

Registering ^{18}F FDG/PET Mouse and AMYViD/PET-CT Rat Studies to Brain VOI Atlases

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Preclinical NeuroPET is employed widely in studies of stroke, ischemia, addiction and neurodegenerative diseases. A wide range of tracers are used in NeuroPET studies. In both clinical and preclinical imaging, ^{18}F FDG is frequently used as a biomarker of brain function in models of neurological disorders (Balsara et al., 2014, Sobrado et al., 2011, Pozo et al., 2008). Targeted tracers such as the recently FDA approved Florbetapir F18 (AMYViD) amyloid tracer provide specific activity (Bonet-Costa et al., 2015). Additionally, using both post synaptic and pre synaptic specific tracers, researchers can make *in vivo* measurements of neurotransmitter function.

To facilitate the analysis of preclinical NeuroPET data, several rat and mouse brain VOI (volume-of-interest) atlases have been developed and are available for use today. A brain atlas consists of a set of VOIs (outlining brain regions) and requires a template brain image for processing. The template mouse or rat brain may be based on an image derived from a single mouse or rat image or an average of multiple mouse or rat brain images. The approach for applying an atlas to study data can vary depending on the tracer and the accompanying anatomical modality employed, but typically requires a spatial registration of study data to a template image. Here we will

provide an overview of the procedures for applying a brain VOI atlas using images acquired on Bruker preclinical PET imaging systems and analyzed using the PMOD analysis software.

^{18}F FDG/PET, Without Anatomical Image

Because PET images alone do not supply anatomical information necessary for alignment to a template brain image, a matching CT or MR study image is usually used as an intermediary to align data. However, Harderian glands provide a distinct spatial anatomical landmark in ^{18}F FDG/PET images suitable for registration. (Harderian glands are metabolically active glands present in the orbit of certain animals including mice and rats). ^{18}F FDG/PET study data can be aligned to an ^{18}F FDG/PET template brain image by registering these landmarks without the need for an intermediary anatomical study image (Balsara et al., 2014). The steps for processing ^{18}F FDG/PET study data are shown below using a typical dataset acquired with the Bruker Albira Si PET system and analyzed using the Mouse M. Mirrone atlas (Ma et al., 2005) included in with the PMOD analysis software (V 3.9, PMOD Technologies LLC, Zurich Switzerland).

¹⁸FDG/PET Sample Preparations and Acquisitions

Several aspects of animal preparation and handling (e.g. fasting, warming) will affect the uptake of ¹⁸FDG in the brain. Fueger et al. (2006) evaluated the uptake of ¹⁸FDG in different tissues under various physiological conditions and reported that mice that were fasting, warmed and conscious during ¹⁸FDG injection had the highest brain uptake. More recently, Van der Veen et al. (2008) reported that mice had a significantly higher ¹⁸FDG uptake in the brain during the evening, consistent with the nocturnal nature of mice. For PET studies, mice and rats commonly receive 100-200 µCi ¹⁸FDG with a 30-90 minute uptake. Acquisition times can range from 5-15 minutes for static acquisitions. To achieve peak sensitivity for brain studies, the animal head should be positioned within the center field of view during imaging.

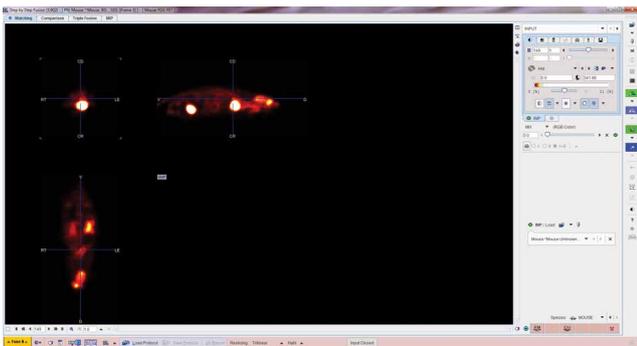
Step 1: Load Study Data

Launch the PMOD PFUSEIT software module.

Set the Species to MOUSE (Arrow 1).

Set the processing stage menu to INPUT (Arrow 2), and open the ¹⁸FDG/PET image to be analyzed. Bruker PET detectors acquire with an extended axial FOV that may cover the entire length of the animal anatomy.

Figure 1



Step 2: Load the Template Image

Next, change the processing stage menu from INPUT to REFERENCE.

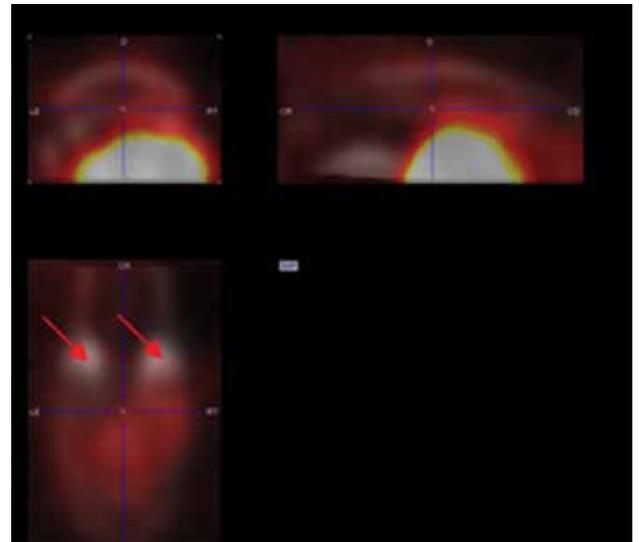
Then, load the Mouse (M. Mirrone) – FDG template.

Figure 2



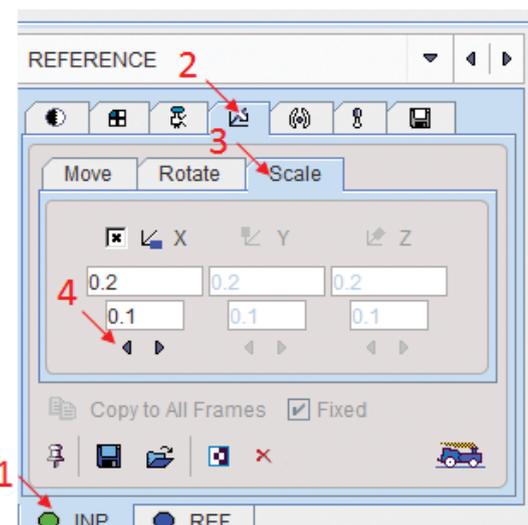
The Mouse - FDG Template (gray) and Study image (fire) will be displayed, but not spatially aligned. The Mouse – FDG Template image is cropped to the mouse brain only. Note the location of Harderian glands clearly visible in the Mouse – FDG Template image. (Shown with arrows on the image below).

Figure 3



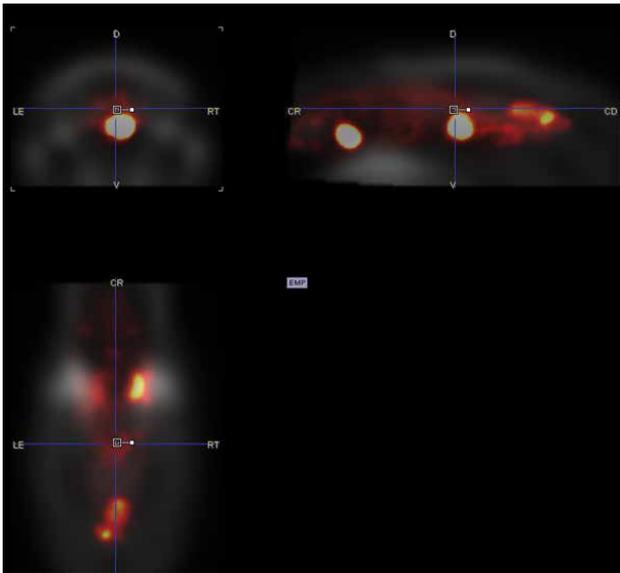
Select the Green INP tab (Arrow 1). Select, the Reslicing (Arrow 2) and Scale tab (Arrow 3). Adjust the image Scale (Arrow 4) to 0.2 to bring the whole image into view.

Figure 4



Note the location of the Harderian glands in the Study image (Shown with arrows on the image).

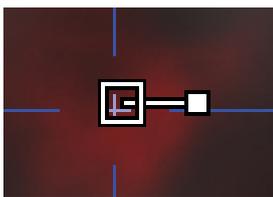
Figure 5



Step 3: Register the Study Data to the Template Data

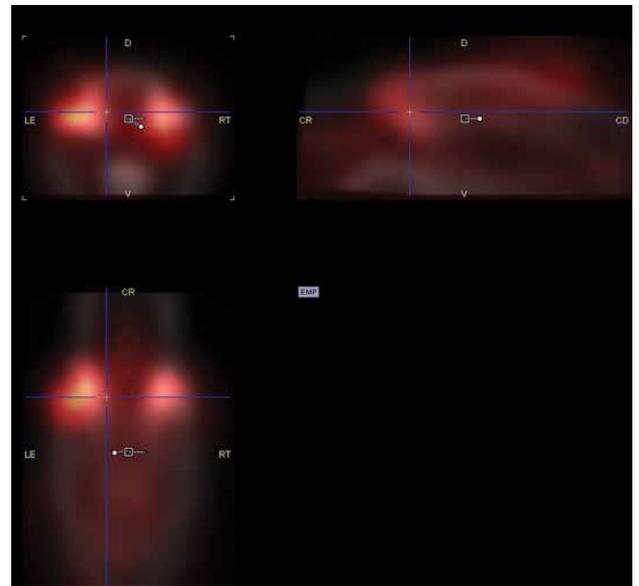
Use the control in the center of each orthogonal view to drag (grab control by the large square) and rotate (grab the control by the small square) the Study image to approximate the orientation of the Mouse FDG - Template image.

Figure 6



Finally, set the Study PET image Scale back to 1. Further adjust the image to align the Harderian glands of the Study PET image with the Harderian glands of the Mouse FDG – Template image. The body region of the mouse image will now be outside the available view.

Figure 7



Automated matching algorithms may be used that can improve the alignment.

Figure 8

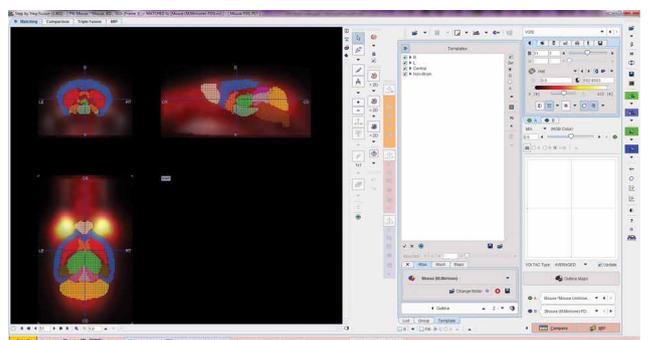


Step 4: Apply the VOI Atlas

The PET Study image should now be spatially aligned with the VOI Atlas. Change the processing stage menu setting from REFERENCE to VOIS (Arrow 1). Select the Template tab (Arrow 2) and then Atlas tab (Arrow 3). Be sure that the Green "A" tab (Arrow 4) is selected, and the PET Study image (Arrow 5) is selected at the Green "A" (select VOI study) menu.

VOI readouts and SUV calculations can be made as usual.

Figure 9



Any Tracer, Multimodal PET with Registered CT or MR Image

Because PET imaging provides little anatomical information, a two-step process is commonly used to align study data to atlas template data. Here, the anatomical Study image (CT or MR) is first spatially aligned to a MR template. The spatial transformation can then be automatically applied to the PET Study data. For this processing to be accurate it is critical that the PET/CT or PET/MR study data is already precisely aligned. Bruker's integrated PET/CT and PET/MR systems produce functional-structural datasets with precise anatomical registration appropriate for these protocols.

Figure 10



The steps for processing are shown below using an AMYViD-PET/CT rat brain dataset acquired using the Bruker Albria Si PET system and analyzed using Rat Schiffer atlas (Schiffer et al., 2006) available with the PMOD analysis software (V3.9, PMOD Technologies LLC, Zurich Switzerland).

Sample Preparation and Acquisition

A representative animal from a recent study is used here to demonstrate the process for applying a rat brain atlas. In this study, TgF344-AD transgenic rats were imaged using an FDA approved compound Florbetapir F18 (AMYViD), that binds with A β plaques. 400-500 μ Ci of tracer compound, dissolved in 300-500 μ l normal saline (0.9% NaCl), was administered through single (tail vein) bolus injection, 45-60 minutes before imaging. The Bruker Albria Si PET/SPECT/CT, located at University of Virginia Molecular Imaging Core, was used (funded by NIH grant 1S10OD021672, SS Berr). Imaging was performed while animals were anesthetized and placed in the prone position at center of the scanner bed. PET acquisition times were between 5-15 minutes. Followed by PET scanning, a computer tomography (CT) of the whole brain was performed. The system provides automated PET-CT data registration on image reconstruction.

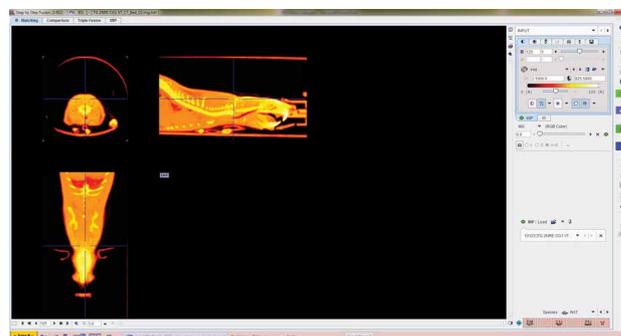
Step 1: Load Anatomical (CT or MR) Study Image

Launch the PMOD PFUSEIT software module.

Set the Species to RAT (Arrow 1).

Set the processing stage menu to INPUT (Arrow 2), and open the CT Study image.

Figure 11

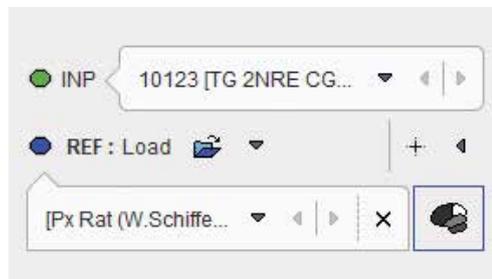


Step 2: Load the Template Image

Next, change the processing stage menu from INPUT to REFERENCE.

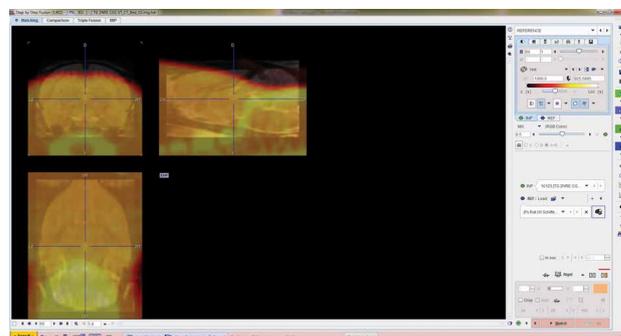
Then, load the PX Rat (W. Schiffer) – T2 template.

Figure 12

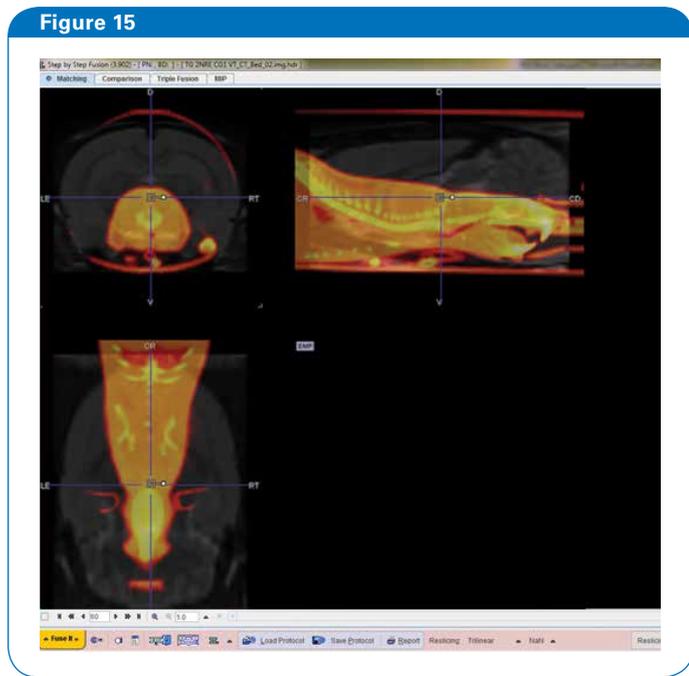
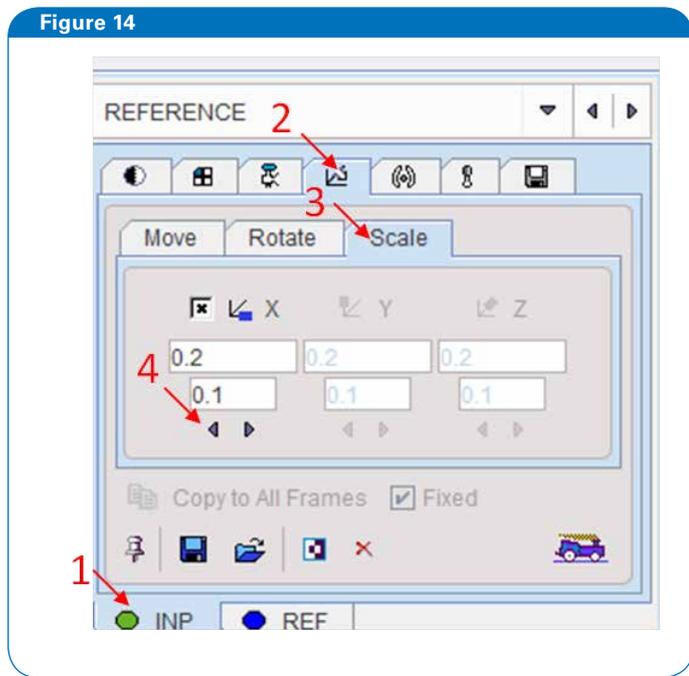


The Rat – PX Schiffer Template (gray) and Study image (fire) will be displayed, but not spatially aligned. The Rat – PX Rat Template image is cropped to the rat brain only.

Figure 13

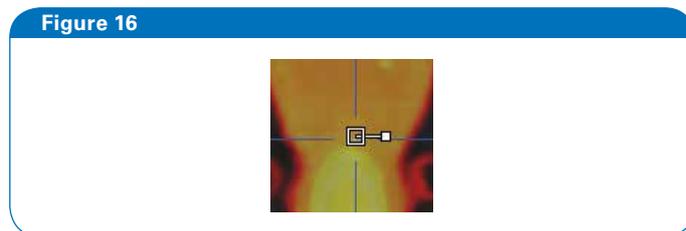


Select the Green INP tab (Arrow 1). Select, the Reslicing (Arrow 2) and Scale tab (Arrow 3). Adjust the image Scale (Arrow 4) to 0.2 to bring the whole image into view.

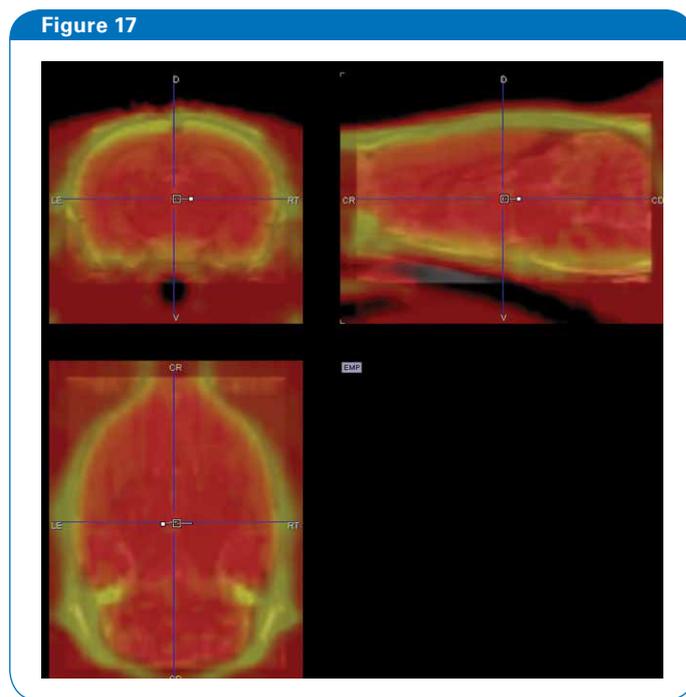


Step 3: Register the Anatomical Study (CT or MR) Data to the Template MR Data

Use the control in the center of each orthogonal view to drag (grab control by large square) and rotate (grab the control by the small square) the Study image to approximate the orientation of the Rat – PX Schiffer Template image.



Finally, set the CT Study image Scale back to 1. Further adjust the image to align the margins Rat – PX Schiffer Template image. The body region of the Rat image will now be outside the available view.



Automated matching algorithms may be used that can improve the alignment, however carefully inspect the margins of the alignment before proceeding.

Finally, save a transformation file for subsequent recall.

Figure 18



Step 4: Apply the Transformation and VOI Atlas to the PET Study Image

Close the existing studies. Set the processing stage menu to INPUT and open the PET Study image.

Next, change the processing stage menu from INPUT to REFERENCE.

Then, load the PX Rat (W. Schiffer) – T2 template.

Finally, load the transformation file generated in the previous step.

Figure 19



The PET Study image should now be spatially aligned with the VOI atlas. Change the processing stage menu setting from REFERENCE to VOIS (Arrow 1). Select the Template tab (Arrow 2) and then Atlas tab (Arrow 3). Finally, select the Rx Rat (W. Schiffer) Atlas. Be sure that the Green "A" tab is selected, and the PET Study image is selected at the Green "A" (select VOI study) menu.

Figure 20

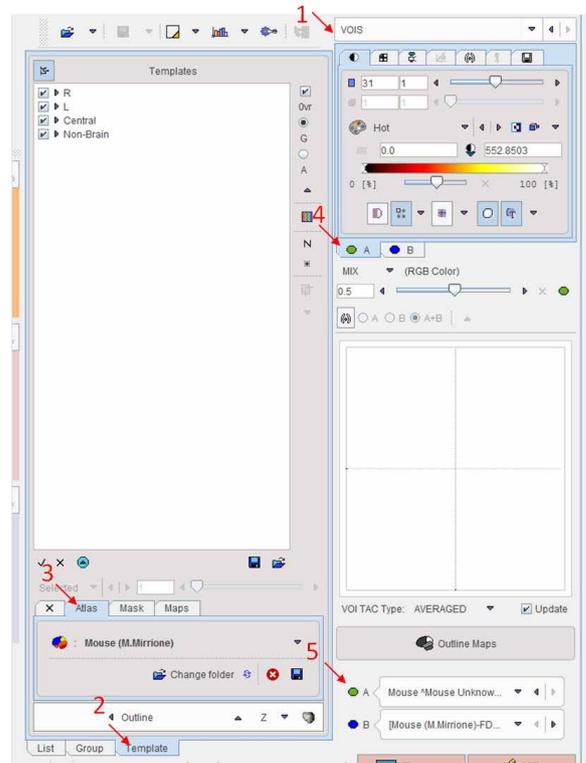
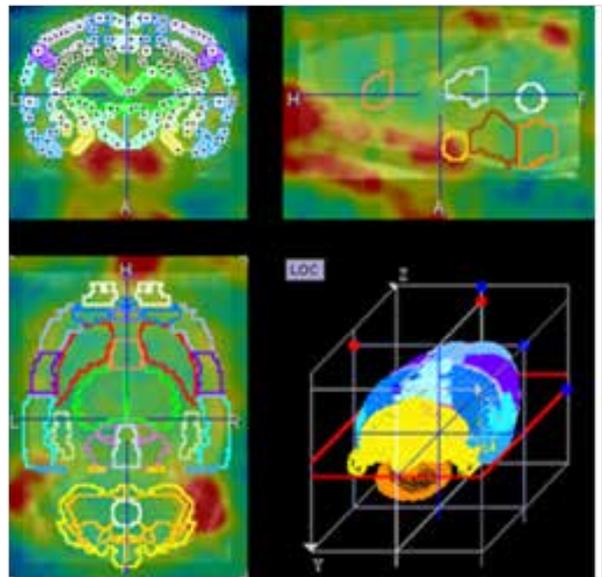
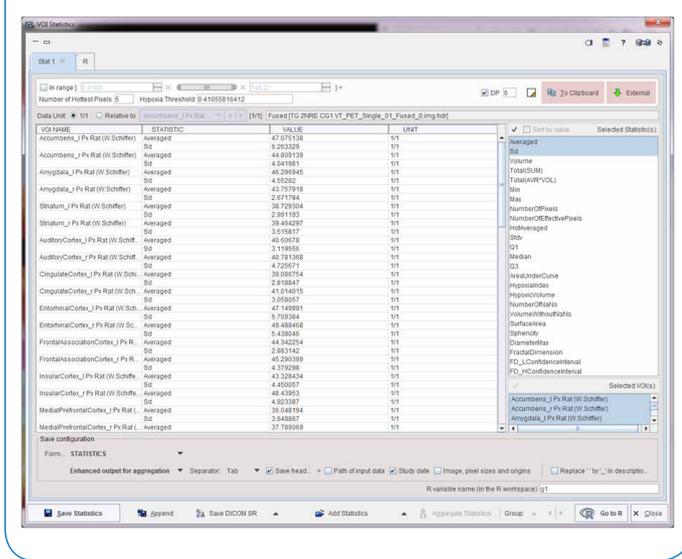


Figure 21



VOI readouts and SUV calculations can be made as usual.

Figure 22



References

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