8	Dysgranular Insula area 8
	Area Id9	Dysgranular Insula area 9
	Area Id10	Dysgranular Insula area 10
Metathalamus	CGM	Corpus geniculatum mediale
	CGL	Corpus geniculatum laterale
Temporal lobe	Area CoS1	Colateral sulcus 1
	Area TPJ	Temporo-parietal junction
	Area Ph1	Parahippocampal area 1
	Area Ph2	Parahippocampal area 2
	Area Ph3	Parahippocampal area 3
Frontal lobe	Area ifs1	Inferior frontal sulcus area 1
	Area ifs2	Inferior frontal sulcus area 2
	Area ifs3	Inferior frontal sulcus area 3
	Area ifs4	Inferior frontal sulcus area 4
	Area ifj1	Inferior frontal junction area 1
	Area ifj2	Inferior frontal junction area 2
	Area 8d1	Superior frontal gyrus
	Area 8d2	Superior frontal gyrus
	Area 8v1	Middle frontal gyrus
	Area 8v2	Middle frontal gyrus
Ventral striatum	BST	Bed nucleus of the stria terminalis

<sup>d</sup> <https://doi.org/10.1126/science.abb4588>

In addition to the volumetric maps defined in the MNI 152 2009c nonlinear asymmetric and Colin 27 single-subject reference spaces, the maximum probability map is now also provided as a surface map in the widely used freesurfer ([Fischl et al., 2012<sup>2</sup>](#)) average reference space (Figure 4). The surface projection was computed by J.-F. MANGIN and D. RIVIÈRE and [publicly released as a derived dataset<sup>e</sup>](#). The procedure is described in detail in the included [data descriptor<sup>f</sup>](#). In short, the [volumetric maximum probability map in MNI Colin 27 space<sup>g</sup>](#) was projected onto the cortical surface mesh using the [freesurfer software pipeline<sup>h</sup>](#) by assigning each vertex the majority label along the surface normal. After moderate morphological cleaning, the parcellation was transformed to the fsaverage surface via a folding-based surface registration ([Fischl et al., 1999<sup>3</sup>](#)), and additionally downsampled to fsaverage6 (~40k vertices/hemisphere) and fs\_LR (~32k vertices/hemisphere; [Van Essen et al., 2012<sup>4</sup>](#)). To facilitate exploration of the new surface map together with the volumetric maps, the interactive atlas viewer [siibra-explorer<sup>i</sup>](#) has been extended by a new surface-rendering component (cf. Section 2.2.1), which offers separate views of the "white matter", "pial" and "inflated" surfaces, and is tightly integrated into the already known user interface.

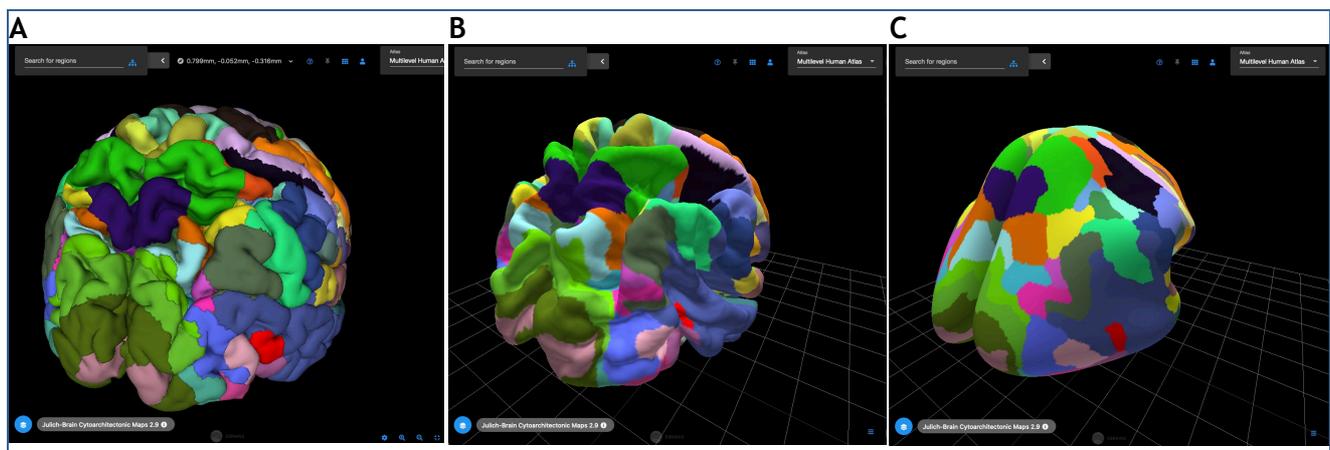


Figure 4: Cytoarchitectonic maximum probability maps of Julich-Brain v2.9 projected to freesurfer surface space

Cytoarchitectonic maximum probability maps of Julich-Brain 2.9 have been projected to freesurfer surface space and are supported by a new surface rendering engine in the interactive viewer siibra-explorer (Section 2.2.1). A: MNI Colin27 surface; B: Freesurfer average pial surface; C: freesurfer average inflated surface.

## 2.1.2 New version of Waxholm Space Rat Brain Atlas (v4)

The Waxholm Space (WHS) rat brain reference atlas is defined in a high-resolution volumetric magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) template of an adult (80 days old) Sprague Dawley rat brain ([Papp et al., 2014<sup>5</sup>](#)). The first version of the WHS rat brain atlas contained 76 delineations, covering most major brain regions ([Papp et al., 2014<sup>5</sup>](#)). Version 2 contained 89 delineations and features detailed delineations of the hippocampus and parahippocampal region ([Kjonigsen et al., 2015<sup>6</sup>](#)). Version 3 contains 118 structures and includes detailed delineations of the ascending auditory system ([Osen et al., 2019<sup>7</sup>](#)).

Now, a comprehensive new version of the WHS rat brain atlas has been released ([https://search.kg.ebrains.eu/instances/413794ff-e7ad-4aef-b57c-0dab29c93c7e<sup>j</sup>](https://search.kg.ebrains.eu/instances/413794ff-e7ad-4aef-b57c-0dab29c93c7e)) (October 2021, M19) and [integrated into the interactive viewer<sup>k</sup>](#). The new version 4 of the atlas features 222

<sup>e</sup> <https://search.kg.ebrains.eu/instances/ff1bae02-857d-4d1b-8b2d-b9dbd583a459>

<sup>f</sup> [https://object.cscs.ch/v1/AUTH\\_227176556f3c4bb38df9feea4b91200c/hbp-d000060\\_SurfaceMaps\\_freesurfer\\_JulichBrain\\_pub/v2.9/EBRAINS-DataDescriptor\\_v2\\_SurfaceMaps-Freesurfer-JulichBrain.pdf](https://object.cscs.ch/v1/AUTH_227176556f3c4bb38df9feea4b91200c/hbp-d000060_SurfaceMaps_freesurfer_JulichBrain_pub/v2.9/EBRAINS-DataDescriptor_v2_SurfaceMaps-Freesurfer-JulichBrain.pdf)

<sup>g</sup> <https://search.kg.ebrains.eu/instances/a8932c7e-063c-4131-ab96-996d843998e9>

<sup>h</sup> <https://surfer.nmr.mgh.harvard.edu/>

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

<sup>j</sup> <https://search.kg.ebrains.eu/instances/413794ff-e7ad-4aef-b57c-0dab29c93c7e>

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

delineated brain regions, including 112 new structures and 56 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-SA license (Kleven et al., in preparation).

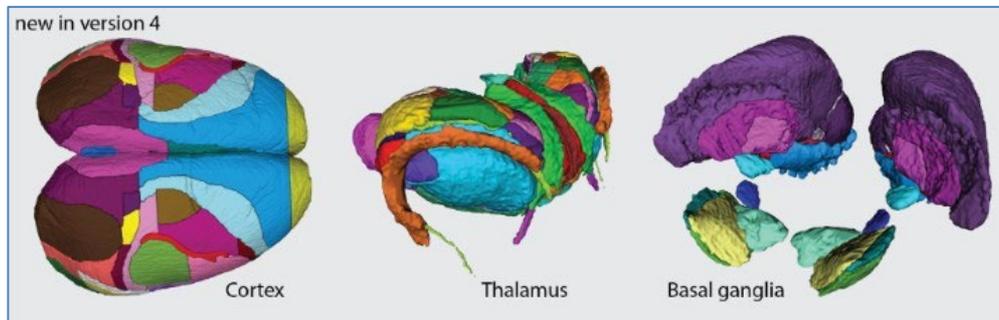


Figure 5: Waxholm Space Rat Brain atlas version 4

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

### 2.1.3 Atlas Ontology Model ‘AtOM’

Since October 2020, an ontology model for the reference atlases ‘AtOM’ has been developed in a collaboration between University of Oslo, [KnowledgeSpace](https://knowledge-space.org/)<sup>1</sup>, and INCF (International Neuroinformatics Coordinating Facility). This Atlas Ontology Model provides a theoretical basis for specifying the following 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. 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 will be provided in a manuscript by Gillespie, Kleven et al. (in preparation).

In addition, the AtOM was adopted by the new openMINDS SANDS metadata model, which was released in November 2020 (M8) and revised over the past year. The third version of the openMINDS SANDS metadata model hosts besides the AtOM schema definitions also metadata implementations for selected brain atlases (ongoing effort; cf. instances folder on [https://github.com/HumanBrainProject/openMINDS\\_SANDS/tree/v3](https://github.com/HumanBrainProject/openMINDS_SANDS/tree/v3); which will include SANDS models for, e.g. "Waxholm Space Brain Atlas of the Sprague Dawley rat", "Allen Mouse Brain Atlas", "Julich-Brain Cytoarchitectonic Atlas" (human)). A tight connection to the AtOM is guaranteed via linkages to the respective ontological instantiations (in preparation).

### 2.1.4 MEBRAINS: An anatomical template of the macaque brain

EBRAINS is developing a new Non-Human Primate (NHP) atlas which is now integrated in the EBRAINS atlas services as a pre-release (<https://atlases.ebrains.eu/viewer/saneurl/mebrains>). As a first important result towards the first release, a new reference template - MEBRAINS - has been developed which represents a population average of structural (T<sub>1</sub>, T<sub>2</sub>) and diffusion weighted magnetic resonance image data from 10 macaque brains (Figure 6). The reference image template

<sup>1</sup> <https://knowledge-space.org/>

was constructed from co-registered structural MRI images by combined voxel intensity information using the multi-brain toolbox for SPM12 (<https://github.com/WTCN-computational-anatomy-group/diffeo-segment>).

The volumetric templates are complemented with the surface template built with freesurfer (Fischl et al., 2012<sup>2</sup>). Recently published 3D maps of the macaque monkey inferior parietal lobe (Niu et al. 2021<sup>8</sup>) were warped to the MEBRAINS surface template, thus not only establishing a link with the Yerkes 19 template (Donahue et al., 2016<sup>9</sup>), but also populating our template with a parcellation scheme based on a cyto- and receptor architectonic analysis (Figure 7).

Traditional neuroimage analysis pipelines involve computationally intensive, time-consuming optimisation steps, often requiring additional manual interventions. We adapted FastSurfer for human subjects (<https://github.com/Deep-MI/FastSurfer.git>) to the macaque. 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 (Figure 8).

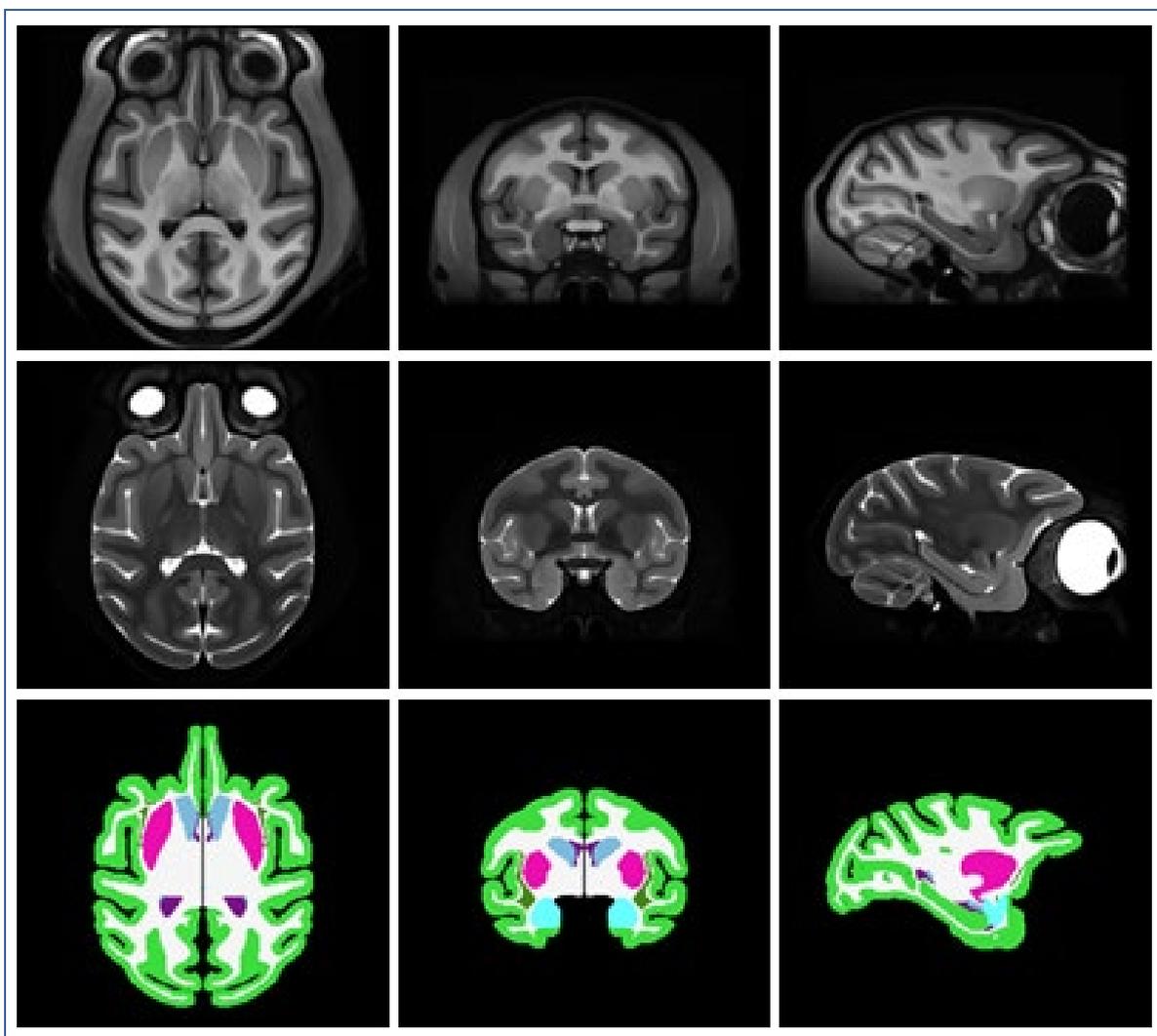


Figure 6: Anatomical template of the macaque monkey ‘MEBRAINS’

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

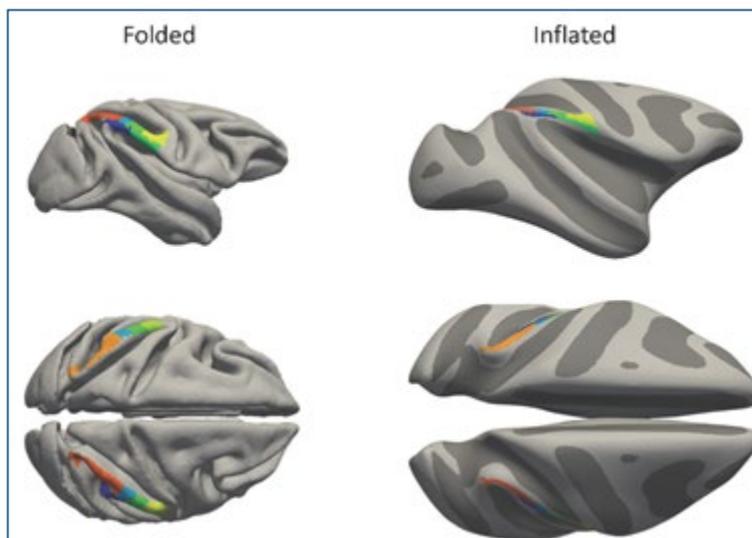


Figure 7: Folded and inflated surface representations of the MEBRAINS template

Folded and inflated surface representations of the MEBRAINS template, onto which areas of the inferior parietal lobule (Niu et al., 2021<sup>8</sup>) have been warped.



Figure 8: White and grey matter segmentation of the MEBRAINS template

Surface segmentation based on the FastSurfer software (<https://github.com/Deep-MI/FastSurfer.git>) which has been adapted and retrained with limited training samples for the MEBRAINS template.

## 2.2 Software interfaces to atlases

### 2.2.1 *New version of interactive atlas viewer (siibra-explorer)*

With its new release, the interactive atlas viewer hosted at <https://atlases.ebrains.eu/viewer> is now built on shared software components with a dedicated web API and programmatic Python client, responding to our strategy of offering both programmatic and interactive access to atlases without duplicating software code. This more tightly integrated tool suite is called *siibra* (*software interfaces for interacting with brain atlases*). The codebase of the interactive atlas viewer has been renamed and is now maintained at <https://github.com/FZJ-INM1-BDA/siibra-explorer>. Besides many internal software improvements, there are several new features visible to users:

- An interactive “quick tour” guides new users in ten steps through the main navigational elements and features of the viewer (Figure 9A). The quick tour is launched when a user visits the viewer for the first time and can be accessed any time via the help menu on the top right of the user interface.

- An annotation mode has been added for drawing points, lines and polygons onto the view (Figure 9B). It is activated via the plugin menu on the top right. Annotations can be described with a name and a description and are directly linked to the selected reference space. The annotations can be shared and downloaded in openMINDS-SANDS compatible format. Exported annotations can be directly loaded in *siibra-python* for programmatic processing (via the *siibra.from\_sands()* function, see next section).
- Users can now display image volumes from their local computer superimposed with the parcellation maps without uploading them to a server (Figure 9C, D). The volumes need to be in a compatible NIfTI format with a valid affine matrix pointing to the physical reference space. The superimposition is as easy as dragging the NIfTI file from the local file system explorer onto the browser window (Figure 9C). It provides an easy way for the immediate comparison of imaging signals with atlas information even for sensitive data, since the image data stay on the user's local computer. This feature has been added to v2.5.0 and released in October 2021 (M19).

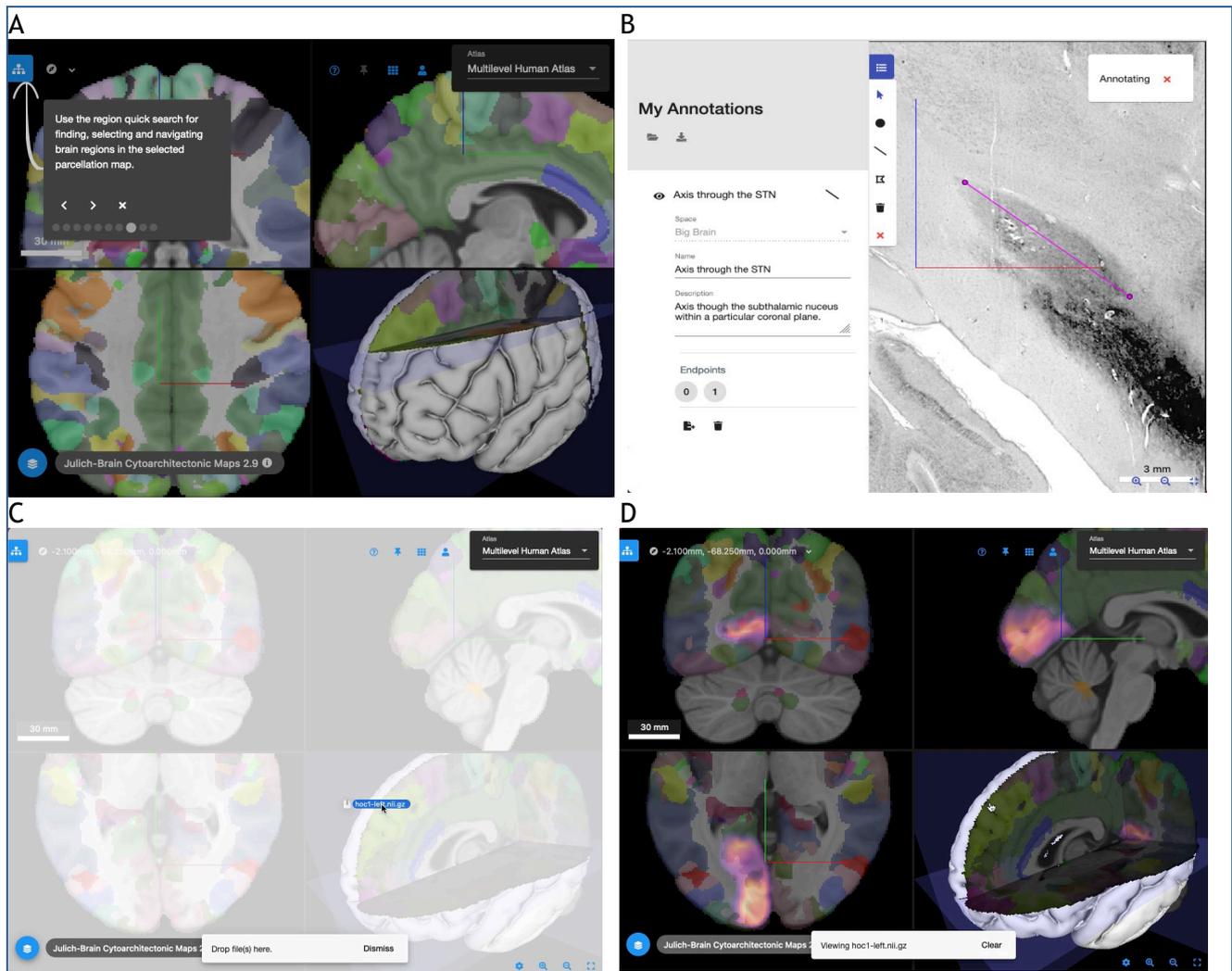


Figure 9: New user-facing features of *siibra-explorer*, the interactive atlas viewer

A: Quick tour, interactively guiding new users through basic navigational elements. B: Interactive annotation mode. C, D: Superimposition of image volumes stored locally on the user's computer by simple drag and drop of a NIfTI file.

## 2.2.2 New atlas programming interface (*siibra-python*, *siibra-API*)

As part of the new *siibra-toolsuite*, we are developing *siibra-python*, a comprehensive Python client providing access to EBRAINS atlases and offering an easy and well-structured way to include maps, reference templates, region definitions and linked datasets into reproducible programmatic workflows. The software is developed in the public domain under Apache2 licence and maintained

at <https://github.com/FZJ-INM1-BDA/siibra-python>, with regular releases of development snapshots on <https://pypi.org/project/siibra/>, and a growing documentation at <https://siibra-python.readthedocs.io>. The library is already used by different HBP researchers and some external scientists. Since it is under very active development, users are encouraged to be in close interaction with the development team. *Siibra-python* has been presented in several workshops and educational events during 2021, so that a range of tutorial videos (e.g. [https://youtu.be/H\\_6-RPLZkYM](https://youtu.be/H_6-RPLZkYM)) and a set of interactive tutorials (<https://github.com/FZJ-INM1-BDA/siibra-tutorials>) are available.

*Siibra-python* has been designed to allow safe and convenient interaction with brain regions from different parcellations, to provide streamlined access to multimodal data features linked to brain regions, and to perform basic analyses of region-specific data features. The intention is to unify interaction with brain atlas data at different spatial scales, including parcellations and datasets at the millimetre scale in the MNI space, as well as microstructural maps and microscopic data in the BigBrain space. Most of the concepts and datasets in *siibra* are maintained in the E BRAINS Knowledge Graph (<https://kg.ebrains.eu>), and designed to support the OpenMINDS metadata standard ([https://github.com/HumanBrainProject/openMINDS\\_SANDS](https://github.com/HumanBrainProject/openMINDS_SANDS)). However, *siibra* also gives access to additional maps and resources, including a direct interface to the Allen brain atlas for retrieving regional gene expressions.

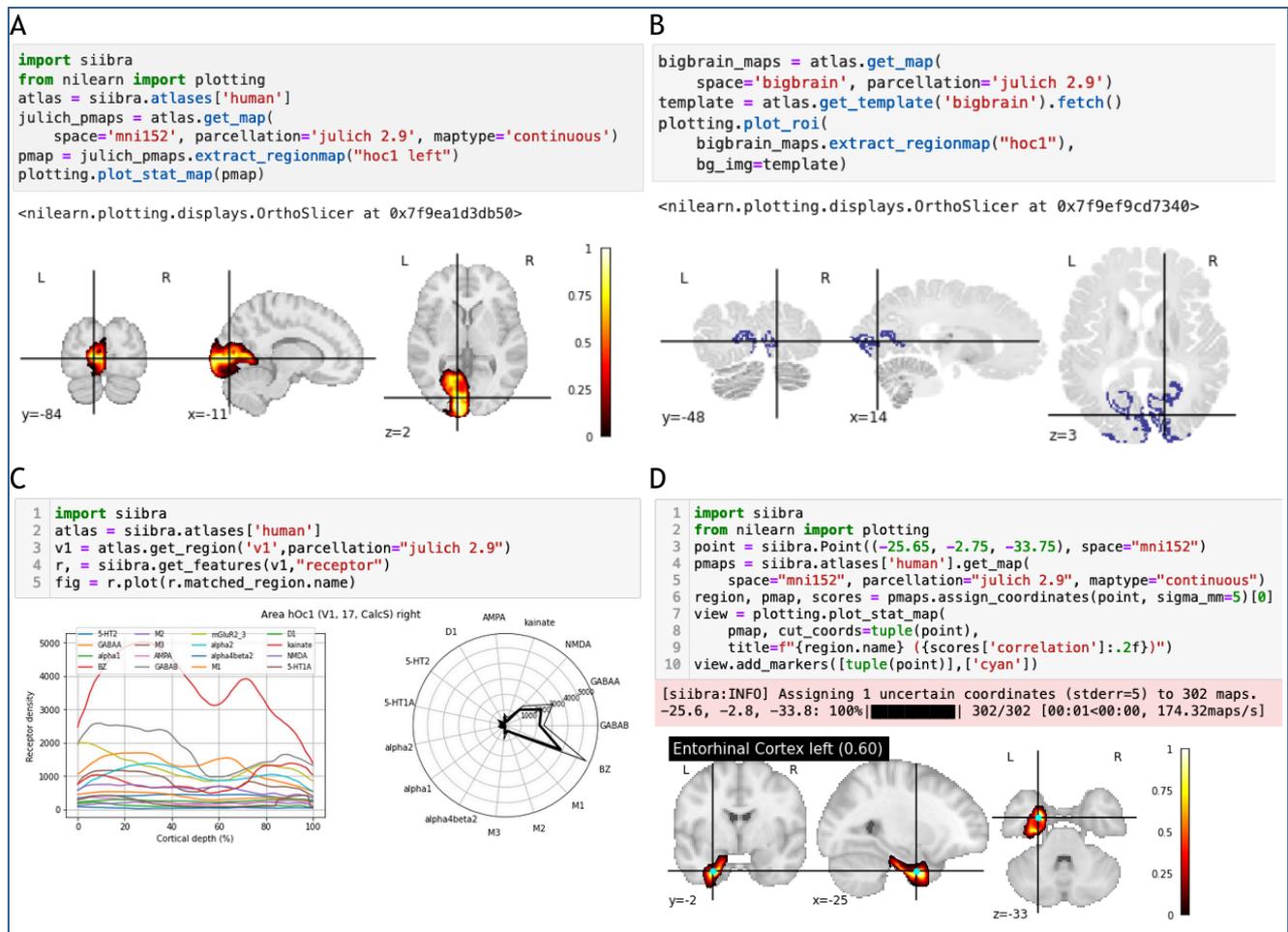


Figure 10: Minimal code examples of simple use cases in *siibra-python*

Minimal code examples of simple use cases in *siibra-python* ([Development version 0.2a4<sup>m</sup>](https://github.com/FZJ-INM1-BDA/siibra-python/releases/tag/v0.2a4)) A: Download and display the Julich-Brain probabilistic map at version 2.9 of the left primary visual cortex in MNI152 space; B: Download and display the corresponding high-resolution individual map of V1 in BigBrain space; C: Find and retrieve neurotransmitter receptor measurements for the primary visual cortex; D: Perform probabilistic assignment of a brain region to a coordinate with location uncertainty and display the most likely match. (More examples can be discovered in the tutorials at <https://github.com/FZJ-INM1-BDA/siibra-tutorials>).

<sup>m</sup> <https://github.com/FZJ-INM1-BDA/siibra-python/releases/tag/v0.2a4>

Among the key features are streamlined queries for multimodal data features linked to coordinates or brain regions; rich data types for brain parcellations, regions and maps; safe handling of geometric elements defined in different brain coordinate spaces and spatial transformations between them; explicit links between semantic region objects and labelled images in different spaces; efficient assignment of locations to brain regions; and well-structured dynamic multi-resolution access to big image data like the BigBrain.

In *siibra-python*, all forms of data features can be queried using the same mechanism (“`siibra.get_features()`”) which takes as an argument a specification of a semantic concept (region, parcellation, spatial location) and a feature modality. Currently available modalities include neurotransmitter densities, regional connectivity profiles, connectivity matrices, gene expressions, distributions of neuronal cells, and spatial properties of brain regions. *Siibra* hides much of the complexity that would be required to interact with the individual data repositories that host the associated data. By encapsulating many aspects of interacting with different maps and reference templates spaces, it also minimises common risks like misinterpretation of coordinates from different reference spaces, or utilisation of inconsistent versions of parcellation maps - aiming to provide a safe and reproducible way of using maps defined across multiple spatial scales.

A few simple code examples of *siibra-python*'s current development version ([v0.2a4<sup>n</sup>](#)) are given in Figure 10.

To share implemented functions with the interactive viewer *siibra-explorer* (Section 2.2.1), we are developing *siibra-api* (<https://github.com/FZJ-INM1-BDA/siibra-api>), which exposes most of the functionalities for interacting with the atlases in a RESTful http API. While *siibra-api* is still under active development, the current version of the interface is documented at [https://siibra-api-stable.apps.hbp.eu/v1\\_0/docs#](https://siibra-api-stable.apps.hbp.eu/v1_0/docs#).

### 2.2.3 *Coordinate transformation service for human reference spaces*

HBP researchers have developed a method for robust spatial alignment of different human brains, which uses sulcal constraints to drive a diffeomorphic alignment ([Lebenberg et al., 2018<sup>10</sup>](#)). The algorithm, which is part of the [brainvisa<sup>o</sup>](#) software platform, has been used to determine accurate deformation fields between the different reference template spaces used in the EBRAINS human brain atlas. These deformation fields are very helpful for establishing spatial relationships across these different spaces, implementing cross-template queries for spatial coordinates, simplifying cross-template navigation, and enabling the warping of imaging data from one space to another. To allow EBRAINS atlas services to make use of these transformations, the [brainvisa](#) software has been containerised together with the computed transformations and extended by an http back-end service which allows the conversion of coordinates between the spaces through a REST API. This back-end service is now available, and has been integrated with the *siibra toolsuite* (cf. Section 2.2.1 and 2.2.2) for enabling different cross-template functionality.

At its core, the spatial transformation service is hosting a containerised installation of a software stack including the [brainvisa<sup>p</sup>](#) 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<sup>11</sup>](#), [Glaunés et al. 2004<sup>12</sup>](#), [Lebenberg et al. 2018<sup>10</sup>](#)), and maximising the overlap of grey- and white matter segmentations, using the established method DARTEL ([Ashburner et al. 2007<sup>13</sup>](#)). Coordinates can be transferred conveniently between those spaces using a simple and convenient REST API. Detailed documentation of the REST API is accessible at <https://hbp-spatial-backend.apps.hbp.eu/redoc>. The source code of the back end is available at <https://github.com/HumanBrainProject/hbp-spatial-backend>.

---

<sup>n</sup> <https://github.com/FZJ-INM1-BDA/siibra-python/releases/tag/v0.2a4>

<sup>o</sup> <https://brainvisa.info/web/>

<sup>p</sup> <https://brainvisa.info/web/>

Using this service, the interactive atlas viewer *siibra-explorer* (Section 2.2.1) 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 11A, B). In *siibra-python* (Sec. 2.2.2), the same service is employed to warp coordinates across spaces, and realise, for example, automatic cross-space feature queries.

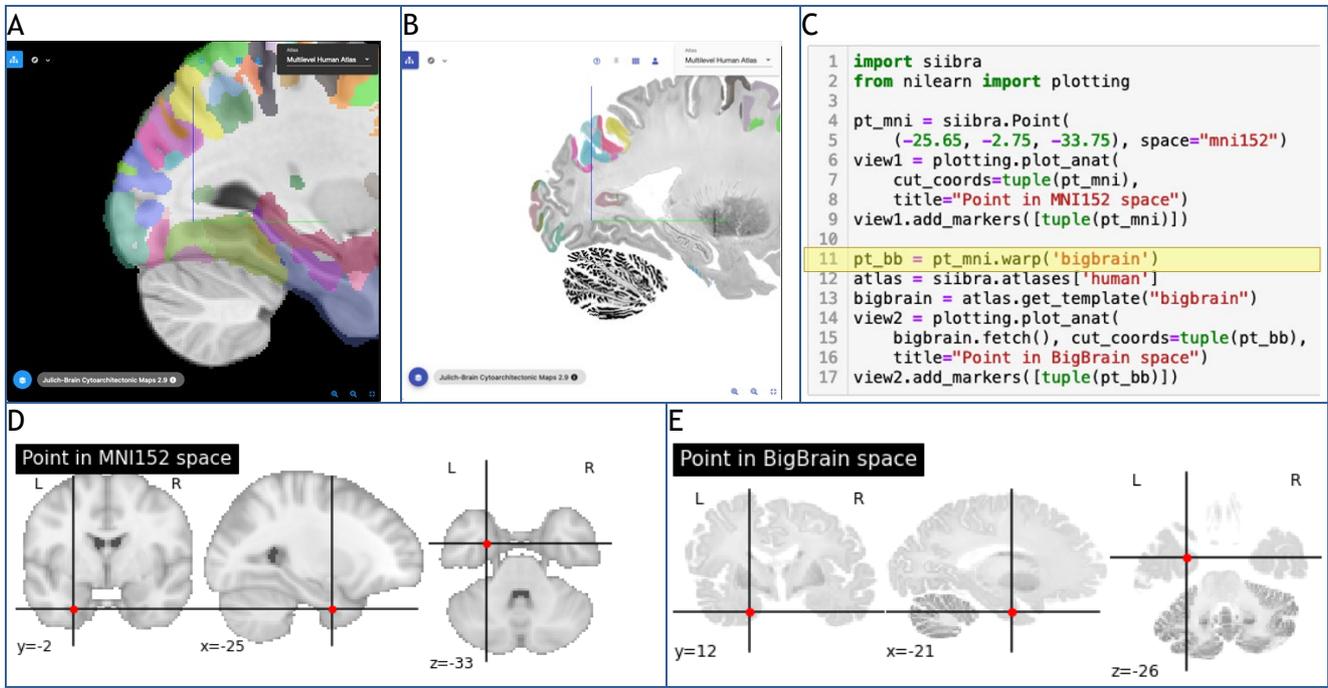


Figure 11: The spatial transformation service employed by the *siibra* toolsuite

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.

## 2.3 Integration of multimodal data to atlases

### 2.3.1 Integration of dataset collections using QuickNII / VisuAlign

Several large mouse dataset collections, shared through (or in preparation for sharing through) the EBRAINS Knowledge Graph, have used the registration tools QuickNII and VisuAlign for image registration to the EBRAINS reference atlas. The [DOPAMAP](https://search.kg.ebrains.eu/instances/Project/97bb7313-f6e8-4d62-b2df-4fa542c6a496)<sup>q</sup> and [Calbindin / Parvalbumin](https://search.kg.ebrains.eu/instances/Project/d9f5a0b1-70d9-410e-88c9-9e17906c50d5)<sup>r</sup> dataset collections (referred to as Projects in the EBRAINS Knowledge Graph) are now publicly available. More projects are in the pipeline.

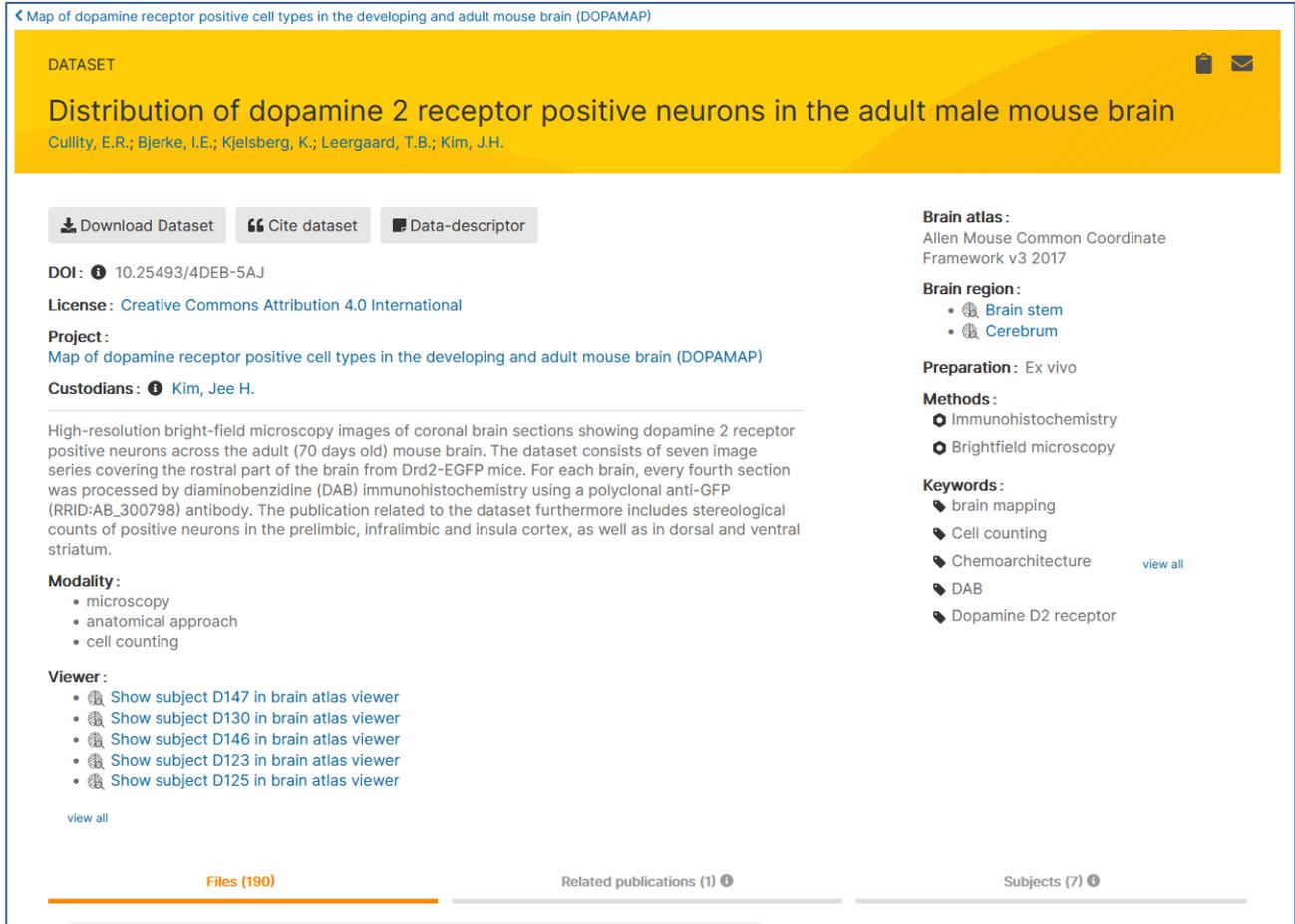
### The DOPAMAP project

DOPAMAP is an HBP Partnering Project. The project integrates a large body (n=4,600) of immunolabelled microscopy images in the mouse reference atlas to provide brain-wide data of the developing mouse dopaminergic system. The images show distribution of dopamine D1 and D2 receptor-positive neurons in the mouse brain, with age groups ranging from postnatal day 17 to 70. The age groups included correspond to key developmental milestones, defined as follows (+/- 1 day

<sup>q</sup> <https://search.kg.ebrains.eu/instances/Project/97bb7313-f6e8-4d62-b2df-4fa542c6a496>

<sup>r</sup> <https://search.kg.ebrains.eu/instances/Project/d9f5a0b1-70d9-410e-88c9-9e17906c50d5>

for each age group): juvenile (17 days), preadolescent (25 days), adolescent (35 days), late adolescent (49 days) and adult (70 days). A manuscript in preparation by I.E. BJERKE and co-workers<sup>s</sup> will present the collection, consisting of 20 datasets, in detail. Through the [EBRAINS portal](#)<sup>t</sup> users can also access the registration information through the Localizoom viewer. For this project, we created a version of QuickNII for mouse development atlases which is planned to be released on the EBRAINS platform before the end of the project period.



Map of dopamine receptor positive cell types in the developing and adult mouse brain (DOPAMAP)

**DATASET**

**Distribution of dopamine 2 receptor positive neurons in the adult male mouse brain**  
Cullity, E.R.; Bjerke, I.E.; Kjelsberg, K.; Leergaard, T.B.; Kim, J.H.

Download Dataset | Cite dataset | Data-descriptor

**DOI:** 10.25493/4DEB-5AJ  
**License:** Creative Commons Attribution 4.0 International  
**Project:** Map of dopamine receptor positive cell types in the developing and adult mouse brain (DOPAMAP)  
**Custodians:** Kim, Jee H.

High-resolution bright-field microscopy images of coronal brain sections showing dopamine 2 receptor positive neurons across the adult (70 days old) mouse brain. The dataset consists of seven image series covering the rostral part of the brain from *Drd2-EGFP* mice. For each brain, every fourth section was processed by diaminobenzidine (DAB) immunohistochemistry using a polyclonal anti-GFP (RRID:AB\_300798) antibody. The publication related to the dataset furthermore includes stereological counts of positive neurons in the prelimbic, infralimbic and insula cortex, as well as in dorsal and ventral striatum.

**Modality:**

- microscopy
- anatomical approach
- cell counting

**Viewer:**

- Show subject D147 in brain atlas viewer
- Show subject D130 in brain atlas viewer
- Show subject D146 in brain atlas viewer
- Show subject D123 in brain atlas viewer
- Show subject D125 in brain atlas viewer

view all

**Brain atlas:** Allen Mouse Common Coordinate Framework v3 2017  
**Brain region:** Brain stem, Cerebrum  
**Preparation:** Ex vivo  
**Methods:** Immunohistochemistry, Brightfield microscopy  
**Keywords:** brain mapping, Cell counting, Chemoarchitecture, DAB, Dopamine D2 receptor

Files (190) | Related publications (1) | Subjects (7)

**Figure 12: Representative dataset card of the DOPAMAP project on the EBRAINS data knowledge portal**

Users have access to author information, description of the dataset, metadata, direct links to viewers and data file download, license and citation information.

## Calcium-binding proteins Calbindin and Parvalbumin in mice and rats

This project provides brain-wide quantifications and distributions of calbindin neurons and parvalbumin interneurons in mice and Parvalbumin interneurons in rats (Bjerke et al. 2021<sup>14</sup>). The data collection, fully available on the EBRAINS portal, consists of 6 whole brain series of adult C57Bl6/J mice labelled with immunohistochemistry (IHC) for calbindin (Dataset DOI [10.25493/KHNT-KV8<sup>u</sup>](#)); 4 whole brain IHC parvalbumin series of adult Sprague Dawley female rats (Dataset DOI [10.25493/8KQC-3C7<sup>v</sup>](#)) and 4 whole brain IHC parvalbumin series of adult PVCre x Rosa26eYFP mice (Dataset DOI [10.25493/BXGX-WM4<sup>w</sup>](#)). The project is accessible through the [EBRAINS portal](#)<sup>x</sup>. As the researchers were able to achieve a precise registration of all section images to the reference atlases

<sup>s</sup> Co-workers: E.R. CULLITY, K. KJELSBURG, K.M. CHARAN, T.B. LEERGAARD, J.H. KIM

<sup>t</sup> <https://search.kg.ebrains.eu/instances/Project/97bb7313-f6e8-4d62-b2df-4fa542c6a496>

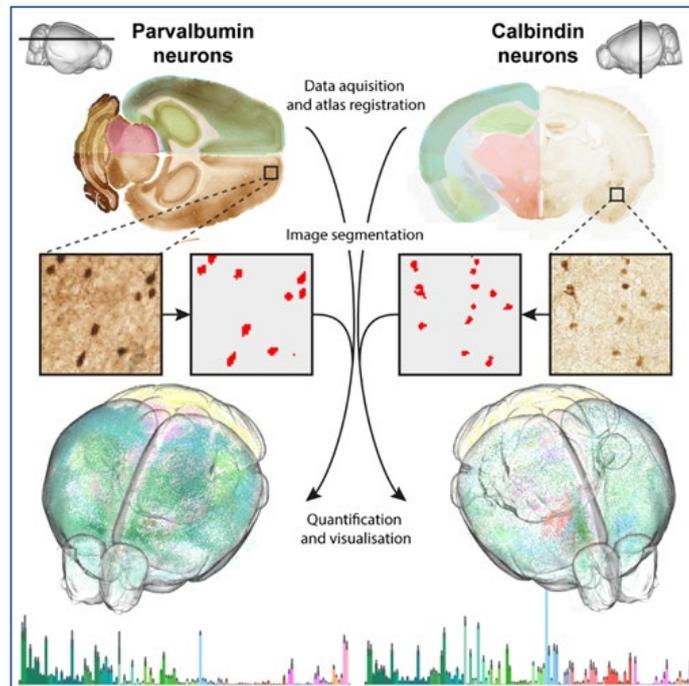
<sup>u</sup> <https://search.kg.ebrains.eu/instances/Dataset/d0d2e25f-029c-495a-b34a-5598dc0e6f65>

<sup>v</sup> <https://search.kg.ebrains.eu/instances/Dataset/e88b6e2d-80dd-484c-9093-0be66ae264ae>

<sup>w</sup> <https://search.kg.ebrains.eu/instances/Dataset/39eefa7b-8f96-48a1-97b9-f752d4eb5f62>

<sup>x</sup> <https://search.kg.ebrains.eu/instances/Project/d9f5a0b1-70d9-410e-88c9-9e17906c50d5>

combining linear and nonlinear registration in QuickNII and VisuAlign, they obtained precise distribution maps for both neuron types as well as precise quantifications of the neurons, which could be validated by comparison with literature data.



**Figure 13: Brain-wide analysis of calbindin neurons and parvalbumin interneurons in adult mice**

Brain-wide analysis of calbindin neurons and parvalbumin interneurons in adult mice using the QuickNII and VisuAlign registration tools allowing precise 2D histological image registration to the 3D mouse atlas. (Bjerke et al. 2021, <https://doi.org/10.1016/j.isci.2020.101906>)

## The BRAINSPACE project

BRAINSPACE is an HBP Partnering Project. The external collaborator is The Jackson Laboratory, Maine, USA. The project aims to develop a capacity for brain-wide spatial analysis of regional and cell-type correlates of resilience to Alzheimer’s disease in the AD-BXD mouse population. The AD-BDX mouse model incorporates human familial AD mutations (5XFAD) on a well-characterised background of genetic diversity (the BXD genetic reference panel; [O’Connell et al. 2019<sup>15</sup>](#)). In a pilot study, all section images from 40 mice immuno-labelled for 4 different markers (NeuN, Gfap, Abeta and Iba-1) were registered to the mouse CCFv3\_2015 reference atlas with both QuickNII and VisuAlign tools. The data are being prepared for sharing via EBRAINS Data and Knowledge services. In the context BRAINSPACE, a new tool for quality assessment of registration results has been developed (Section 2.4.4 below).

## 2.4 Tools for analysing data using EBRAINS atlases

### 2.4.1 *Prototype of web-ilastik: Interactive image segmentation*

The online image segmentation tool, web-ilastik, has completely been reworked. The previous version relied on implementation details of the underlying viewer (Neuroglancer, the basis of NeHuBa). A new front-end architecture was conceived that allows the ilastik Pixel Classification interaction pattern on (in principle) any web-image-viewer, making it future-proof with respect to potential new developments in EBRAINS and in the Quint workflow. This includes rendering of pixel-

perfect brush annotations (with respect to the underlying data) even on oblique cross-sections - an important application for 3D brain data where features might be best visible at oblique angles.

The authentication layer has been changed from Collab authentication to EBRAINS authentication. Every EBRAINS user can allocate an individual Pixel Classification session (currently on a single VM on CSCS Castor). Given the session ID the back end now (experimentally) supports the rejoining of running sessions, and the training of classifiers on multiple images, opened in different browser tabs. Allocation of compute sessions on the Castor VM currently limits scaling with respect to the number of concurrent sessions. We plan to implement allocation of sessions on the “interactive computing” resources Piz Daint Hybrid to allow for better scaling and work on more complex data. The github repository of the web-ilstik architecture can be found here: <https://github.com/ilastik/webilastik/tree/dev>.

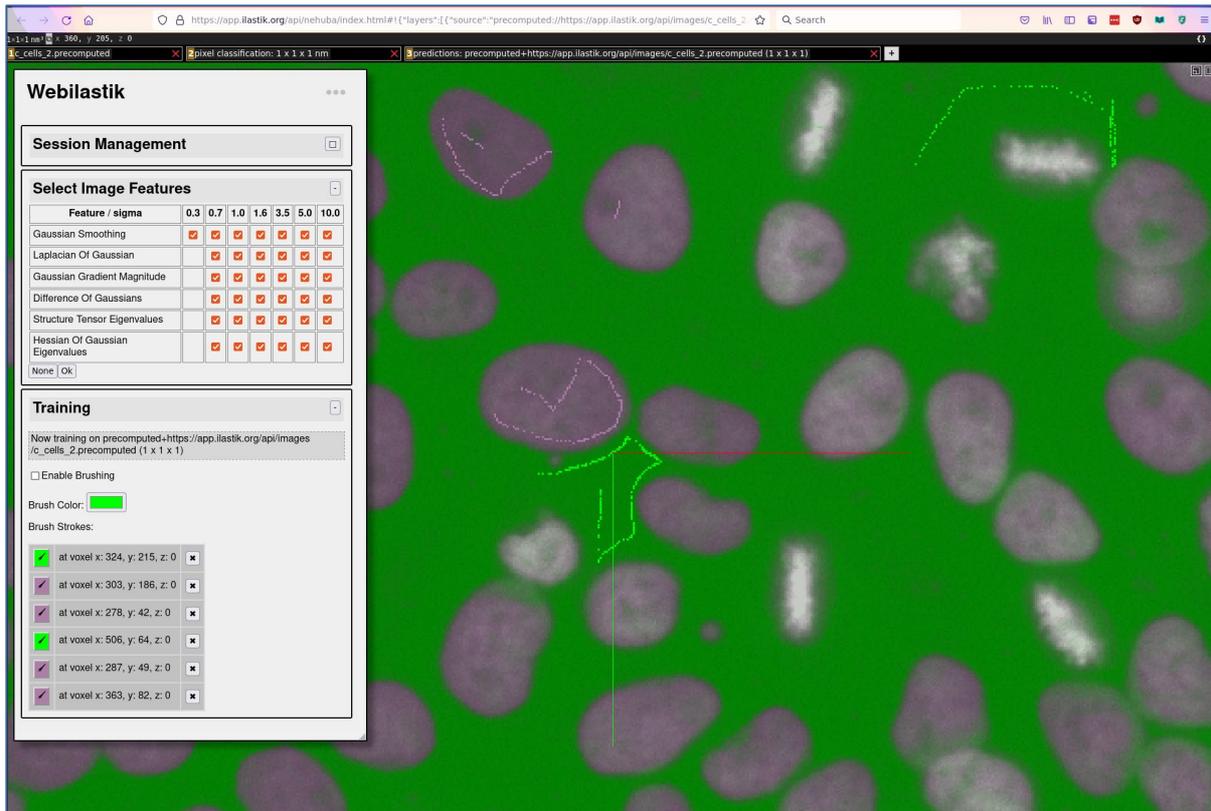


Figure 14: Screenshot of web-ilstik front end on top of Neuroglancer

Predictions from the back end overlaid in colours: green for background, and in lavender for foreground (nuclei). Classifier trained on the annotations visible in the screenshot. The left shows the generic panel for configuration of the session management, features used in the back end as well as adding, removing, and navigating to annotations.

## 2.4.2 NeuroSuites and neurogenpy

NeuroSuites (<https://neurosuites.com/>) 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. 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 web interface of this service has undergone a complete 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 will be the basis to connect this functionality to the EBRAINS atlas services for convenient computation and visualisation of such networks for specific brain regions. This will exploit the already existing capabilities of *siibra-python* (cf. Section 2.2.2) to extract gene expression levels, and the capability of *siibra-explorer* (cf. Section 2.2.1) to allow the implementation of plugins. In

the past months, there have been several improvements to the core functionalities, and the reliability and availability of the servers has also been improved.

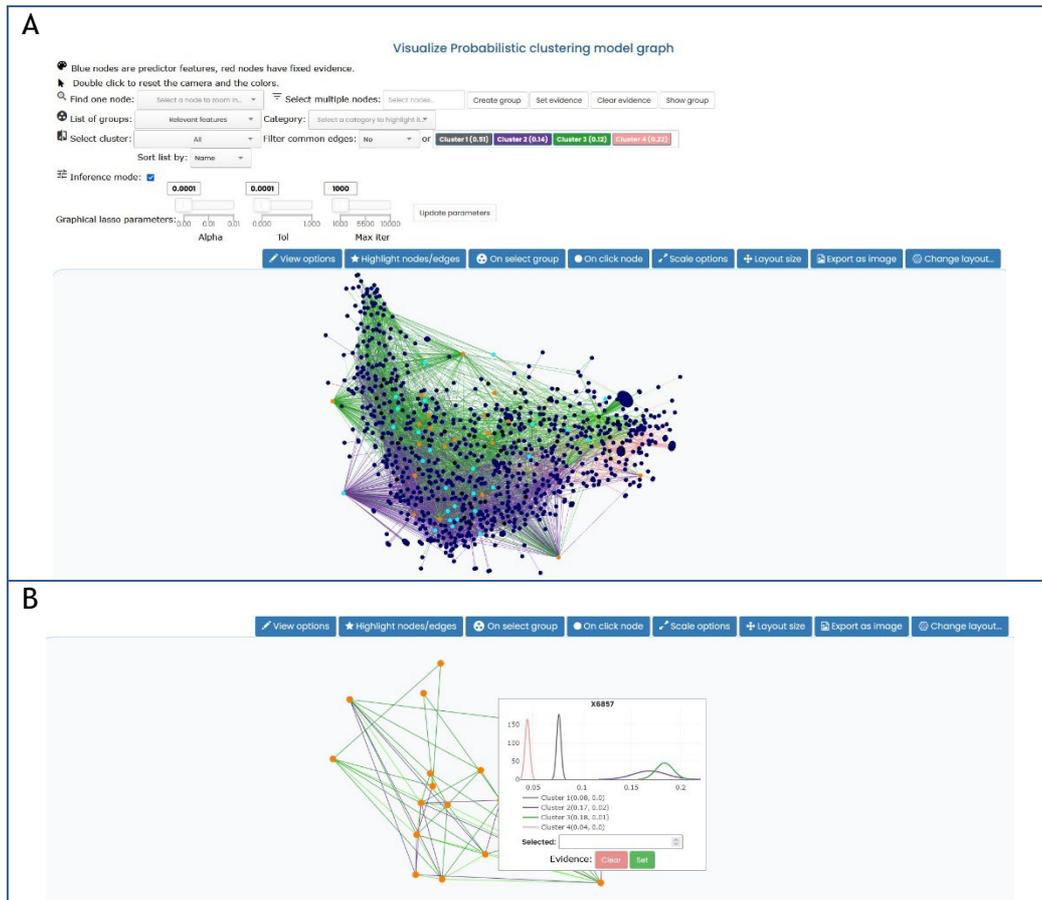


Figure 15: User interface of Bayessuites

A: Visual representation of the probabilistic clustering of the example data set Allen model ([https://neurosuites.com/morpho/ml\\_probabilistic\\_clustering](https://neurosuites.com/morpho/ml_probabilistic_clustering)). B: Selection of a group with the 20 most relevant nodes according to the uploaded metadata of the data set in A.

### 2.4.3 Nilearn and NiBabel libraries for neuroimaging analysis

Nilearn enables approachable and versatile analyses of brain volumes. It provides statistical and machine-learning tools, with instructive documentation and an open community. The Nilearn Library prototype (v0.8.0) has been released in June 2021 <https://nilearn.github.io/>. 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, or connectivity analysis. An associated python package that provides read and write access to some common medical and neuroimaging file formats, Nibabel, has been released in October 2020 (v3.2) <https://nipy.org/nibabel/>. This tool is part of the *nipy* community (<https://nipy.org>). In May 2021, the Nilearn-Nibabel Development Days have been held to onboard new contributors to our communities and to explore future directions for development (<https://nilearn.github.io/dev-days-2021/>).

We have now completed the conception of the integration of Nilearn with the EBRAINS Knowledge Graph and the *siibra-python* client based on an [interactive notebook](#)<sup>y</sup>. While the integration is in progress, the notebook already demonstrates how the combination of EBRAINS atlases and data with Nilearn and Nibabel makes it easy to run a functional connectivity analysis to study brain architecture

<sup>y</sup> <https://github.com/NicolasGensollen/EBRAINS-Connectivity-Analysis>

or compare groups of individuals. Current efforts include a better handling of surface data and the integration of outputs of standard pre-processing pipelines for signal cleaning.

### 2.4.4 QUINT workflow

Two new versions of the Nutil software have been released to improve usability and support for the anchoring descriptor file in json format coming from the nonlinear registration tool VisuAlign. The QUINT workflow has been successfully employed for quantifications and distribution analyses on large dataset collections from the DOPAMAP and BRAINSPACE projects, as well as a study on calcium-binding proteins.

The current stable version of Nutil v0.6.0 includes an automatic testing module on [GitHub](https://github.com/Neural-Systems-at-UIO/nutil)<sup>z</sup>. With this module, each new release candidate is tested and has to pass test datasets before being released. Furthermore, the documentation for Nutil and QUINT has been improved and is now hosted at <https://nutil.readthedocs.io/en/latest/>.

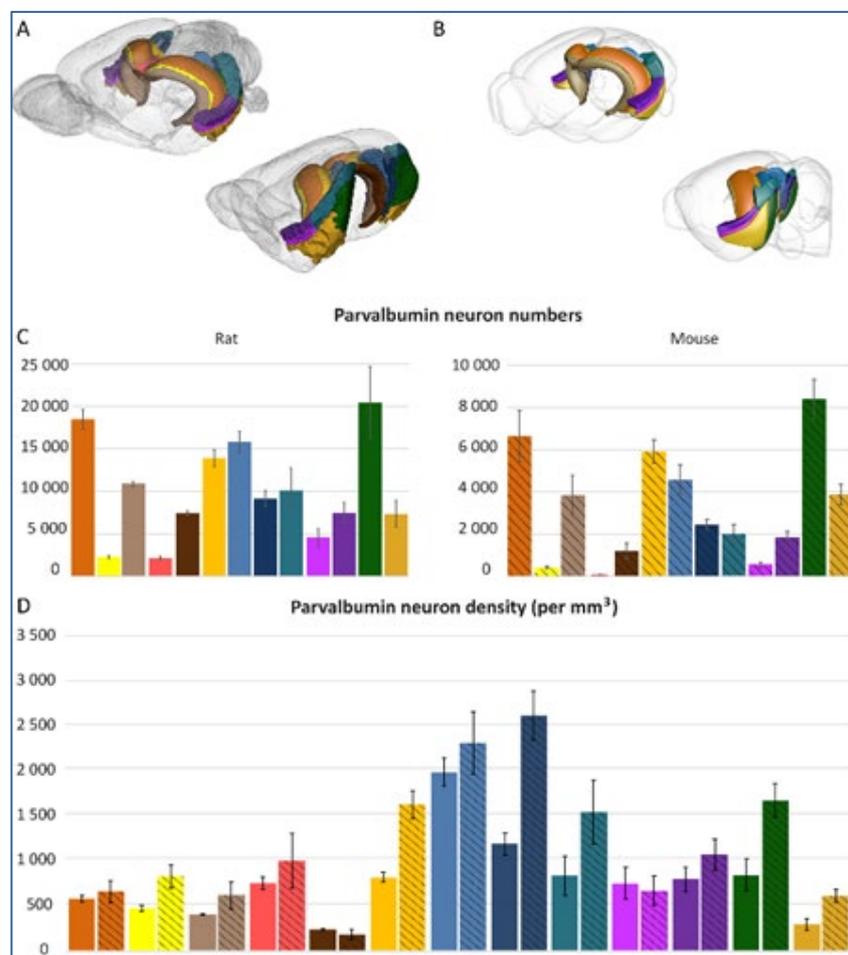


Figure 16: Illustration of results obtained with the QUINT workflow

Brain-wide analysis of calbindin neurons and parvalbumin interneurons in adult mice and rats allow comparisons of cell numbers and distributions across species. (Bjerke et al. 2021 iScience, <https://doi.org/10.1016/j.isci.2020.101906>).

<sup>z</sup> <https://github.com/Neural-Systems-at-UIO/nutil>

### 3. The EBRAINS Atlas Community

Users of the EBRAINS atlas services are provided with various opportunities to network, interact and collectively learn, with the aim of not only disseminating knowledge and technical know-how regarding the atlases, but to also encourage user feedback and immersion for a more user-centric development of the atlases. The goal is to build a strengthened, independent and sustainable atlas community that can facilitate and enrich the much-needed discussions that will progress the future development of the atlases.

A large part of this community building is centred around the organisation of regular live tutorials and workshops through which users are interactively introduced to the main features and applications of atlas tools. For example, the BigBrain dataset has an active community, managed by the [BigBrain Project](https://bigbrainproject.org/)<sup>aa</sup>, which is a partner of the HBP. This community has organised a [winter school](https://bigbrainproject.org/winter-school.html)<sup>bb</sup> and workshops (BigBrain Workshop [2020](https://bigbrainproject.org/hiball-launch.html)<sup>cc</sup> and [2021](https://www.youtube.com/playlist?list=PLGwf8gkzAzj0tYH9rdNjtYARwPxHHudp)<sup>dd</sup>) focusing on the role of the BigBrain in relation to the EBRAINS atlases, and will organise regular follow-up events. Similarly, the EBRAINS atlas services have been demonstrated at several events organised by the HBP Education Programme. An example is the Young Researchers Event, where hands-on trainings on the atlas infrastructure have been provided to students and early career researchers (e.g. <https://www.humanbrainproject.eu/en/education/YRE21/>). At the HBP Student Conference on Interdisciplinary Brain Research 2021, presentations have been given on image registration, the QUINT workflow, and key features of the different interfaces of the EBRAINS atlas (e.g.: <https://www.humanbrainproject.eu/en/education/HBPSC2021/media/>). At the international conference INCF Neuroinformatics Assembly, brain atlas analysis tools have been demonstrated in an interactive session at the virtual booth “Brain atlas based analysis tools: Q and A” (<https://www.humanbrainproject.eu/en/incf-neuroinformatics-assembly/>). Initiated by HBP’s participation in the International Brain Initiative, the HBP Education Programme has also partnered with the International Brain Research Organization (IBRO) and the International Neuroinformatics Coordinating Facility (INCF) to organise Master Classes on Brain Atlasing and Simulation Services ([1<sup>st</sup> Masterclass](https://www.humanbrainproject.eu/en/education/virtual-masterclass-1/)<sup>ee</sup>, [2<sup>nd</sup> Masterclass](https://www.incf.org/training-week/ebrains-ibro-master-class-brain-atlasing-and-simulation-services)<sup>ff</sup>), which are live training sessions focused on senior PIs and educators throughout the world. The University of Oslo has organised a dedicated study course on “[Neuroscience data integration through use of digital brain atlases](https://www.uio.no/studier/emner/medisin/med/IMB9345/)”<sup>gg</sup> where several of the EBRAINS atlas services were used in practical exercises.

Users of EBRAINS atlas services have access to **interactive online community spaces** for discussions around the brain atlases and their services, and participation in the growing user community. Most importantly, EBRAINS has developed its own [Community Space](https://wiki.ebrains.eu/bin/view/Collabs/quint), which is currently in its ‘soft launch’ phase and intends to serve as a social media-like forum where users can join different ‘subcommunities’ to learn about and participate regularly in the EBRAINS infrastructure discussions. A ‘[Brain Atlases](https://github.com/FZJ-INM1-BDA/siibra-python)’ subcommunity within the EBRAINS Community Space has been created very recently, which will provide regular dissemination of atlas developments, workshops, informational material, as well as creative interactive engagement exercises with the user community (Figure 17). For some specific workflows, dedicated **spaces for technical user discussions, user guidance and support** are offered. Examples are the [QUINT workflow collaboratory](https://github.com/FZJ-INM1-BDA/siibra-python)<sup>hh</sup>, the GitHub forums for programming libraries offered by EBRAINS atlas services (e.g. [siibra-python](https://github.com/Neural-Systems-at-UIO/nutil)<sup>ii</sup>, [nutil](https://github.com/nilearn/nilearn)<sup>jj</sup>, [nilearn](https://github.com/nilearn/nilearn)<sup>kk</sup>), and the [ilastik discussion forum at image.sc](https://forum.image.sc/tag/ilastik)<sup>ll</sup>.

aa <https://bigbrainproject.org/>

bb <https://bigbrainproject.org/winter-school.html>

cc <https://bigbrainproject.org/hiball-launch.html>

dd <https://www.youtube.com/playlist?list=PLGwf8gkzAzj0tYH9rdNjtYARwPxHHudp>

ee <https://www.humanbrainproject.eu/en/education/virtual-masterclass-1/>

ff <https://www.incf.org/training-week/ebrains-ibro-master-class-brain-atlasing-and-simulation-services>

gg <https://www.uio.no/studier/emner/medisin/med/IMB9345/>

hh <https://wiki.ebrains.eu/bin/view/Collabs/quint>

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

jj <https://github.com/Neural-Systems-at-UIO/nutil>

kk <https://github.com/nilearn/nilearn>

ll <https://forum.image.sc/tag/ilastik>

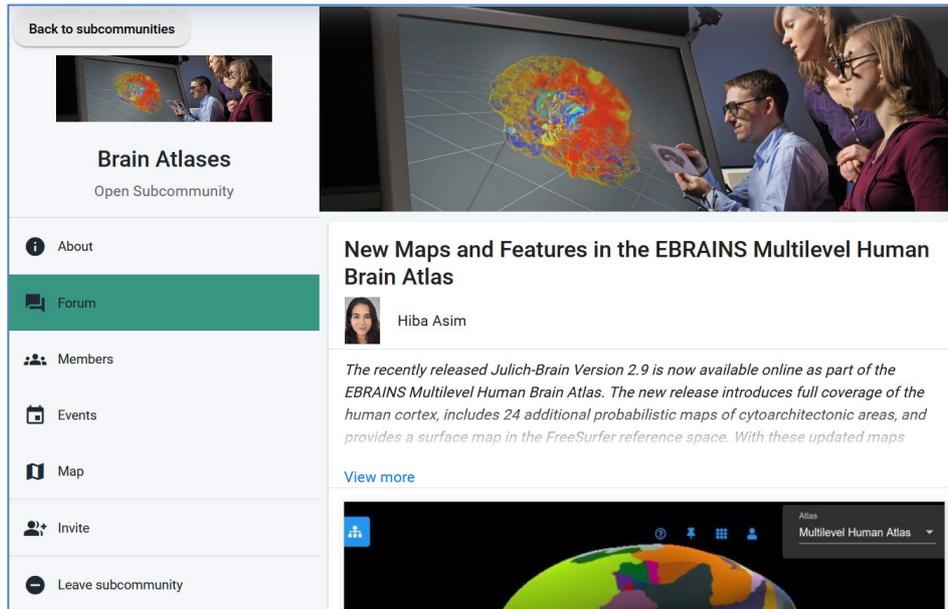


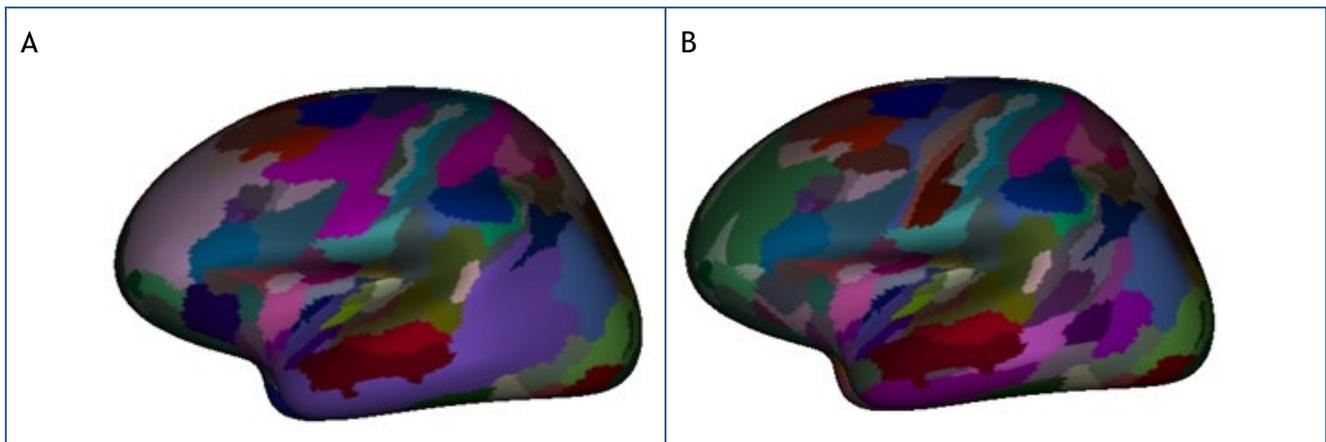
Figure 17: EBRAINS Brain Atlas subcommunity within the EBRAINS Community Space

## 4. Selected ongoing developments

### 4.1 Reference atlases

EBRAINS reference atlases are being continuously refined and extended. Some ongoing developments are the following:

- In addition to the maximum probability map, surface projections of the individual probabilistic maps of Julich-Brain are being added to the human atlas, allowing to perform more precise analyses based on the cytoarchitectonic maps. A release of these maps is expected early 2022.
- Julich-Brain provides a probabilistic parcellation of the grey matter of the human brain into cytoarchitectonic areas ([Amunts et al., 2020<sup>1</sup>](#)), which means that it embeds a model of the variability of the localisation of these areas computed across a group of post-mortem brains. While the Julich-Brain is already employed for a variety of neuroscience studies, its use for simulation is still challenging because of the dominant size of some GapMaps, which mark remaining regions to be mapped from microscopic sections. This work is in progress (cf. Section 2.1.1) because of the huge amount of data to be processed, but also because 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 (Figure 18A). To overcome this difficulty, we have adapted an algorithmic technology developed in earlier project phases ([Lefranc et al., 2016<sup>16</sup>](#)) 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 during SGA2. 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 Julich-Brain maps, will allow modellers a complete parcellation of the cortex homogeneous from the point of view of the size of the nodes (Figure 18B).
- Measurements of layer-specific cell densities from more than 100 tissue samples in about 10 different brain regions will be released in the EBRAINS Knowledge Graph, and tightly integrated with the atlas with explicit anchoring points in the BigBrain space and direct access via the viewer and Python clients. These data features will be released in November 2021.
- The new NHP atlas will be complemented with more brain region maps and a first selection of linked datasets by end of 2021.



**Figure 18: Julich-Brain probabilistic parcellation in fsaverage inflated view**

A: Julich-Brain with GapMaps; B: Julich-Brain with connectivity-based parcellation of the GapMaps.

## 4.2 Software interfaces to atlases

Besides adding additional features for different user communities, we are working towards a closer integration of atlas interfaces with the EBRAINS infrastructure and among each other. Some currently ongoing developments are:

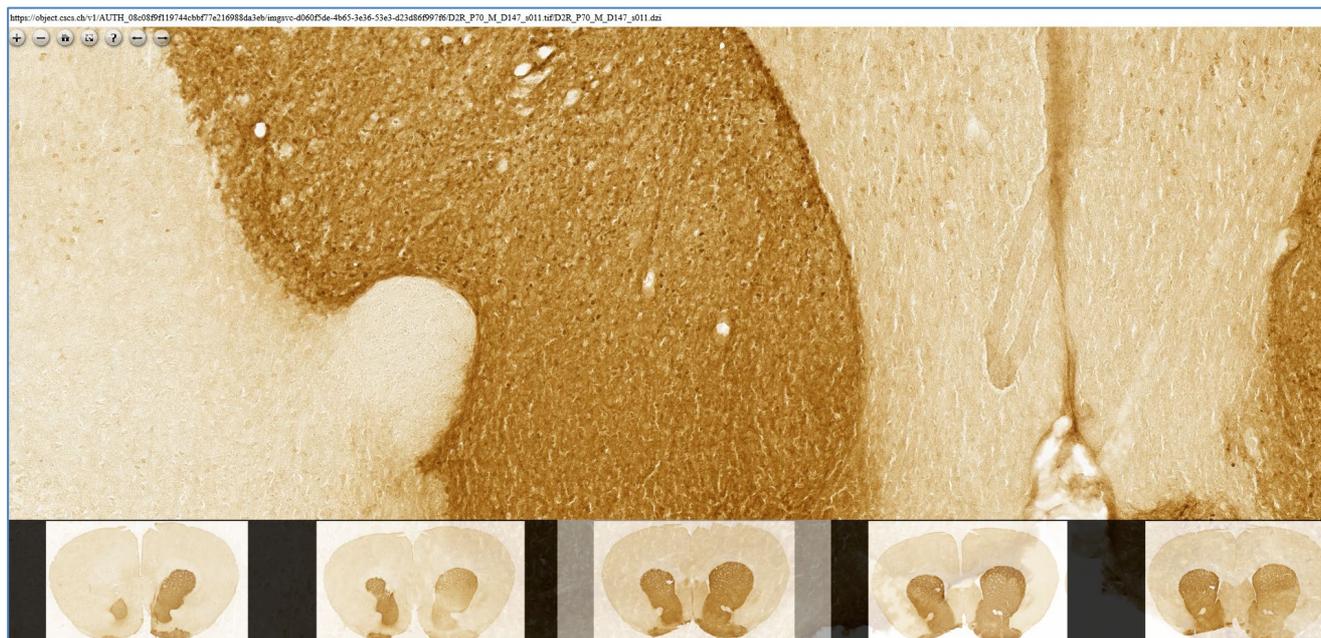
- Support for superimposing local NIfTI files in *siibra-explorer* (cf. Sec. 2.2.1) will be further extended, especially to allow the adjustment of colour and contrast, and downloading the combined scene for future reference. This is planned for release early 2022.
- A tighter integration of *siibra-explorer* (Sec. 2.2.1) and *siibra-python* (Sec. 2.2.2) will be implemented on several levels. For example, landmark annotations created interactively in *siibra-explorer* will be directly used in the Python client, and spatial structures computed in *siibra-python* (like signal peaks, feature locations, or bounding boxes of custom structures) will be easily opened in *siibra-explorer* for 3D visualisation in the atlas context and for sharing with other users. This compatibility will be based on the new openMINDS standards and is expected in spring 2022.
- A [draft extension](#)<sup>mm</sup> to [datalad](#)<sup>nn</sup> has been implemented, which allows the downloading of public EBRAINS datasets in a highly reproducible fashion with explicit tracking of file versions using hashes, and according to the same principles used by [git-annex](#)<sup>oo</sup> for safe versioning of software. This extension is currently a proof of principle based on a draft Knowledge Graph query. In the future, it will further improve the possibilities of attaching EBRAINS atlas services to highly reproducible computational workflows.
- A version of Localizoom image viewer running on CSCS OpenShift will soon be released (Nov 2021, M20). It is a viewer for 2D image datasets present on EBRAINS that have been registered to the atlases. This version is reading the ingested image chunks stored in the image service containers. The links will be accessible to the users from the dataset cards (Figure 12) and display the same view as the present links. In a central window, the section image with atlas overlay can be examined at multiple resolutions down to the cellular level. Each brain region's name will be displayed when the cursor is pointing at the region. At the bottom, a filmstrip shows all images in the series, allowing the users to easily jump to another section for examination.
- An OpenSeaDragon viewer for high-resolution 2D image datasets is currently in preparation. This viewer has the same configuration as the Localizoom image viewer mentioned above and is

<sup>mm</sup> <https://github.com/datalad/datalad-ebrains>

<sup>nn</sup> <https://www.datalad.org>

<sup>oo</sup> <https://git-annex.branchable.com/>

expected to be available end of December 2021 (M21). It will be linked to from the Knowledge Graph entries of suitable datasets



**Figure 19: OpenSeaDragon viewer for 2D image series visualisation**

The viewer reads ingested chunks from the Image service.

- A Localizoom tool will be available through the EBRAINS brain atlas tool pages. It will allow the users to see the same 2D images as in the viewer, but in addition allow users to perform annotations or simple analyses. The tool already described in D4.2, Section 2.2.2 (Figure 8), will be available through the EBRAINS brain atlas tool pages in spring 2022.

### 4.3 Tools for integrating data to EBRAINS atlases

The WebAlign tool for image registration will be integrated into the EBRAINS services before the end of the project period. WebAlign will allow users to register their images in a similar manner as QuickNII, but without the need for image pre-processing steps. The user interface resembles the one from QuickNII with a main central window, where the histological section is shown in transparency with the cut atlas. Three smaller windows showing the main sectioning planes (coronal, sagittal and horizontal) allow the users to orient themselves in the 3D space of the atlas. A status bar allows users to store registration of the section and move to the next section. The new feature is the presence of a filmstrip view at the bottom, showing the other sections in the series. The filmstrip is showing both the histological images and the anchoring result. Anterio-posterior positioning of the sections is propagated along with the progress in registration. Status bar and filmstrip are resizable, filmstrip can go completely hidden as it also reduces vertical screen space when visible. The planned use-case scenario will allow users to work in a private Collaboratory, where they will be able to: 1) upload images; 2) perform the ingestion with the image service; 3) register their images with WebAlign; 4) adjust the registration non-linearly with VisuAlign (if desired); 5) Segment their images with web-ilastik; 6) perform quantification analysis with Nutil Quantifier.

In the BRAINSPACE Partnering Project, a new tool for the assessment of atlas registrations and statistical analysis of confidence levels in the different atlas regions is in development. The prototype is being tested and is expected to be ready for use towards 2023.

## 4.4 Tools for analysing data using EBRAINS atlases

The ongoing developments of atlas analysis tools and workflows are especially characterised by bringing interfaces from standalone installations of established tools to the web browser, and thereby improving accessibility and integration with the data infrastructure of EBRAINS:

- A fully web-hosted interface to the interactive segmentation toolkit [ilastik](https://ilastik.org)<sup>PP</sup> is in development, which will allow the segmentation of image datasets stored in EBRAINS. This implementation is integrated with several levels of EBRAINS infrastructure, including to schedule training of image classifiers to FENIX compute resources, to access image data hosted by the image service, and downloading trained models. A first release of web-ilastik is planned before April 2022.
- Following the same use-case scenario described in Section 2.3.1, a web-integrated version of the Nutil Quantifier is being developed. The web application will be available through the EBRAINS Collaboratory as a community app by the end of the project period. Users will be able to activate the Nutil Quantifier web app after creating a Collaboratory and perform a Quantifier analysis after having processed the ingested image files through the two first steps of the QUINT workflow using WebAlign for registration and Webilastik for segmentation. The results of the spatial analysis will be stored in the private bucket of the users' Collaboratory.
- Preparation of Jupyter notebooks for analyses of results from the QUINT workflow. The users will be able to plot the obtained quantifications according to desired brain regions (as illustrated in Figure 16) and visualise the obtained 3D point clouds (as illustrated in Figure 13). The notebooks will be available to users in the Collaboratory environment by the end of the project period in 2023.

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## 6. Annex

### 6.1 List of known problems, possible risks and delays

We have mostly encountered challenges to keep up with integration of data to brain atlases, and making such links easily discoverable. This is mostly due to the large heterogeneity of datasets collected in EBRAINS, coupled with the fact that reference atlases are under continuous development. The main difficulties are presently the following:

- A remaining challenge for the mouse and rat brain atlases is the so far limited opportunities for discovering the data that have been integrated into the atlases. The ongoing openMINDS implementation and atlas tools improvements aim to mitigate these limitations during the first half of 2022.
- Spatial integration of high-resolution volumetric data from histological experiments and high-field imaging in humans remains a challenge, since the process requires considerable anatomical expertise and technical understanding to be carried out with good precision, and since those datasets are typically the ones scheduled for rather late delivery in the project. Our strategy is to work in increments here, using the intuitive VoluBA workflow to achieve linear alignments, and working on dedicated nonlinear alignments for selected experiments.
- Implementing access to pseudonymised human data in the EBRAINS Knowledge Graph via downstream applications like the atlas viewer is slightly delayed as a consequence of previous delays of setting up a secure access to those data (“human data gateway”) and offering an API to this service. Such API is now available, but still needs to be implemented into downstream applications and tested. As a consequence, the atlas viewer is currently not offering direct access to the files connected with e.g. human fMRI or IEEG datasets. As a temporary solution however, it provides the links to the corresponding Knowledge Graph landing pages, which allow using the Human Data Gateway.