PMOD Rodent Brain Tool (PNROD)

USER MANUAL
Version 4.4

PMOD is a software
FOR RESEARCH USE ONLY (RUO)
and must not be used for diagnosis or treatment of patients.

π.pmod

1 PMOD Rodent Brain Tool (PNROD)

Precise knowledge of the functional brain areas in the individual subject is crucial for the accurate quantitative analysis of brain PET images and their meaningful interpretation. Often however, functional regions are manually outlined in a casual manner, with subjective results as the outcome. For rodent brain images, this fundamental flaw can be overcome with PMOD's PNROD tool which offers objective region outlining via easy step-by-step procedures.

Automatic Rodent Brain Regions by Atlas Adjustment

A well established way of obtaining brain region outlines automatically is by adjusting brain atlases to a subject brain. This is achieved by calculating a spatial transformation which maps the brain anatomy represented in the atlas to the actual brain anatomy of the subject. The transformation is called "spatial normalization", and correspondingly its estimation step "normalization". Various types of normalizations are supported in PNROD: elastic procedures which warp the entire anatomy, affine matching which only scales and shears the brain as a whole, and rigid matching which assumes that the imaged animal brain is practically identical to the atlas brain. If all automatic procedures fail, rigid matching can be manually performed as a last resort. Naturally, the estimation of the atlas transformation is crucial for the whole analysis.

Once a successful normalization has been found, the spatial transformation between the anatomies can be used to project the brain areas encoded in the atlas to the subject brain. The user should always inspect the adequacy of the resulting outlines (called VOIs i.e. Volumes-of-Interest) and has tools available to adjust them locally.

Finally, statistics can be calculated within the brain regions resulting in signal average, volume, and other statistics. In case of dynamic acquisitions, the average regional signal is conveniently obtained as a time curve and can directly be transferred to the kinetic modeling tool (PKIN) for absolute quantification of tissue function.

Parametric Mapping

If the pixel-wise modeling tool PXMOD has been licensed, PNROD also embeds the PXMOD Parametric Mapping[52] workflow which can be run after regional outlining has been completed. This integration has several advantages: (1) The regions generated by PNROD can be used during the PXMOD model configuration. (2) The resulting parametric maps can immediately be regionally analyzed. (3) The parametric maps can be calculated in the subject or the atlas space.

Workflows

PNROD supports two different workflows:

1. **Dual-image workflow with two images from the same subject brain**: In such studies, the target image for analysis is typically a functional (PET, SPECT), and an anatomical image (MR, CT) serves as the anatomical backdrop and is normally used for the spatial normalization. In hybrid studies, the two images are inherently aligned. If the two brain images were acquired in separate scans, an additional rigid matching step is required to bring them into alignment. Once the transformations have been determined, each image can be transformed into the space of any other image or the atlas. Similarly, the atlas regions can be transformed to any of the images. This has the advantage that the user can calculate the regional statistics in the original functional image, in the image transformed to the anatomical image space, or in the image transformed to the atlas space. It is .
2. **Single image workflow**: If only a single image is available, the transformation to the atlas anatomy has to be determined directly. In this situation, statistics can be calculated in the original image or in the image transformed to the atlas space.

Starting the PNROD Tool

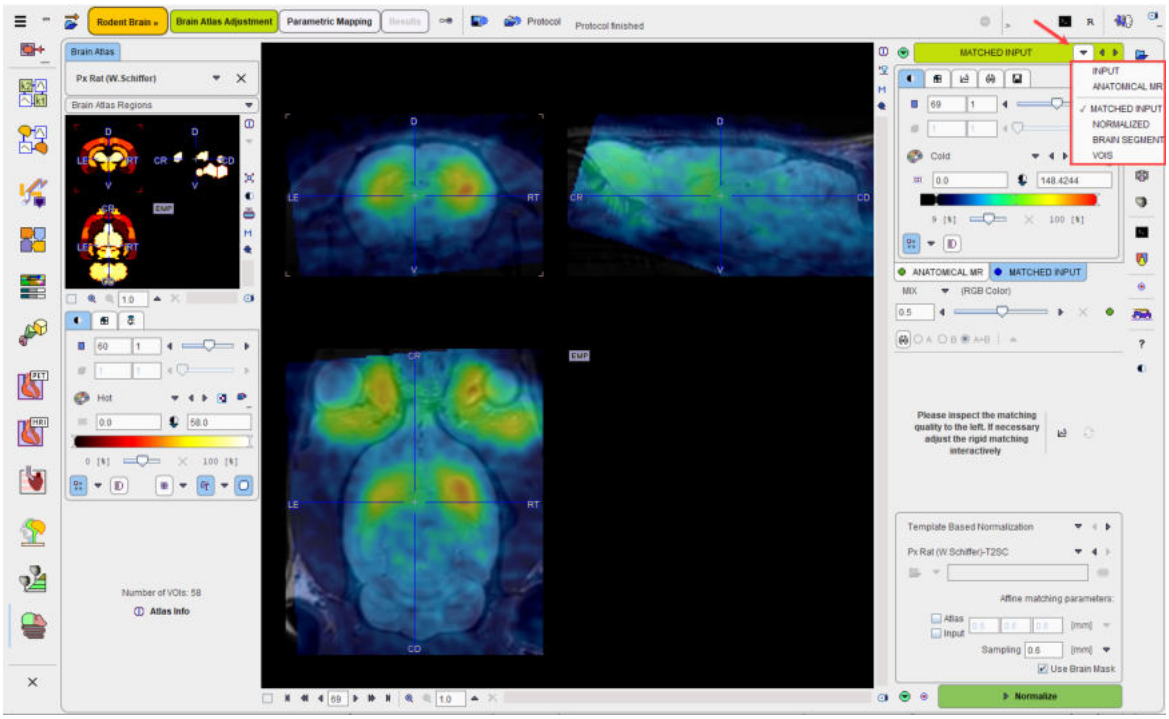
The PNROD tool is started with the **Rodent Brain** button

from the PMOD ToolBox or by directly dragging image files onto the above button.

2 PNROD Organization and User Interface

The PNROD tool organizes the analysis of the rodent brain images as a sequence of processing stages, which together form a workflow targeted at ease of use and consistency of results.

The user interface explained below is organized accordingly.



Further Information

This guide is focused on the brain analysis functionality of PNROD. Please refer to the *PMOD Base Functionality Guide* for details about general functions such as data loading, image display controls, and VOI definition tools.

2.1 PNROD Sub-Pages

The PNROD interface includes three sub-pages:

Brain Atlas Adjustment

This is the main page to select a brain atlas and adjust it to the brain of the subject which has been imaged. During the workflow, it shows a sequence of layouts for performing the different tasks.

Parametric Mapping

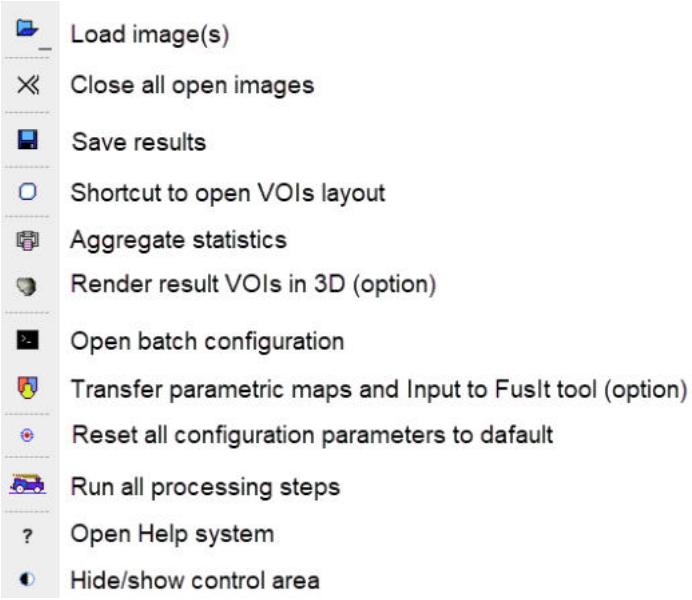
This page is only available, if the pixel-wise modeling tool PXMOD has been licensed. It allows the user to perform parametric mapping as part of the analysis of dynamic data.

Result

This page shows the statistical results of the analysis. Depending on the data, it contains a table listing the regional average in the adjusted brain regions, or a plot of curves representing the regional averages along a dynamic acquisition.

2.2 PNROD Taskbar

The taskbar to the right of the user interface provides shortcuts and additional functionality.



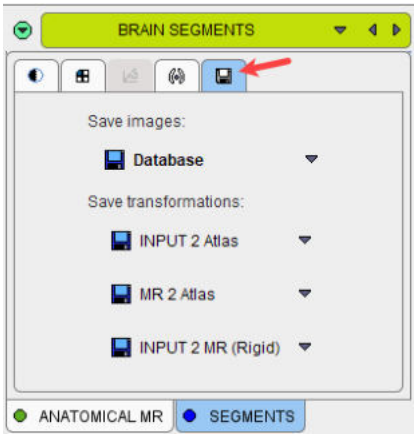
2.2.1 Loading Images from Taskbar

The loading button in the taskbar allows loading of one or two images in all supported formats:

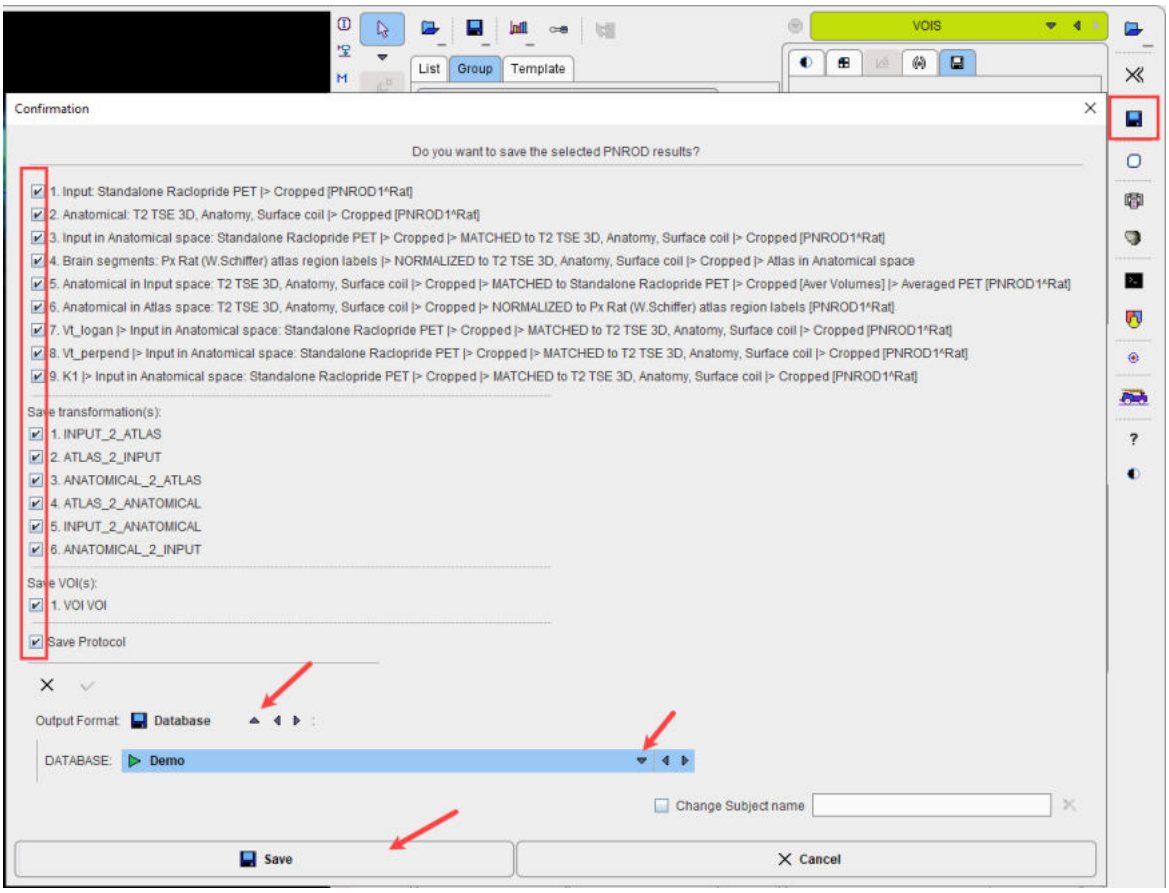
- If only a single image is selected and loaded, it takes the role of the **Input** image.
- If two images are loaded, PNROD tries to figure out the roles from the DICOM attributes: Images from an anatomical modality (MR, CT) are assigned the role of the **Anatomical**. Dynamic images are assigned the role of the **Input**, assuming that it is the functional image to analyze. If the pairing is not clear it is recommended using the loading buttons in the workflow layouts to ensure proper assignments.

2.2.2 Saving Intermediate Results

Intermediate results such as transformed images and the various spatial transformations can be saved from the dedicated saving panels.



The complete set of intermediate information for a PNROD workflow can be saved at once using the **Save all** button from the lateral taskbar.



This information may be valuable in order to further exploit the outcome in the viewing and fusion tools.

2.2.3 Run All Processing Steps

The "Run All" button  has two uses.

Re-calculate with Modified Parameters

The **Run All** functionality is useful when testing the impact of parameters. Simply change the target parameter on any panel and run the full processing.

Re-calculate with New Data

If the desired workflow has proven to be reproducible (i.e. equivalent VOIs can be generated with a stable set of configuration parameters), there is no need to interactively step through the different stages. Rather, the data can be loaded, all processing steps performed unattended, and then the results inspected and saved.

To do so please proceed as follows:

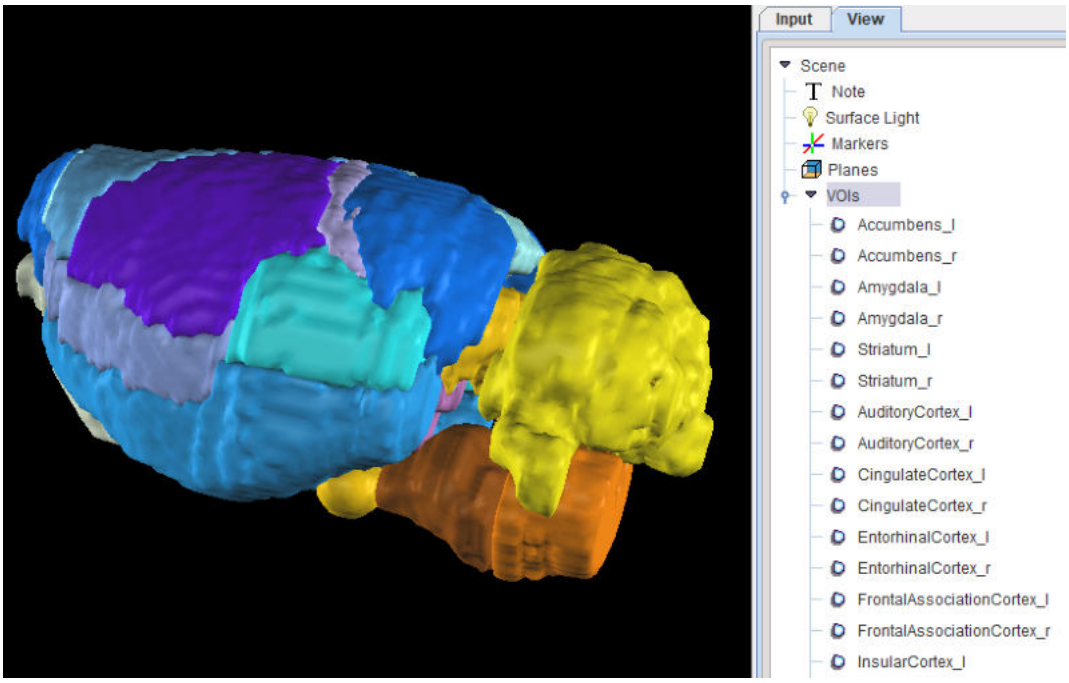
1. Make sure the parameters on the all stages are set appropriately. This can also be ensured by loading a specific protocol file.
2. Load the **Input** image, and define the crop box if necessary.
3. If there is an **Anatomical** image as well, load the image, and define the crop box.
4. Activate the "Run All" button  from the lateral taskbar. All steps up to the VOI outlining will be performed.

5. Inspect the relevant intermediate results such as matching and spatial normalization to ensure the resulting VOIs are meaningful.
6. Save the VOIs and calculate the statistics.
7. Save a protocol file.

If this mode of operation is successful, the data can alternatively be processed using the batch mode.

2.2.4 3D Rendering of Brain VOIs

Once a set of brain VOIs has been calculated it can be visualized in the 3D tool (option) as full surface by activating the button in the lateral taskbar. The result illustrated below can be used for exploring the spatial relationships and preparing documentation slides.



Please refer to the *PMOD 3D Rendering Tool Users Guide* for information about the operation of this tool.

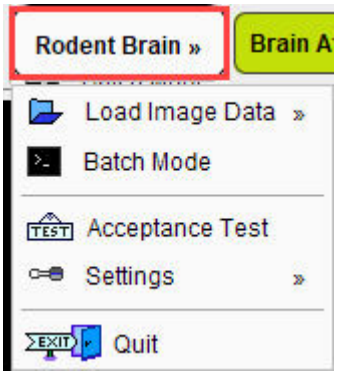
2.3 PNROD Menu Line

The PNROD menu line is located at the top of the docking interface. It consist of the yellow menu button, **Rodent Brain**, followed by the main module pages, functional buttons, an area for progress information and other buttons common for all PMOD modules. The currently active page, e.g. **Brain Atlas Adjustment** in the example above, is highlighted in green color.

Only the local menu, the configuration and protocol functionality are documented in this section, the other elements are standard in PMOD and documented in the *PMOD Base Functionality Users Guide*.

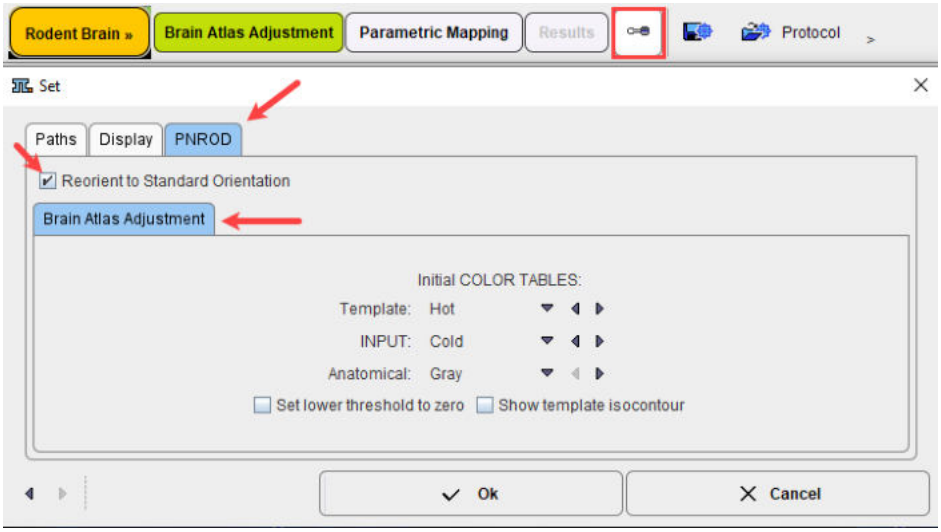
2.3.1 Menu Content

The yellow menu button allows accessing: data loading interface, PNROD batch processing interface, the acceptance test, the local configuration and the PNROD **Quit** button.



2.3.2 Configuration

The PNROD tool can be configured according to user preferences in a dialog window as illustrated below.



The common configurations are available on the **Paths** and **Display** tabs, and in the upper part of the **PNROD** tab. Note the **Reorient to Standard Orientation** box. If it is checked, PNROD tries to orient the brain images such that they appear in the radiological Head First Prone (HFP) order with subject left on the image left. For instance, MR images acquired in sagittal orientation will automatically be reformatted and presented with axial slices if the orientation encoding in the data is correct. The correct HFP orientation of the data after loading is important for the automatic procedures to work properly.

The **COLOR TABLES** selections allow the user to set the initial color tables applied for the different image roles in the process. The two check boxes allow enabling overlay of the template iso-contour display, ant the automatic setting of the lower color threshold at the value of zero.

2.3.3 Protocols

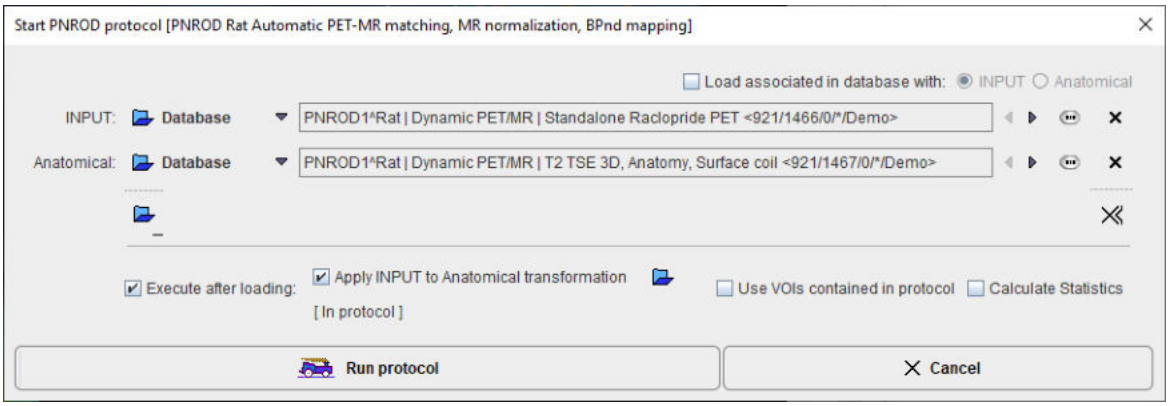
PNROD allows saving the final processing configuration as a protocol.

Such a protocol includes definition of the input data as well as the parameters of the different processing stages, including parametric mapping. The user is advised to save a protocol after every completed data processing workflow, so that at any later time the configuration can be retrieved, verified and modified to try variations of the processing parameters.

Note: If parametric mapping should be part of the protocol, page **Parametric Mapping** must be active when saving the protocol.

Protocol Execution

When loading a PNROD protocol a dialog window offers several options.

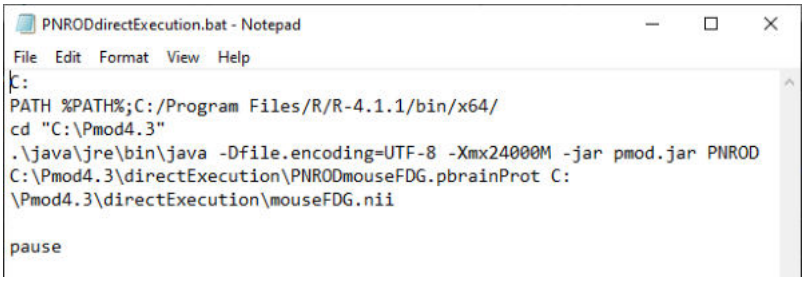


If **Execute after loading** is enabled, not only the configuration is retrieved, but the processing is also performed with the following options:

- The **Apply INPUT to Anatomical transformation** allows using a transformation instead of repeating the actual rigid matching in a dual-modality workflow. Either the transformation saved with the protocol can be used (default), or an external transformation file can be specified.
- If the **Use VOIs contained in protocol** option is enabled, region outlining is not executed, but rather the saved VOIs are retrieved. This has the advantage that any manually adjusted VOIs are recovered.
- With **Calculate Statistics** the statistics in the VOIs will be calculated at the end of the protocol.

Please note that if information is retrieved from the protocol instead of repeating all processing, not all processing options will be active.

Note that protocols may also be executed from the command line using a modified PMOD start script:

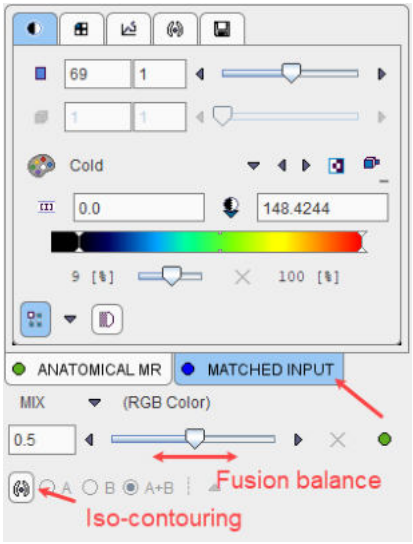


The tool must be defined immediately following "pmod.jar", separated by a space, then the paths to the protocol and input data defined, also separated by spaces.

2.4 Fusion Image Display

The display of the images is controlled in the upper right. In many cases two images contribute to a fusion display. Each of these images has its own set of controls. In order to change the appearance of an image, the corresponding control tab has to be first activated.

The control section for the combining the two images into a fused image is located below the image control tabs. In the configuration illustrated below the colors of both images are mixed, whereby the weighting can be changed with the slider.



Please refer to the *PMOD Base Functionality Guide* for a documentation of the multitude of available fusion options.

3 PNROD Data Processing

Data processing is mostly done on the **Brain Atlas Adjustment** page, which is described next. The succeeding sections detail the workflow this page for the dual-modality and the single-modality situation.

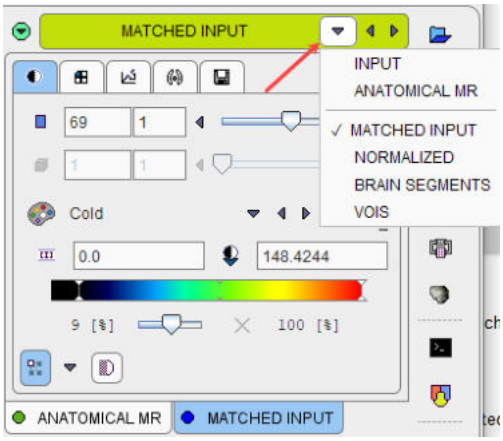
3.1 Brain Atlas Adjustment Page

Step-wise Processing

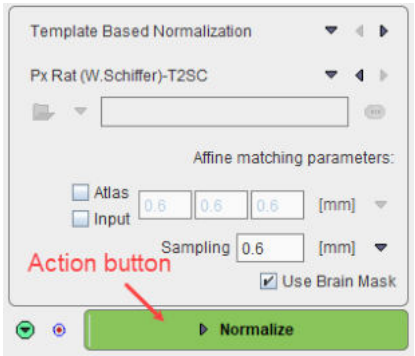
The adjustment of the atlas to the subject brain is organized on the **Brain Atlas Adjustment** page as a processing sequence. On each processing stage the user has to take some action such as data loading, alignment inspection or parameter configuration, and then start the next processing step.

Sequence of Page Layouts

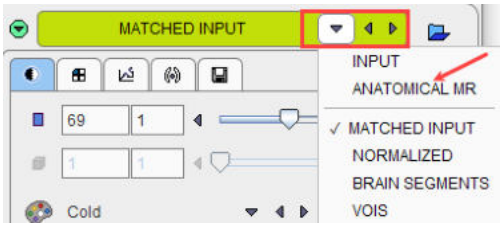
The processing stages are implemented as different layouts of the **Brain Atlas Adjustment** page. The list element in the upper right indicates the current stage. When the list is opened as illustrated below, the sequence of stages is shown. Note that the sequence list depends on the type of data to be processed.



In each layout, some actions have to be performed, such as checking the alignment. Then the next processing step has to be configured with the parameters in the lower right. Processing is finally started with the green action button below the parameters e.g. **Normalize** as illustrated below.



As soon as the result is calculated, it will be shown in the subsequent layout. If the result is not satisfactory, please return to the previous layout using the list selection



Then change the processing parameters, and activate the green button again.

Note that by using the left/right arrows or by directly selecting a list element no processing is started. This conveniently allows inspecting the results of the different stages. If there is a need to repeat a calculation with modified parameters, the action button in the lower right has to be activated again on the actual and all following pages.

Convenience Buttons

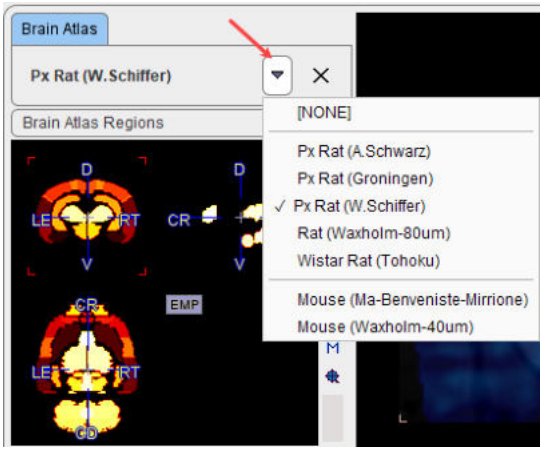
Next to the action button in the lower right there is an area with two buttons

offering the following functions:

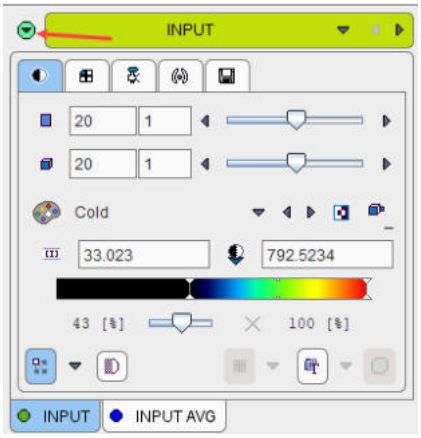
/ toggle	Hide the parameters panel to free some space in the user interface. With the panel hidden, the icon changes to . When this button is activated, the panel is shown again.
	Resets the parameters on the panel to their default values. If the same button in the taskbar to the right is activated, the defaults are reset on all panels.

3.1.1 Atlas Selection

The atlas to be used for the analysis can selected in the **Select Atlas** panel.



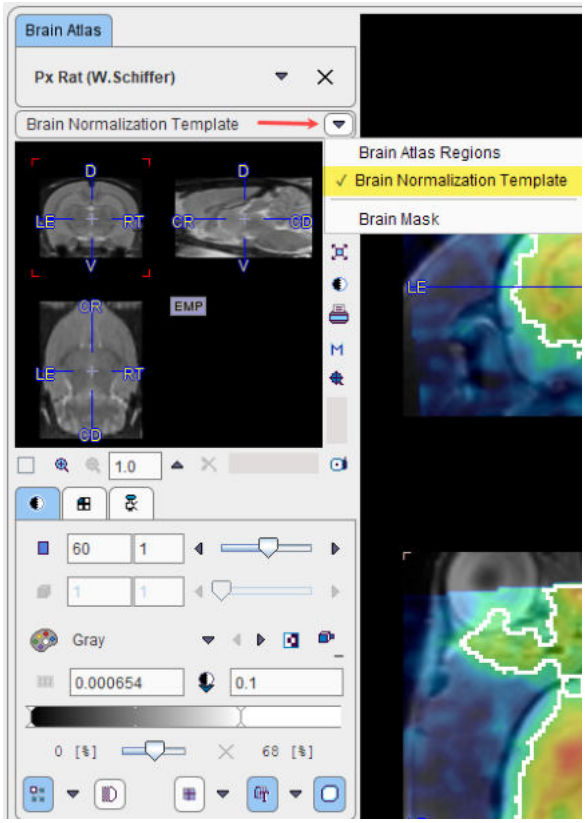
If the panel is not visible, please activate the toggle button illustrated below in the upper right of the **Brain Atlas Adjustment** page.



Note that all rodent atlases in the sub-directory *resources/templates/voitemplates* are listed.

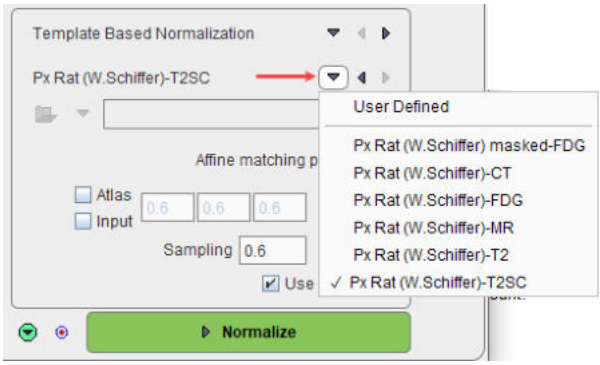
Atlas Information

An atlas consists of three different parts. The displayed information can be selected as illustrated below.

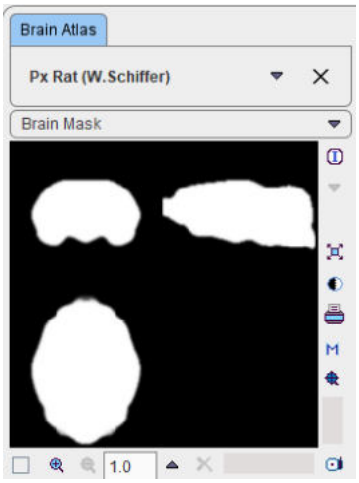


The **Brain Atlas Regions** are shown per default. They represent the brain regions encoded in the atlas.

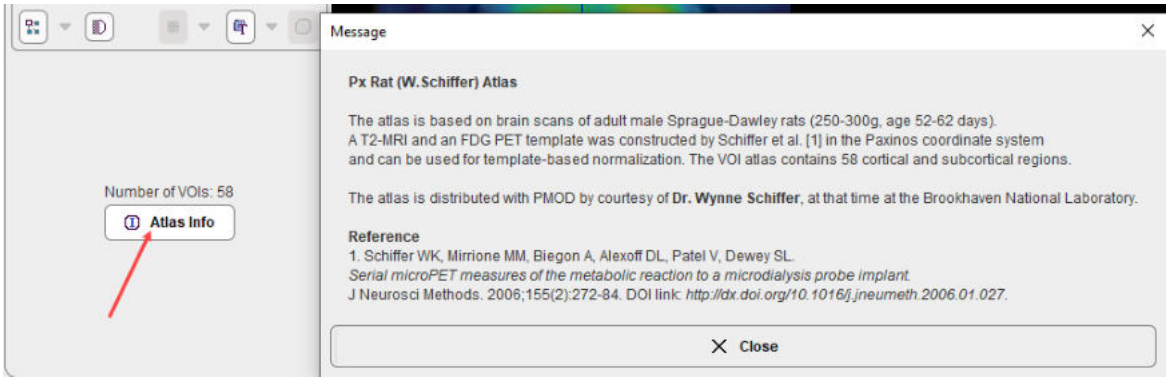
Brain Normalization Template shows the anatomical image in the atlas space which is currently configured for the normalization. Note that some atlases offer several modality-specific templates, among which the user should choose the most adequate one in the parameter section of the atlas normalization. In the example below the T2 MR template acquired with a surface coil was selected.



Brain Mask shows the mask in the atlas space which is applied during spatial normalization to limit the optimization procedure to the brain information. All non-negative pixels will be taken into account.

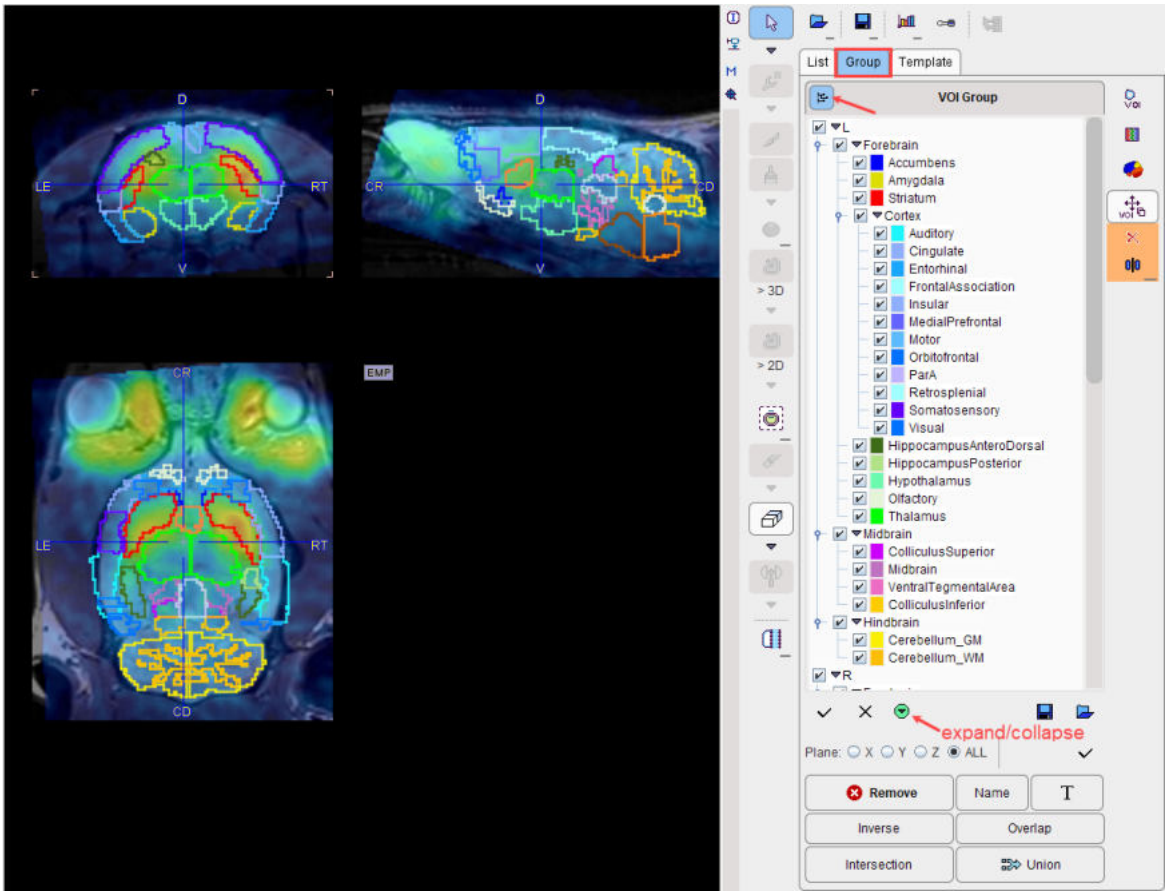


The **Atlas Info** button brings up a dialog window with a short summary of the atlas characteristics.



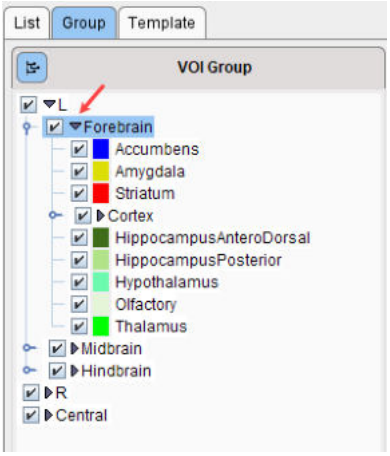
3.1.2 Atlas VOI Interface

The brain VOIs are structurally organized in a tree on the **Group** tab of the VOI editing page. When collapsed, the tree can be fully expanded using the arrow button below the VOIs. Note the check box beside each VOI or each leaf. Only the selected elements are shown in the image and will be used for the VOI statistics.

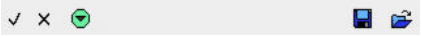


VOI Tree Selections

Branches can be selectively opened/collapsed by clicking at the leaf arrows



Click specific check boxes to select parts of the VOI tree. The shortcuts in the area below the VOI list



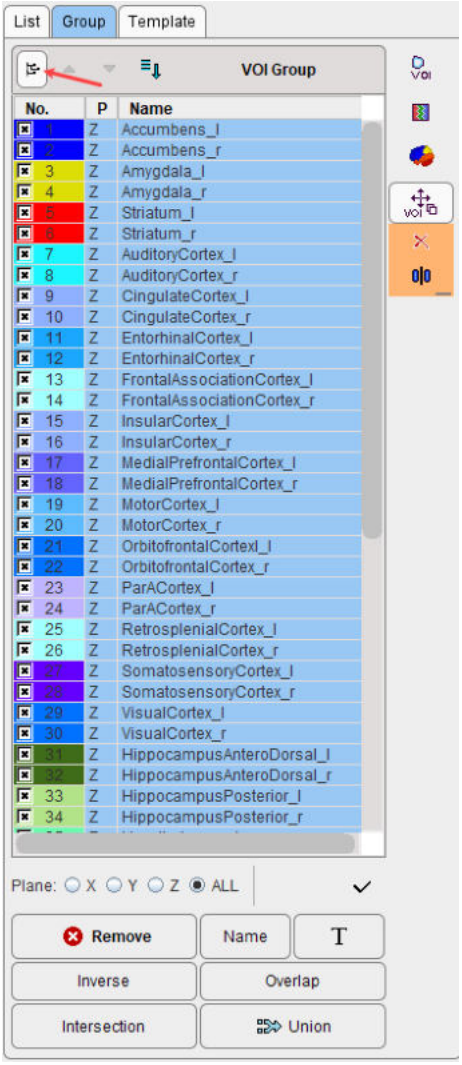
have the following functionality:

✓	Set the selection check of all VOIs
✕	Remove the selection check of all VOIs.

	Save the current selection to a file.
	Load a selection set from a file.

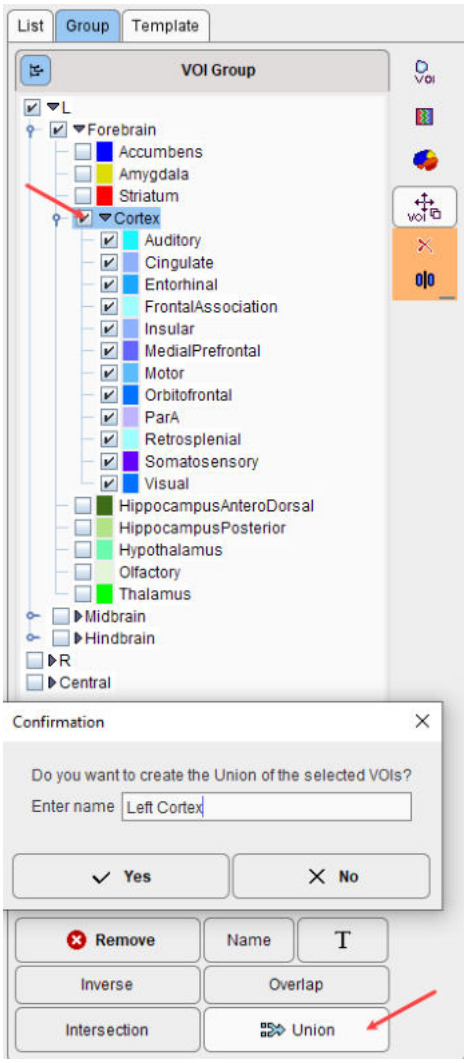
Flat View of VOI Tree

The VOIs can also be shown as a list with the "Flat view " button. Use the check box of each individual VOI to define which VOIs are shown and included in the statistics.

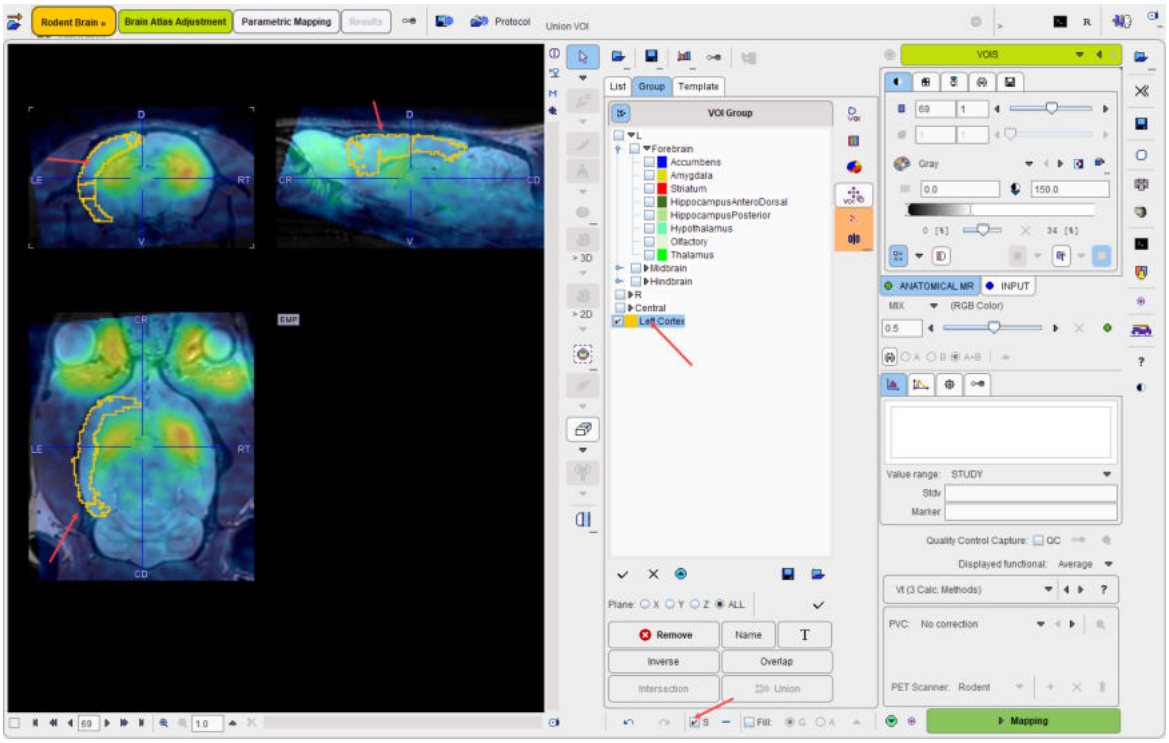


Union of Atlas VOIs

Larger structures can be formed by combining VOIs using the **Union** button. In the example below a Left Cortex VOI is created. The selection was first reset by ✕, then the Cortex entry in the Forebrain of the Left hemisphere branch was checked.



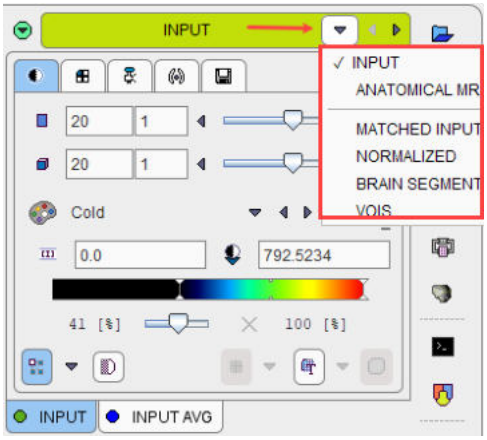
When activating **Union** and accepting the **Confirmation** dialog, a new VOI named **Left Cortex** is created and added at the end of the tree, whereas the original VOIs are removed.



Removal of the original VOIs is necessary for partial volume correction to function correctly. However, the VOIs could easily be recovered by stepping to the prior page and activating the **Outline** button again. Saving the original VOI set and reloading them using **Load Append** can also be useful after creating larger **Union** VOIs.

3.2 Workflow for dual-Modality Studies

The workflow will run through the following layouts of the **Brain Atlas Adjustment** page:



Note that the labeling depends on the selection of the **Anatomical** modality (**PET**, **MR**, **CT**)

However unlike in PNEURO the processing options are the same for PET, MR or CT anatomical reference.

Note: This section will use the data of two standalone scans, PET and MR, for the documentation. PET will be the **Input** image to be analyzed, and MR the **Anatomical** image to derive the brain regions from. The modality of the **Anatomical** series is reflected in the labels shown in the interface. In the case of a CT **Anatomical** series, the interface will display CT instead of MR on the appropriate pages, and likewise for PET.

3.2.1 Processing Overview

The two images of the same subject brain which are used during processing are called **Input** and **Anatomical**:

Input Image

The **Input** image series is the target of the analysis. It will be used for VOI statistics as well as parametric mapping. Note that in the user interface the label occasionally appears capitalized **INPUT** for clarity.

Anatomical Image

The **Anatomical** image is used for deriving the brain VOIs by adjusting it to an atlas. Use of an **Anatomical** reference image is recommended if it supports better normalization than using the **Input** directly.

The processing steps, reflected by the user interface, are the following (with the **Anatomical** image being MR):

1. **Brain Atlas Adjustment** page, **INPUT** layout:
   a. Loading of the **Input** image series which may be static or dynamic.
   b. Dynamic **Input** image case: Averaging of the series in a specified acquisition range. The averaged image will be used in all following steps except for the final statistics calculation and parametric mapping.
   c. Cropping of the image to retain mainly the brain part, potentially with some neighboring tissue which helps the normalization (e.g. skull for CT, Harderian glands for PET).
2. **Brain Atlas Adjustment** page, **ANATOMICAL MR** layout:
   a. Loading of the **Anatomical** image series.
   b. Cropping of the brain area to a similar extent as for the **Input** image.
   c. Start of the automatic rigid matching of the **Input** image to the **Anatomical** image.
3. **Brain Atlas Adjustment** page, **MATCHED INPUT** layout:
   a. Visual, interactive assessment of the alignment.
   b. Manual improvement of the alignment if necessary.
   c. Configuration of the atlas, the normalization method and the normalization template.
   d. Start of the normalization procedure which matches the **Anatomical** image to the selected atlas template.
4. **Brain Atlas Adjustment** page, **NORMALIZED** layout:
   a. Visual assessment of the normalization.
   b. In case of a bad match, return to the **MATCHED INPUT** layout, change the normalization approach, and normalize again. Repeat until a satisfactory match is obtained. If no automatic procedure works, resort to manual rigid matching.

c. Start transformation of the atlas brain regions so that they can be overlaid on the **Anatomical** image as segments.

5. **Brain Atlas Adjustment** page, **BRAIN SEGMENTS** layout:
   a. Visual assessment of the segments overlaid on the **Anatomical** image.
   b. Selection of the image space (**Atlas**, **Input**, **Anatomical**) where the VOIs are generated.
   c. Start generation of the outline VOIs in the result space.
6. **Brain Atlas Adjustment** page, **VOIS** layout:
   a. Visual assessment of the brain VOI outlines overlaid on a fusion of the **Anatomical** and the **Input** image by the user. If the match is not satisfactory, return to steps 3 and 4 and improve matching and/or normalization.
   b. If needed, manually adjust the whole VOI set or individual structures. For instance, all VOIs can be scaled at once.
   c. Start calculation of the VOI statistics on the **Input** image.
7. **Results** statistics page:
   a. Inspect the results.
   b. Save the statistics table (or time curves in dynamic case).
   c. In the dynamic case transfer the curves (usually PET tissue time-activity curves) to the PKIN tool (option) and continue there with modeling.
8. Save the complete configuration of the processing with **Save** protocol icon in the top line 10.

Parametric Mapping of Dynamic Data

In the case of a dynamic **Input** series, return to

9. **Brain Atlas Adjustment** page, **VOIS** layout:
   a. Select an appropriate parametric mapping method.
   b. Start parametric mapping.
10. **Parametric Mapping** page:
    a. Perform the Parametric Mapping 52 workflow as in PXMOD.
    b. Save the parametric maps.
11. Save the complete configuration of the processing including parametric mapping with **Save** protocol icon in the top line 10.

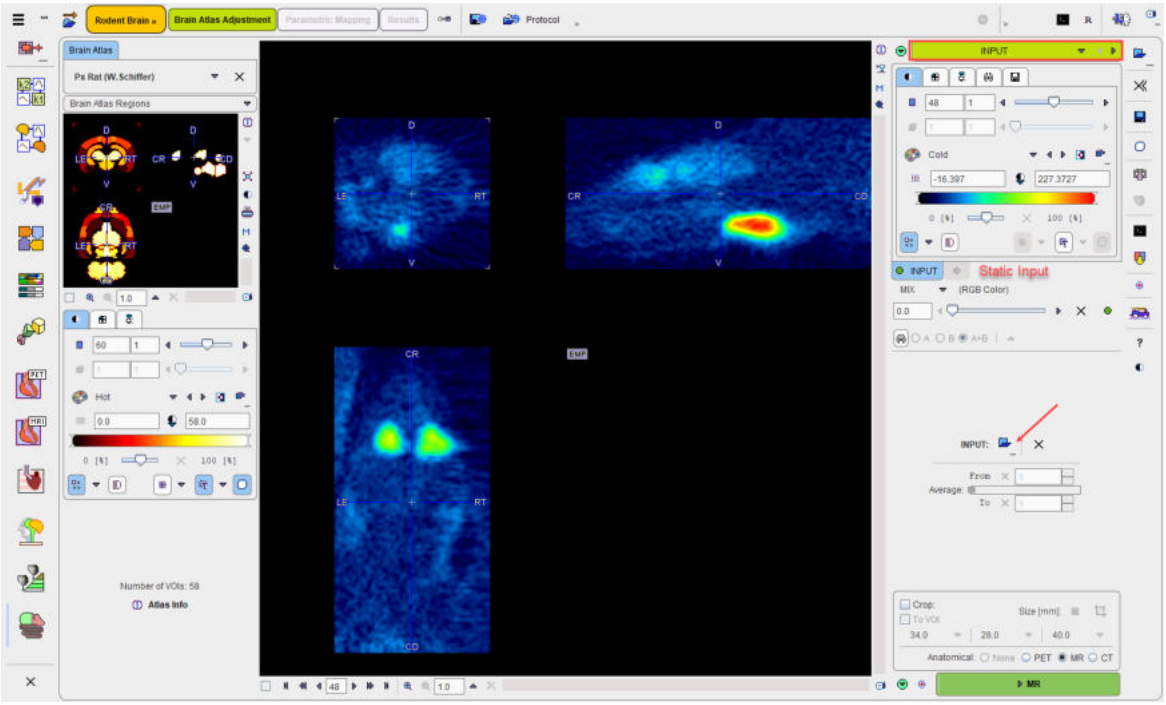
3.2.2 Input Image Loading, Time Averaging, Cropping

Stepwise processing is started by selecting the **Brain Atlas Adjustment** page.

Static Input Image Loading

On the **INPUT** panel, use the **Load INPUT** button in the right control area for loading the **Input** image. As usual it is an option button which needs to be set to the appropriate data format with the indicated arrow. For loading images which are not saved in a PMOD database it is recommended to use the **Autodetect** loader.

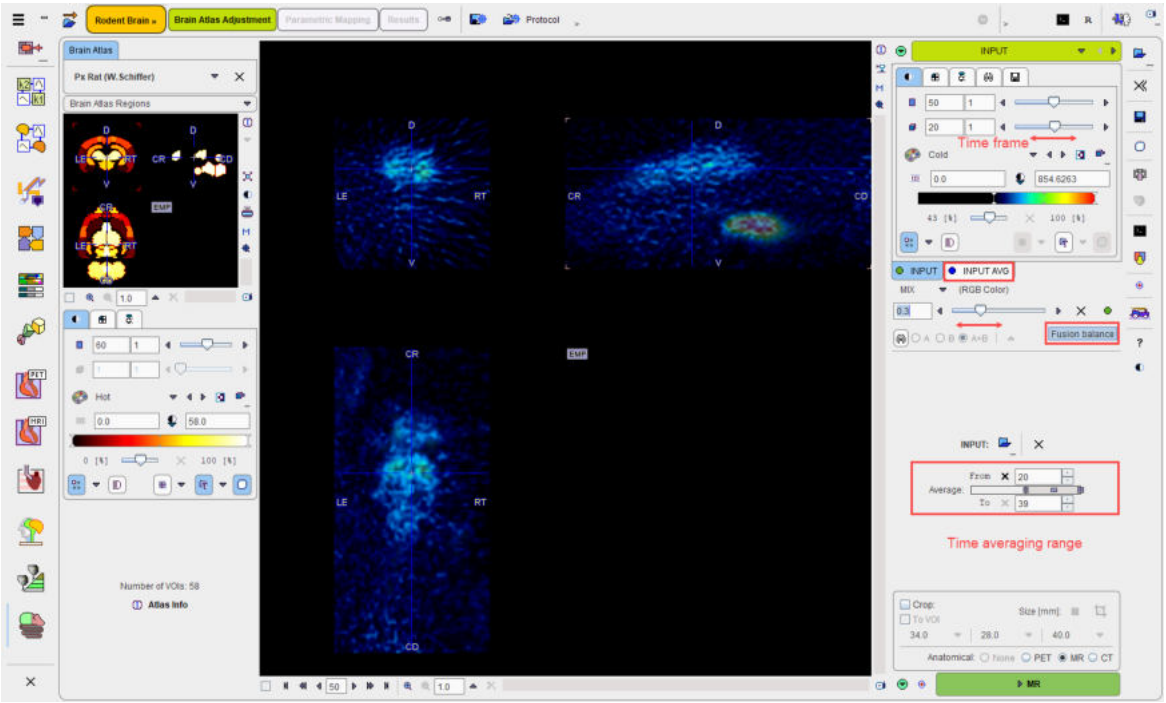
The situation after loading a static **Input** image series is illustrated below. The appearance of the **Input** image is controlled by the elements on the **INPUT** tab.



Dynamic Input Image Loading

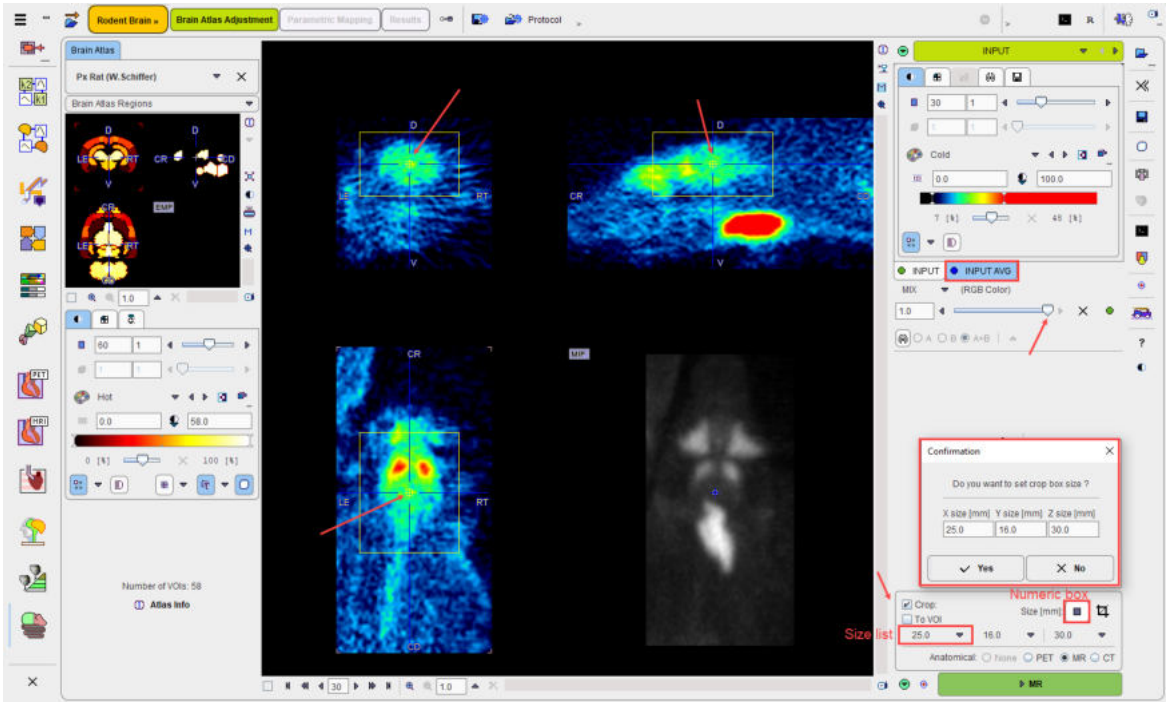
In contrast, when loading a dynamic image, an additional image series is generated by averaging a range of time frames. The appearance of this series is controlled via the additional tab labeled **INPUT AVG**. The image display shows a Fusion[11] of the original **Input** with **INPUT AVG**.

The averaging range can be defined by the **From** and **To** number fields, or dragging the range indicators in the **Average** bar. After any modification of the range, the average is recalculated and the display updated. The aim of the averaging is to generate an image with as detailed anatomy as possible for the rigid matching with the **Anatomical** image.



Input Image Cropping

If the field-of-view is larger than the brain, the image volume should be reduced to improve the reliability of processing. This can be achieved by enabling the **Crop** box and defining a crop box which appears as yellow rectangles in the image overlay.



The size of the crop box can be changed by opening a configuration window for entering the three edge dimensions. Alternatively, the edge sizes can be modified using the size list elements which are available for the X, Y and Z dimensions.

The position of the crop box needs to be defined interactively by clicking into the image. The center of the crop box is placed at the clicking point. Place the crop box by clicking at the brain center so that the brain is fully enclosed. Depending on the template used, it may aid the normalization procedure if some neighboring tissue such as the Harderian glands are included.

Caution: The triangulation plane of the image can't be changed while the **Crop** box is enabled. Please disable the box to change the slice planes, and re-enable **Crop** again for positioning if needed.

The actual cropping can be performed on demand with the  button. However, this is not necessary because when proceeding, cropping will automatically be applied. Note that cropping can only be performed once, thereafter it is disabled and the data needs to be loaded again for defining a different crop box.

Anatomical Modality Specification

As a next step, set the **Anatomical** radio button according to the image which will be used for the atlas normalization, in the example **MR**. The label of the action button is changed accordingly.

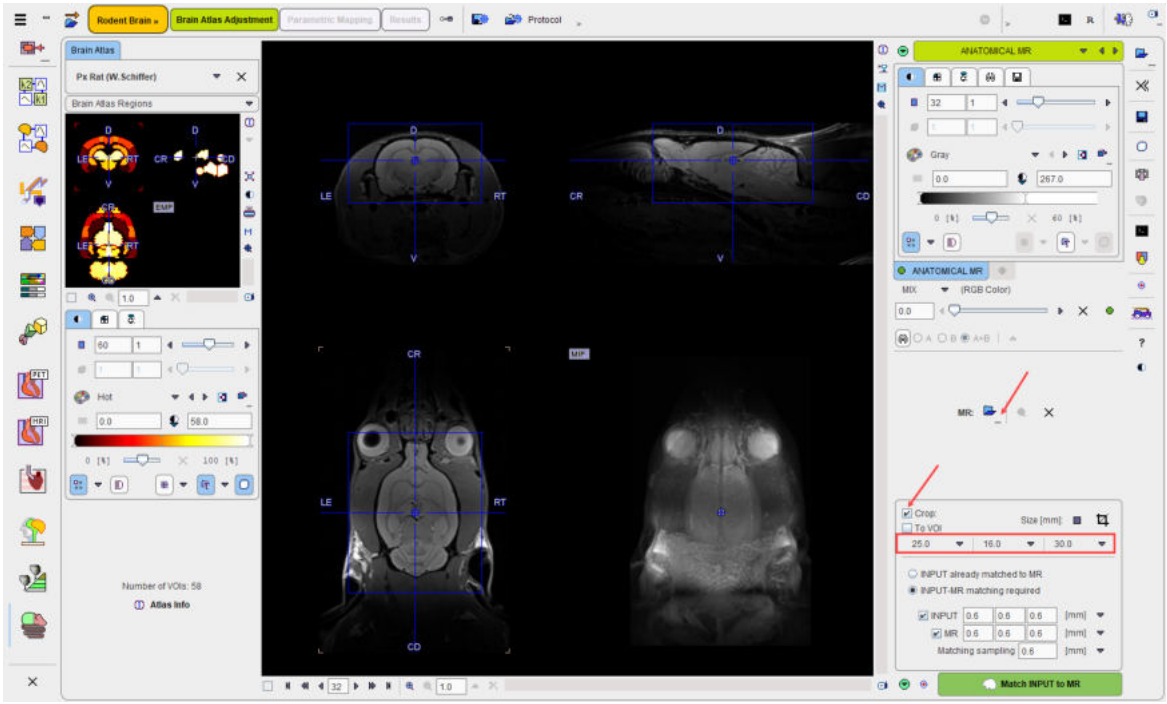
Please activate the green **MR** action button to switch to the next layout for loading the **Anatomical** images.

3.2.3 Anatomical Image Loading, Cropping

The labels of the **ANATOMICAL** layout correspond to the setting of the **Anatomical** modality selection, in the documentation example **MR**. In the case of a different modality they will appear accordingly.

Anatomical Image Loading

Load the brain MR image series of the same subject using the load **MR** button and adjust the controls so that the image appears with appropriate contrast.



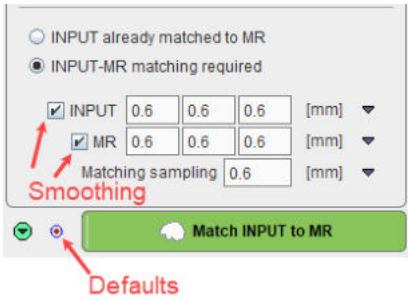
Anatomical Image Cropping

Crop the **Anatomical** image in a similar way as the **Input** image. In this case the crop box appears as blue rectangles in the image. The box size is initialized to the size used for the **Input** image.

3.2.4 Rigid Matching Input to Anatomical

Rigid Matching of Input to Anatomical

In order to transfer the atlas regions determined with the **Anatomical** image to the **Input** image, they have to be matched. The matching configuration is available in the lower right.



Only in the case of a hybrid scan without cropping, the matching procedure can be omitted by setting the **INPUT already matched to MR** radio button. In that case the action button label

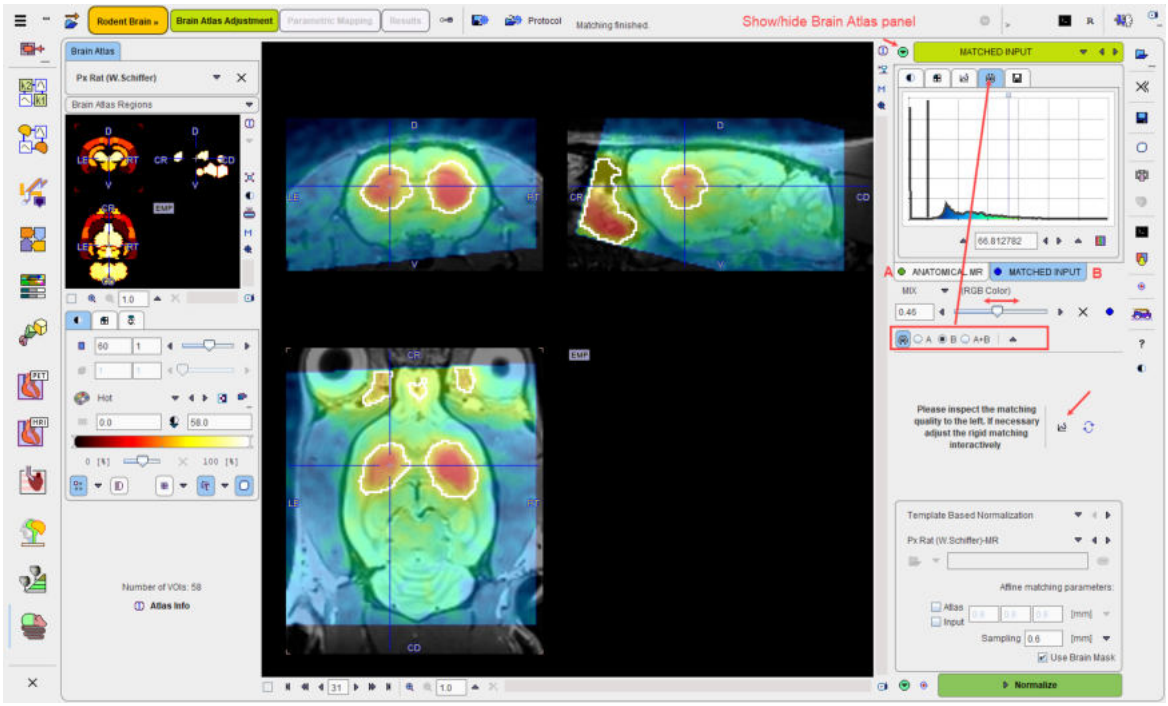
changes to **Resample INPUT to MR**, meaning that the **Input** series will simply be resampled at the resolution of the **Anatomical** series.

Most cases will require matching and thus **INPUT-MR matching required** should be set. With this setting PNROD will attempt an automatic rigid matching which has three configuration parameters:

- **INPUT** and **MR** checks: If a check is enabled, the image is smoothed before starting the matching process using the specified Gaussian half-widths in X, Y, and Z. However, further processing will proceed with the non-smoothed images.
- **Matching sampling**: Density of the information used for the matching.

The default parameters can be recovered by the" Defaults" button indicated above.

The action button **Match INPUT to MR** starts the automatic rigid matching and shows the result as a fusion of the **Anatomical** image with the resampled **Input** image in the **MATCHED INPUT** layout. The task for the user is to ensure that the matching is accurate. Otherwise the matching can be adjusted manually, or the user can return to the previous layouts and try again with modified parameters.

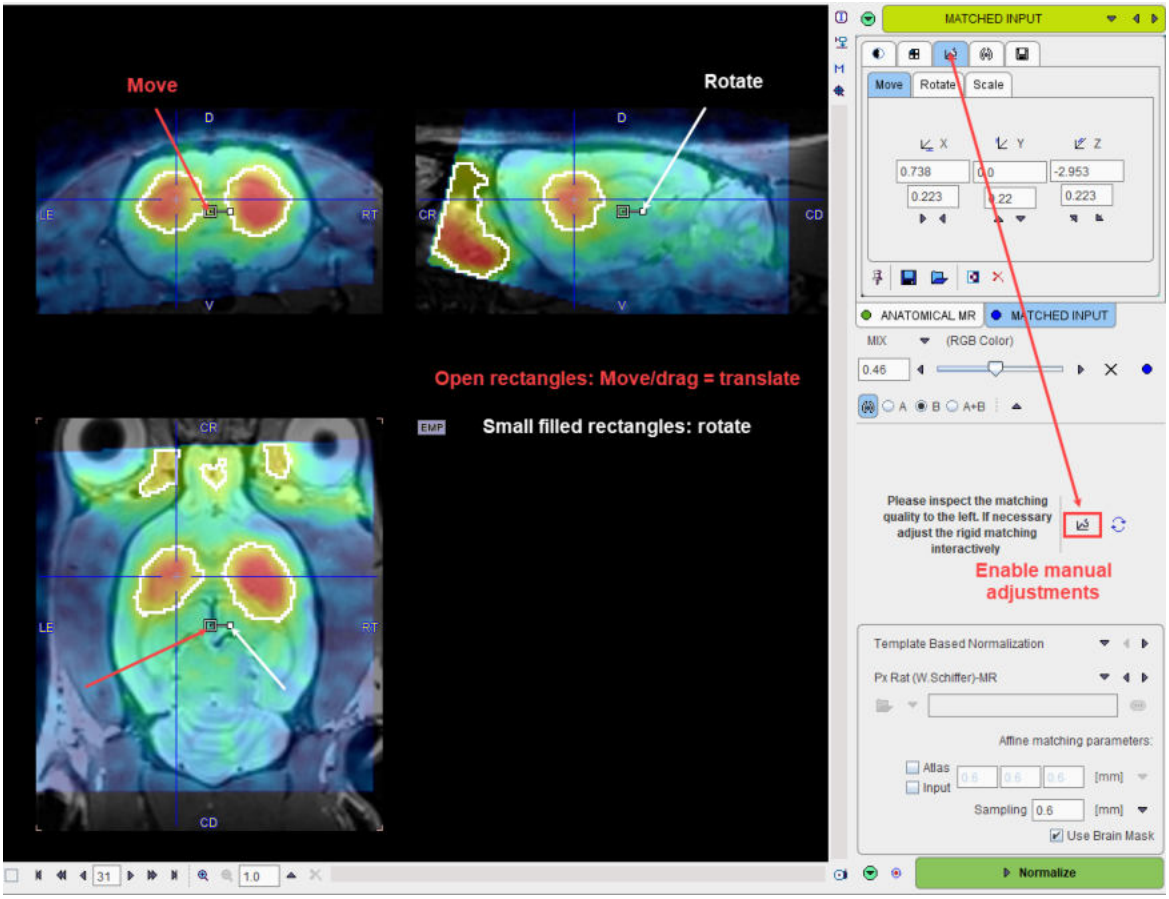


Evaluation of Matching

The fusion functionality can be used for assessing the alignment of the images. In the example above, iso-contours of the **Input** image are overlaid. To this end the contouring has been enabled, the **B** contours selected (corresponding to the matched **Input**), and the iso-contouring level adjusted. Useful is also the fusion balance slider, and other fusion modes explained in the Fusion Image Display 11.

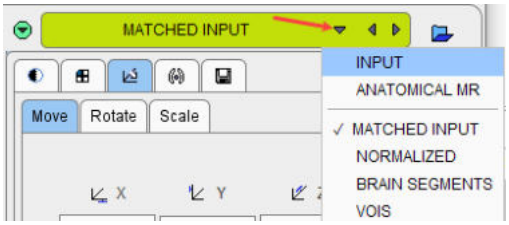
Manual Adjustments

To adjust the matching result please activate the reslicing button indicated below. The control panel with sections **Move**, **Rotate** and **Scale** is opened on the **MATCHED INPUT** tab, and handles for mouse-operated dragging and rotations appear in the image overlays. Please use the handles for interactive adjustments or enter numerical translation/rotatione values until the match is satisfactory.

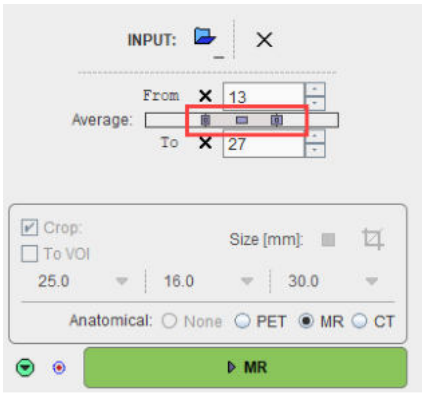


Repeating the Prior Steps

An alternative to (subjective) interactive adjustments is to try improving at the earlier stages. In the dynamic example, a different frame range can be averaged to obtain better brain contours. To do so, select **INPUT** from the list of layouts

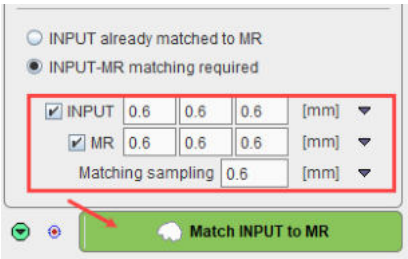


Define an averaging range which focuses more on the time before the late uptake, then use the action button **MR** to continue to the **ANATOMICAL MR** layout.

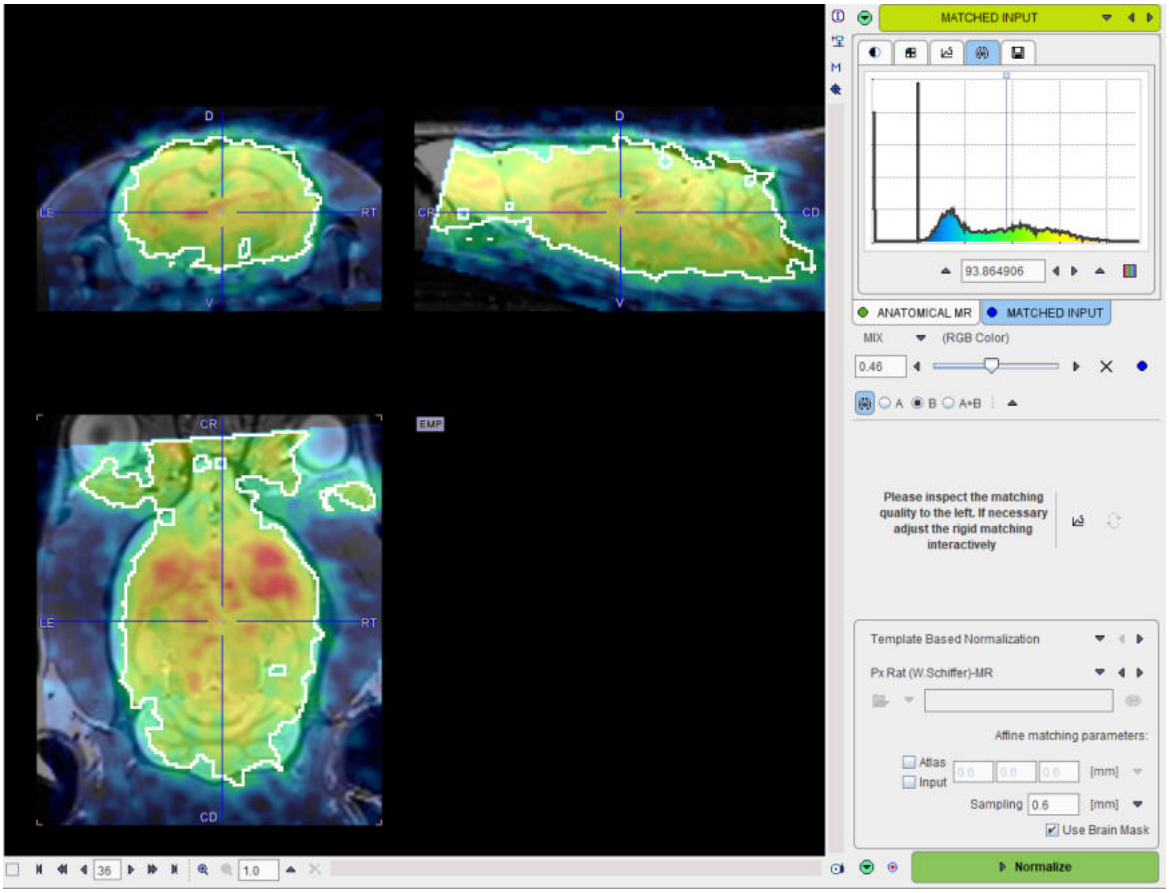


Caution: Don't switch to **ANATOMICAL MR** via the layout list, because otherwise the new data will not be propagated.

On the **ANATOMICAL MR** layout continue with the action button **Match INPUT to MR**.



In the example the result is a bit easier to evaluate because the PET iso-contour now also includes the cerebellum.

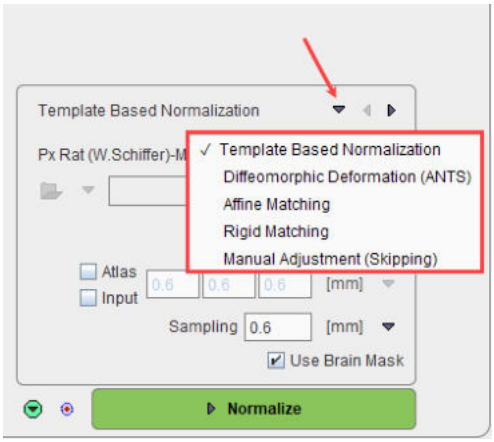


If the match is still not yet ok, it is worth trying with different matching parameters. Return to the **ANATOMICAL MR** layout, modify the smoothing and resampling parameters, and start the matching again.

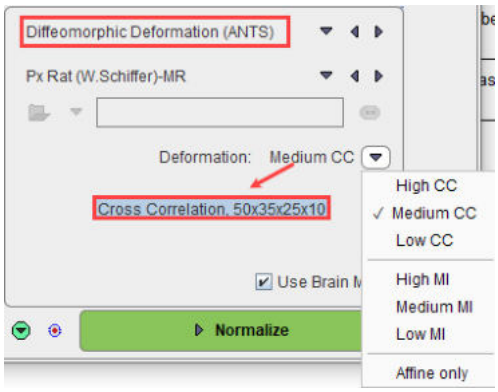
The next processing step, atlas normalization, is configured on the same page and described in the next section.

3.2.5 Normalization of the Anatomical Image

The spatial normalization to the atlas is configured on the **MATCHED INPUT** layout in the lower right.



There are four methods available which can be selected as list illustrated above. They are ordered by decreasing complexity.

Template Based Normalization	Performs an SPM5-type normalization between the **Anatomical** image of the subject and the selected atlas template image with the usual options. This method first applies scaling and shearing of the subject brain, then iterative elastic adjustments to bring it into agreement with the atlas brain.
Diffeomorphic Deformation (ANTS)	Implements the Advance Normalization Tools in the PNROD work flow. Please note, that this method is much slower than the SPM based elastic mapping. It will depend on the image, whether the improved accuracy is worth the long waiting times.Various options are available as illustrated below:  After selection, hoovering with the mouse button above the selection, a tool tip will be displayed, indicating the **Deformation** method (cross correlation=**CC**, mutual information=**MI** or **Affine only**) and the parameters that are going to be used for the selection. Please note that this parameters cannot be modified. The **High** deformation methods are the most time consuming calculations as they represent the most accurate ones. The calculation time is shorter for the **Medium** and **Low** deformation methods.
Affine Matching	Performs only the affine part of an SPM5-type normalization between the **Anatomical** image of the subject and the selected atlas template image. This method applies scaling and shearing of the subject brain to bring it into agreement with the atlas brain.
Rigid Matching	Performs an automatic rigid matching between the **Anatomical** image of the subject and a selected atlas template image. The result can be adjusted manually. This method assumes a close similarity of the subject brain with the atlas brain.

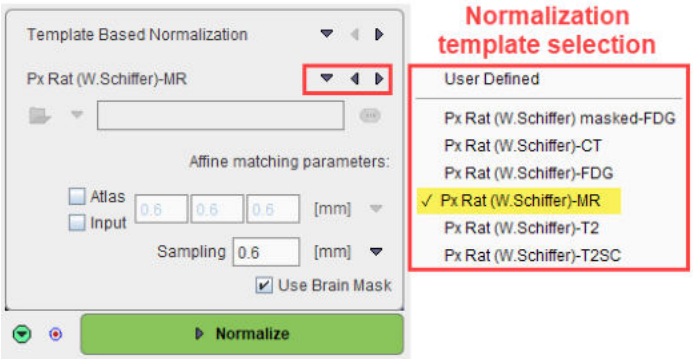
Manual Adjustment (Skipping)	No automatic matching procedure is applied. The user will have to interactively match the **Anatomical** image of the subject to the selected atlas template image.

Atlas Configuration

Now is the last chance to select the atlas[14] which is used for the analysis. Each atlas has its own set of normalization templates which will be available when configuring the normalization procedure.

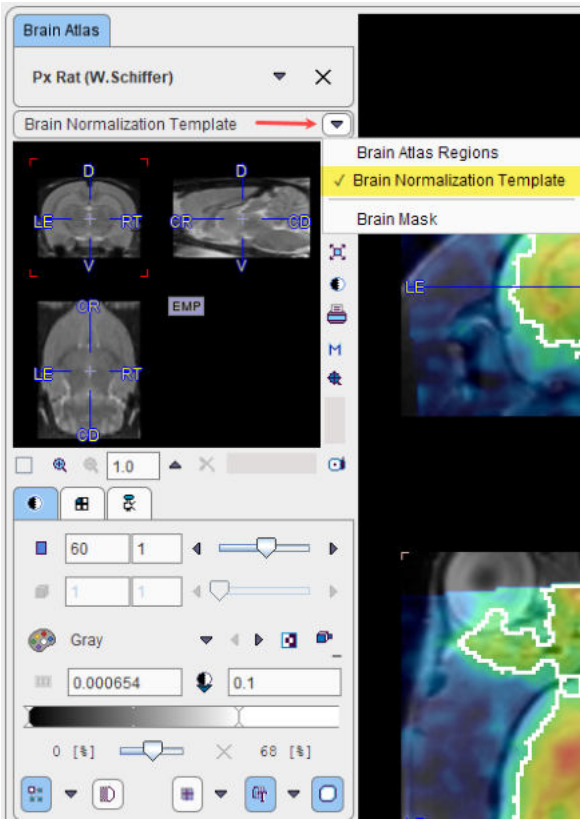
Normalization Configuration

Select the normalization method to be used from the list. The matching parameters below the selection are adjusted correspondingly. All of them require selecting an appropriate normalization template from the available choices as illustrated below.

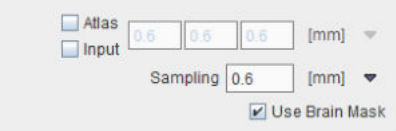


The **User Defined** entry allows an arbitrary file to be defined as normalization template, which naturally needs to fit the atlas anatomy.

Note that the selected template can be visualized in the Brain Atlas[14] panel by selecting **Brain Normalization Template**.



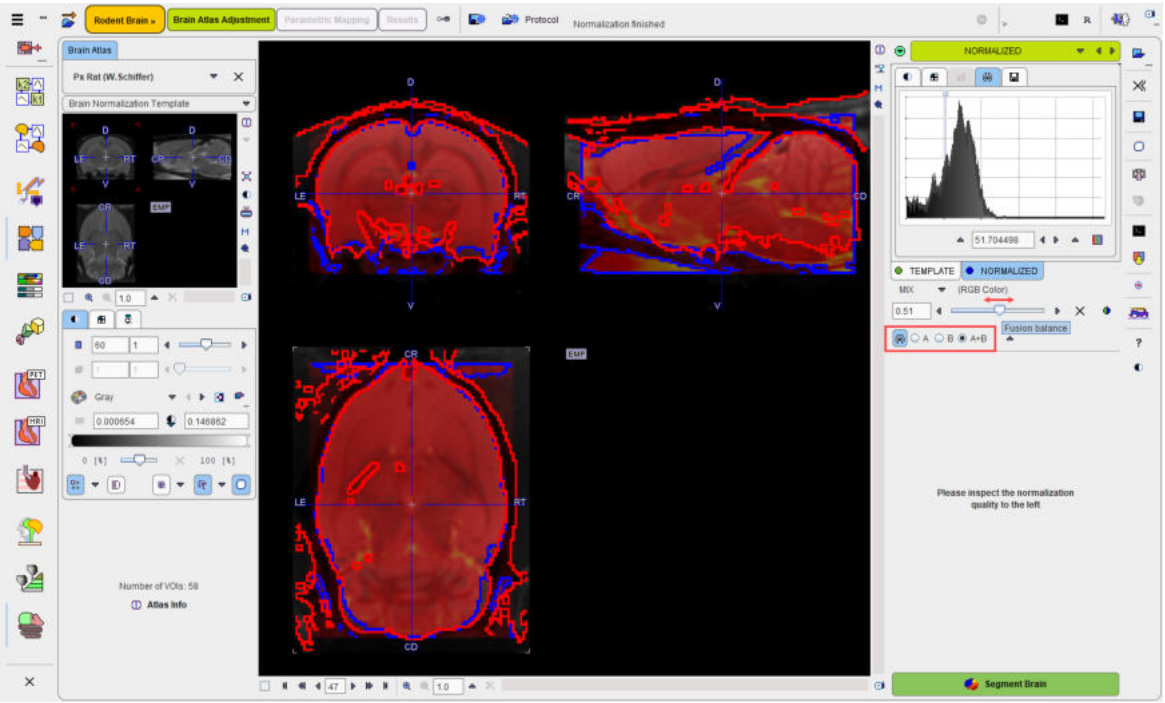
The automatic normalization methods have several additional parameters



- **Atlas** and/or **Input**: Gaussian filtering of the selected series before the procedure starts.
- **Sampling**: Density of image resampling for the matching procedure.
- **Use Brain Mask**: if enabled, applies the template masking. The mask can be visualized in the Brain Atlas[14] panel by selecting **Brain Mask** entry.

Start the Normalization

The action button **Normalize** starts the configured procedure and shows a fusion of the template with the normalized **Anatomical** image in the next layout **NORMALIZED**.



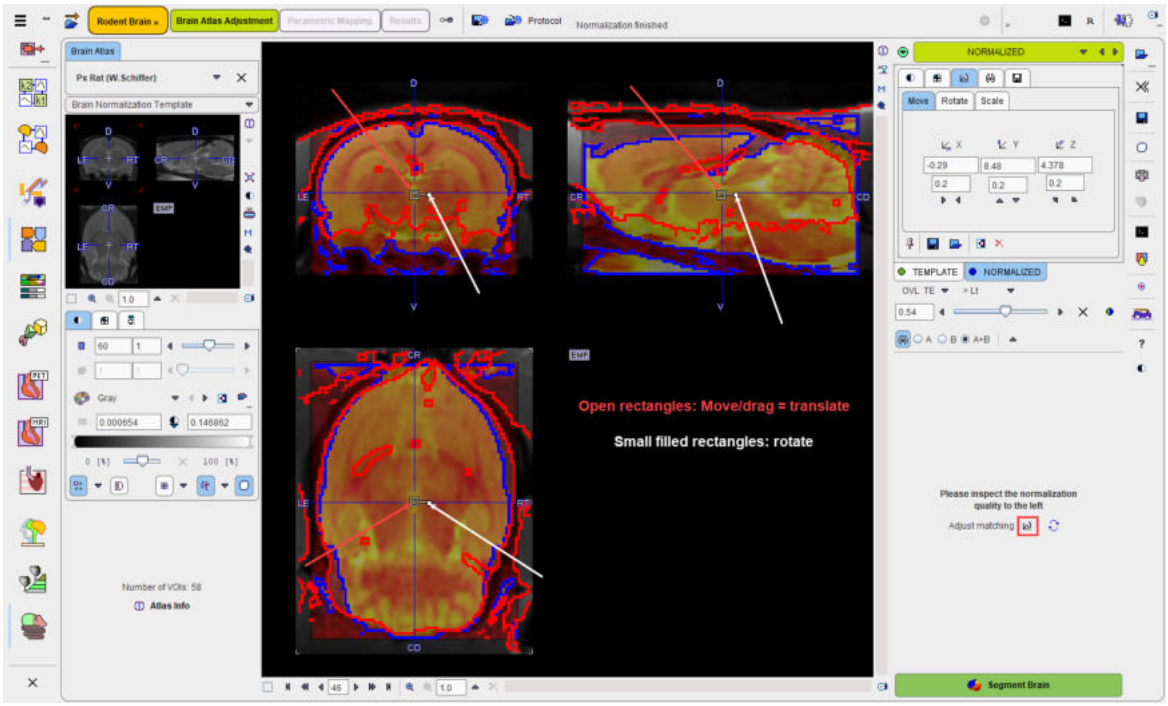
Assessment of the Normalization Quality

In the case of an automatic normalization it is the responsibility of the user to evaluate the normalization quality.

First, the color table and contrast of the individual images should be optimized. Then, the iso-contour lines, the fusion balance slider, and various fusion modes explained in the Fusion Image Display[11] can be used to assess the degree of the brain alignment. In the example above, the correspondence of the blue (template) and red (Anatomical) iso-contours indicate a good agreement.

Manual Rigid Template Matching

In the case of the **Manual Adjustment (Skipping)** method the **NORMALIZED** layout simply shows an overlay of the template with the **Anatomical** image. As explained before[25] the user has to manually shift and rotate the **Anatomical** image until the best fit with the template is found. If a fully satisfactory result cannot be achieved the VOIs may be edited on the **VOIs** page.



3.2.6 Brain Segments Calculation

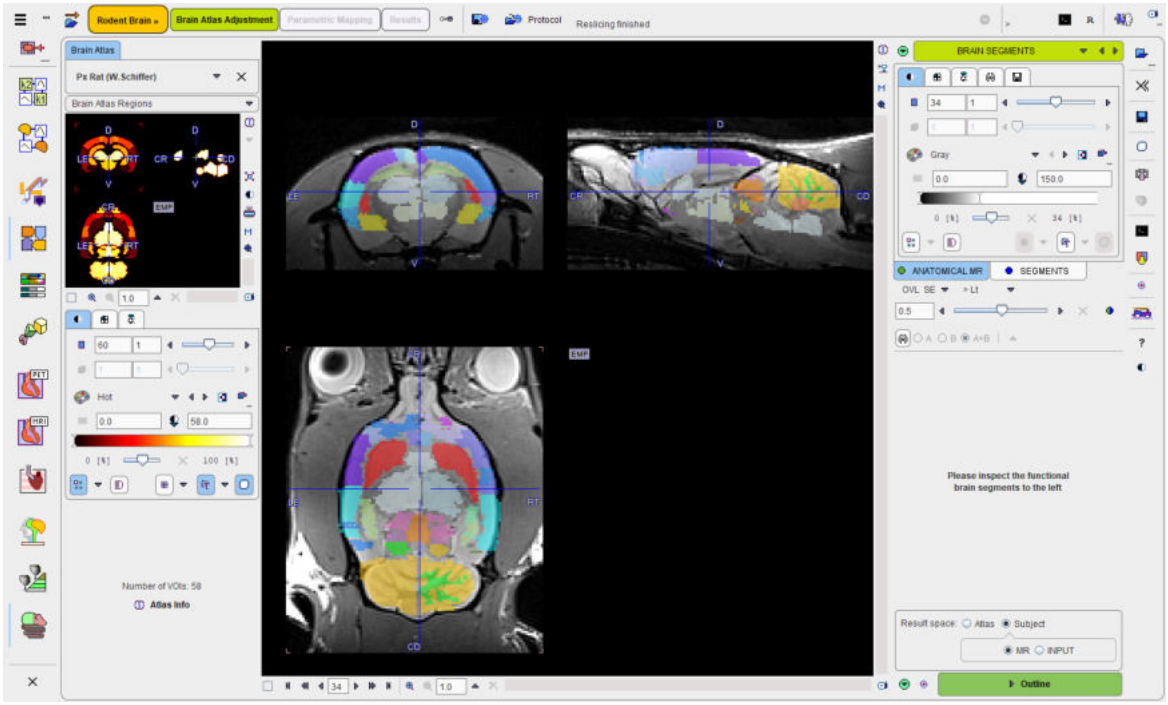
After successful rigid matching and normalization the mapping between the different image spaces is established:

- the normalization transform maps the **Anatomical** MR to the atlas space;
- the rigid transform maps the **Input** to the **Anatomical** space;
- the rigid transform combined with the normalization transform maps the **Input** to the atlas space.

As all the transformations can be inverted, the atlas space can also be mapped to the **Input** and the **Anatomical** MR image space. Consequently, the brain structures which are defined in the atlas space can be mapped to the **Input** and **Anatomical** MR subject space and shown in the overlay.

Calculate the Brain Segments

Activate the **Segment Brain** action button at the right bottom of the **NORMALIZED** layout to prepare the images in all possible spaces. As a result, the original **Anatomical** image is overlaid with an image of the transformed atlas regions called **Brain Segments**. Please perform a final validation of the region placement. As mentioned before, a certain degree of deviation can't be avoided and needs to be handled by adjusting the generated brain VOIs.

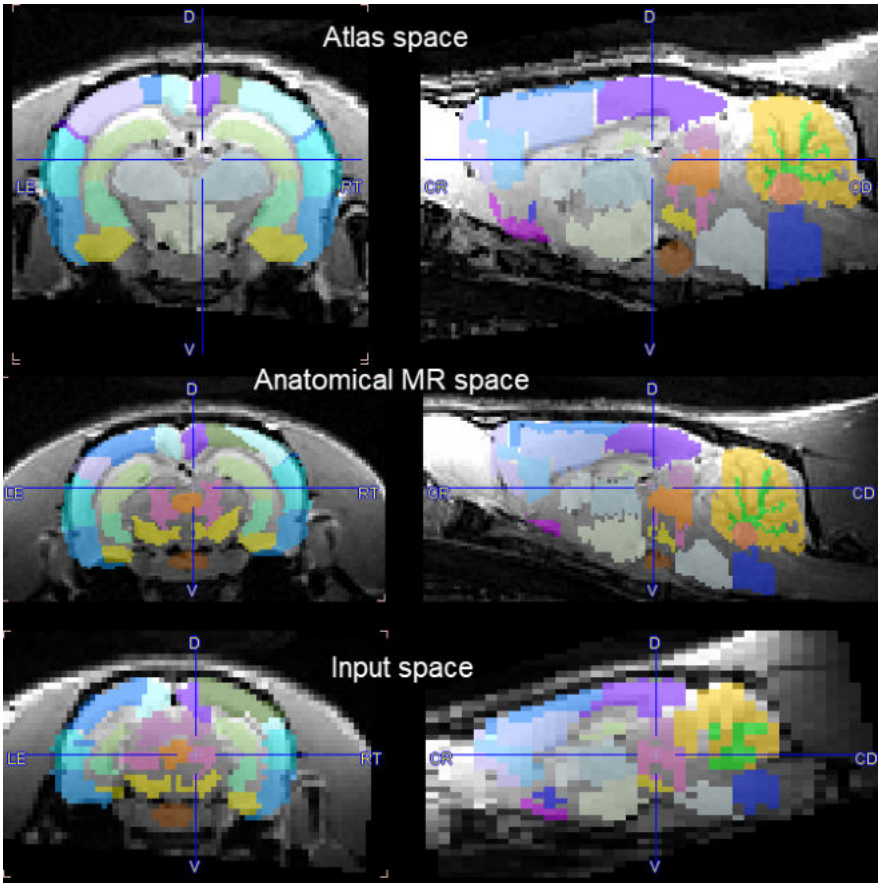


Result Space Definition

There are three image spaces where the results can be generated and the statistics calculated:

1. **Atlas** space: The **Input** and the **Anatomical** images are transformed to the space of the atlas. This option is preferable for pooling the resulting images (functional image, parametric map) of a group of subjects and performing an analysis such as SPM.
2. **Subject/MR**: The **Input** image and the brain VOIs are transformed to the **Anatomical** space. This option can be preferable for visualization purposes if **Anatomical** has better resolution than the **Input**.
3. **Subject/INPUT**: The **Anatomical** image and the brain VOIs are transformed to the **Input** space. This option has the advantage that the statistics are calculated on the original **Input** data, whereas in the other choices the data has been resampled.

The information visualized on the page is updated as soon as the configuration is changed. The illustration below shows the effec when selecting the different spaces. Clearly, the PET **Input** series has the lowest resolution so that the resliced **Anatomical** image appears heavily pixelated.

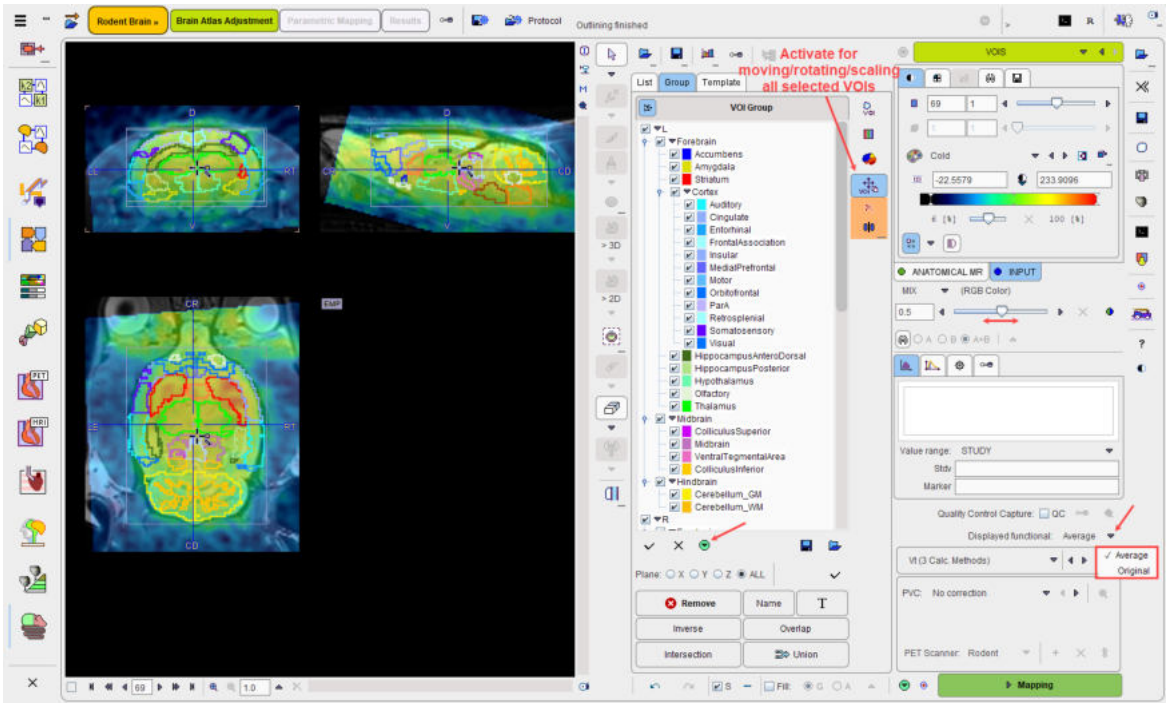


Brain Structure Outlining

Once the result space has been specified, the brain structures are fully defined and can be outlined to create contour VOIs. This process is started with the **Outline** action button.

3.2.7 Brain VOI Editing, Statistics Calculation

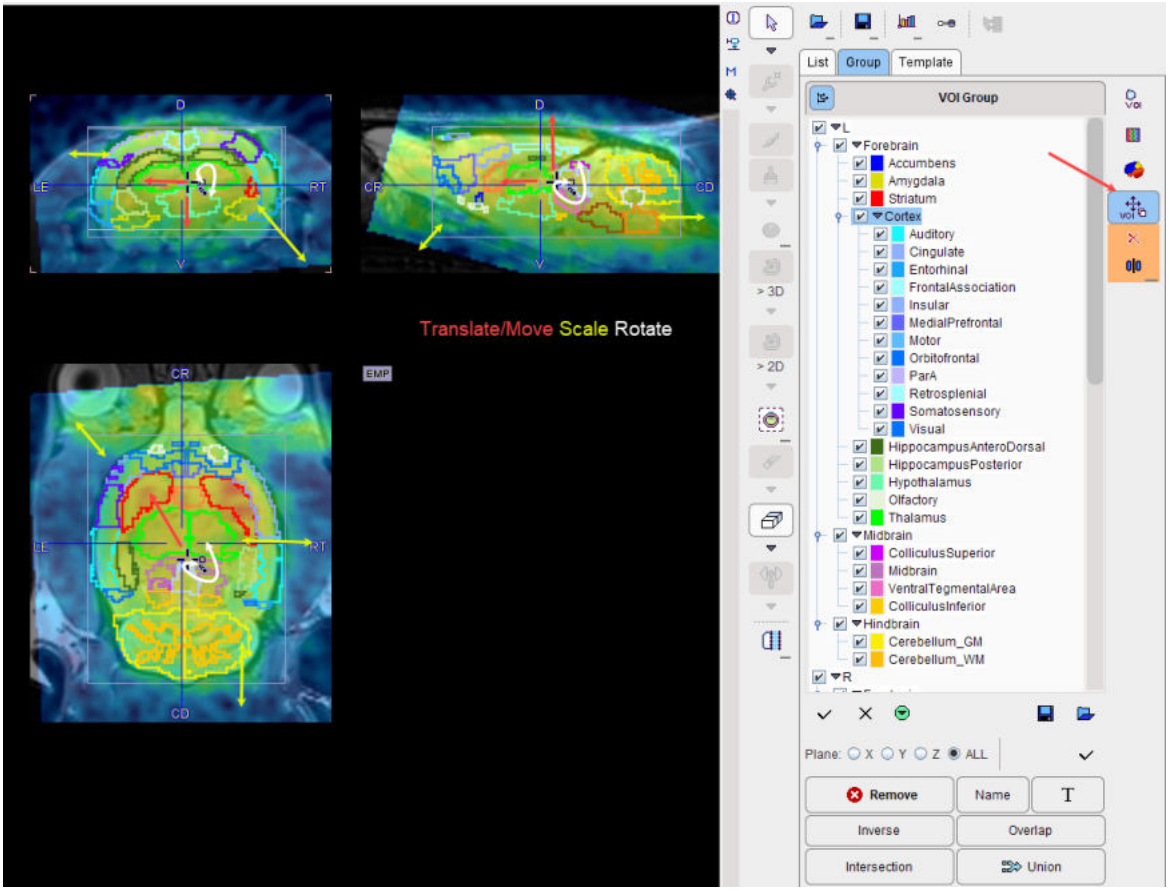
The result of structure outlining is shown in the **VOIS** layout. The generated contours are presented in the overlay of a fusion of the averaged **Input** and the **Anatomical** image in the result space. Note that the dynamic series can be used instead of its average by the **Displayed functional** selection illustrated below.



Please use the fusion balance slider to change the weight between the image contributions, and use the image control tabs for the changing the individual image displays.

VOI Editing and Selection

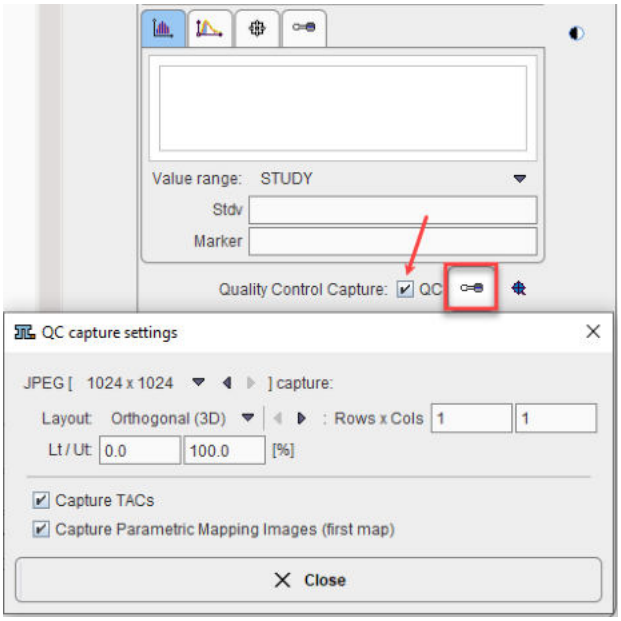
At this time the contour VOIs can be interactively adjusted using the VOI features of PMOD, which are described in the *PMOD Base Functionality Guide*. Particularly useful is the scaling of a group of VOIs which is possible after enabling the VOI button illustrated below. By dragging the center handle the VOIs can be shifted and rotated, by dragging the edges of the VOI bounding box they can be scaled.

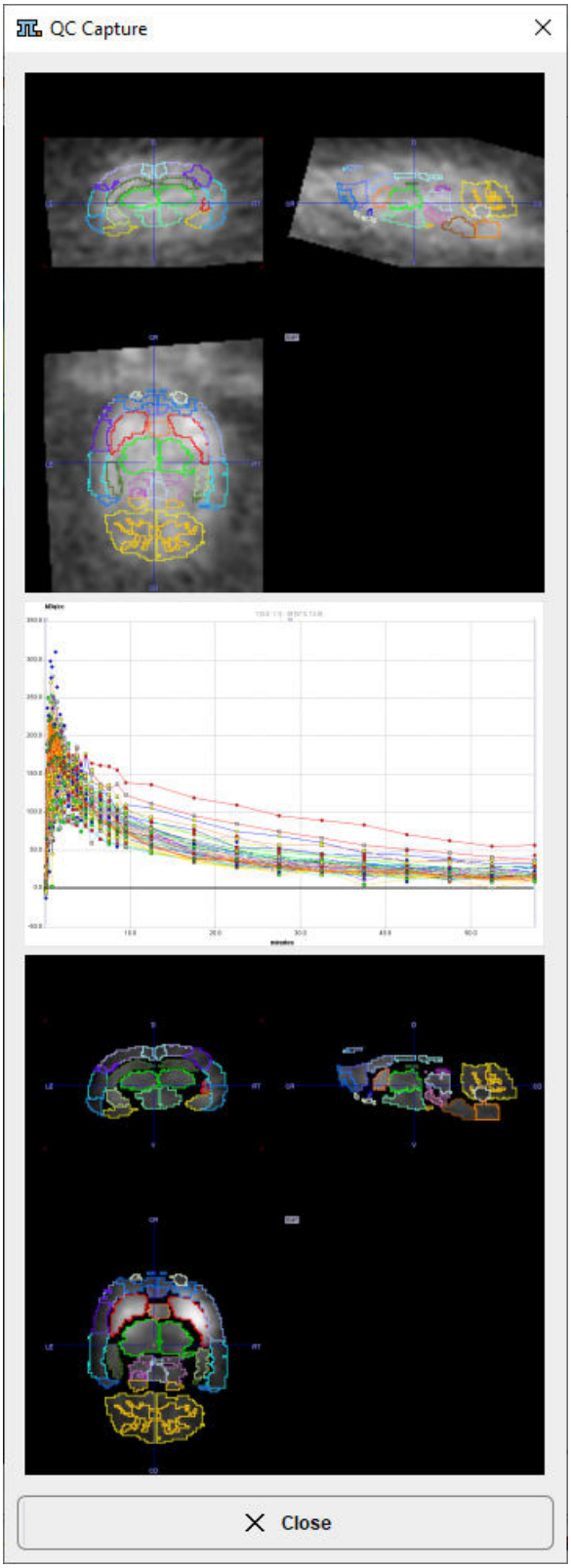


A subset of the VOIs can easily be selected on the **Group** tab as described above[16] .

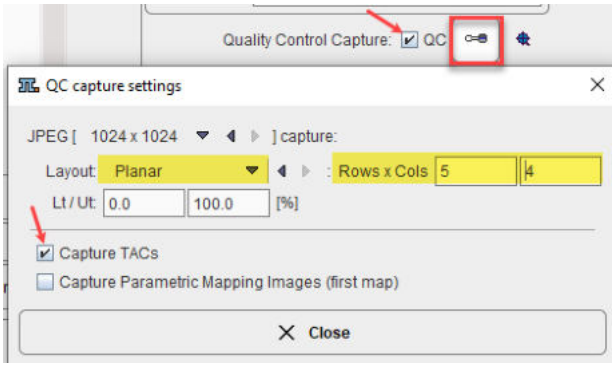
Quality Control Capture

The **QC** box is particularly relevant when batch processing is planned (i.e. the current interactive workflow will be used to save a Protocol that is later Cloned for Batch Processing). It allows checking whether the automatic VOI placement was successful and the processing results are valid. The capture image will show the VOIs overlaid on the functional image using display settings which can be configured as illustrated below.

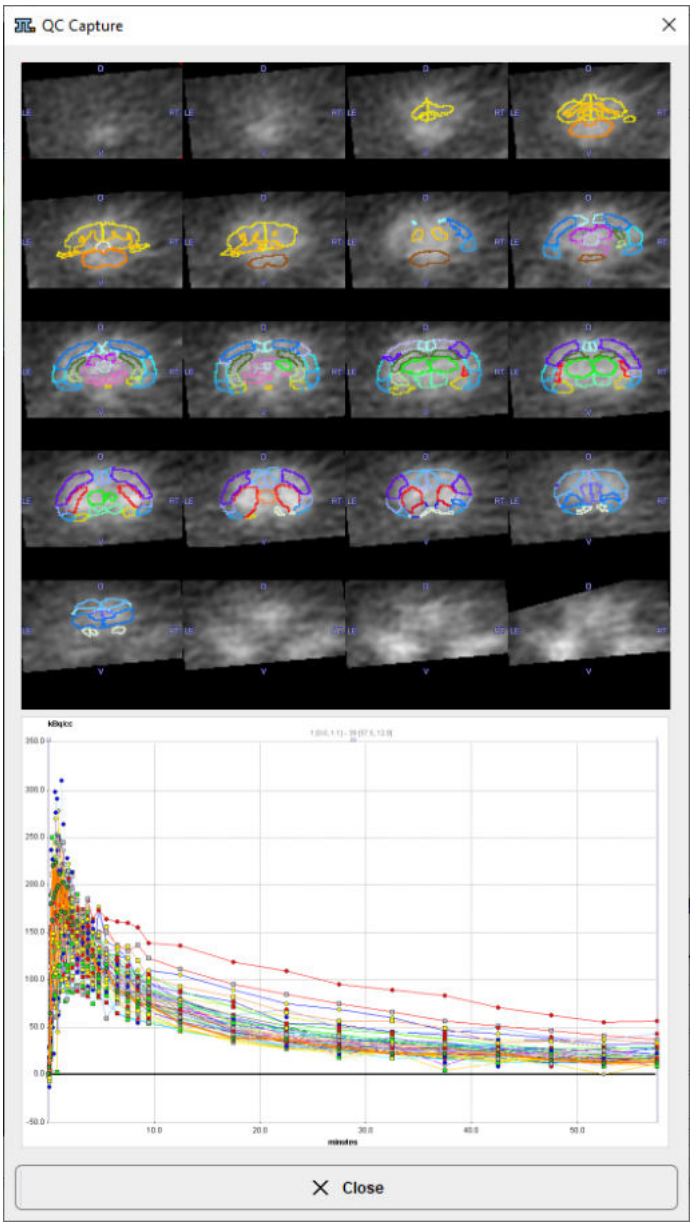




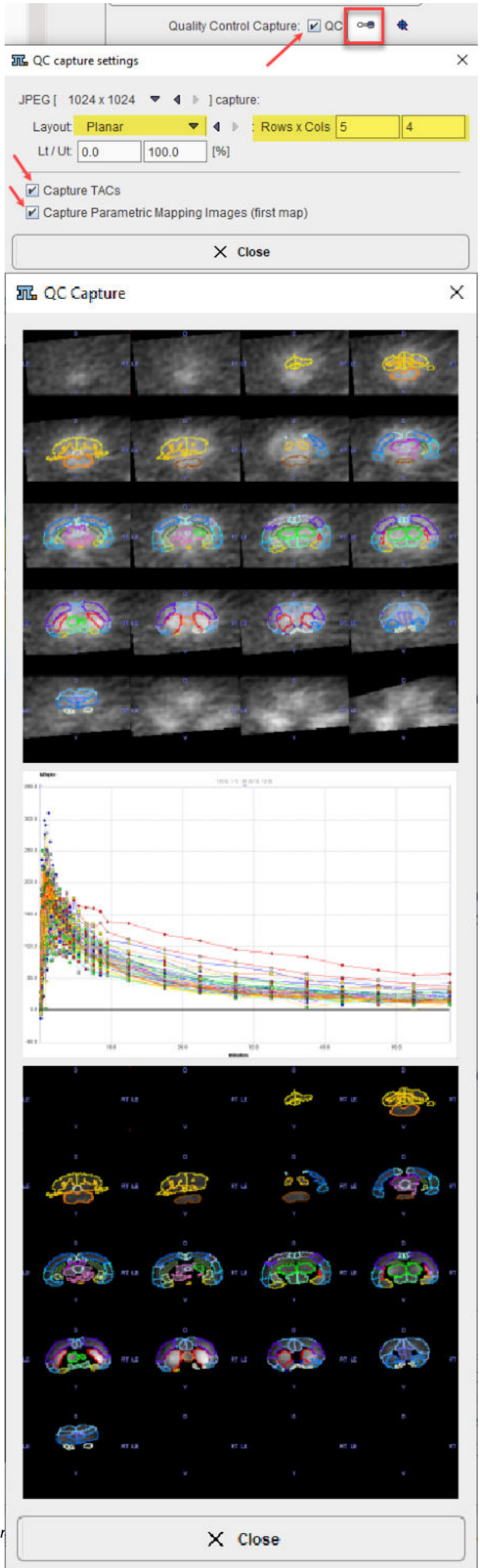
The **Planar** layout requires a choice of image display matrix. The slice gaps between displayed images are automatically calculated so that the full field-of-view is covered.



If dynamic data is analysed, a QC capture of the resulting TACs may be added.

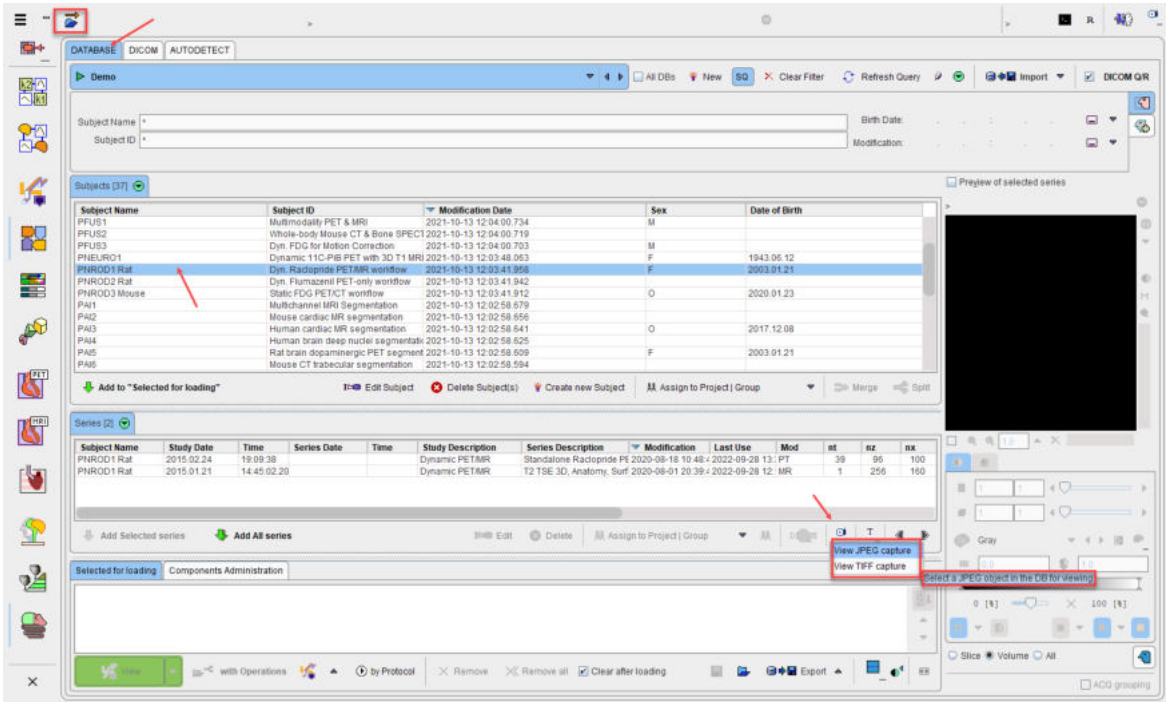


Likewise if parametric mapping is included in the workflow, a QC capture of the first map in the list calculated may be added.


Quality Control Capture: QC
QC capture settings
JPEG [1024 x 1024] capture:
Layout: Planar
Rows x Cols 5 4
Lt / Ut: 0.0 100.0 [%]
Capture TACs
Capture Parametric Mapping Images (first map)
Close
QC Capture
Close

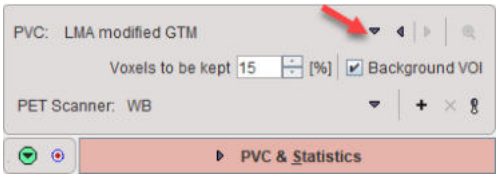
These settings are stored in the protocol which forms the basis of batch processing.

The QC captures resulting from the PNROD Batch Processing may be viewed in the **DATABASE** panel via the **Select data and application** icon available to the left in the top line of the docking interface.



Partial-Volume Correction (PVC)

The PNROD tool supports the GTM-based partial-volume correction[72] (PVC) of the PET signal. Note that the corrections are sensitive to the signal-to-noise ratio and might produce large artifacts for noisy dynamic data.



The **PVC** selection has various choices:

- **No correction:** No partial-volume correction is applied (default).
- **Rousset VOI based GTM:** The original Rousset GTM correction[73] method is applied.
- **LMA modified GTM:** A variant[74] of the Rousset correction method is applied, whereby only a percentage of the pixels in the inner of the VOI is used to calculate the VOI average. This percentage can be set using the **Voxels to be kept** parameter.
- **Region-based Voxel Wise**:extends the GTM method and performs a voxel-wise correction of the entire image. Note that the pixelwise correction may be problematic for dynamic data with low signal/noise ratio.
- **Fast VOIs-based GTM**: it is actually the LMA modified GTM method which contains some speed-up improvement for the smoothing. The speed performance might be observe when the selected atlas contain a low number of regions.

If PVC correction is enabled the action button label becomes **PVC & Statistics**. In this case, both the original and the corrected statistics are calculated. Note that for a high number of VOIs and fine resolution the PVC calculation may take long and consumes a significant amount of RAM.

NOTE: When **Parametric mapping** is enabled, only the **Region-based Voxel Wise** PVC method will be active.

Statistics Calculation

Once the VOIs have been outlined and carefully checked by the user, they may be saved independently

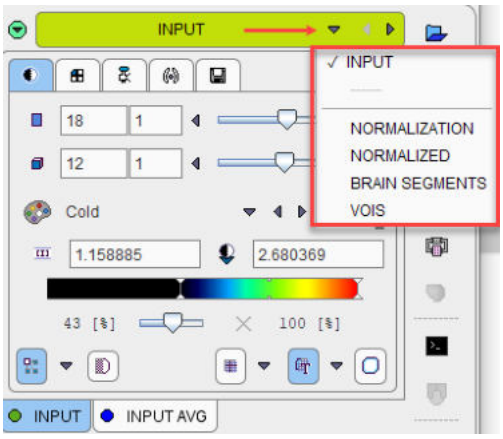
and then statistics calculated by proceeding with the **Statistics** or **PVC & Statistics** action button. The result (for the selected VOIs only) is shown on the separate Result[48] page, from where it can be further evaluated.

Parametric Mapping

If the **Input** images are dynamic and the PXMOD option is included in the license, parametric mapping using pixel-wise models can be directly applied within PNROD, as described in a separate section[52] .

3.3 Workflow for single-Modality Studies

If no Anatomical images are available for the atlas normalization, the workflow for a brain image analysis will run through a shorter sequence of layouts of the **Brain Atlas Adjustment** page:



Note: This section will use the data of a dynamic FDG PET rat brain scan for the documentation.

3.3.1 Processing Overview

The brain image to be analyzed is called **Input**. In the user interface the related label occasionally appears capitalized **INPUT** for clarity.

The processing steps, reflected by the user interface, are the following:

1. **Brain Atlas Adjustment** page, **INPUT** layout:
   a. Loading of the **Input** image series which may be static or dynamic.
   b. Dynamic case: Averaging of the series in a specified frame range. The averaged image will be used in all following steps except for the final statistics calculation and parametric mapping.
   c. Cropping of the (averaged) **Input** image to retain mainly the brain part, potentially with some neighboring tissue which helps the normalization (e.g. Harderian glands for PET).

2. **Brain Atlas Adjustment** page, **NORMALIZATION** layout:
   a. Configuration of the atlas template and the normalization method.
   b. Start of the normalization procedure which matches the (averaged) **Input** image to the selected atlas template.
3. **Brain Atlas Adjustment** page, **NORMALIZED** layout:
   a. Visual assessment of the normalization.
   b. In case of a bad match, return to the **NORMALIZATION** layout, change the normalization approach, and normalize again. Repeat until a satisfactory match is obtained. If no automatic procedure works, resort to manual rigid matching.
   c. Start transformation of the atlas brain regions so that they can be overlaid on the (average) **Input** image as segments.
4. **Brain Atlas Adjustment** page, **BRAIN SEGMENTS** layout:
   a. Visual assessment of the overlaid segments.
   b. Selection of the image space (**Atlas** or **Subject**) where the VOIs are generated.
   c. Start generation of the outline VOIs in the result space.
5. **Brain Atlas Adjustment** page, **VOIS** layout:
   a. Visual assessment of the brain VOI outlines overlaid on the (average) **Input** image by the user. If the match is not satisfactory, return to step 3 and try to improve the normalization.
   b. If needed, manually adjust the whole VOI set or individual structures. For instance, all VOIs can be scaled at once.
   c. Start calculation of the VOI statistics on the **Input** image.
6. **Results** statistics page:
   a. Inspect the results.
   b. Save the statistics table (or time curves in dynamic case).
   c. In the dynamic case transfer the curves (usually PET tissue time-activity curves) to the PKIN tool (option) and continue there with modeling.
7. Save the complete configuration of the processing with **Save** protocol icon in the top line 10.

Parametric Mapping of Dynamic Data (PXMOD Option)

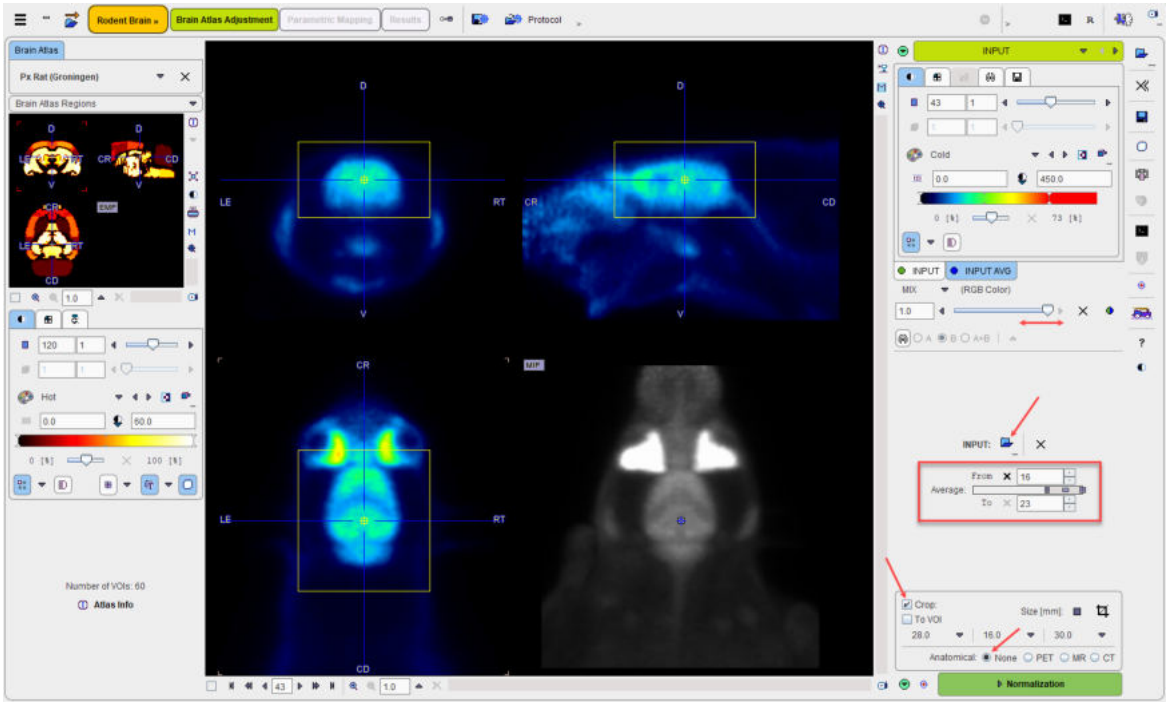
In the case of a dynamic **Input** series, return to

8. **Brain Atlas Adjustment** page, **VOIs** layout:
   a. Select an appropriate parametric mapping method.
   b. Proceed to parametric mapping.
9. **Parametric Mapping** page:
   a. Perform the Parametric Mapping 52 workflow as in PXMOD.
   b. Save the parametric maps.
10. Save the complete configuration of the processing including parametric mapping with **Save protocol icon** in the top line 10.

3.3.2 Input Image Loading, Time Averaging, Cropping

The **Input** image loading, time averaging and cropping are performed on the first layout **INPUT** of the **Brain Atlas Adjustment** page exactly as described for the dual-modality workflow above 22.

The only difference is, that the **Anatomical** modality is not available and the radio button therefore set to **None**.

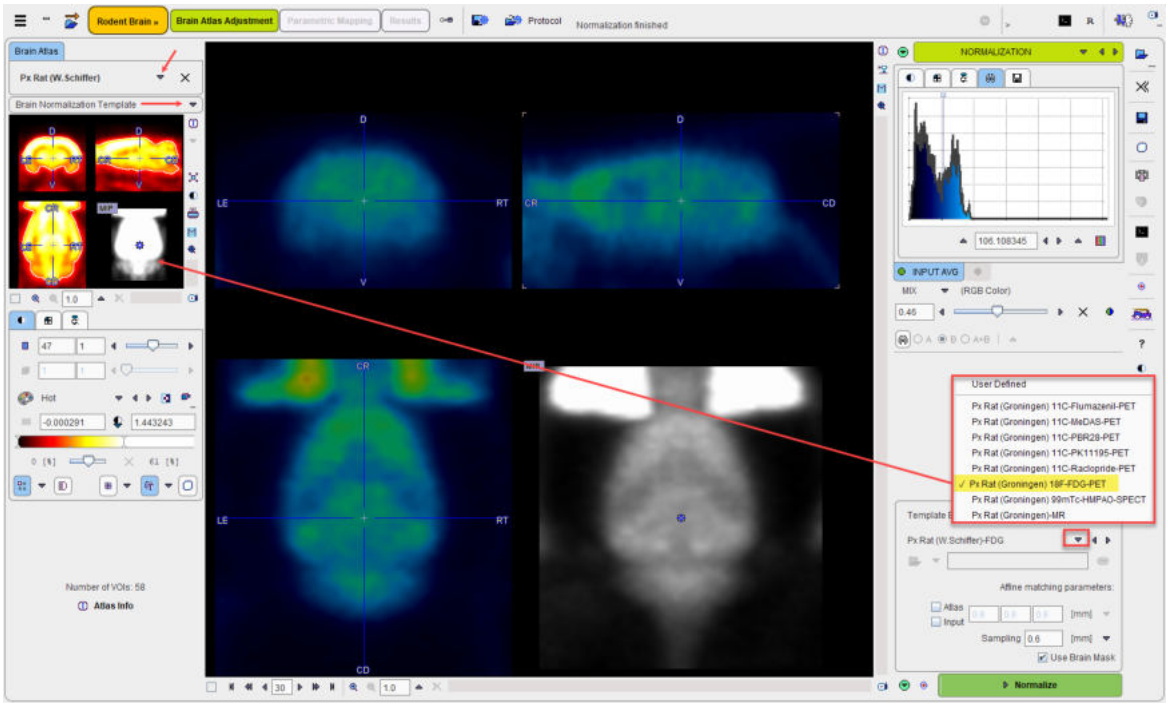


Activate the **Normalization** action button in the lower right to proceed to the **NORMALIZATION** step.

3.3.3 Normalization of the Input Image

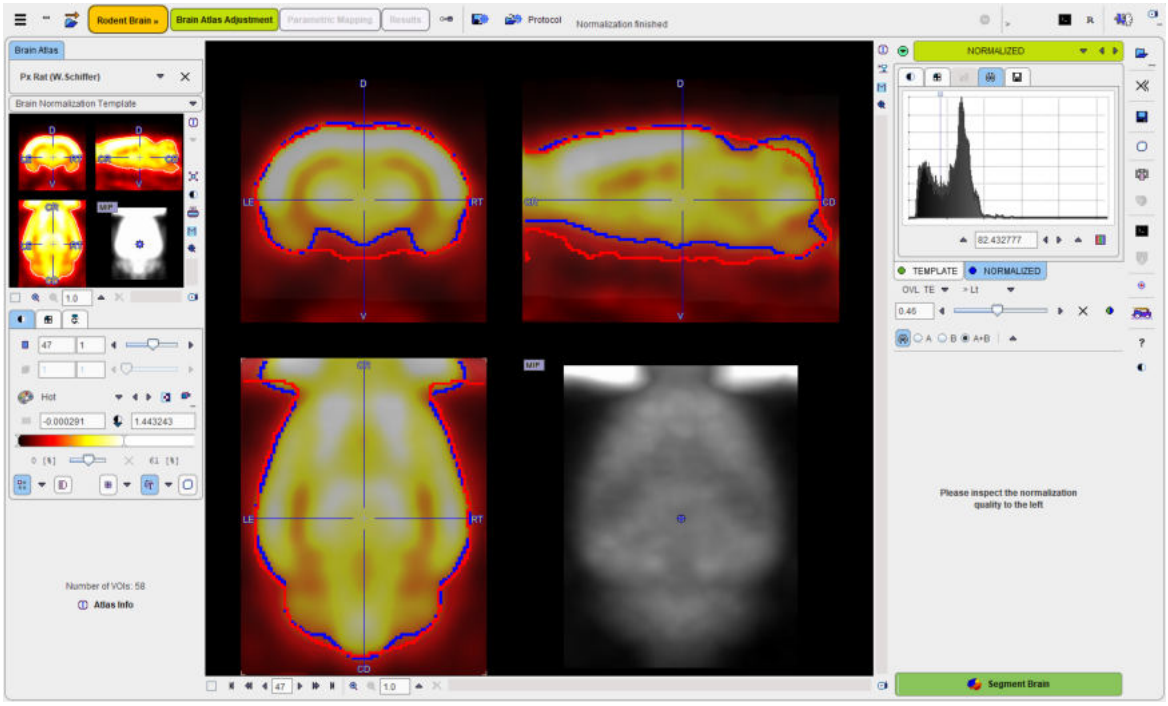
The exactly same atlas normalization methods are available as described above 28 for the dual-modality workflow, but the normalization is directly performed using the **INPUT** image, or if it is dynamic using the frame average labeled **INPUT AVG**.

First select the atlas (e.g. **Px Rat(W.Schiffer)**), then the normalization method (e.g. **Template Based Normalization**), and finally an appropriate normalization template (e.g. **FDG**). The more resemblance between the template and the (averaged) **Input**, the better the chance that an automatic procedure works.



Start the Normalization

The action button **Normalize** starts the configured procedure and shows a fusion of the template with the normalized (average) **Input** image in the next layout **NORMALIZED**.



Assessment of Normalization Quality

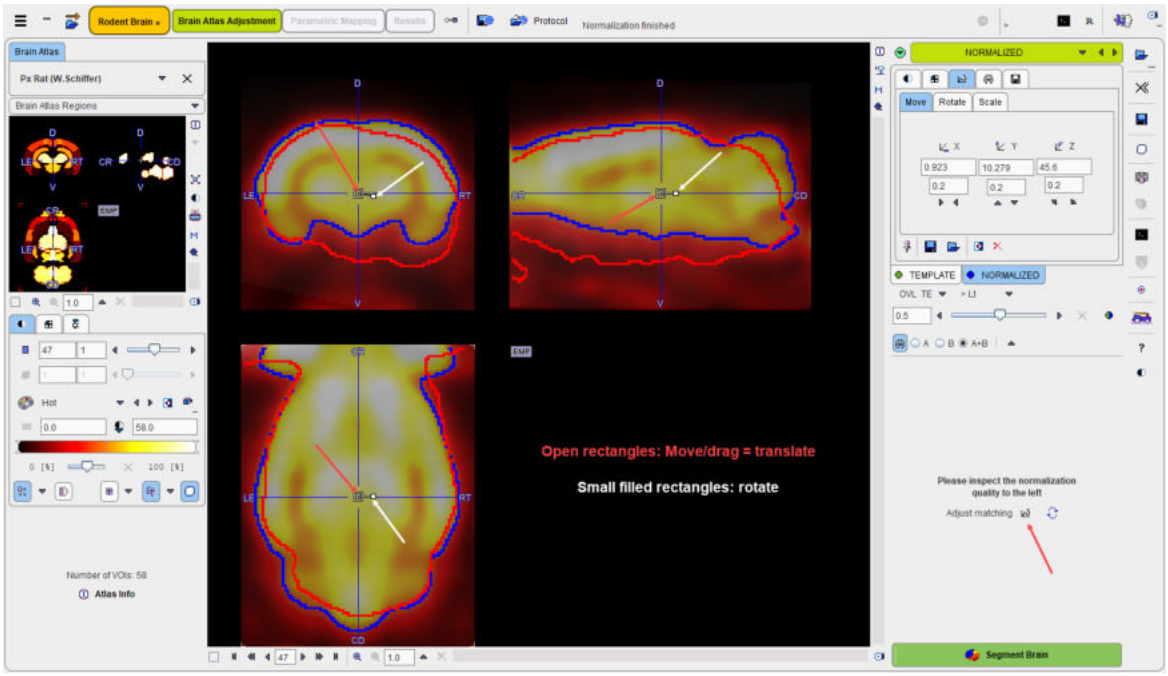
In the case of an automatic normalization it is the responsibility of the user to evaluate the normalization quality. Unfortunately, a fully accurate match can not be expected. Therefore, the assessment is an interactive, subjective task for which the expertise has to be gradually built up.

First, the color table and contrast of the individual images should be optimized. Then, the iso-contour lines, the fusion balance slider, and various fusion modes explained in the Fusion Image Display 11

can be used to assess the degree of the brain alignment. In the example above, the correspondence of the blue (template) and white (**Input**) iso-contours indicate an acceptable agreement.

Manual Rigid Template Matching

In the case of the **Manual Adjustment** method the **NORMALIZED** layout simply shows an overlay of the template with the **Input** image. As explained before[25] the user has to manually shift and rotate the **Anatomical** image until the best fit with the template is found. Naturally, the agreement will not be ideal. Note however, that after generating the outline VOIs of the brain regions, they can be further adjusted ig needed.

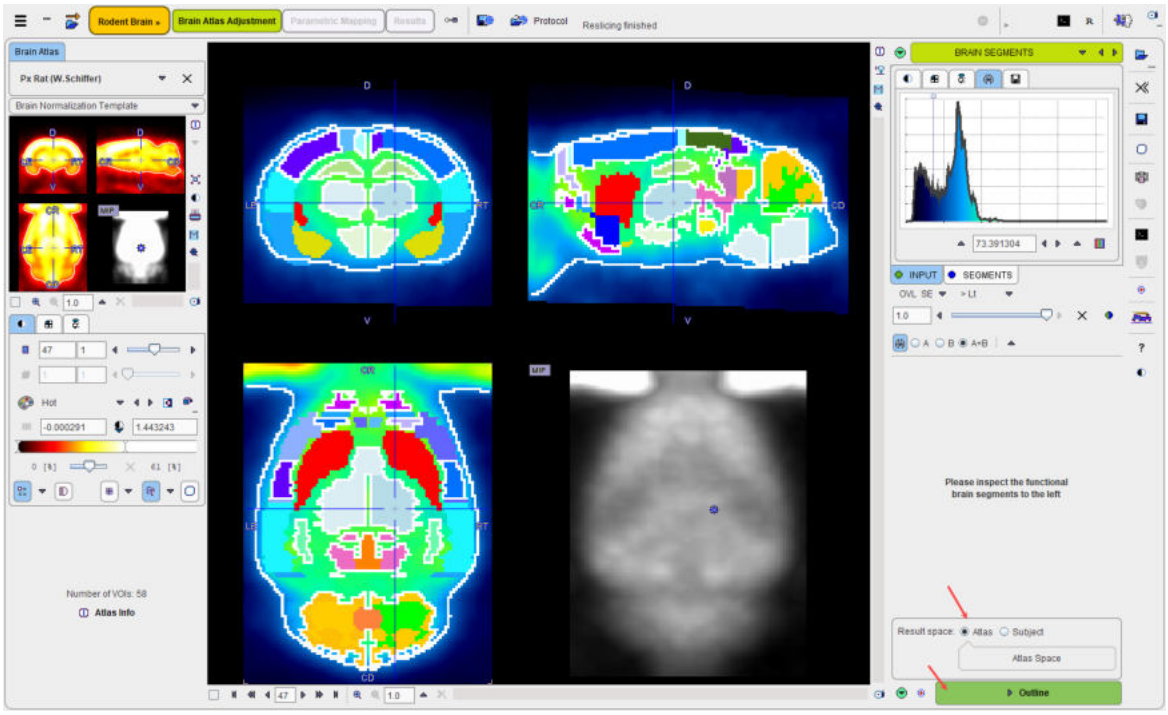


3.3.4 Brain Segments Calculation

After successful normalization the mapping between the **Input** and the atlas space is established. Consequently, the brain structures which are defined in the atlas space can be mapped to the **Input** subject space and shown in the overlay.

Calculate the Brain Segments

Activate the **Segment Brain** action button at the right bottom of the **NORMALIZED** layout to prepare the images in the two spaces. As a result, the (averaged) **Input** image is overlaid with an image of the transformed atlas regions called **BRAIN SEGMENTS**.



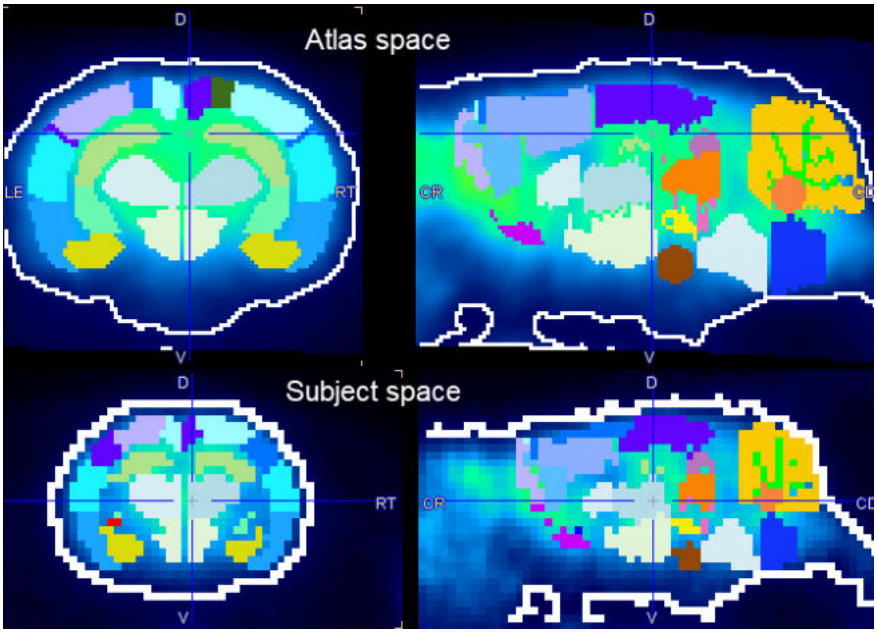
Please perform a final validation of the region placement.

Result Space Definition

There are two image spaces where the results can be generated and the statistics calculated:

1. **Atlas space**: The **Input** image is transformed to the space of the atlas. This option is preferable for pooling the resulting images (functional image, parametric map) of a group of subjects and performing an analysis such as SPM.
2. **Subject**: The atlas brain VOIs are transformed to the **Input** space. This option has the advantage that the statistics are calculated on the original **Input** data, whereas in the atlas space the data has been resampled.

The information visualized on the page is updated as soon as the **Result space** configuration is changed. The illustration below shows the results when selecting the two spaces. Clearly, the PET **Input** series has a much lower resolution than the **atlas** and correspondingly the segments appear heavily pixelated.

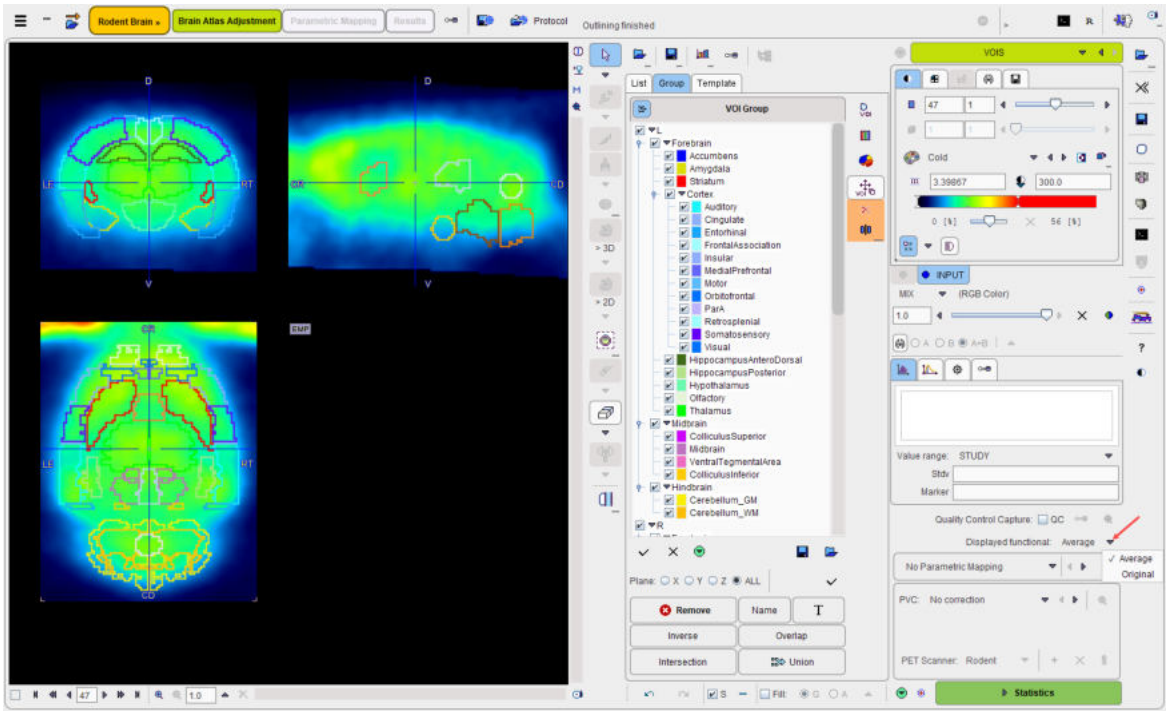


Brain Structure Outlining

Once the result space has been specified, the brain structures are fully defined and can be outlined to create contour VOIs. This process is started with the **Outline** action.

3.3.5 Brain VOI Editing, Statistics Calculation

The result of structure outlining is shown on the **VOIS** layout. The generated contours are presented in the overlay of the (averaged) **Input** image in the result space. Note that the full dynamic series can be shown instead of its average by the **Displayed functional** selection illustrated below.



From here on, all further operations like adjusting and saving the VOIs, ensuring that QC Captures are made, partial volume corrections, statistics calculation and parametric mapping are exactly the same as described for the dual-modality situation. Please refer to the related section above 34.

3.4 Result Statistics Page

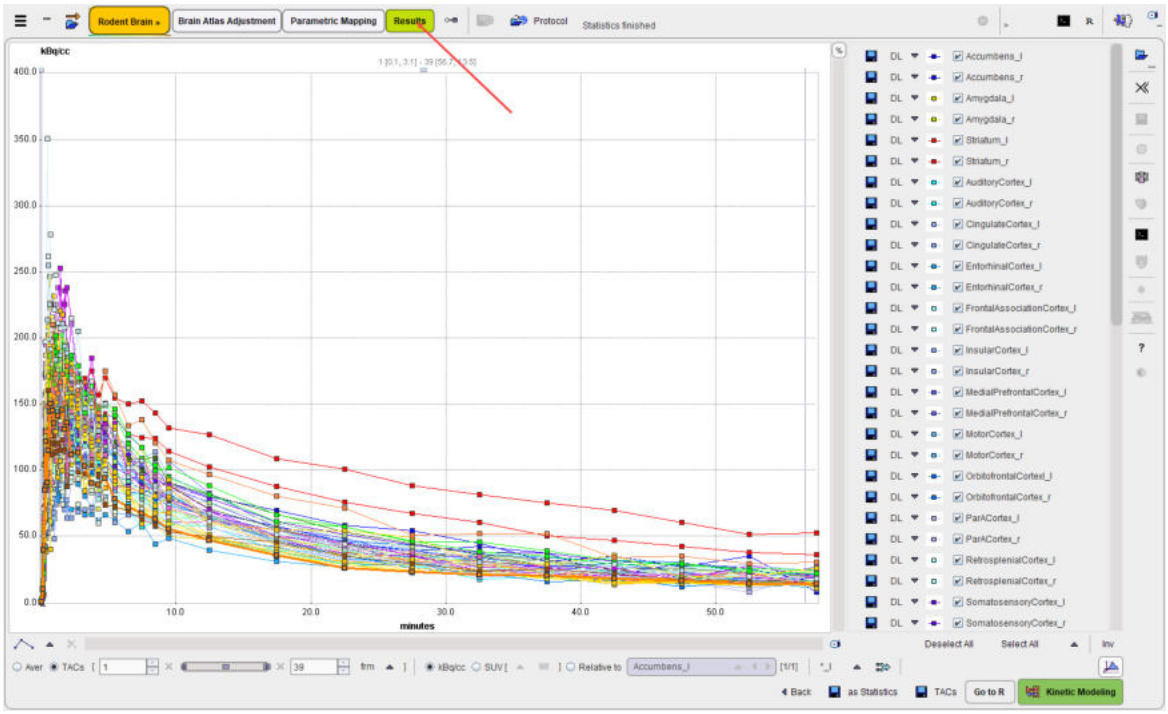
The statistics output from PNROD is shown on the **Result Statistics** page. It shows

- time-activity curves in the case of a dynamic **Input** series,
- average regional uptake in the case of static **Input** series.

Note: In PNROD, when new VOIs are created, the VOI voxel classification mode is forced to binary 100% (in preparation for partial-volume correction which doesn't permit overlaps).

3.4.1 Statistics of Dynamic PET Data

The example below illustrates the result for a dynamic 11C-Raclopride PET/MR example. In this case the statistics is the set of regional TACs.

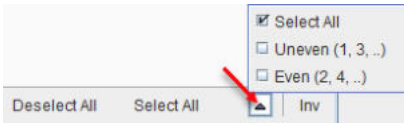


The **Back** arrow in the lower part is a convenience button for switching back to the PNROD workflow which generated the statistics.

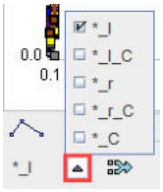
Selection of Curve Subsets

Depending on the atlas, PNROD may create a large number of VOIs. If only a subset is needed for further processing, the checks of the unneeded ones can be removed in the curves list.

There are some convenience buttons supporting selection in the list: **Deselect All** switches all curves off. **Select All** switches all curves on. **Inv** inverts the current selection. Additionally, there is a list which allows the user to quickly select the even or uneven numbers in the list.



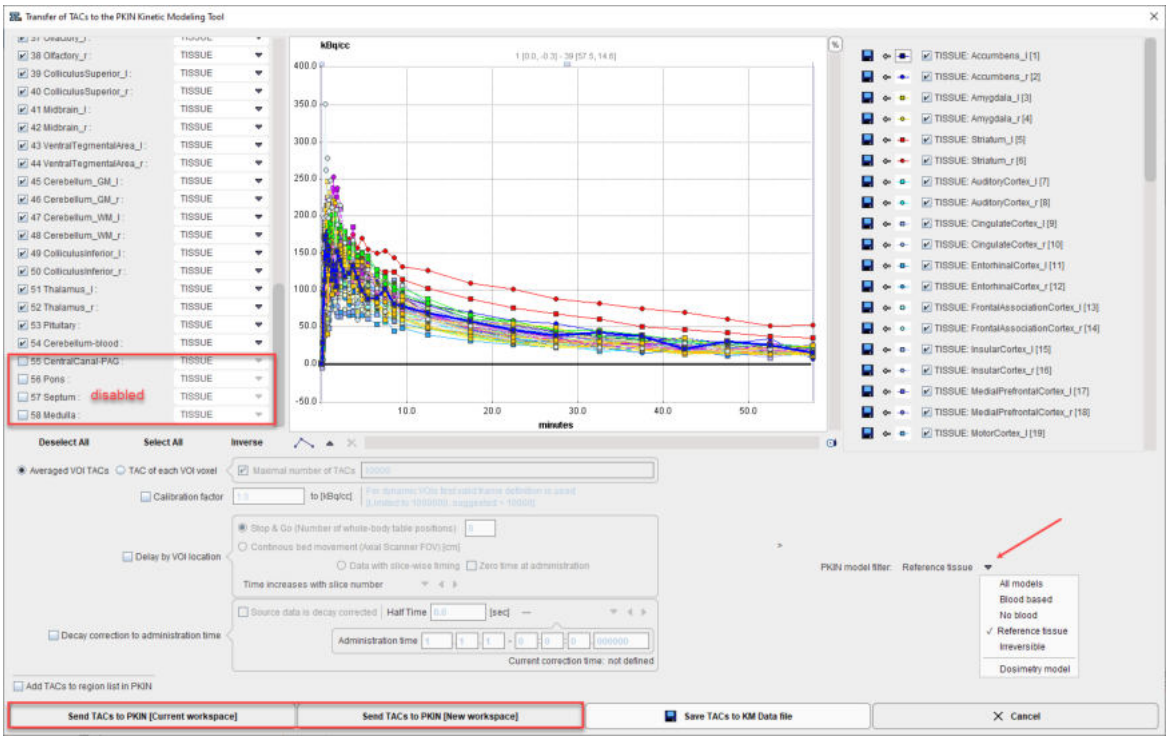
Yet another selection method is available next to the merge button allowing to select curves from the right (_r), the left (_l), or curves resulting after partial value correction (_C).



Note: An alternative reduction mechanism is to select only the relevant VOIs on the VOIs page[34] before calculating the actual statistics.

Transfer of TACs to the PKIN Tool

The **Kinetic Modeling** button allows dynamic tissue TACs to be directly transferred to the PKIN tool for modeling. It opens the following dialog window.



The TACs to be transferred can be selected by checking the box in the left column. The right side lists the currently selected TACs. **Send TACs to PKIN [Current workspace]** transfers the selection to the active workspace in PKIN. If the **Add TAC to region lis in PKIN** is enabled, the TACs will be added as additional tissue regions, otherwise the existing tissue data is overwritten. **Send TACs to PKIN [New workspace]** first creates a new workspace in PKIN before actually transferring the selection.

Save TACs to KM Data file creates a *.kmData* file ready to be used in the PKIN processing. The **PKIN model filter** selection is stored in the file.

Saving the Statistics

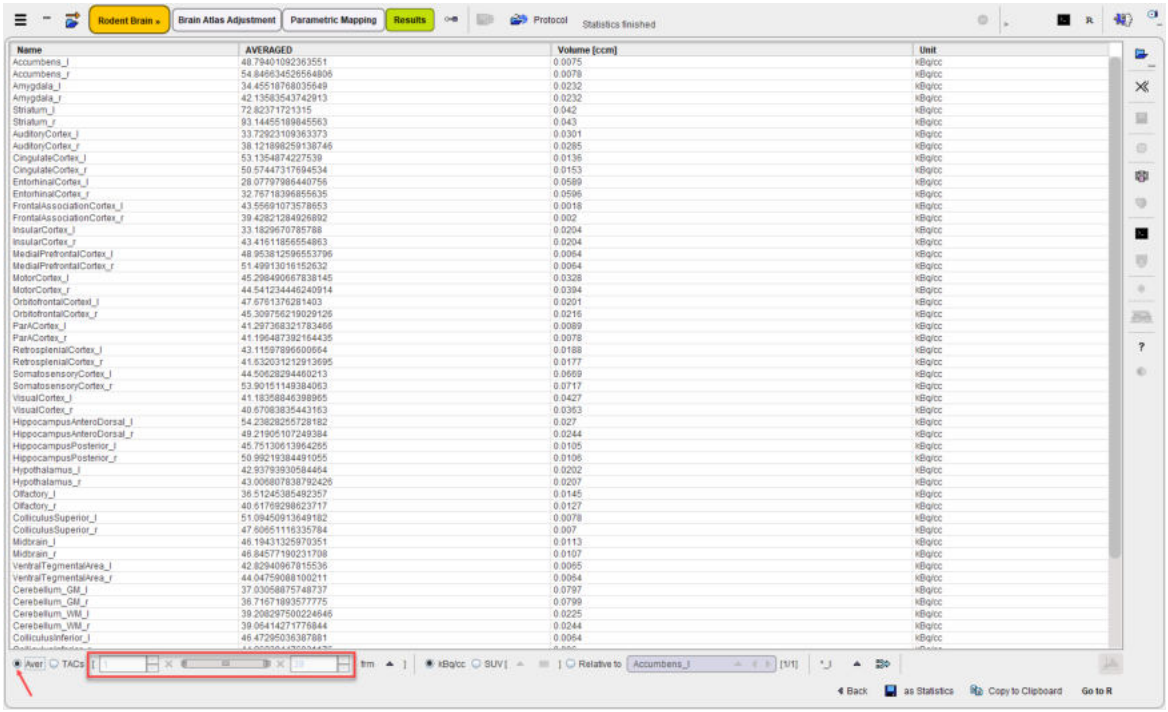
The save **TACs** button allows saving all curves in a simple tab-delimited text file as illustrated below. Such a file can easily be imported into other programs for processing and visualization.

start[seconds]	end[kBq/cc]	Accumbens_l	Accumbens_r	Amygdala_l	Amygdala_r	Striatum_l	Striatum_r	AuditoryCort
0	5	-0.854138361	1.842165297	-0.383517652	-0.147350651	-0.182233398	0.085621835	0.156494
5	10	0.563399638	1.996727172	-1.249460648	1.181134643	6.475534308	3.742047692	1.374395
10	15	28.2263985	17.15168257	41.75306365	47.74493908	31.6717491	48.60429618	28.69721
15	20	137.0943749	49.82483189	76.07024526	78.75507247	106.2900221	100.8557281	77.1733
20	25	170.599668	186.8340419	107.7752003	138.1484127	106.416208	113.1138174	98.84208
25	30	173.0115029	140.2353223	118.6526126	109.3649873	121.5509435	113.9891499	83.40529
30	35	178.6826748	122.0738514	96.28569095	131.9692792	130.943909	139.8472429	89.64717
35	40	113.0916325	191.8384339	116.1562503	78.10795687	129.9327171	142.2497993	82.23795
40	45	98.28354817	137.5934504	101.2561668	87.44354146	135.8110362	142.0134097	110.7575
45	50	169.3038463	259.1734516	93.4695336	166.3467876	161.0083616	168.3602811	98.52275
50	55	146.1662337	43.41939818	84.49963673	72.42473902	154.2566164	186.2111935	101.7742
55	60	145.3615819	168.5602026	71.98850622	76.2926588	161.6826155	153.9211748	110.6674
60	70	127.8754788	110.8433636	114.4237359	145.0536248	149.6758343	154.7596207	108.8035
70								

Save **as Statistics** button allows storing the information in a different format suitable for statistical analysis.

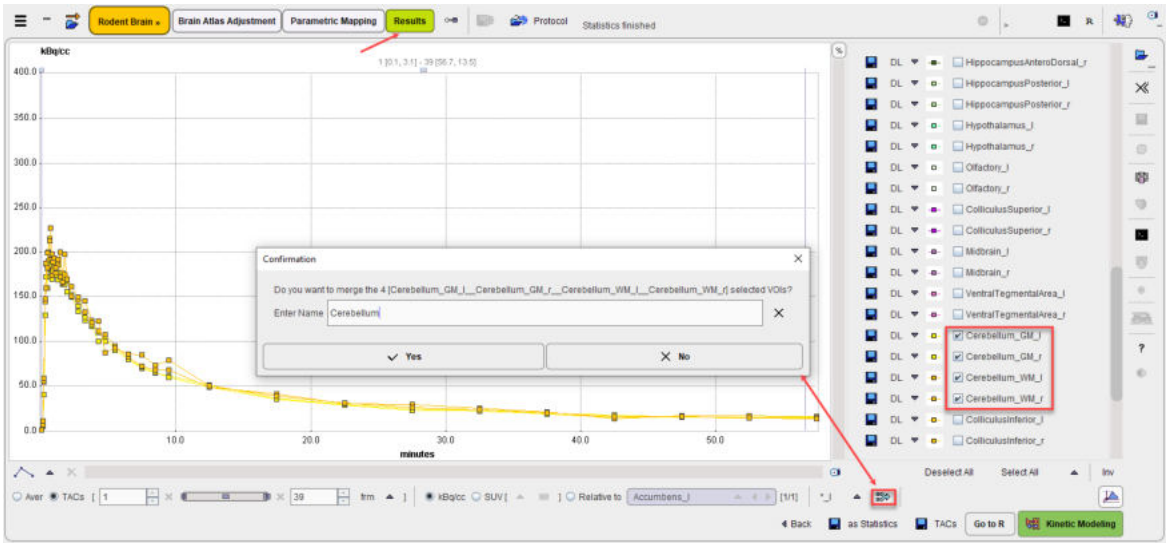
Average in Time Frame Range

For dynamic data there is an easy way to calculate the average regional uptake in the regions in a certain frame range: with the **TACs** radio button selected define the frame range to be averaged. As soon as the **Aver** radio button is switched on the uptake statistics is calculated and listed, replacing the curves display.



Averaging of Regional TACs

The **Merge (volume weighted) selected VOIs** button allows averaging of selected TACs. When the **Selected** option is activated a confirmation window appears.



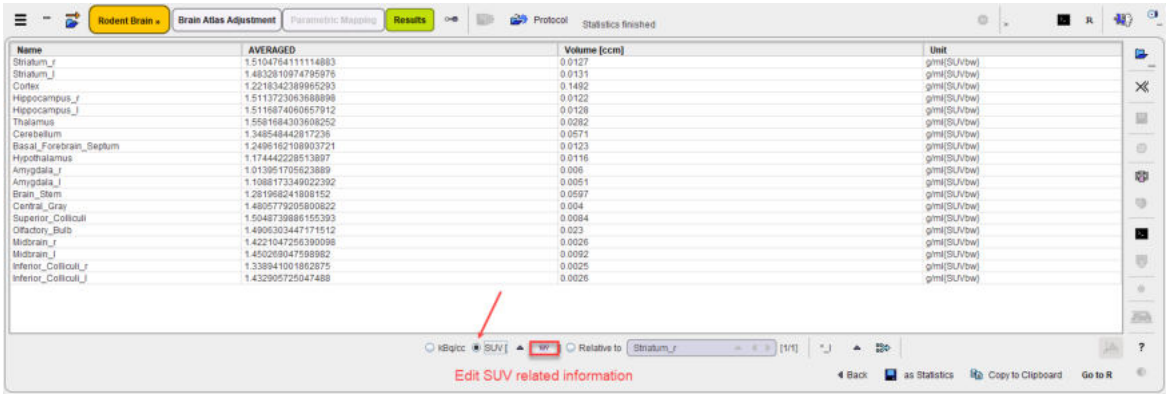
As soon as the **Yes** button is pressed the new TAC is calculated and appended at the list bottom using the specified name.

Transfer of Statistics to R

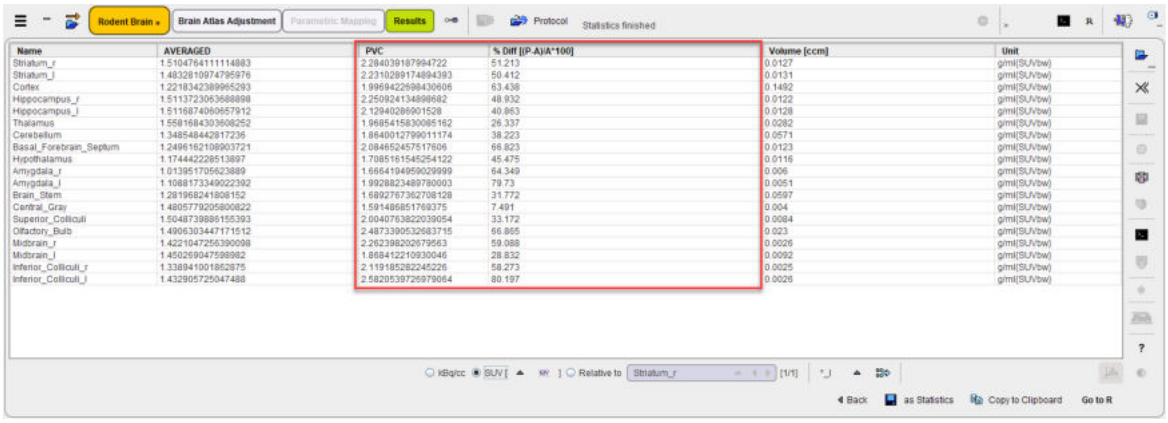
The **Go to R** button transfers the average and volume statistics of the selected TACs to the R server, generating one R variable in the R workspace.

3.4.2 Statistics of Static Data

If the VOIs are applied to static data, the **Statistics** page only shows a table of the main outcome parameter. In the case of a static PET the list shows the tracer average uptake in kBq/cc (**AVERAGED**) and the VOI volume in ccm. The **SUV** radio button allows listing the uptake in SUV units, as illustrated below.



In case a PVC method is applied, two additional columns are available in the list after the tracer average uptake: the tracer average **PVC** corrected value and the percentage difference between the non corrected and the corrected value.



Note: Please use the regular statistics button on the **VOIs** page to get the full statistics output.

SUV Statistics

If the statistics are calculated for activity concentration images, the uptake results can be converted to different types of SUV images, assuming that the related activity information and subject weight/height is available in the image header. If the information is not available in the image header, but is available via lab records etc., it can be entered after activating the SUV button.

SUVR Statistics

The so-called SUVR statistic is the uptake divided by a reference region uptake. It can easily be obtained by the **Relative to** radio button and selecting the reference region from the VOI list. Note that the ratio is also calculated for all the other statistical measures.

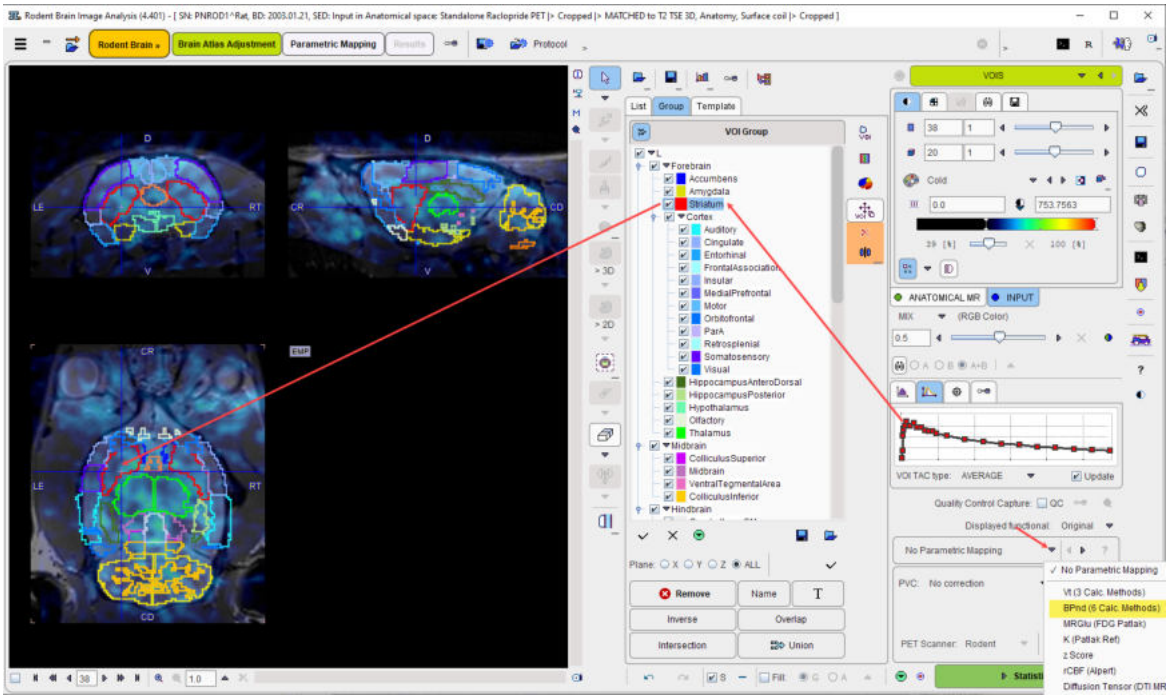
Transfer of Statistics to R

The **Go to R** button transfers the average and volume statistics to the R server, generating one R variable in the R workspace.

3.5 Parametric Mapping

If the pixel-wise modeling tool PXMOD has been licensed, PNROD includes a **Parametric Mapping** page. An advantage of this integration is that the VOIs generated by PNROD can be used during the PXMOD model configuration, and that the resulting parametric maps can immediately be regionally analyzed using those same VOIs. A further advantage is the choice of image space in which parametric maps will be calculated. For example, the **Atlas** space may be useful when a group analysis will be performed later, and the **Input** (original PET) space may be preferred in order to work with the original pixel TACs.

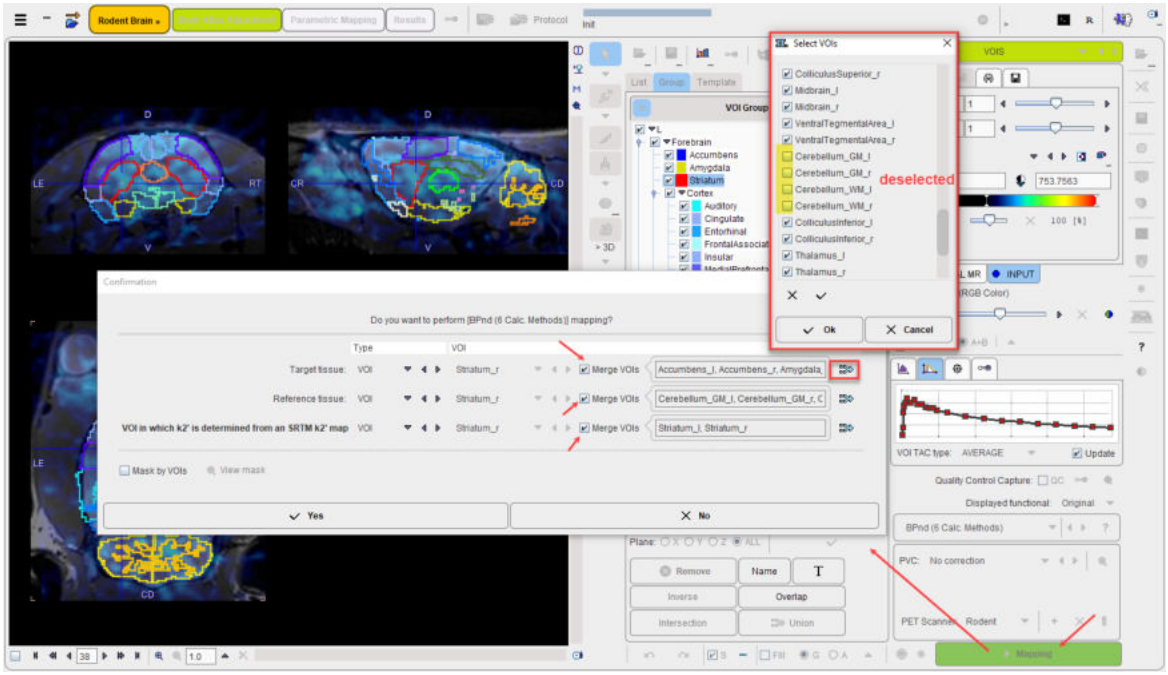
When a dynamic **Input** image (usually PET) is available, parametric mapping can be performed after the PNROD VOI outlining workflow completed as illustrated below. Please refer to the *PXMOD Users Guide* for a full description of the process and the models.



Starting Mapping

The first step is to choose an appropriate model from the list which initially shows **No Parametric Mapping**. As a consequence of model selection, the **Statistics** action button is replaced by a **Mapping** button.

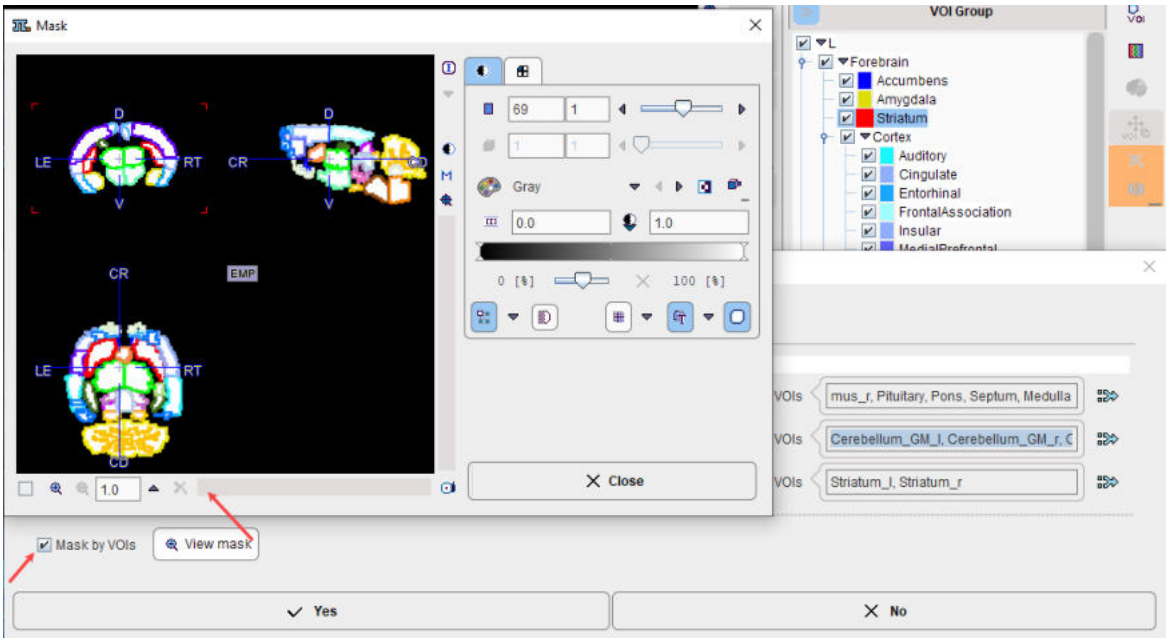
When activating the **Mapping** action button, a model-dependent configuration window is shown. The example below illustrates the case of mapping the binding potential with the **BPnd (6 Calc methods)** model.



It requires two tissue time-activity curves for a preprocessing step, one representing a **Target tissue** region, the other a **Reference tissue** region. There are three ways how to specify them: **FILE**, **VOI** and **TAC(DB)**.

VOI is the obvious choice, as the PNROD-generated VOIs can be employed. Either a VOI can be selected from the list, or the **Merge VOIs** option can be enabled in order to create a VOI from a subset of the existing VOIs. There are two ways to define a VOI subset: (1) by the specification of a comma-separated list of VOIs or a pattern such as **Cere*** in the text field (selects all VOIs with a heading "Cere" in the name), or (2) by selecting the merge button indicated above. With the latter, the selected **Selected button** shows a dialog window within which any VOI combination can be defined.

The **Mask by VOIs** option allows the user to restrict the mapping procedure to pixels within the VOIs. This may substantially reduce the time needed for map calculation, and allows non-specific tracer uptake outside the brain to be ignored. On the other hand, the gaps in the image may be appear unpleasant. The **View mask** button opens a dialog window with a mask preview.

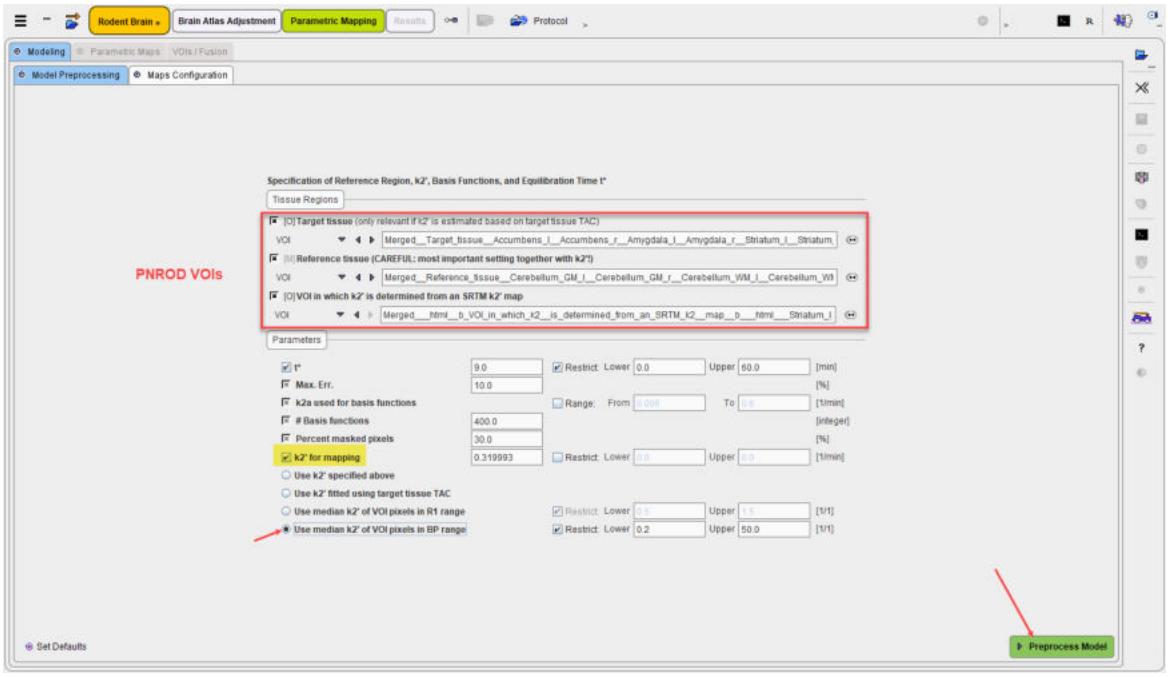


Note: Mapping is performed in the selected result space and can take much longer in a highly-resolved MR space than in the PET space.

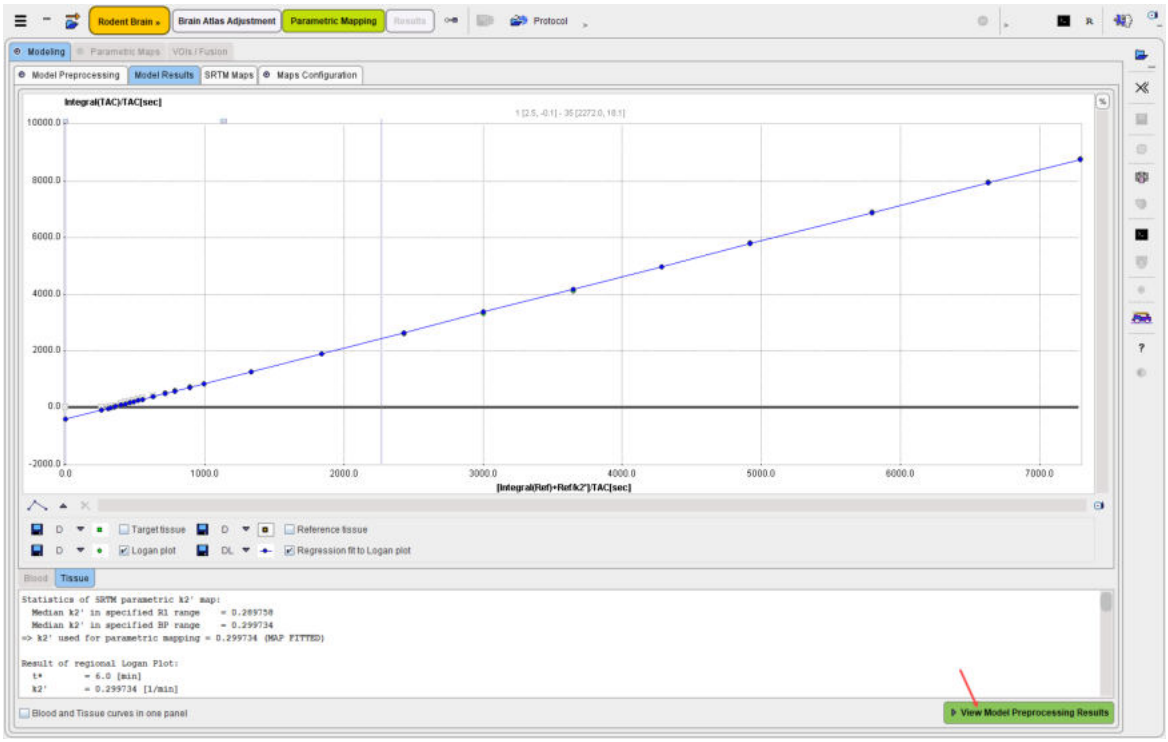
PXMOD Workflow

After confirming with **Yes** the program enters the **Mapping** page which hosts the PXMOD functionality. In the following the workflow is briefly captured. Please refer to the *PXMOD Users Guide* for the modeling-related explanations.

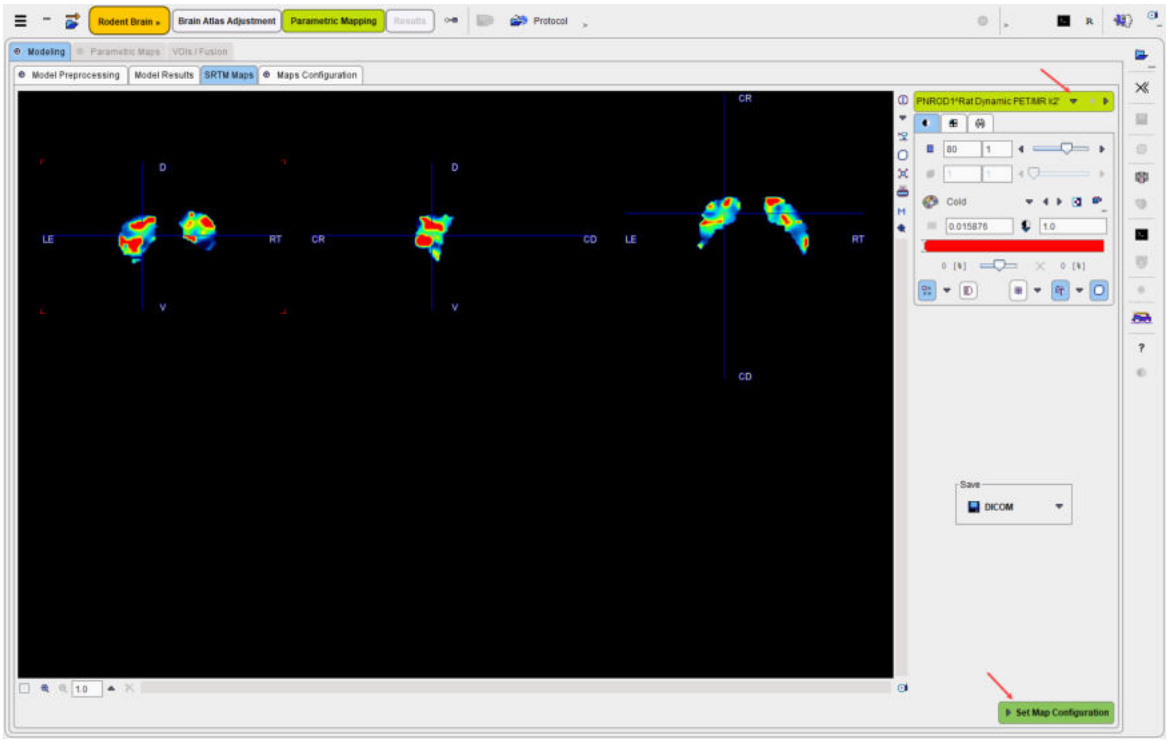
In the example below mapping starts on the **Model Preprocessing** page, because there is no blood data involved. Note that the VOI definitions are already configured according to the definition provided by the user in the previous dialog window.



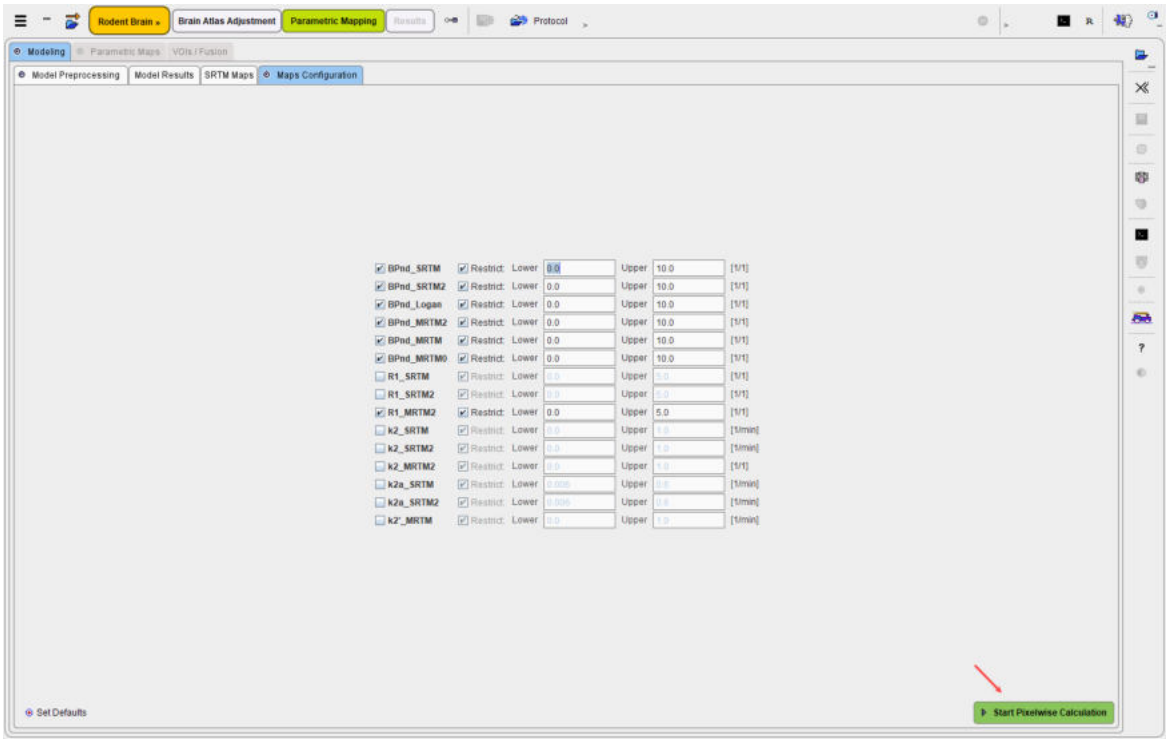
Preprocess Model starts the modeling preparations and displays the results on the next panel. Note that because the scale of the Logan plot is different from the original data, the tissue TACs have been switched off manually in the illustration below.



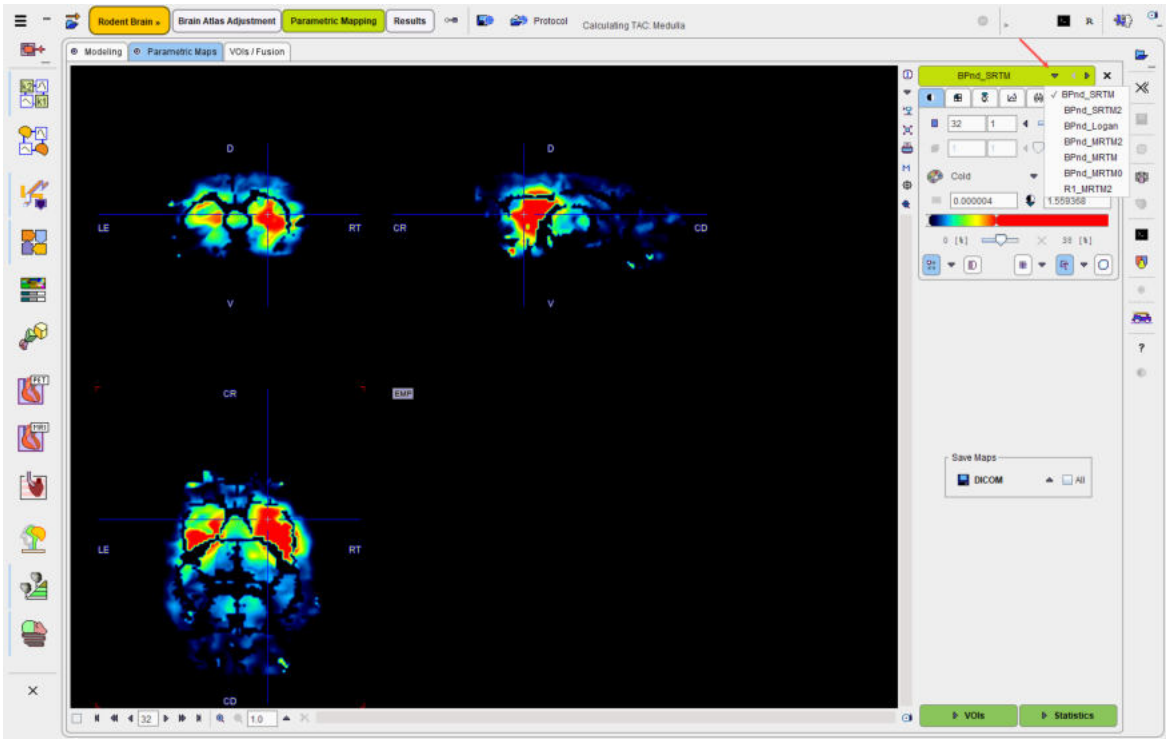
The selected model generates an additional result panel, which is shown on the next panel when proceeding with **View Model Preprocessing Results**. It displays the parametric maps for the VOIs structures configured in the first mapping step as **VOI in which k2' is determined from an SRTM k2' maps:**



Set Map Configuration proceeds to the **Maps Configuration** panel for defining the target parametric maps and their physiologic boundaries.

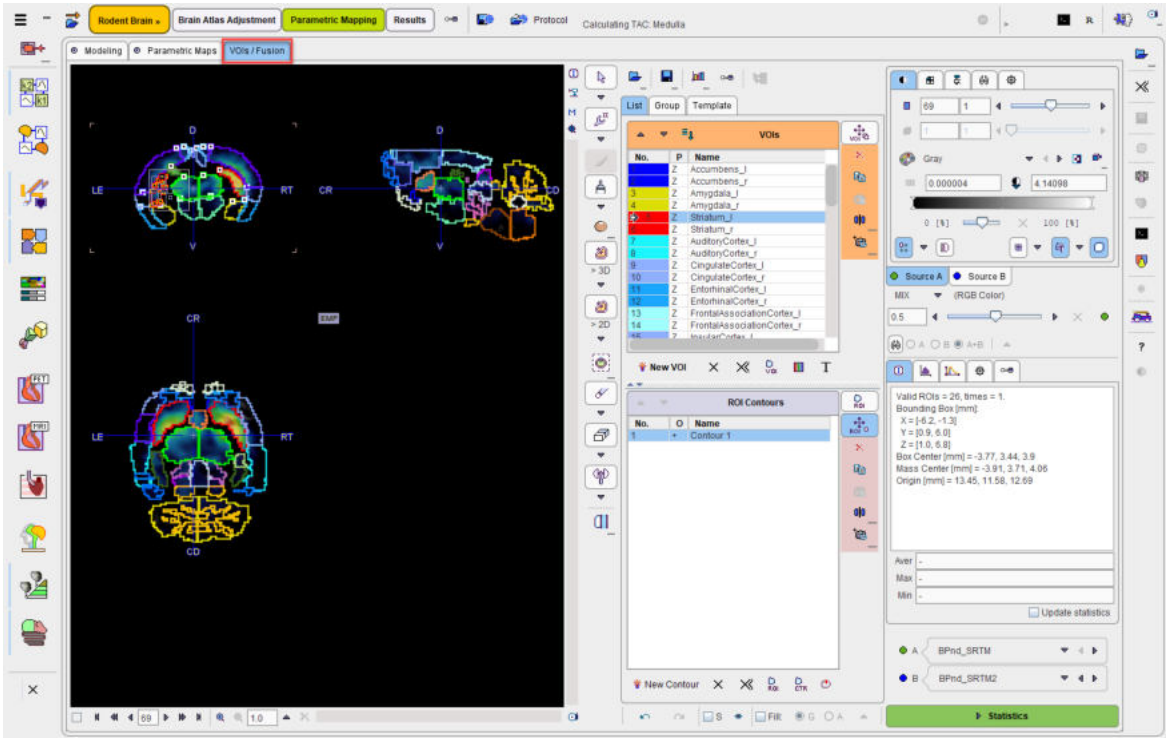


Start Pixelwise Calculation initiates the actual kinetic modeling in every pixel and shows the result on the **Parametric Maps** panel.

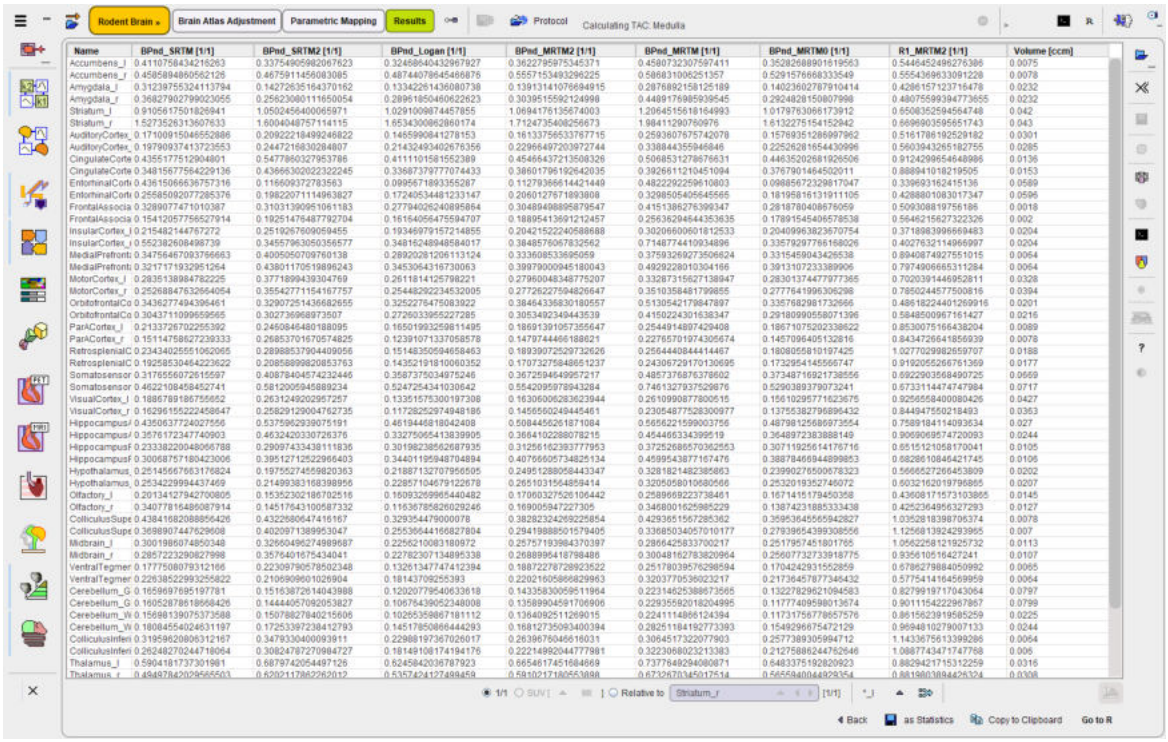


Evaluation of the Parametric Maps

The **VOIs** action button opens the **VOIs/Fusion** panel which shows a fusion of two resulting parametric maps as well as the VOIs in the overlay.



The Statistics action button calculates the regional average of all VOIs in all parametric maps and shows the resulting table in the main **Results** statistics page. Note also the last column which lists the VOI volumes for convenience.



Note: If parametric mapping should be part of the protocol, page **Parametric Mapping** must be active when saving the protocol.

4 PNROD Reference

4.1 Atlas Methodology

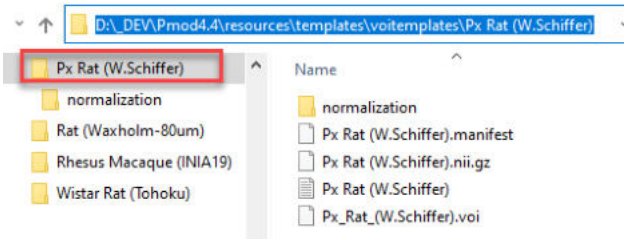
The PNROD tool includes . Dedicated variants can be derived from the atlases, and user-generated atlases can be added if they conform to PMOD's requirements (maps in template space, correctly inserted into the PMOD installation directory - dedicated functionality to facilitate this process is included in the standard VOI functionality of PMOD.

4.1.1 VOI Atlas Organization in PMOD

A VOI atlas in PMOD consists of the following components:

1. **Atlas image**: Image which encodes the atlas VOIs in a stereotactic space as numeric labels.
2. **Label list**: Text file mapping the label values to the VOI names shown in the user interface.
3. **Manifest**: Text file that defines the properties of the atlas.
4. **Normalization files** for calculation of the transformation between the subject anatomy and atlas anatomy (not needed for human MNI atlases).

The atlas information has to be organized in a sub-directory of *resources/templates/voitemplates* exactly as illustrated below for the **PxRat (W.Schiffer)** atlas below.



The atlas name (e.g. **PxRat (W.Schiffer)**) has to be used as the sub-directory name, the atlas image name (**PxRat (W.Schiffer).nii.gz**), the label list name (**PxRat (W.Schiffer).txt**), and the manifest name (**PxRat (W.Schiffer).manifest**). If the atlas is not a human atlas in the MNI space, it needs to include an additional *normalization* folder for the templates as illustrated below[61] .

By conforming to this structure it is possible for users to prepare their own VOI atlases.

4.1.1.1 Atlas Image

The atlas image must be prepared as a NifTI file and encode the atlas VOIs as numeric labels. Each pixel has a value of 0 if it is a background pixel, or otherwise an integer number. We recommend using the HFP anatomical orientation (head first, prone) for rodent data.

4.1.1.2 Label List File

The label list text file has the minimal form:

```
name1   outlined_name1  label_value1
name2   outlined_name2  label_value2
```

where each VOI is represented by a line.

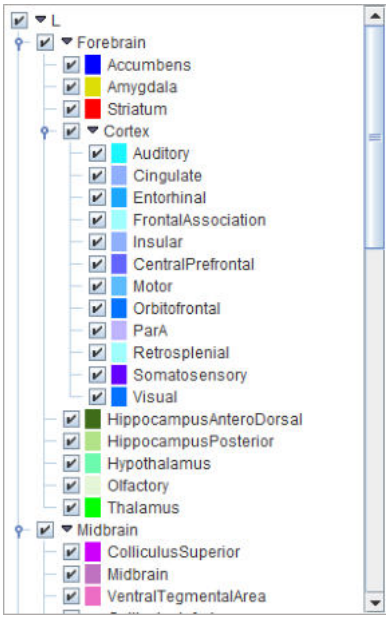
The list can be extended with additional information for the VOI presentation as illustrated below for the **PxRat (W.Schiffer).txt**. The first column starts with the name followed by a bracket construction which encodes a tree structure. For instance, **Auditory** belongs to the **Cortex** in the left **L**eft or right hemisphere of the **Forebrain**. The second column indicates the name of a generated contour VOI. The third column contains the label value in the atlas file. Each pixel in **PxRat (W.Schiffer).nii** with

value 1 will belongs to the **Accumbens_l** VOI, pixels with value **2** to **Accumbens_r**, etc. The fourth column specifies the RGB color values for showing the VOI, and the last column the text to be shown as a tooltip.

Tree organization	Outline name	Label value	RGB Color	Tooltip info
Accumbens[Forebrain[L]]	Accumbens_l	1	(0,0,255)	Nucleus accumbens right
Accumbens[Forebrain[R]]	Accumbens_r	2	(0,0,255)	Nucleus accumbens left
Amygdala[Forebrain[L]]	Amygdala_l	3	(222,222,7)	Amygdala left
Amygdala[Forebrain[R]]	Amygdala_r	4	(222,222,7)	Amygdala right
Striatum[Forebrain[L]]	Striatum_l	5	(255,0,0)	Caudate and Putamen left
Striatum[Forebrain[R]]	Striatum_r	6	(255,0,0)	Caudate and Putamen right
Auditory[Cortex[Forebrain[L]]]	AuditoryCortex_l	7	(28,247,255)	Auditory cortex left
Auditory[Cortex[Forebrain[R]]]	AuditoryCortex_r	8	(28,247,255)	Auditory cortex right
Cingulate[Cortex[Forebrain[L]]]	CingulateCortex_l	9	(143,175,255)	Cingulate cortex left
Cingulate[Cortex[Forebrain[R]]]	CingulateCortex_r	10	(143,175,255)	Cingulate cortex right
Entorhinal[Cortex[Forebrain[L]]]	EntorhinalCortex_l	11	(28,167,255)	Entorhinal cortex left
Entorhinal[Cortex[Forebrain[R]]]	EntorhinalCortex_r	12	(28,167,255)	Entorhinal cortex right
FrontalAssociation[Cortex[Forebrain[L]]]	FrontalAssociationCortex_l	13	(160,255,255)	Frontal association cortex left
FrontalAssociation[Cortex[Forebrain[R]]]	FrontalAssociationCortex_r	14	(160,255,255)	Frontal association cortex right

Note: For all rows, all columns need to be filled. Spaces in the **Name** field are not allowed.

The corresponding atlas VOI structure is illustrated below.



There are additional options to be added to the columns for use in PNROD:

- **O**: Indicates that the VOI is not brain matter.
- **H**: Indicates that the VOI should initially be hidden, i.e. not selected on the **Group** panel.
- **L**, **R**: Indicates that the VOI belongs to the left (L) or right (R) hemisphere.
- **C**: Indicates that the VOI belongs to the cerebellum.

Example as shown in Excel:

Cerebellum_GM[Hindbrain[L]]	Cerebellum_GM_l	45	(250,239,5)	Cerebellum gray matter left	C	
Cerebellum_GM[Hindbrain[R]]	Cerebellum_GM_r	46	(250,239,5)	Cerebellum gray matter right	C	
Cerebellum_WM[Hindbrain[L]]	Cerebellum_WM_l	47	(252,191,6)	Cerebellum white matter left	C	H
Cerebellum_WM[Hindbrain[R]]	Cerebellum_WM_r	48	(252,191,6)	Cerebellum white matter right	C	H
ColliculusInferior[Midbrain[L]]	ColliculusInferior_l	49	(255,204,0)	Inferior colliculus left		
ColliculusInferior[Midbrain[R]]	ColliculusInferior_r	50	(255,204,0)	Inferior colliculus right		
Thalamus[Forebrain[L]]	Thalamus_l	51	(0,255,0)	Thalamus left		
Thalamus[Forebrain[R]]	Thalamus_r	52	(0,255,0)	Thalamus right		
Pituitary[Central]	Pituitary	53	(255,204,0)	Pituitary gland	O	
Cerebellum-blood[Central]	Cerebellum-blood	54	(219,238,243)	Cerebellum blood flow	O	H

4.1.1.3 Atlas Manifest File

The following entries are supported in the manifest text file describing the atlas:

`SPECIES = RAT`	The supported species include `HUMAN, PRIMATE, PIG, RAT, MOUSE`
`SPACE = MNI`	Only the MNI (Montreal Neurological Institute) space for humans is supported as of now. If this line is present, a common set of template files with 2x2x2mm resolution is used.
`APPLICATION = NO_PNEURO` or `NO_PNROD`	If this line is present, the atlas is not listed in PNEURO or PNROD respectively.
`TYPE = PROBABILISTIC, RANGE 0 / 100`	The range specified for the data will be scaled to a probability value in the range [0,1]
`INFO = html text`	Text to be shown if the atlas info button is actived. Example: INFO = <html>Px Rat (W.Schiffer) Atlas The atlas is based on brain scans of adult male Sprague-Dawley rats (250-300g, age 52-62 days). A T2-MRI and an FDG PET template was constructed by Schiffer et al. [1] in the Paxinos coordinate system and can be used for template-based normalization. The VOI atlas contains 58 cortical and subcortical regions. The atlas is distributed with PMOD by courtesy of Dr. Wynne Schiffer, at that time at the Brookhaven National Laboratory.

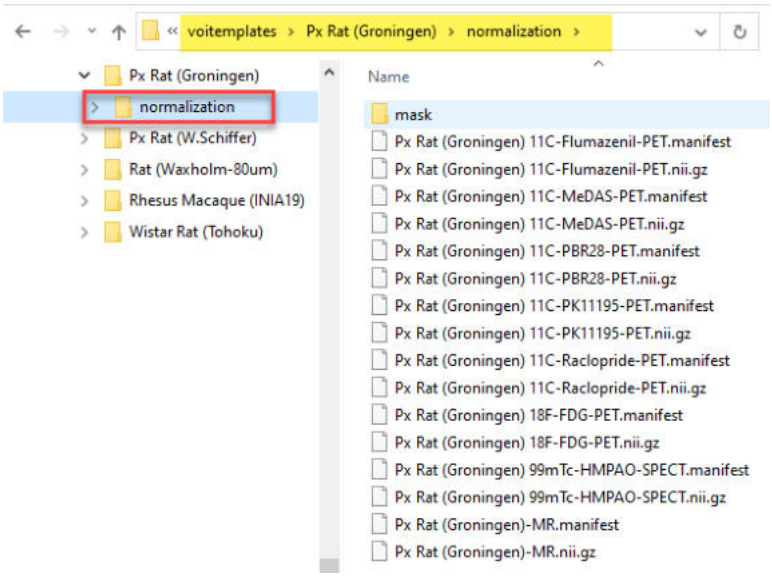
4.1.1.4 Spatial Normalization Methods

Atlases can only be applied to images if they have the same resolution and show the anatomy with the same geometry. Therefore, images originating from real experiments first need a normalization step for the atlas to be applied. This is done by calculating a normalization transform between the subject image and a "template" image representing the standard anatomy imaged with a certain modality, and using it for warping the VOIs to the subject anatomy.

The PNROD tool supports four methods as described in Normalization of the Anatomical Image[28] .

4.1.1.5 Template Files for Spatial Normalization

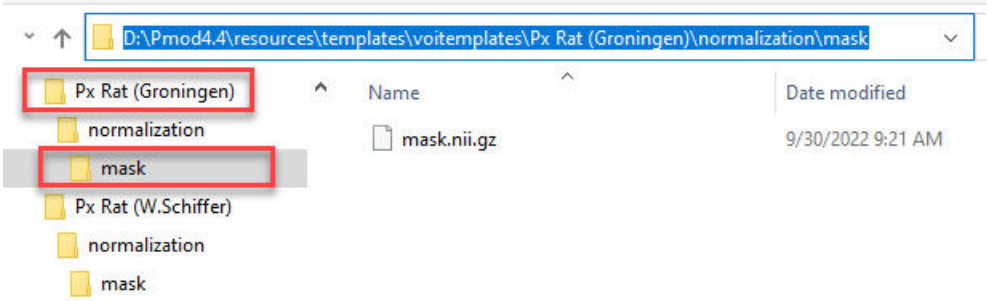
For atlases in other spaces than the human MNI corresponding normalization templates have to be included in a *normalization* sub-folder. As an example, for the **Px Rat (Groningen)** atlas illustrated below many PET templates and MR template are available.



The template files need to be in NifTI format. In the example above they are in compressed Nifti format. They can be accompanied by a simple manifest text file containing
`SPECIES = RAT` (`SPECIES = MOUSE`) for mouse atlas templates.

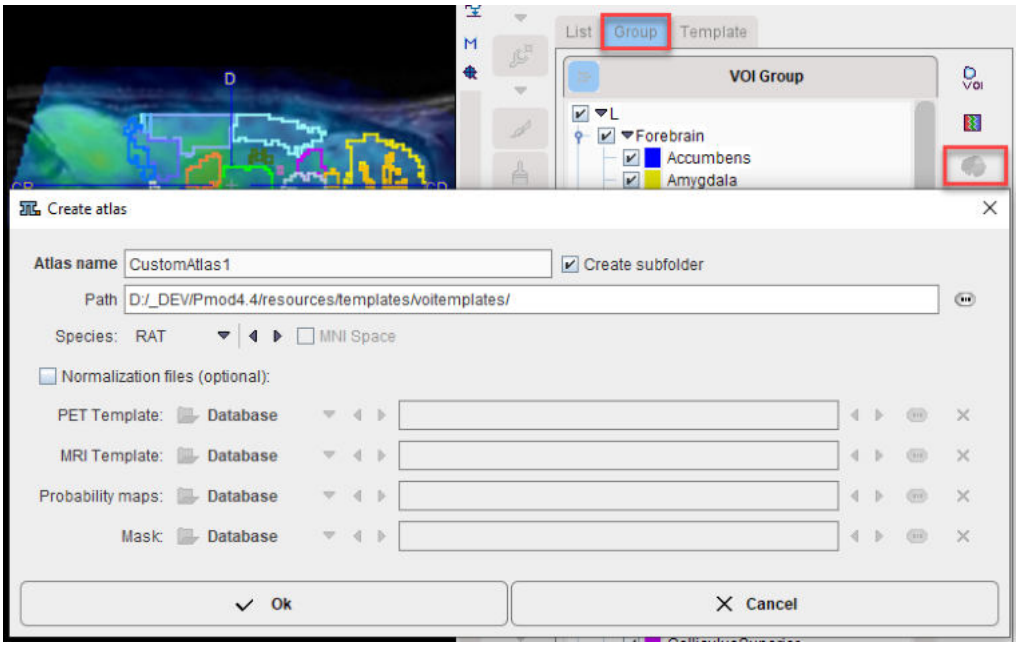
4.1.1.6 Normalization Mask

Normalization works best if the information is restricted to the relevant image part. Therefore, the *normalization* sub-folder should contain a *mask* sub-folder with a mask file called **mask.nii** containing 1 for all relevant pixels and 0 for all others.



4.1.1.7 Atlas Creation from VOIs

The PMOD VOI interface provides a facility easily create the infrastructure of an atlas from a VOI definition. Once a VOI set has been outlined which should become the regions of a new atlas, the button on the **Group** panel can be activated. It opens the dialog window illustrated below which requests the user to specify an **Atlas name**, the location **Path** of the structure (proposing the default atlas location), and optionally template images which will be available for the spatial normalization. They typically correspond to different modalities or different image contrasts (MR pulse sequence, PET tracer), always with the anatomy corresponding to the region definition.



Note that the label list text file which is created needs to be edited in order to implement a tree structure, unless the VOIs are just modified outlines of an existing atlas.

4.1.2 Rodent VOI Atlases in PNROD

Enter topic text here.

4.1.2.1 Sprague-Dawley Rat Brain Atlas (A.Schwarz) & PET/SPECT Templates (Groningen)

Overview

The **Px Rat (A.Schwarz)** atlas is based on 97 anatomical MR images of adult male Sprague-Dawley rats (250-300g). For the original atlas [1] a volumetric reconstruction of the Paxinos and Watson rat brain atlas was created and adapted to the averaged anatomy. This version of the atlas was used as part of a proposed standardized methodology for the creation of small animal brain PET templates [2]. For application in PMOD the atlas and templates were interpolated to 0.1 mm resolution and VOIs merged to avoid small regions, which would result in poor statistics. The VOI atlas contains 60 cortical and subcortical regions. The atlas is distributed with PMOD by courtesy of Dr. Adam Schwarz, Department of Psychological and Brain Sciences, Indiana University, and the PET/SPECT templates courtesy of University Medical Center Groningen, The Netherlands (with thanks to Dr. D. Vallez Garcia, UMC Groningen, Nuclear Medicine & Imaging).

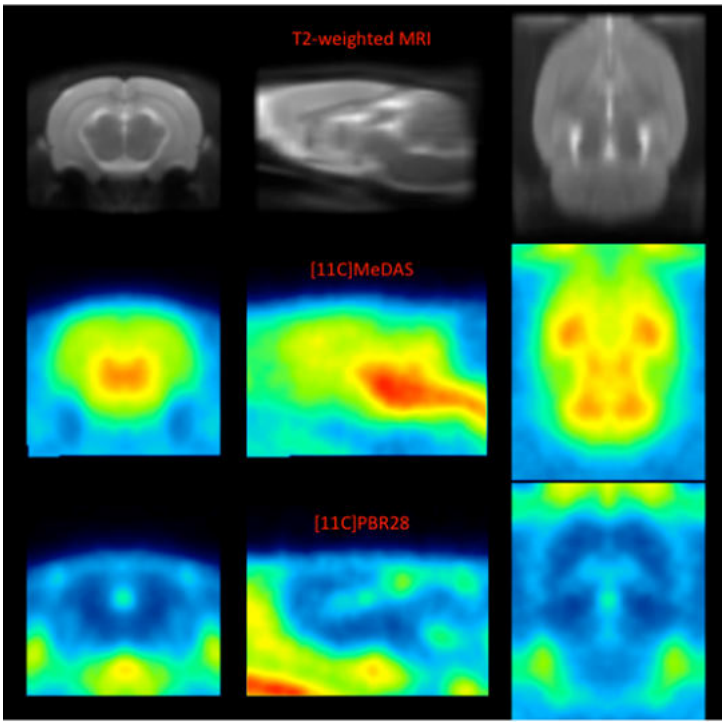
Spatial Normalization

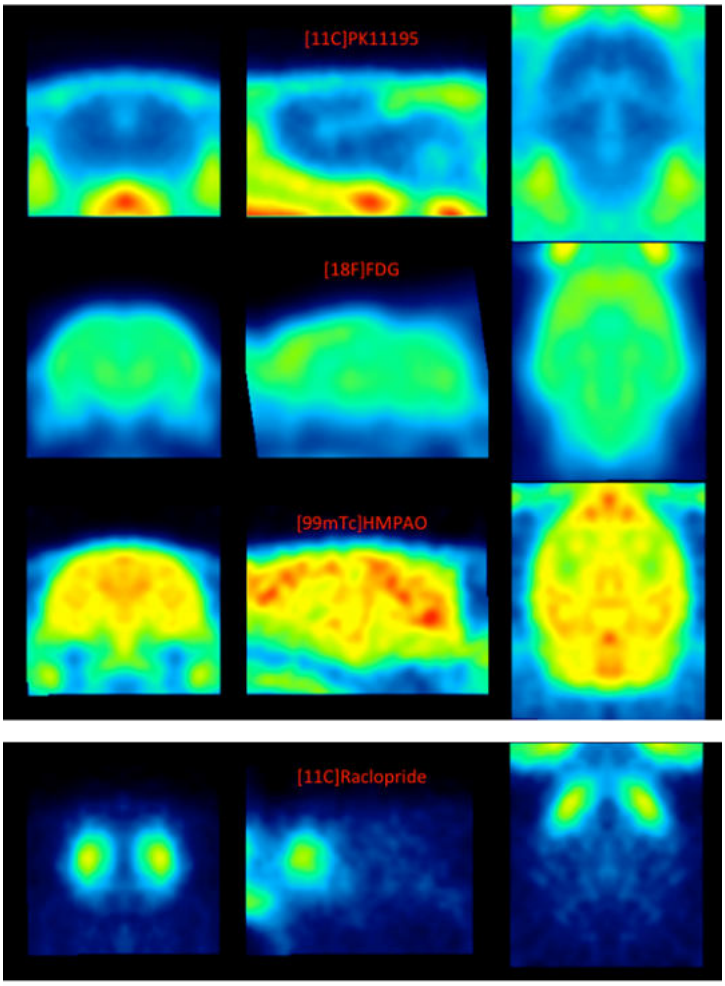
The T_2-weighted MR template, five PET templates and a single SPECT template are available in the Fuse It tool when **Rat** is selected as **Species**.

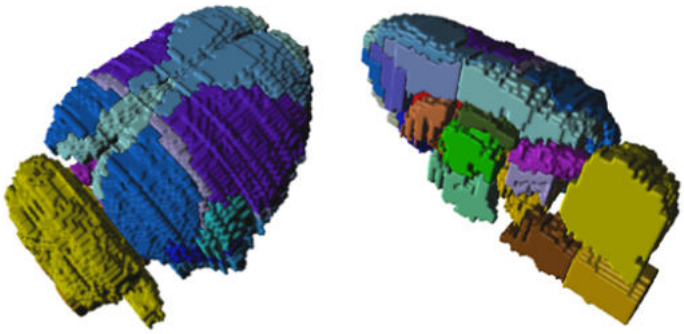
- **Px Rat (A.Schwarz)-T2**, **Px Rat (Groningen)-T2**: This is the T_2-weighted MR anatomical reference for the A.Schwarz VOI atlas.
- **Px Rat (Groningen)-MeDAS**: This is a PET template for the tracer [11C]MeDAS, coregistered to the MR anatomical reference above.
- **Px Rat (Groningen)-PBR28**: This is a PET template for the tracer [11C]PBR28, coregistered to the MR anatomical reference above.
- **Px Rat (Groningen)-PK11195**: This is a PET template for the tracer [11C]PK11195, coregistered to the MR anatomical reference above.

- **Px Rat (Groningen)-Raclopride**: This is a PET template for the tracer [11C]Raclopride, coregistered to the MR anatomical reference above.
- **Px Rat (Groningen)-FDG**: This is a PET template for the tracer [18F]FDG, coregistered to the MR anatomical reference above.
- **Px Rat (Groningen)-SPECT**: This is a SPECT template for the tracer [99mTc]HMPAO, coregistered to the MR anatomical reference above.

The image files corresponding to these templates can be found in the *resources/templates/voitemplates/Px Rat (A.Schwarz)* and *resources/templates/voitemplates/Px Rat (Groningen)* folders, specifically in the **normalization** sub-folder. Mask files for use during normalization and coregistration are also available.







VOI Atlas

The VOI atlas **Px Rat (A.Schwarz)** (and identical atlas through **Px Rat (Groningen)**) can be selected in the list of included VOI atlases. The corresponding map files in Nifti format can be found in the *resources/templates/voitemplates/Px Rat (A.Schwarz)* directory.

The brain VOIs are structurally organized in a tree on the Group tab of the VOI editing page. The selection of a VOI subset is supported by a dedicated **user interface**[16].

Reference

1. Schwarz AJ, Danckaert A, Reese T, Gozzi A, Paxinos G, Watson C, Merlo-Pich EV, Bifone A. A stereotaxic MRI template set for the rat brain with tissue class distribution maps and co-registered anatomical atlas: application to pharmacological MRI. Neuroimage. 2006 Aug 15;32(2):538-50. DOI.
2. Vallez Garcia D, Casteels C, Schwarz AJ, Dierckx RA, Koole M, Doorduin J. A standardized method for the construction of tracer specific PET and SPECT rat brain templates: validation and implementation of a toolbox. PLoS One. 2015;10(3):e0122363. DOI.

4.1.2.2 Sprague-Dawley Rat Brain Atlas (Schiffer)

For the analysis of rat brain data the **Px Rat (W.Schiffer)** [1] VOI atlas is available. We would like to thank Wynne Schiffer for providing the data and helping with the integrations. The atlas incorporates adult male Sprague-Dawley rats (250-300g, age 52-62 days). This template implements the Paxinos coordinates.

Spatial Normalization

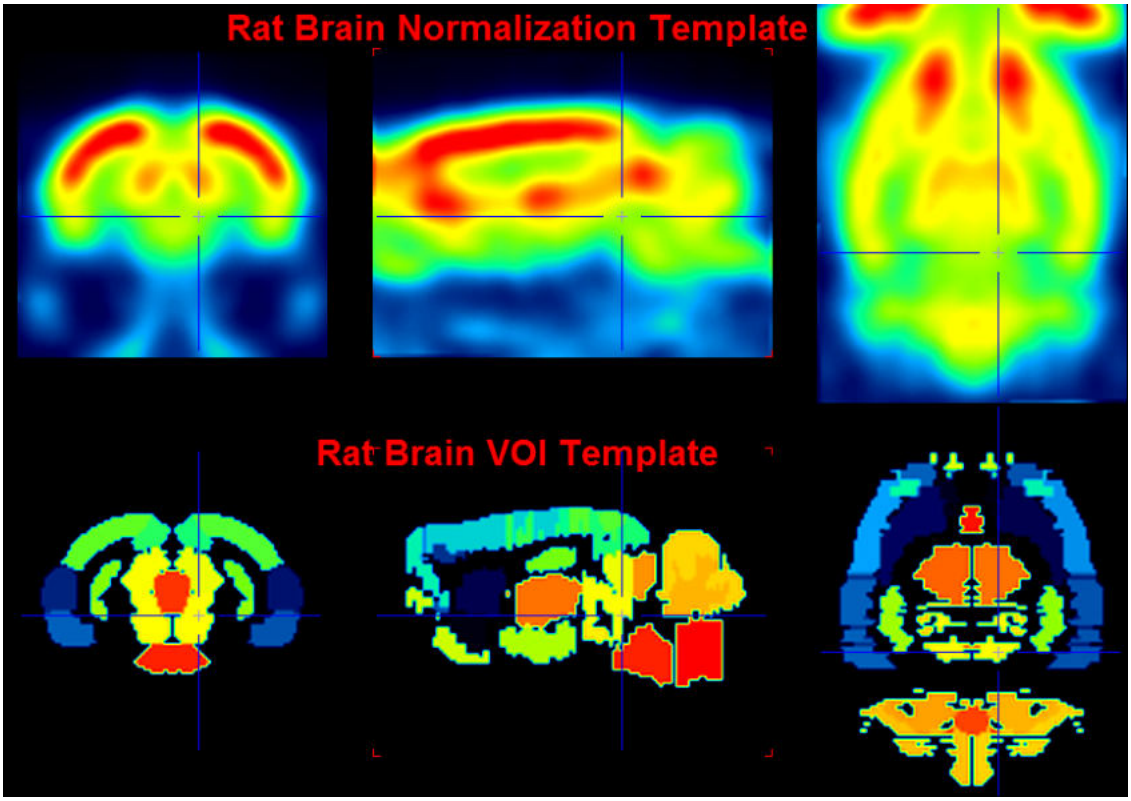
Three normalization templates are available in the fusion tool:

- **Px Rat (W.Schiffer)-FDG**: This is an FDG PET template as illustrated below.
- **Px Rat (W.Schiffer)-FDG masked**: This is a masked version of the FDG PET which has been masked outside the brain. It may be helpful if the additional activity of the Harderian glands is not present in the rat images to be normalized.
- **Px Rat (W.Schiffer)-T2**: This is a T_2-weighted MRI PET template which is in the same space as the PET templates.

The images of these templates can be found in the *resources/templates/voitemplates/Px Rat (W.Schiffer)/normalization* directory.

VOI Atlas

The VOI atlas **Px Rat (W.Schiffer)** can be selected in the list of included VOI atlases. The corresponding files can be found in the *resources/templates/voitemplates/Px Rat (W.Schiffer)* directory.



Reference

[1] Schiffer WK, Mirrione MM, Biegon A, Alexoff DL, Patel V, Dewey SL. Serial microPET measures of the metabolic reaction to a microdialysis probe implant. J Neurosci Methods. 2006;155(2):272-84. DOI

4.1.2.3 Wistar Rat Brain Atlas (Tohoku)

Overview

The **Wistar Rat (Tohoku)** atlas was developed by Valdes-Hernandez et al [1] using 7T T_2-MRIs from 30 Wistar rats. The template image was constructed as a "minimal-deformation" template, and the coordinates are thus not in Paxinos space. In the same space, gray matter, white matter and CSF probability maps were calculated, so that the 3-probability maps normalization can be applied in addition to the template-based normalization. 48 bi-lateral cortical structures were digitized from the Paxinos atlas and registered them to the template image. This atlas can be used for VOI statistics and for the anatomical interpretation of fMRI results.

The atlas is distributed with PMOD by courtesy of Prof. Akira Sumiyoshi, Tohoku University, Japan (**atlas website**).

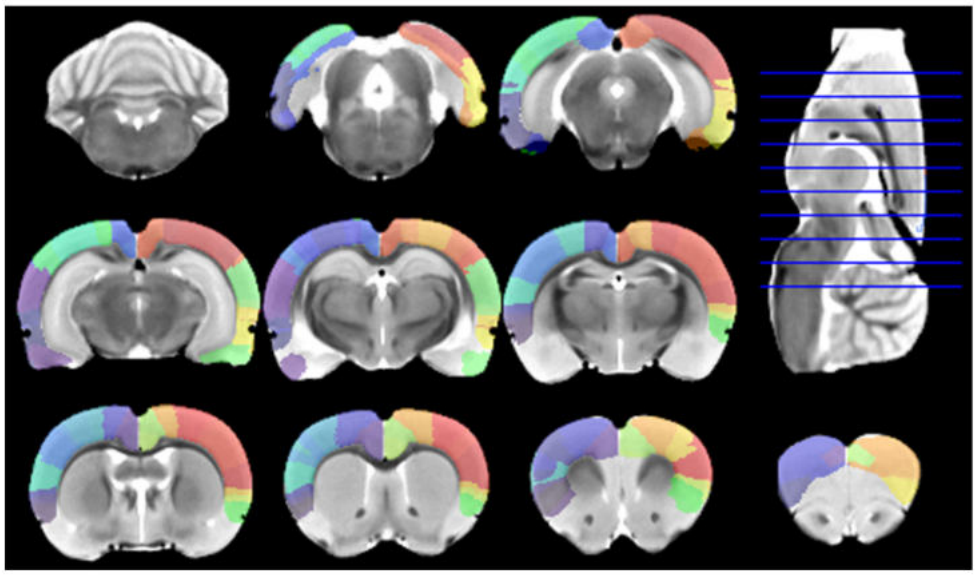


FIGURE 4 | Digitalized Paxinos and Watson atlas, overlaid on the minimal deformation template after being warped to the template space using the approximate thin plate splines (TPS) method, plus further manual corrections.

Spatial Normalization

Two normalization approaches are supported:

- Template-based normalization using the **Wistar Rat (Tohoku)-MR** skull-stripped T_2-MR template illustrated above.
- 3-tissue probability maps normalization using Gray matter, White matter and CSF combined in a single **tpm.nii** file.

The images of these templates can be found in the *resources/templates/voitemplates/Wistar Rat (Tohoku)/normalization* directory.

Reference

[1] Valdes-Hernandez PA, Sumiyoshi A, Nonaka H, Haga R, Aubert-Vasquez E, Ogawa T, Iturria-Medina Y, Riera JJ, Kawashima R: An in vivo MRI Template Set for Morphometry, Tissue Segmentation, and fMRI Localization in Rats. Frontiers in neuroinformatics 2011, 5:26. DOI

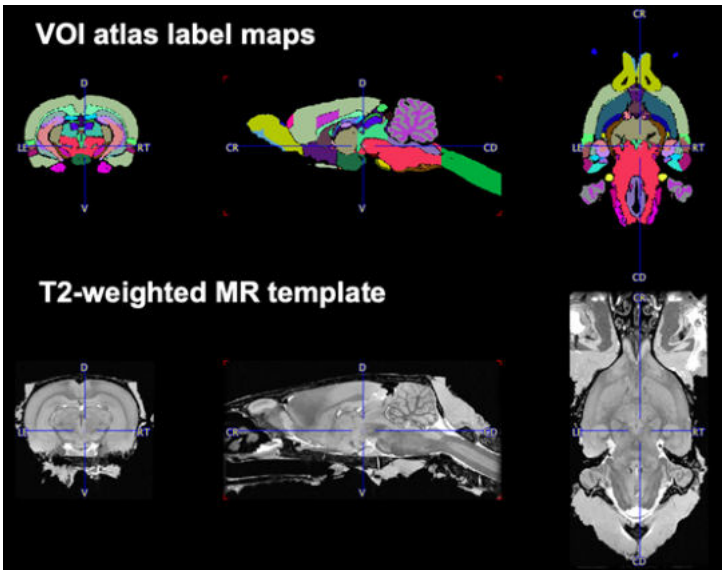
4.1.2.4 Sprague-Dawley Rat Brain (Waxholm-80um)

The **Rat (Waxholm-80um)** atlas is based on the brain of a 397.6 g male Sprague-Dawley rat. The brain was imaged with MR ex vivo, resulting in T_2-weighted gradient echo images with 40 um isotropic spatial resolution. 76 brain structures were segmented [1, 2].

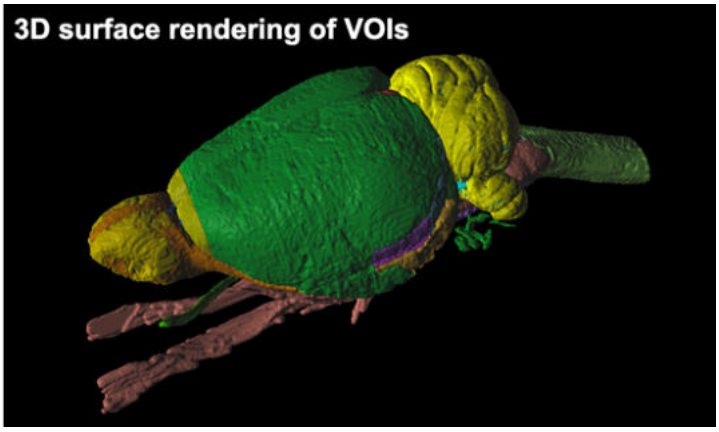
E. A. Papp prepared a version suitable for PMOD and made it available for download on nitrc.org: https://www.nitrc.org/projects/whs-sd-atlas/

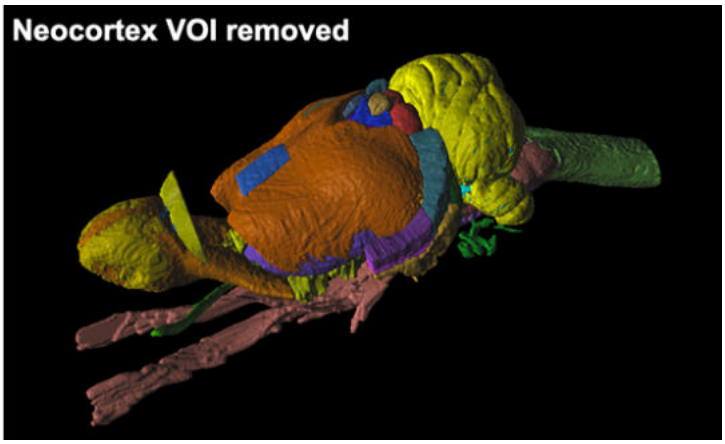
An adapted version of this atlas is distributed with PMOD as a convenience to our users. Because the original 40um isotropic resolution is beyond typical in vivo MR and far beyond the resolution applicable for PET image analysis, it was down-sampled to 80um. The original text file associated with the atlas was re-organized to consecutively number the regions. Note: down-sampling left no actual voxels in regions 6,33,47,49,60,63 as numbered in the atlas text file.

Atlas Label Map and MR Normalization Template



3D Rendering of Atlas Regions





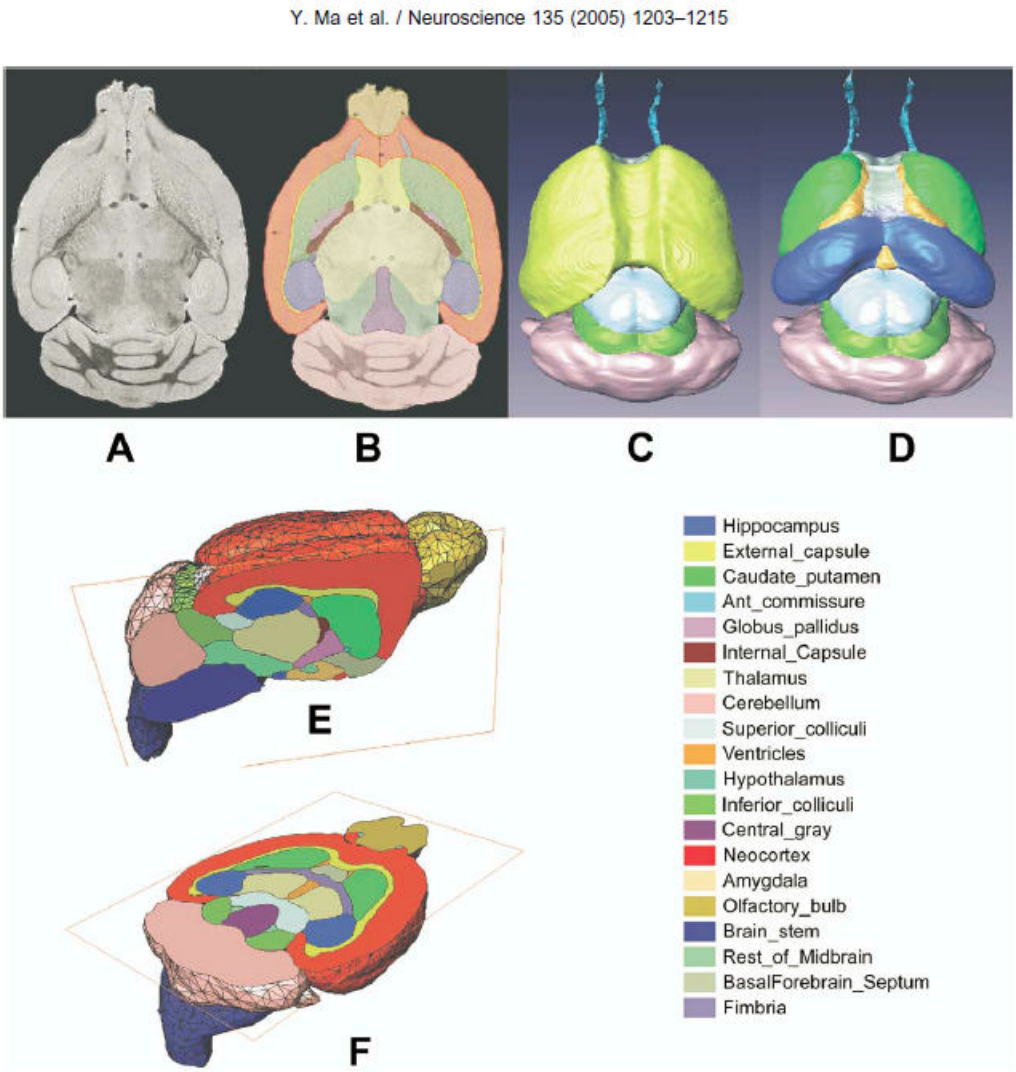
References

[1] Papp EA, Leergaard TB, Calabrese E, Johnson GA, JG (2014). Waxholm Space atlas of the Sprague Dawley rat brain. NeuroImage 97:374-386. doi: 10.1016/j.neuroimage.2014.04.001

[2] Kjonigsen LJ, Lillehaug S, Bjaalie JG, Witter MP, Leergaard TB (2015). Waxholm Space atlas of the rat brain hippocampal region: Three-dimensional delineations based on magnetic resonance and diffusion tensor imaging. NeuroImage 108:441-449. doi: 10.1016/j.neuroimage.2014.12.080

4.1.2.5 Mouse Brain Atlas (Ma-Benveniste-Mirrione)

For the analysis of mouse brain data the **Mouse (Ma-Benveniste-Mirrione)** VOI atlas [1,2] is available. It represents the minimum deformation atlas of 10 C57BL/6J mice (male, 12-14 weeks, 25-30g). We would like to thank Helene Benveniste and Martine Mirrione for providing the data and helping with the integrations.



Spatial Normalization

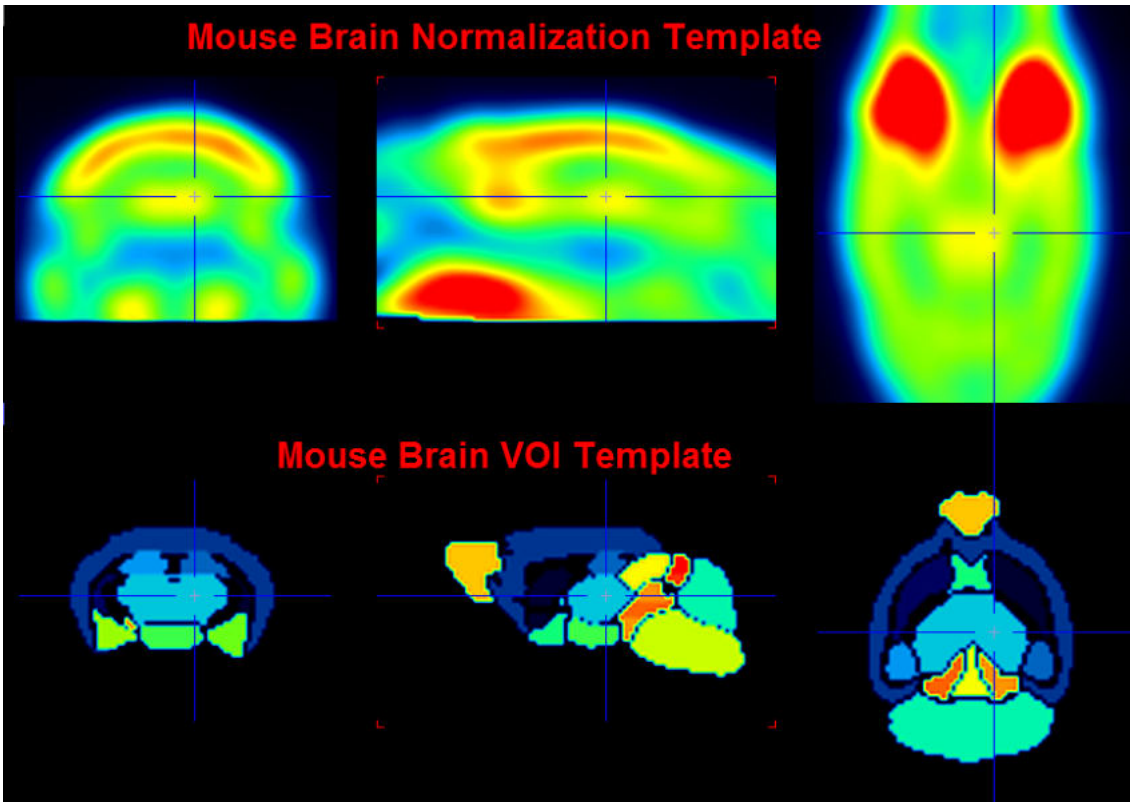
Two normalization templates are available in the fusion tool:

- **Mouse (Ma-Benveniste-Mirrione)-FDG**: This is an FDG baseline PET template as illustrated below.
- **Mouse (Ma-Benveniste-Mirrione)-T2**: This is a T_2-weighted MRI PET template which is in the same space as the PET templates.

The images of these templates can be found in the *resources/templates/voitemplates/Mouse (Ma-Benveniste-Mirrione)/normalization* directory.

VOI Atlas

The VOI atlas **Mouse (Ma-Benveniste-Mirrione)** can be selected in the list of included template VOIs. The corresponding files can be found in the *resources/templates/voitemplates/Mouse (Ma-Benveniste-Mirrione)* directory.



References

[1] Ma Y, Hof PR, Grant SC, Blackband SJ, Bennett R, Slatest L, McGuigan MD, Benveniste H. A three-dimensional digital atlas database of the adult C57BL/6J mouse brain by magnetic resonance microscopy. Neuroscience. 2005;135(4):1203-15. DOI

[2] Mirrione MM, Schiffer WK, Fowler JS, Alexoff DL, Dewey SL, Tsirka SE. A novel approach for imaging brain-behavior relationships in mice reveals unexpected metabolic patterns during seizures in the absence of tissue plasminogen activator. Neuroimage. 2007;38(1):34-42. DOI

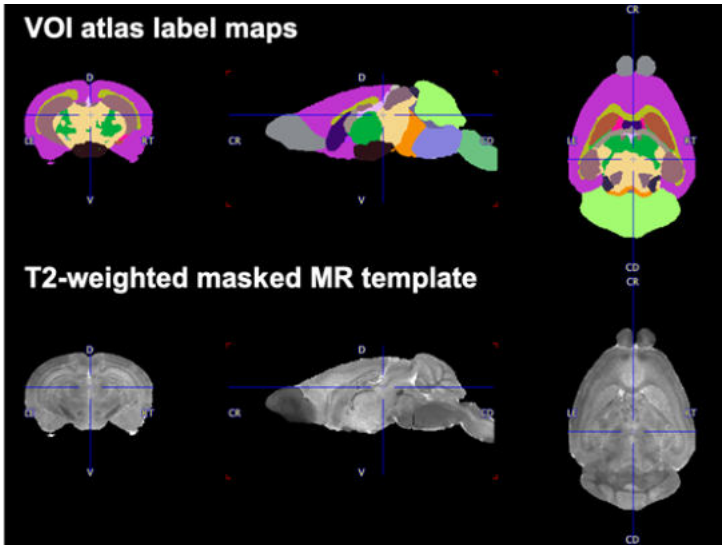
4.1.2.6 Mouse Brain (Waxholm-40um)

The **Mouse Brain (Waxholm-40um)** atlas represents the canonical Waxholm Space (WHS) adult C57BL/6J mouse brain. It is based on histology and high spatial resolution MR of adult male C57BL/6J mice aged 66-78 days [1]. The atlas resources are available at https://www.nitrc.org/projects/incfwhsmouse.

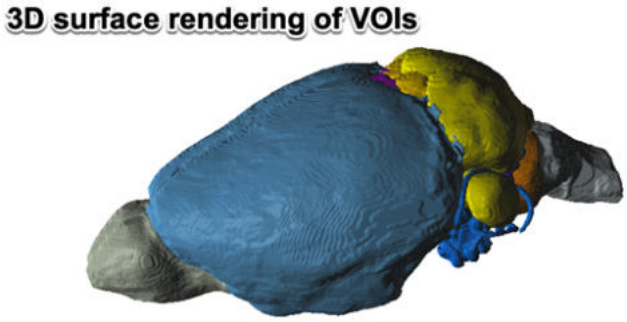
An adapted version of this atlas is distributed with PMOD as a convenience to our users. Because the original 21.5um isotropic resolution is beyond typical in vivo MR and far beyond the resolution applicable for PET image analysis, it was down-sampled to 40um. It provides a higher resolution space than the **Mouse (Ma-Benveniste-Mirrione)** atlas. PET templates corresponding to the mouse Waxholm space have been reported in the literature [2].

The **Mouse Brain (Waxholm-40um)** atlas contains 26 structures (+ inner ear) organized in accordance with the NeuroLex Brain Partonomy scheme. An ex-vivo masked T_2-weighted MR template image is provided for normalization.

Atlas Label Map and Normalization Template



3D Rendering of Brain Regions



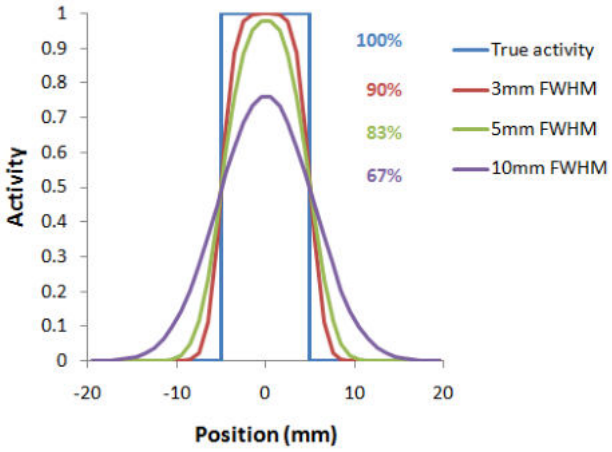
References

[1] G. Allan Johnson, Alexandra Badea, Jeffrey Brandenburg, Gary Cofer, Boma Fubara, Song Liu, Jonathan Nissanov. Neuroimage 53 (2) 365-372, 2010. PMCID: PMC2930145.

[2] Bertoglio D, Verhaeghe J, Miranda A, Kertesz I, Cybulska K, Korat Š, Wyffels L, Stroobants S, Mrzljak L, Dominguez C, Liu L, Skinbjerg M, Munoz-Sanjuan I, Staelens S. Validation and noninvasive kinetic modeling of [11C]UCB-J PET imaging in mice. J Cereb Blood Flow Metab. 2020 40(6):1351-1362. doi: 10.1177/0271678X19864081.

4.2 Partial-Volume Correction (PVC)

PET images are inherently affected by the partial-volume effect. This means that the measured tracer activity concentration is not accurate due to the relatively low image resolution and the limited tissue sampling. The low spatial resolution of the PET system causes a blurring of the image, so that high activities (from a hot lesion) are spread to the surrounding as illustrated below. This effect is called spill-out. The same effect also causes a spill-in of background activity into the volume of interest.



As a consequence, hot lesions tend to appear less aggressive (reduced maximum) but bigger (spreading) than they are in reality.

Spill-in and spill-out depend on the geometry of the objects, the activity distribution of the tracer, and on the resolution of the scanner which may vary across the imaging field-of-view. Therefore, practical correction approaches have to assume certain conditions and can only be approximate. For a nice overview of the topic please refer to the publication of Soret et al. [1].

Partial-volume correction in PNROD can be activated on the VOIs page[34].

NOTE: When **Parametric mapping** is enabled, only the **Region-based Voxel Wise** PVC method will be active.

4.2.1 Rousset VOI-based GTM Method

This correction is based on the assumption that the imaging volume can be separated into tissue volumes (VOIs) with homogeneous uptake. If the resolution of the PET scanner is known, the mutual signal contaminations across the VOIs can be calculated and corrected for. This method is known as the GTM (Geometric Transfer Matrix) method and was introduced by Rousset et al. [1].

The relation of the measured average PET values in the VOIs (affected by the partial-volume effect) to the true PET values is given by the matrix equation

$$\vec{C}_{measured} = [GTM] \times \vec{C}_{true}$$

with the following notations:

C_{true}	Vector of the true average activity concentration in the different VOIs of interest. The vector length n equals the number of object VOIs.
$C_{measured}$	Actually measured average activity concentration in the different VOIs. Each VOI is assumed to have a homogeneous concentration.
GTM	Geometric Transfer Matrix which describes the spill-over among all the VOIs. The matrix is square with nxn weighting elements $w_{i,j}$ which express the fraction of true activity spilled over from VOI_i into VOI_j. In practice, $w_{i,j}$ is calculated as follows: A binary map is created with 1 in all pixels of VOI_i and 0 elsewhere. The map is convolved with the imaging Point-Spread Function (PSF), and in the resulting spillover map the weighted average of all VOI_j pixels calculated.

The GTM equation above represents a system of linear equations. Once the weights have been calculated, the system can be solved for the true average concentration values C_{true} in all VOIs by matrix inversion.

Recommendations

According to Rousset et al. [2,3], the accuracy of the GTM method depends primarily on the proper identification of the tissues which have different functional properties. If this is the case, the GTM algorithm is capable of accurately correcting the regional concentration within small structures such as the human basal ganglia. Furthermore, the propagation of statistical noise during partial-volume correction was found to be easily predictable and suitable for the application in dynamic PET.

4.2.2 LMA Modified GTM Method

The LMA (Local Means Analysis) GTM method [4] uses the homogeneous regions localized by the segmentation and calculates the average uptake in the inner of the structures. The percentage of pixels per segment considered for averaging is a parameter of the method. With 100% pixels included, the LMA GTM method equals the standard GTM method.

4.2.3 Region-based Voxel Wise Method

The RBV correction introduced by Thomas et al [7] extends the GTM method and performs a voxel-wise correction of the entire image.

In a first step the standard GTM[73] correction is performed, resulting in a synthetic image C_{GTM}, which consist of the VOIs filled with the corrected average values.

In a second step a corrected image is calculated, which is not any more homogeneous within the VOIs, and which shows an image of the entire brain, not just the GM pixels. The calculation uses the formula

$$C_{PVC-RBV} = C_{Measured}\left[\frac{C_{GTM}}{C_{GTM} \otimes PSF}\right]$$

whereby the measured PET image $C_{Measured}$ is multiplied by a correction term calculated from the GTM corrected image and the point-spread function.

Note that the pixelwise correction may be problematic for dynamic data with low signal/noise ratio.

4.2.4 Fast VOIs-based GTM Method

This is actually the LMA modified GTM method which contains some speed-up improvement for the smoothing. The speed performance might be observe when the selected atlas contain a low number of regions.

4.3 System Requirements

For productively working with the parcellation tool, the following workstation system requirements should be met:

- 64-Bit operating system (Windows, Mac OS, Linux)
- ≥ 32 GB RAM
- ≥ 8 processing cores (hyper-threading is also viable)

16 GB RAM and 4 cores is at the edge of practicability.

4.4 References

1. Soret M, Bacharach SL, Buvat I. Partial-volume effect in PET tumor imaging. J Nucl Med. 2007;48(6):932-45.
2. Rousset OG, Ma Y, Evans AC. Correction for partial volume effects in PET: principle and validation. J Nucl Med. 1998;39(5):904-11.
3. Rousset OG, Collins DL, Rahmim A, Wong DF. Design and implementation of an automated partial volume correction in PET: application to dopamine receptor quantification in the normal human striatum. J Nucl Med. 2008;49(7):1097-106.
4. Maroy R, Viel T, Boisgard R, Comtat C, Trebossen R, Tavitian B. Fast and Accurate PET Preclinical Data Analysis: Segmentation and Partial Volume Effect Correction with no Anatomical priors. IEEE Nuclear Science Symposium; 2008:5498-5001.

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