New release of interactive spatial alignment tool (D5.3.1 – SGA2)

Figure 1: Web-based graphical user interface of the spatial anchoring tool.

After uploading a volumetric dataset, the user can position the volume on top of a reference brain (here: the BigBrain template) by shifting (drag) and rotating (shift-drag) the incoming datasets 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.

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Deescription in GA	We will deploy the 2nd release of the interactive spatial alignment tool started in SGA1. The release will provide a significantly streamlined user interface, especially a much better user experience in terms of landmark management and interactive navigation. (T5.3.3)

Abstract:	A very practical yet largely unsolved problem in high-resolution brain atlasing is spatial anchoring of high-resolution volumes of interest from specific imaging experiments into the detailed anatomical context of a high-resolution reference model like the BigBrain, to allow integration of volumetric data at the level of individual cortical layers and more. Downloading and interacting with high-resolution reference datasets is out of reach for many neuroscientists due to the size of the data and the lack of practical tools. The HBP provides a novel interactive volumetric alignment tool, VoluBA (previously landmark-reg), that allows anchoring of user data to very large reference volumes. It is implemented as a web service that allows uploading data from imaging experiments and perform anchoring by interactive manipulation of the incoming volume's position and rotation, flipping of coordinate axes, and entering of point landmarks. The resulting transformation parameters can be downloaded, and the aligned image directly opened in HBP's interactive atlas viewer to see it in the full atlas context. This deliverable describes the current release at https://voluba.apps.hbp.eu/.

Keywords:	Human atlas, Neuroinformatics Platform, Big Brain, Image Registration, Tier 2 curation, Spatial Anchoring, Atlas Viewer, Affine Transformation
Target Users/Readers:	Neuroanatomics, Data curation teams

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1. Introduction

Comparable to the way geographical information systems organise data in the 2D coordinate system of the earth's surface, the HBP provides reference atlases and online services as a framework for topographical organisation of neuroscience data relative to locations in the brain: cortical and subcortical areas, layers, fibre pathways and other spatial entities of brain organisation. By integrating a broad range of neuroscience data from different sources into the system and assigning them appropriate spatial location in one of HBP's reference atlases, we continuously build up a multilevel atlas that provides a multimodal characterisation of the brain from the microscopic to the macroscopic scale and can be explored interactively online. The process of assigning locations to new data is modelled as Tier 2, Atlas Integration, of the Curation Service. More information about the Curation Service can be found on the project website: https://www.humanbrainproject.eu/en/explore-the-brain/share-data/, and in SGA2 Deliverables D5.1.1 (D28.1 D72) and D5.2.1 (D29.1 D73).

Most imaging data of the brain is given in the form of 2D sections and 3D volumes. For aligning 2D sections (e.g. from histology) to reference volumes, HBP provides the well-established QuickNII tool developed at the University of Oslo. The alignment of whole-brain MRI scans to whole-brain reference volumes is nowadays typically performed using nonlinear image registration software. This is a particularly involved task especially in the human brain, due to its complex folding patterns and high variability. Several established algorithms have been proposed. In the HBP, such algorithms are investigated for the use with HBP atlases in Subproject 2 (SP2), with the notable example of the DISCO framework (Lebenberg *et al*. 2018; P1391) which explicitly introduces sulcal constraints into a nonlinear alignment based on the DARTEL method (Ashburner, 2017).

A very practical yet largely unsolved problem is the spatial anchoring of high-resolution volumes of interest from specific imaging experiments into the detailed anatomical context of a high-resolution reference model like the Big Brain (Amunts *et al*. 2013). This is a rather new problem, because such high-resolution models are only available since a few years. They allow to integrate volumetric data at the level of individual cortical layers and more. Typical application examples are laminar resolution functional MRI (DeMartino *et al*. 2013), microscopic resolution structural connectivity as derived from 3D Polarized Light Imaging (Axer *et al*. 2011), or 2-Photon fluorescence imaging (e.g. Silvestri *et al*. 2014), which would all be appropriately organised in the detailed anatomical context of the Big Brain microscopic brain model. Unfortunately, downloading this huge (~1 Terabyte) dataset and working on a proper positioning of new imaging data is out of reach for many neuroscientists due to the sheer size of the data, as well as the lack of practical tools.

HBP provides a novel interactive volumetric alignment tool, **VoluBA** (previously denoted as landmark-reg), that allows anchoring of user data to very large reference volumes. This tool is currently implemented as an online web service that provides the BigBrain model as a fixed reference dataset and allows users to upload data from their own imaging experiment to perform interactive anchoring. Anchoring is possible by direct manipulation of the incoming volume's position and rotation using the mouse pointer, flipping of any of the 3D coordinate axes, as well as entering of point landmarks for refined alignment with affine components. The resulting transformation matrix can be downloaded for reference and for submission to HBP data curation (curation-support@humanbrainproject.eu). In the latter case, the curation team can directly apply this information for Tier 2 curation, since it represents the user's input about the location of the dataset relative to a reference atlas. The aligned image volume can be directly opened in the HBP interactive atlas viewer to see it in the full atlas context and compare it to atlas regions as well as other data linked to the same reference atlas.

This deliverable describes the current release of the software, which is available at https://voluba.apps.hbp.eu/. Please note that this URL might change in the upcoming months, since we are still working on even closer integration of HBP tools. VoluBA will then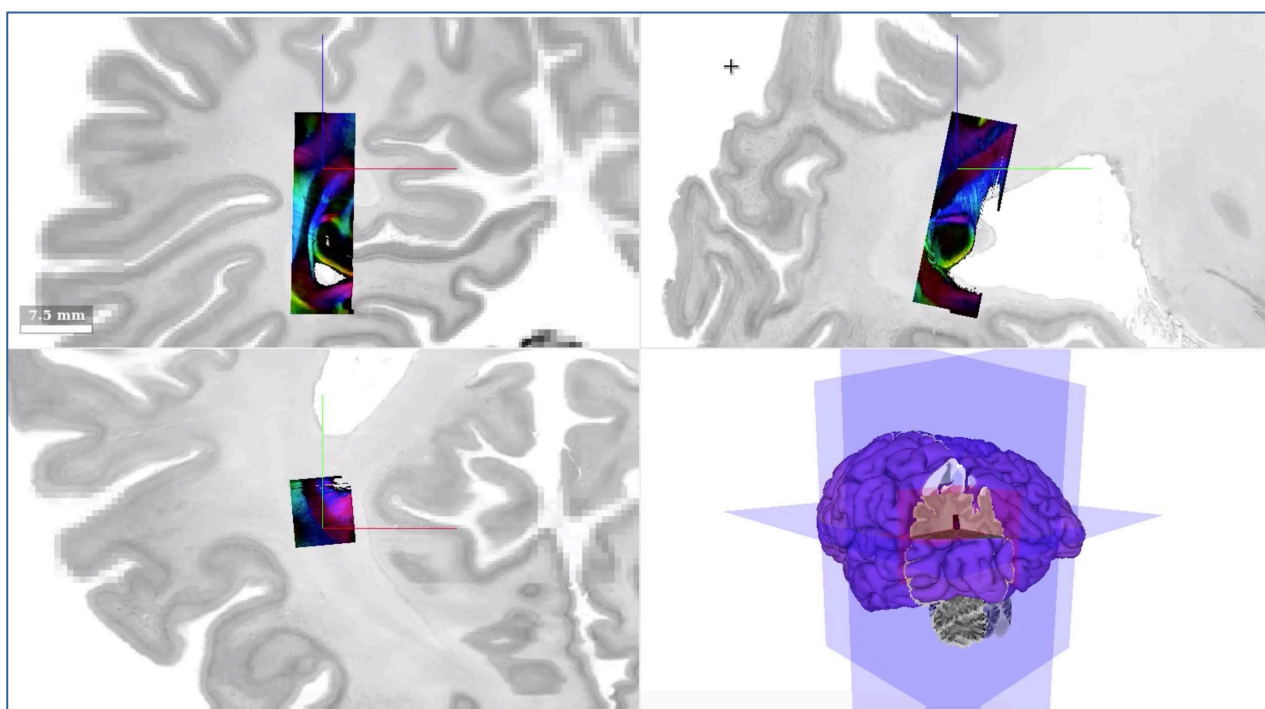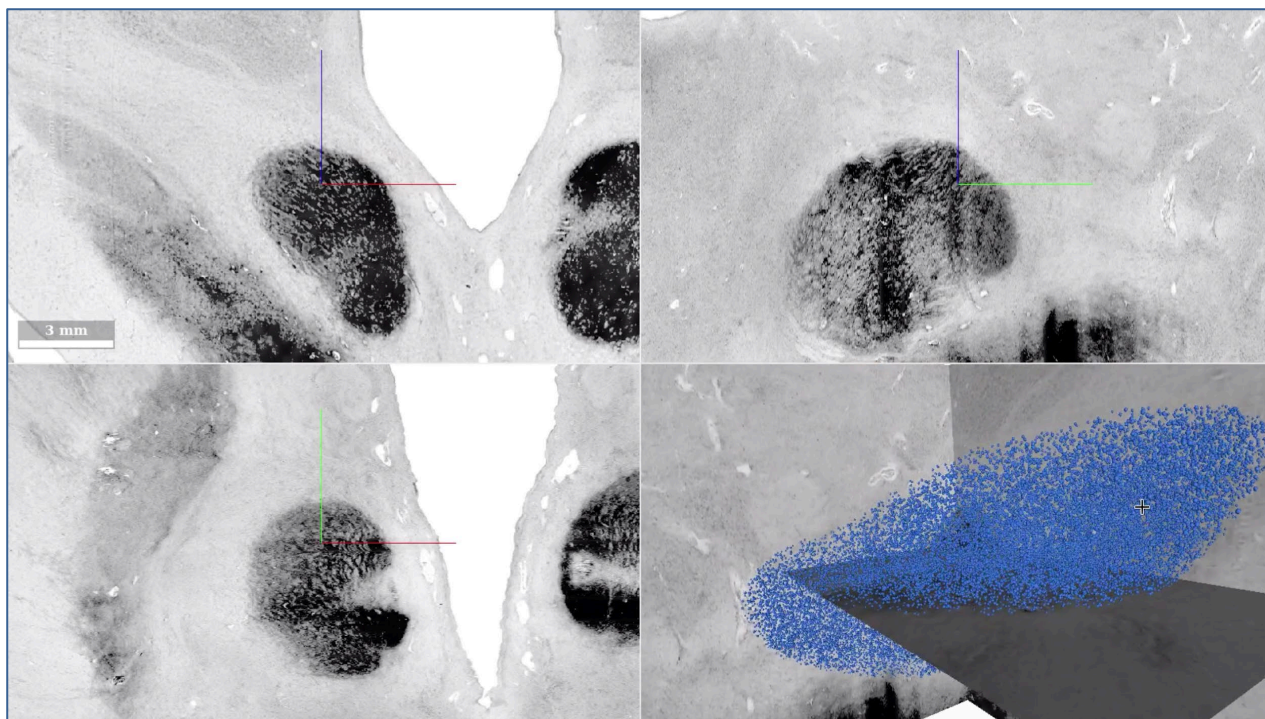 be prominently linked directly from the HBP atlas website (https://www.humanbrainproject.eu/en/explore-the-brain/atlases/).

Figure 2: Example results or partial volumetric alignment, achieved using the VoluBA tool

A 3D neuronal cell distribution (top) and volume of interest from Polarized Light Imaging (bottom) collected in a common anatomical context, by spatial anchoring to the BigBrain microscopic reference brain model.
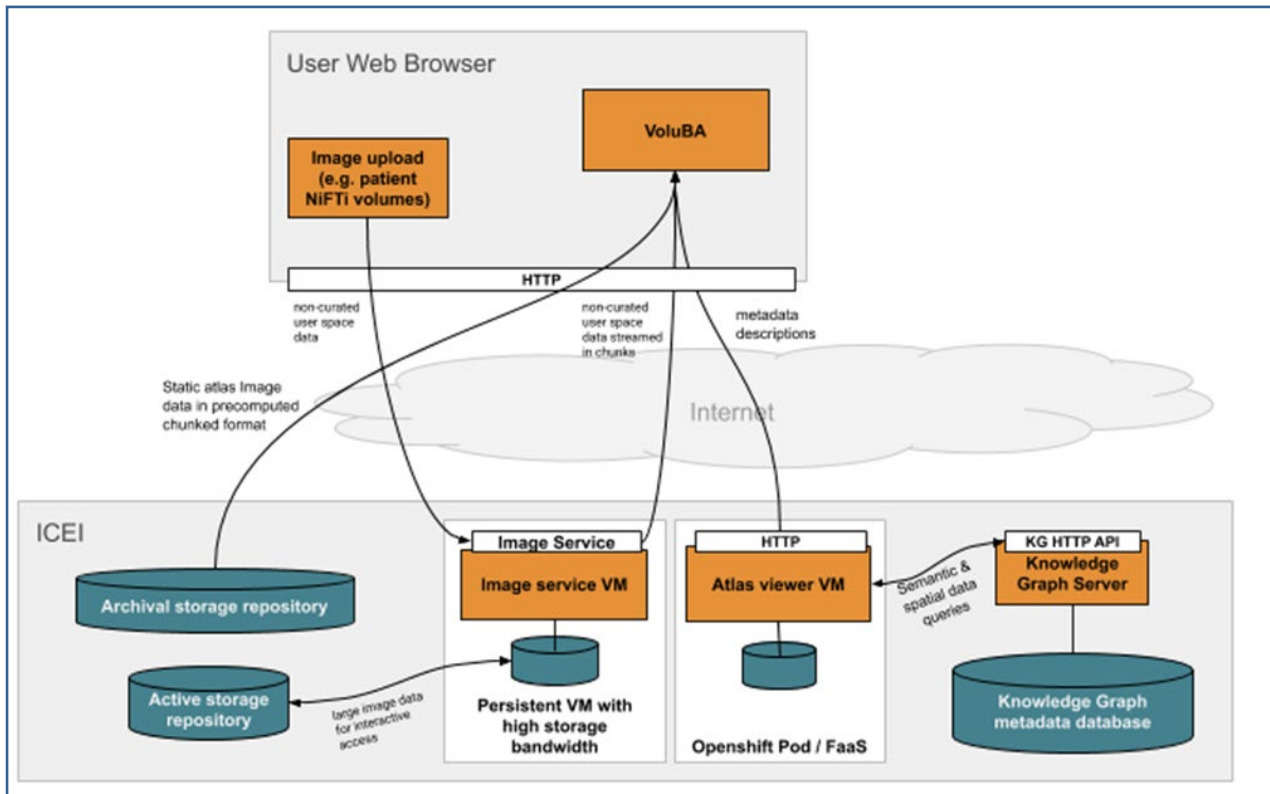
Figure 3: Interaction of the interactive volumetric alignment service VoluBA with other HBP services and infrastructure components

2. Software architecture

VoluBA is implemented as a JavaScript-based web application which allows visual interaction with a reference brain volume and an incoming volumetric dataset in 3D from a standard web browser. It interacts with several other web services to retrieve data, as illustrated in Figure 3.

The VoluBA front end application is implemented using Vue for the reactive UI layer, Vuex for state management, Bootstrap 4 for layout and font awesome for glyphicons (Figure 4). At its core, VoluBA integrates the web-based volumetric rendering software NeHuBa for fetching and displaying of multiresolution volume data, which is also the core component of HBP's interactive atlas viewer NeHuBa-UI (both developed in SGA2 Task T5.4.3). In this respect, the design of VoluBA answers to the concept of an increasingly unified viewer architecture in HBP, as documented in more detail in SGA2 Deliverable D5.4.1 (D31.1 D75), "First release of software adapted to new viewer architecture". It shares much of the code as well as look & feel of the interactive atlas viewer NeHuBa-UI. The data provided through the image service is directly compatible, so that the user data which is anchored in VoluBA can also be used as an image source for a layer in NeHuBa-UI.

The multiresolution image data of the reference atlas template is retrieved from a data repository hosted by the ICEI infrastructure. For large reference volumes, the data is stored in the neuroglancer precompute tile format (https://github.com/google/neuroglancer/tree/master/src/neuroglancer/datasource/precompu ted) and directly exposed as static chunk files via http. This data format is highly effective for very large datasets that retrieve updates in rare intervals, as it allows for very quick retrieval with small communication overhead via http but requires explicit conversion.
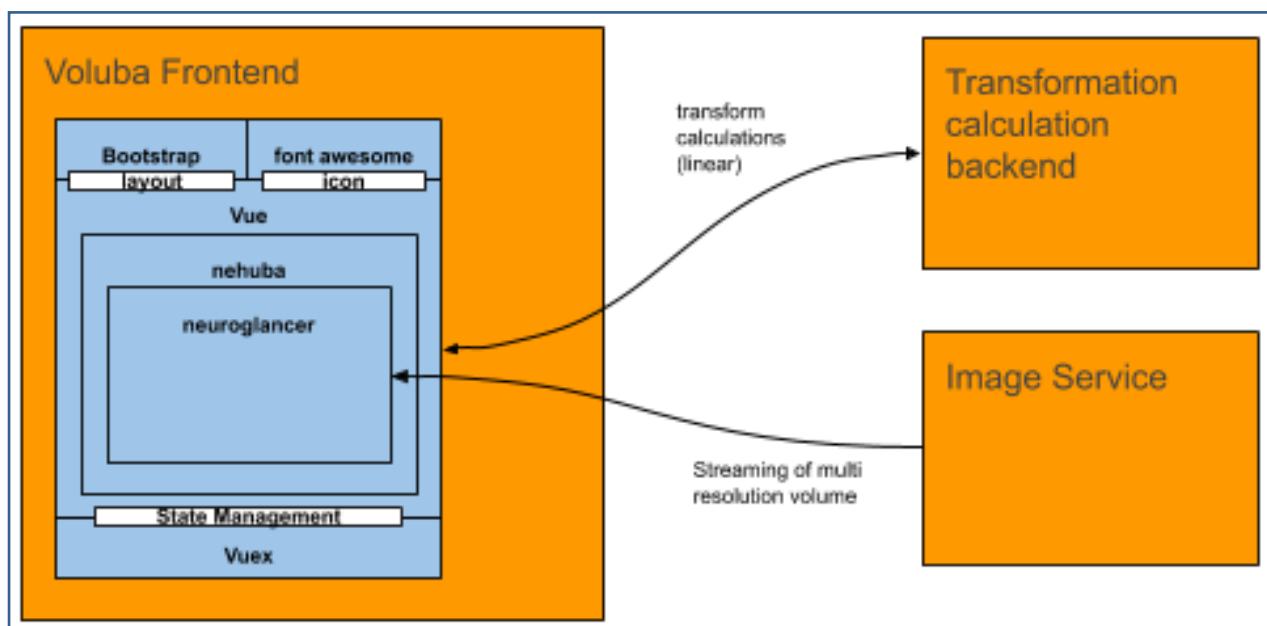

Figure 4: Internal software architecture of VoluBA.

The incoming data is uploaded to an image service by the user, and then provided to VoluBA through the image service. This way, the user can superimpose his or her volumetric data with HBP reference atlases without prior passing through the HBP data curation process. However, VoluBA is designed to be tightly integrated with HBP data curation: The anchored image data can be submitted to data curation by the user, and VoluBA will be used vice versa in the HBP Curation Workflow for Tier 2 curation tasks.

VoluBA's image service was developed to enable secure and efficient streaming of private user - uploaded data to the viewer. It provides a REST API which allows an upload of volumetric image and segmentation data, initially in NIfTI format with future plans to add support for image stacks,

HDF5 and other less common but equally important scientific formats. Uploaded data can be inspected by the user and streamed back to the NeHuBa viewer in an efficient, chunked [neuroglancer precomputed format](). Other data representations could be easily plugged in when needed. Image service takes care of generating volume chunks at different scales to construct a multi-resolution pyramid, which allows easy navigation and display of large data volumes at the desired level of detail. Data conversion and chunk/pyramid generation could be performed by image service in advance or happen "on-the-fly" when requested by the user. Even if the former mode of operation is chosen, data processing and ingestion happens concurrently while uploading the data. This way, by the time when the last byte sent by the user reaches the image service, the whole dataset is already processed and ready to be served. Thus, the best possible user experience is achieved without any interruptions and waiting time avoiding lengthy ingestion phase. In order to provide security and confidentiality of user data, Image Service requires the user to be authenticated via HBP or ORCID authentication services (other ID providers could be easily added later). Digitally signed ID token is passed along with other parameters to every API endpoint. The authenticity of the token is verified using independently obtained public keys of HBP or ORCID before the access is granted to the private space of the user denoted by validated token. Currently authentication using HBP service is disabled due to insufficiently secure cryptographic key. RFC 7518, Section 3.3 (https://tools.ietf.org/html/rfc7518#section-3.3) clearly states that "A key of size 2048 bits or larger MUST be used" where HBP public key is only 1024 bits long. HBP service will be available for user authentication as soon as it complies with the standard. The image service is designed to be hosted on an ICEI VM with fast, direct access to an active storage repository to efficiently handle interaction with large "active" image data, which changes frequently. This infrastructure configuration currently serves as an early use case for the ICEI developments.

3. User workflow

Anchoring an incoming image volume to the reference volume in VoluBA consists of 1) uploading data, 2) adjusting coordinate axes orientations and scalings, 3) visually supported interactive translation and rotation of the incoming data volume, and 4) affine refinement of the transformation by entering additional corresponding pairs of anatomical landmarks. All but the data upload steps can be performed and repeated in arbitrary order and are supported through a history browser which allows to undo actions and roll back to any previous status of alignment.

The visual interface can be used in two different modes at any time, by clicking the "mode" button in the upper right part of the "overlay mode" (Figure 5 top), which displays the incoming and reference volumes in a semitransparent overlay as known from the interactive atlas viewer, as well as a "side-by-side mode" (Figure 5 bottom) which shows the two volumes side-by-side. All actions can be performed in both modes, although for some actions it is advisable to use a specific mode. For example, adding corresponding landmarks is typically more intuitive in the two-pane mode, while interactive shifting of the incoming volume is more easily performed in the overlay mode.
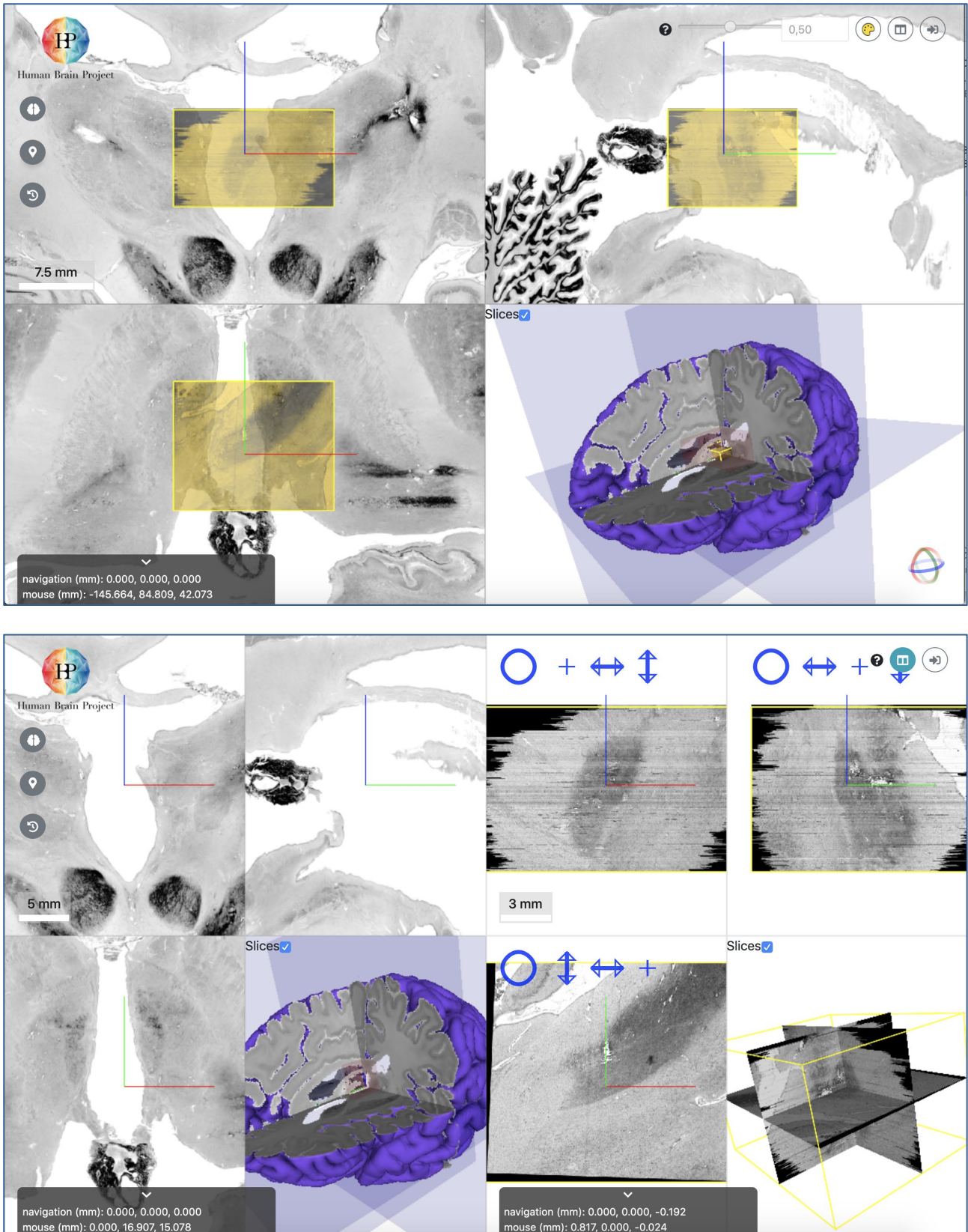
Figure 5: Overlay mode (top) and side-by-side mode (bottom) in VoluBa can be switched by clicking the mode button in the upper right of the user interface.

3.1   Uploading a dataset

The anchoring process starts by selecting an existing dataset from the image service or uploading a new dataset (Figure 6). Users need to authenticate themselves to access or upload data in their user data space in the image service. In the present version, HBP and ORCID logins are accepted.
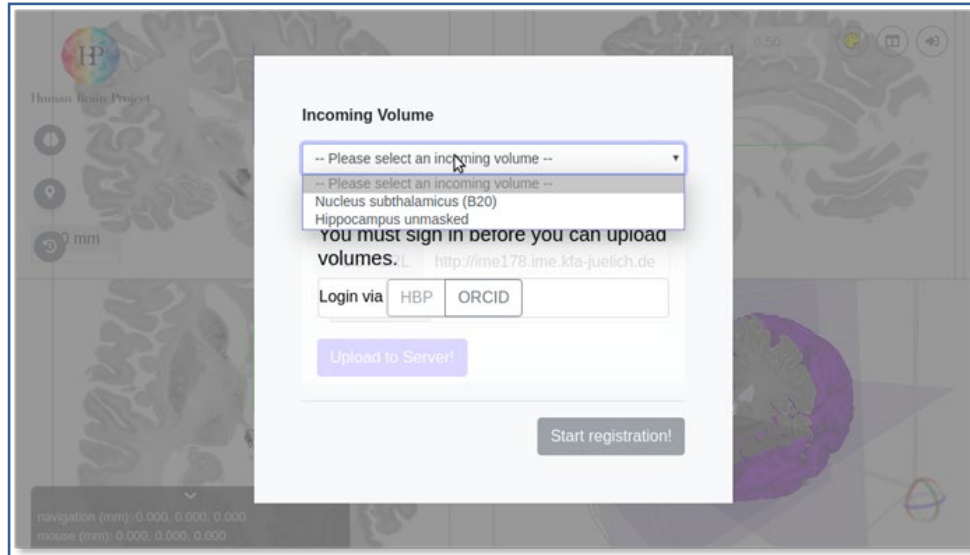

Figure 6: Incoming image selection and upload dialogue

3.2   Initial alignment

After upload and selection of an incoming data volume, VoluBA starts in overlay mode where it allows direct manipulation of the incoming volume's position and orientation using the mouse pointer (Figure 7). The position is changed by clicking & dragging the incoming volume in any of the orthogonal views. By pressing shift while clicking & dragging, a rotation is applied.
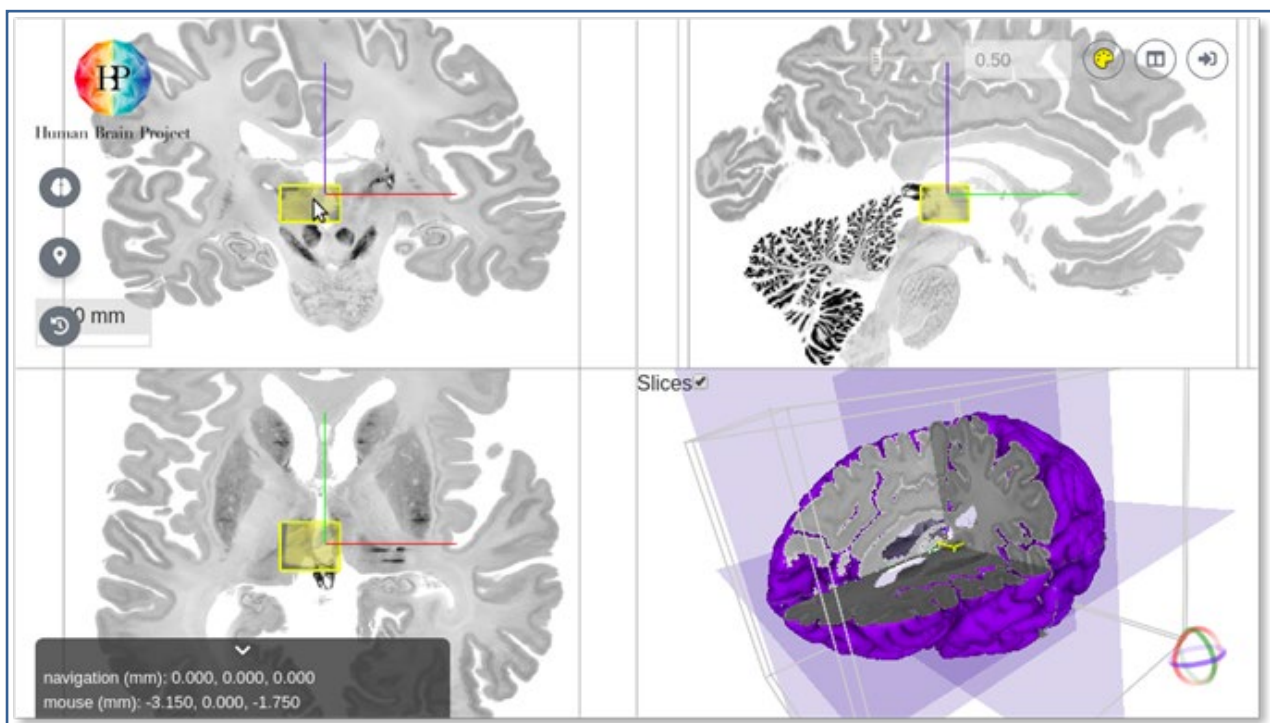

Figure 7: Initial alignment of incoming volume by mouse manipulation of position and orientation.

The scale and orientation of the axes can be changed using the "Transform" dialog box (see Figure 8 top), which also allows a precise manipulation of translation and orientation parameters. In two-pane mode, axis flips are directly accessible in the orthogonal views (see Figure 8 bottom).
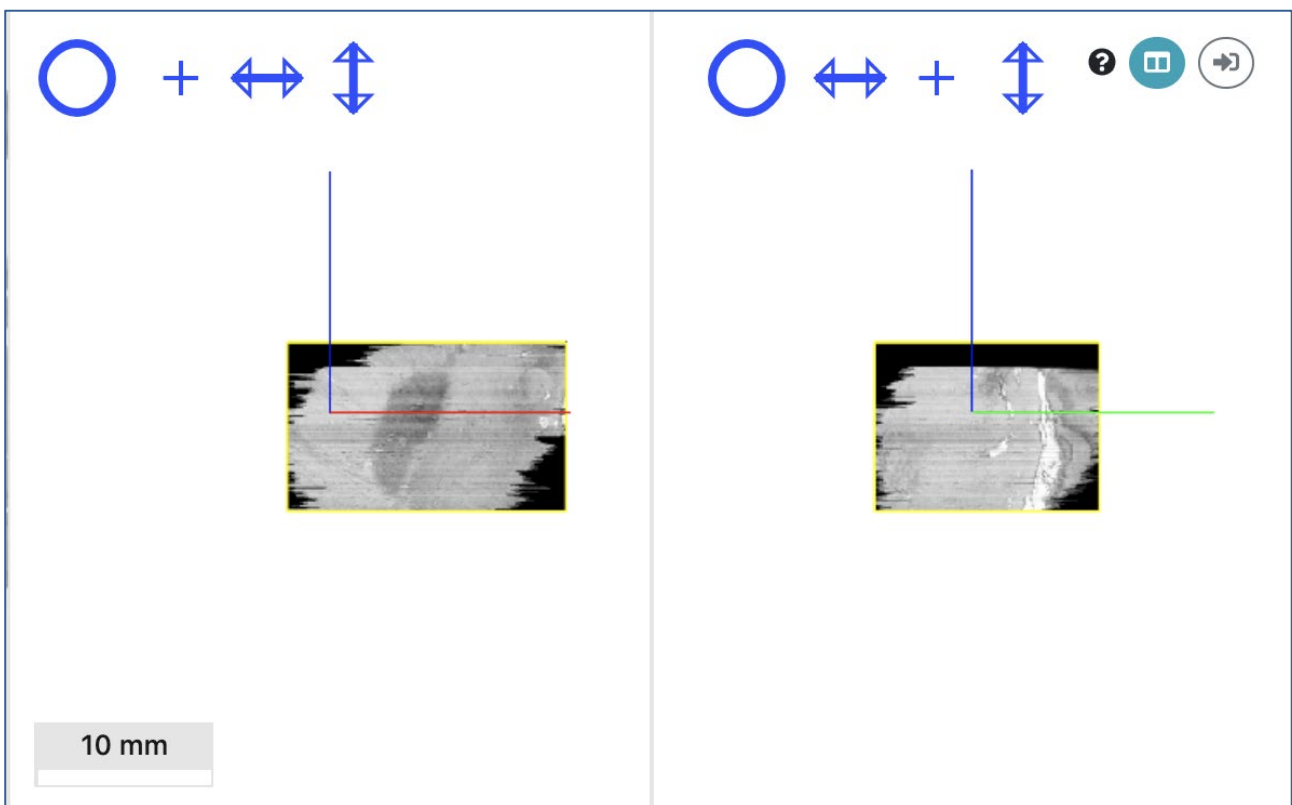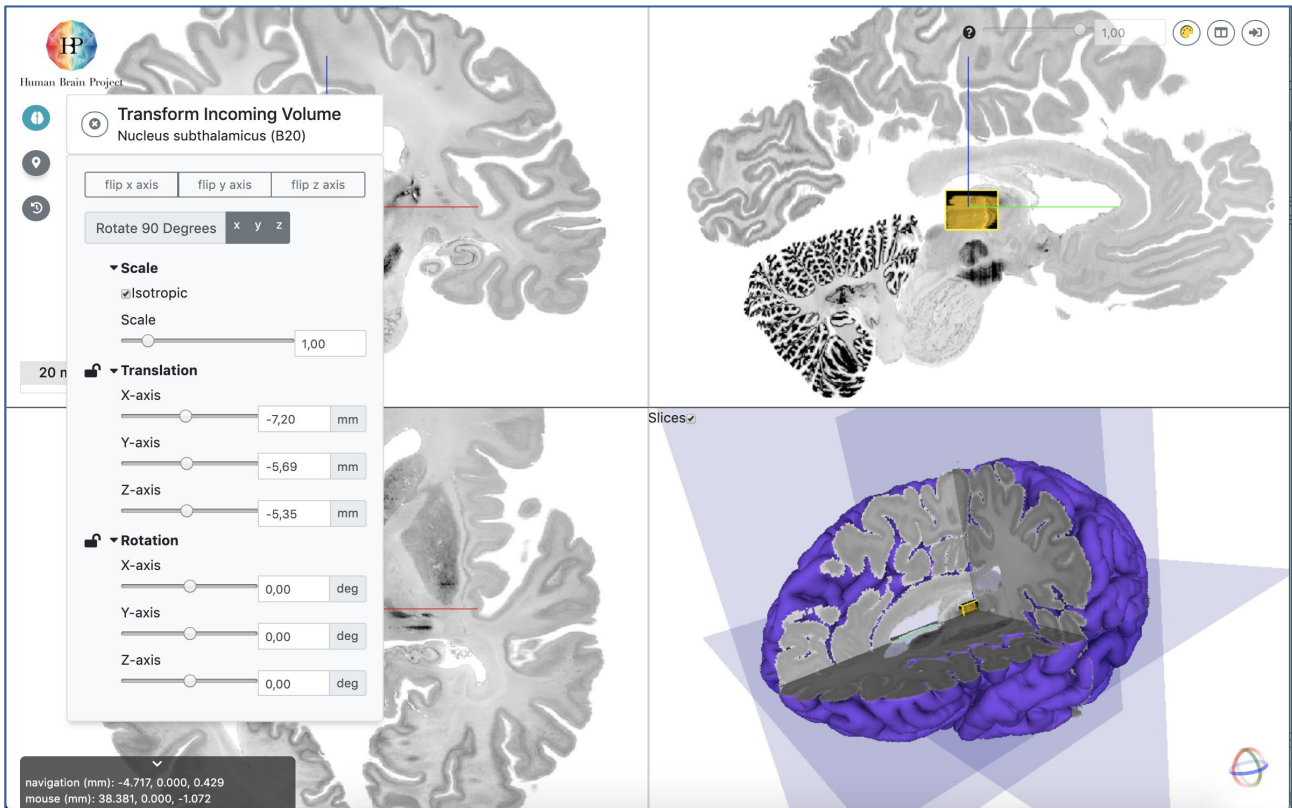

Figure 8: Manipulation of the incoming volume's scale (top) and axis orientation (bottom)

3.3 Refined alignment using landmarks

Once an acceptable alignment has been achieved based on the rigid transformations described above, users can start entering anatomical landmark pairs in either overlay or two-pane mode (Figure 9):
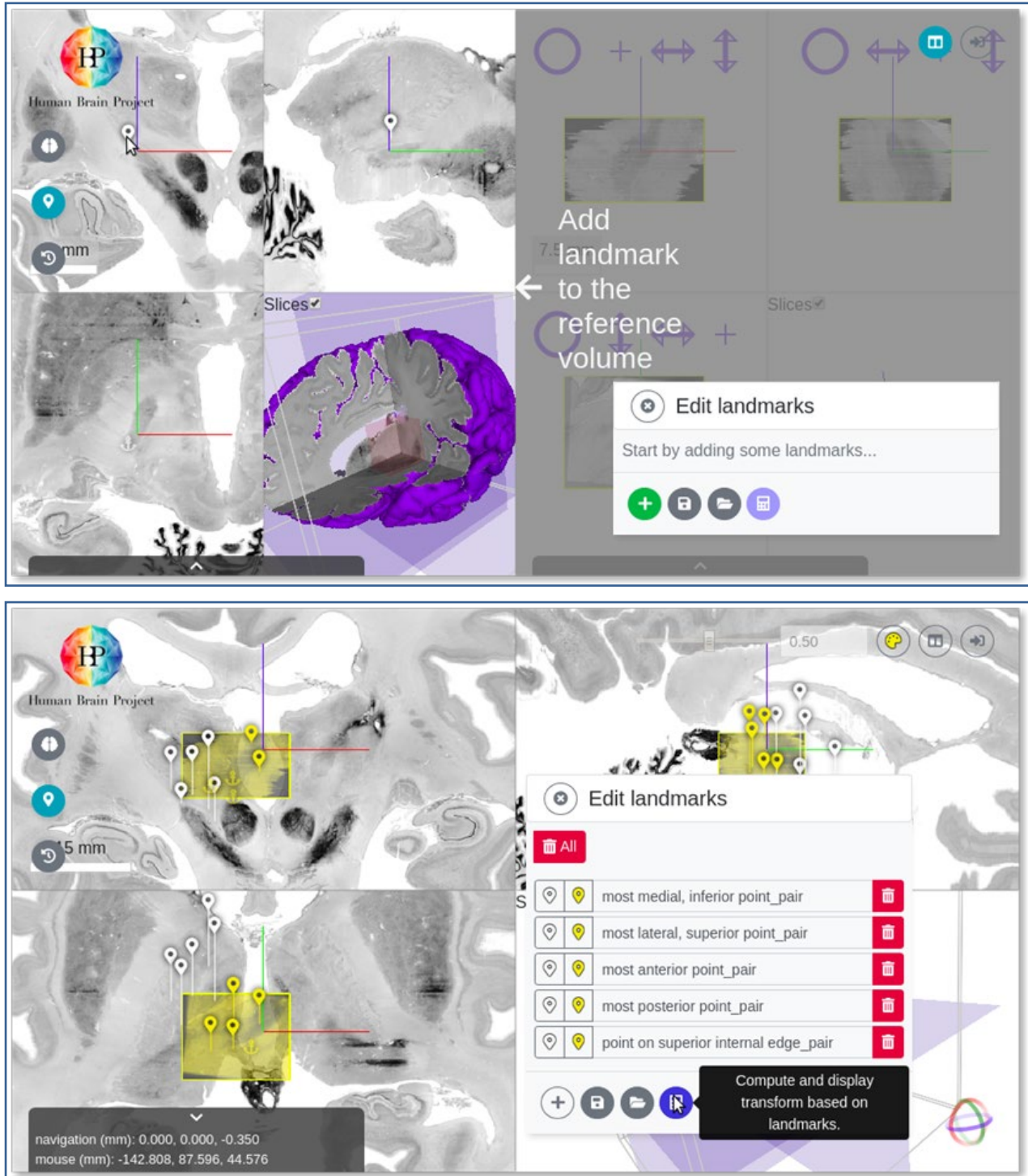

Figure 9: Adding and editing pairs of corresponding landmarks for refined affine alignment (top: two-pane mode, bottom: overlay mode).

Each landmark can be given a name, and the list of landmarks can be downloaded as a json file for reference. Conversely, an existing list of landmarks can be loaded from the user's computer. The entering of landmarks does not immediately influence the position of the incoming volume. Only when computing a transform based on the current list of landmarks, an affine transformation

of the incoming volume is estimated and applied. Just as the previous interactive adjustments of position, scale, rotation or axis orientation, the application of the affine transformation will then be recorded in the history browser and can be undone.

It is important to note that the interactive rigid transformations described above have no influence on the computation of the affine transformation. The affine transformation estimation depends exclusively on the landmark pairs. Hence, when using landmark-based alignment, other actions only serve the purpose of a better visual orientation for entering landmarks.

3.4   Undoing actions using the history browser

Any action on the incoming volume in VoluBA is recorded as an entry in the history browser (Figure 10), which is accessible via the corresponding button ("rollback" arrow) on the left of the user interface. This includes translations, axis flips, rotations, scalings, and application of affine matrices that have been estimated from landmark pairs. As known from undo functions in many software products, the history is implemented as an infinite stack, from which the top element can be removed at any time, resulting in a rollback to the previous version of the work.

As long as no new action is applied to a recovered history version, the "undone" actions can be recalled again ("redo"). This allows users to easily navigate forward and backward along their changes and inspect the development of the spatial alignment.
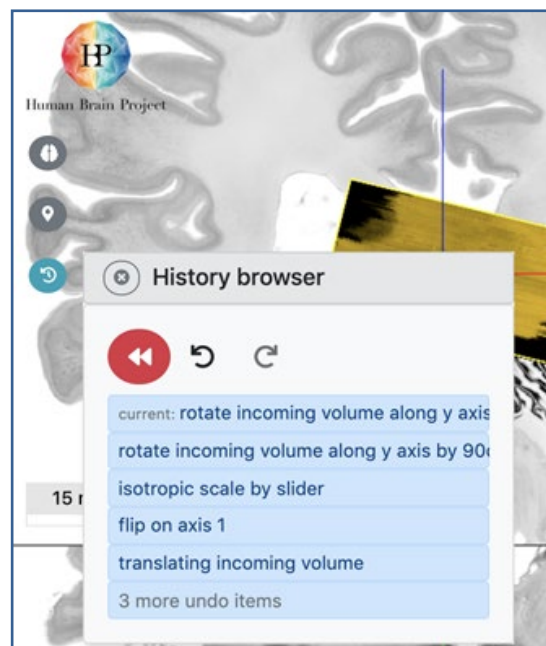

Figure 10: Browsing the history of actions with the option of undoing and reapplying actions.

3.5   Using the result

The spatial anchoring results are inherently useful, since the incoming volume is then visible on top of the reference atlas volume. However, there are two ways of using the results beyond VoluBA:

1) The affine matrix of the current alignment can be downloaded as a json file for personal reference, or for submission to the HBP curation workflow with the dataset.

2) The result can be opened as a semi-transparent layer directly in the HBP interactive atlas viewer. This way, the user can investigate the aligned image volume relative to all the data that is registered with the corresponding HBP reference atlas.

4. Conclusion

This first publicly accessible release of the volumetric spatial alignment tool "VoluBA" allows users to interactively position their own volumetric image dataset in the coordinate system of the high-resolution BigBrain reference template. The tool supports interactive adjustment of axis orientations, translation, scale, and rotation, as well as full 3D affine alignment on the basis of entering corresponding anatomical landmark pairs. The resulting transformation parameter can be downloaded for reference or submission to the HBP curation teams with the data. The aligned image can be directly opened as a layer in the interactive atlas viewer to relate it to the wealth of information that is accessible there. It is the first tool available to our knowledge, that allows direct manipulation of the linear 3D alignment of high-resolution volumes of interest to a Terabyte-scale high-resolution reference volume like the BigBrain, in particular without the need of installing additional software or downloading this large dataset to the local computer - which in most cases will not have enough free disk space.

The software is designed to match the increasingly unified viewer and service architecture of the HBP atlas ecosystem. Most notably, it reuses software components of the interactive atlas viewer and provides full compatibility of the data sources.

Although currently fixed to the Big Brain reference volume, VoluBA is designed to work with any of HBP's reference atlas templates. Upcoming releases in SGA2 will allow to select any of them. Current research regarding high-resolution spatial volumetric alignment in HBP is addressing nonlinear transformations driven by topological cues such as cortical depth and retinopy. Once implemented and tested for feasibility and usability, these will be integrated into future updates of the online tool.

VoluBA will be addressed in several upcoming educational and dissemination events on the HBP to provide user training and collect practical feedback, amongst others during the FENS Cajal course on whole brain imaging, 8-28 September 2019 in Bordeaux (https://www.fens.org/Training/CAJAL-programme/CAJAL-courses-2019/WBI-2019/). The education material that is currently prepared will be made available online together with the tool during the remainder of SGA2.

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