User manual for Partial Volume Correction Toolbox

1. Introduction

PET is an imaging technique that allows observation of specific biological processes in vivo. These processes effectively occur at a molecular level as is underlined with a very simplified example of FDG-PET. The tracer, FDG, has a chemical composition that is similar to glucose but has been radiolabelled with the positron emitting isotope fluorine-18 (18F). Glucose is the main substrate for supplying energy in the brain. Like glucose, FDG is carried into tissues via the blood stream following intravenous bolus injection and undergoes phosphorylation, but no significant further metabolism. It therefore accumulates in brain tissues in proportion to the local cerebral metabolic rate of glucose (lCMRglc) over the first 10–20 min post-injection and approximates lCMRglc over the next 40 min. Hence, FDG PET images acquired 20 to 90 min post injection represent lCMRglc in the brain. LCMRglc provides energy that sustains ion gradients and is also used in the synthesis of neurotransmitters. It also plays an essential role in the synthesis of glutamate and its recycling through the neuroglia. LCMRglc hence reflects neuronal activity, more specifically synaptic activity.

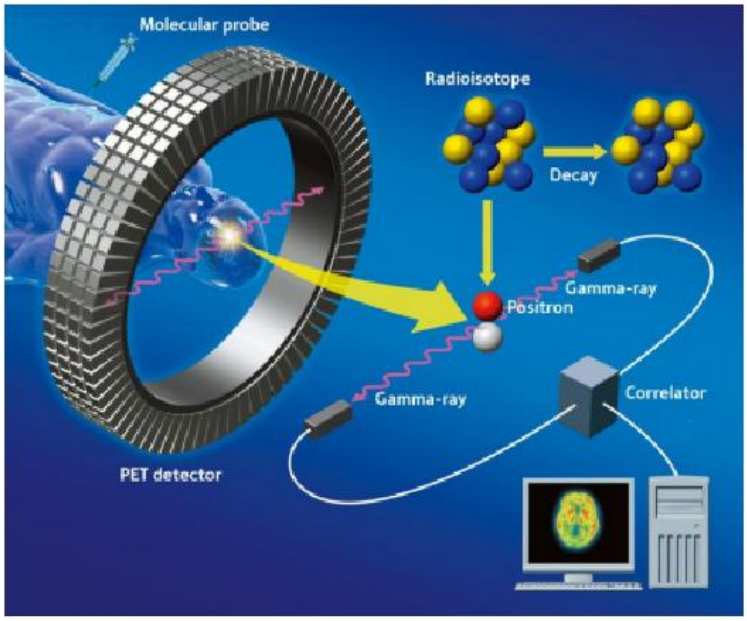


Figure 1. Schematics of a brain PET scan procedure

The radio-labelled 18F serves to facilitate the measurement of the distribution of the FDG from the PET scanner. Like all positron emitting isotopes, 18F has a nuclear mass that is smaller than the stable isotope of fluorine and decays via emission of a positron. This positron then travels in tissue for a short distance (1–2 mm) from the decaying nucleus before hitting an electron. The resulting annihilation produces a

pair of photons (gamma-rays, each 511 keV) travelling in opposite directions. The PET scanner contains scintillation detectors that detect these photon pairs also referred to as events, which are stored in a computer system. The line of response is 2 the line that connects the 2 points of photon detection and it is known that the event originated along or close to that line. With the appropriate reconstruction method, the events (several millions in a typical PET scan) are reconstructed to provide local activity concentration within the field of view (FOV) of the PET scanner (Figure 1).

PET has high sensitivity (i.e., it takes a small concentration of imaging agent to detect quantities above background level and is in 10-10 mol/l in this case), good depth of penetration (through the whole body) and reasonable temporal resolution (5–10 s per update). However, from a structural point of view, PET's spatial resolution lags behind that of structural imaging modalities like MRI. The High Resolution Research Tomograph, a dedicated brain-PET scanner, offered the highest possible spatial resolution in PET at the time of its introduction with an isotropic resolution of 2.5 mm at full-width-half-maximum (FWHM). Conventional clinical and research scanners have a spatial resolution that varies between 4 and 10 mm according to how old they are. The limited resolution of PET scanners gives rise to what is termed Partial Volume Effects (PVEs) whereby the images look blurred due to a loss of signal to the surroundings. Partial volume effect leads to signal dilution especially in small regions, and results in overestimating and underestimating activity concentration in the adjacent regions. Figure 2 is a mathematical phantom and simulated PET image, demonstrating the impact of partial volume effect in terms of signal dilution. In the observed PET image, there is activity from gray and white matter spilling into the ventricles leading to quantitative overestimation while it should be zero based on our true image. On the other hand, in a hot region like caudate nucleus signal loss is obvious (spill out form grey matter to white matter and ventricle), and it leads to underestimating tracer uptake in this region.

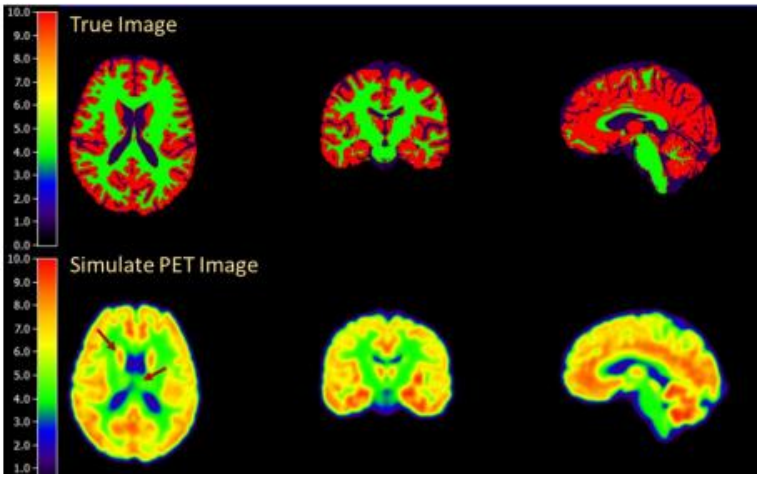


Figure 2. Mathematical brain phantom (first row) and simulated PET image (second row) in transverse, axial, and

So to avoid bias in activity estimation and consequently misinterpretation of PET data, it is necessary to apply partial volume correction method to minimize the error and improve the accuracy of quantification. Partial Volume Correction (PVC) is the method used to correct for the signal loss due to PVEs and emerged in the late 1970s and early 1980s. PVC methods can be 1) phantom-based, where a recovery coefficient is calculated and applied to VOIs whose sizes are estimated to be comparable to that of the phantoms; 2) reconstruction-based, where the PSF of the scanner is modelled within the reconstruction of the PET image; and 3) post reconstruction methods: where the algorithms require accurate delineation of the VOI using higher resolution anatomical images like MRI or CT. The most popular PVC methods are post reconstruction ones and are widely used in clinical studies. They can be voxel-based, like the Lucy-Richardson; regionbased or a combination of both. PVC is particularly important in the study of neuropsychiatric diseases when researchers aim at understanding how the functional activity of a region varies with volumetric changes. For example, in a dementia context, with progressing atrophy, the objective is to determine the true loss of metabolism in FDG PET studies within VOIs that would represent loss in tissue function as opposed to an artefactual decrease of the PET signal due to PVEs. The impact of PVEs and its correction has been widely reported in literature, especially in conditions where the pathology is accompanied by shrinkage within the brain [1].

2. Partial Volume Correction Toolbox

Due to the importance of partial volume correction for quantifying and analyzing PET images, a toolbox for PVC designed. This toolbox implements four different post reconstruction based partial volume correction methods.

1. Muller Gartner
2. Rousset
3. Lucy Richardson
4. Partially Segmented Lucy Richardson

This toolbox also is able to perform quantitative scaling as well as regional quantification. All these options will be detailed in the next section.

The main advantage of this toolbox is the ability to perform PVC for a group of PET data, no matter how many subjects you have in each group. It means that in contrast with software like PMOD, user won't need to pass the data one by one for each subject. All that is needed for implementing this toolbox is just arranging data properly and passing required inputs.

***Note: All the preprocessing including segmentation, normalization, coregistration and reslicing are done using SPM12.

2.1 Arranging Data

To implement the toolbox user needs to arrange data in the defined way for this toolbox. Suppose that there is a group of alcoholic subjects (4 subjects) scanned by PET scanner in Cyceron. Following steps should be taken to arrange data:

1. Create a folder, for example “AlcoolGroup”.

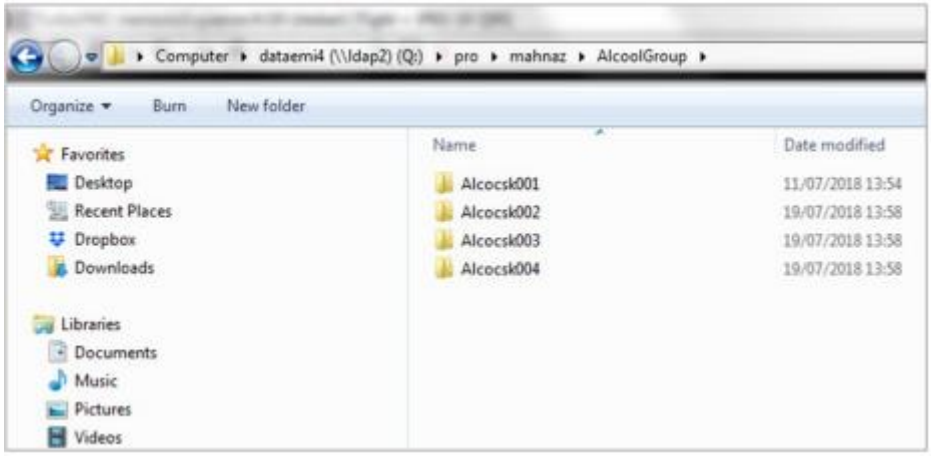


Figure 3. Creating directory and arranging data for using Pipeline

2. Subfolder for each subjects, and add PET and MRI of each subject in the corresponding subfolder.
3. If segmentation is already done for any of the subject, you can add segmented files including C1(GM), C2(WM), C3(CSF), y(Deformation field), and iy (Inverse Deformation field) as well to subfolder of that subject and reduce elapsed time for partial volume correction of that subject (Segmenting of MRI image takes about 10 minutes for each subject). Otherwise it will automatically do the segmentation for each subject.

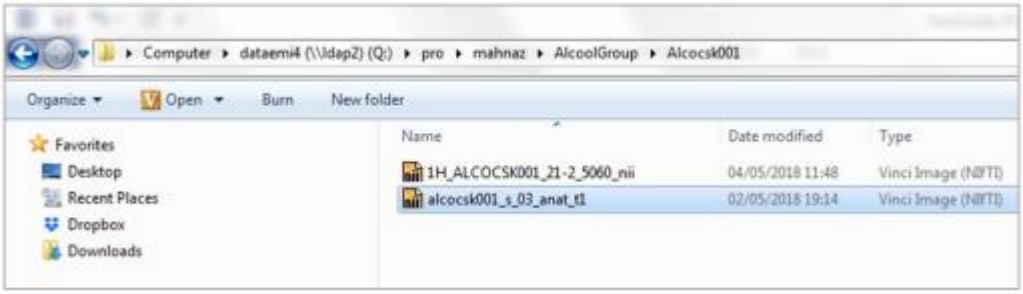


Figure 4. Subfolder of a subject including anatomical and functional images

2.2 Installation and main structure

First, it is necessary to download the file named Partial Volume Correction Toolbox.mlappinstall from the repository.

Open MATLAB. At the top of the screen, locate the APPS button. Click on the button, and then select Install App:

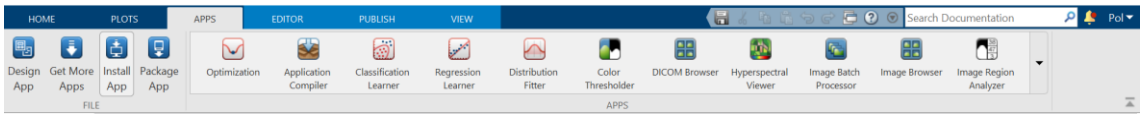


Figure 5. Install App

Once the button is selected, choose the corresponding toolbox installer file from your PC, which was previously downloaded. The following prompt will appear:

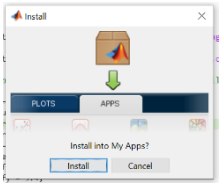


Figure 6. Installation prompt

Select 'Install', and the toolbox will be available in MATLAB.

To use it, click on the corresponding application logo:

Figure 7. Partial Volume Correction Toolbox LOGO

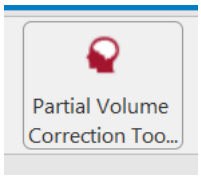
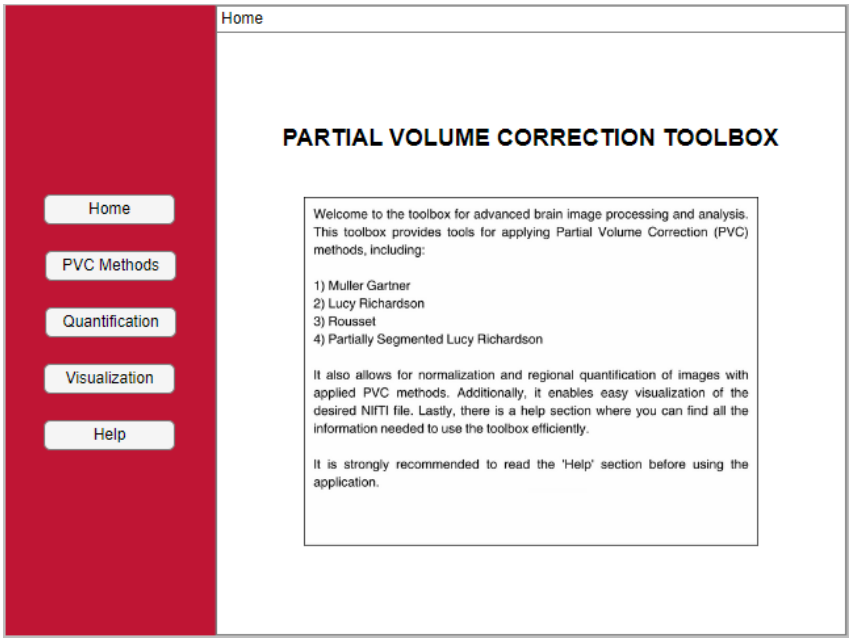
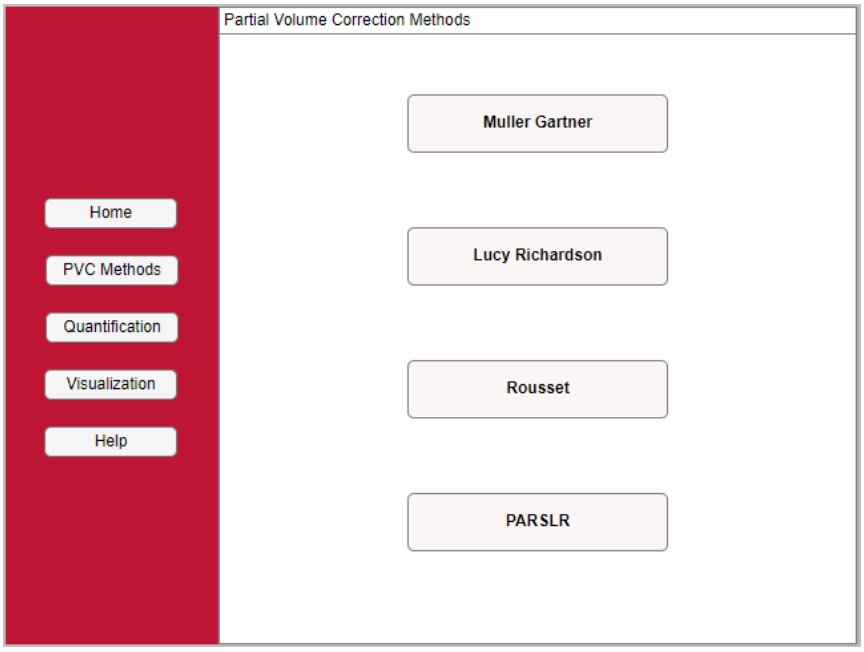


Figure 8. Toolbox installed

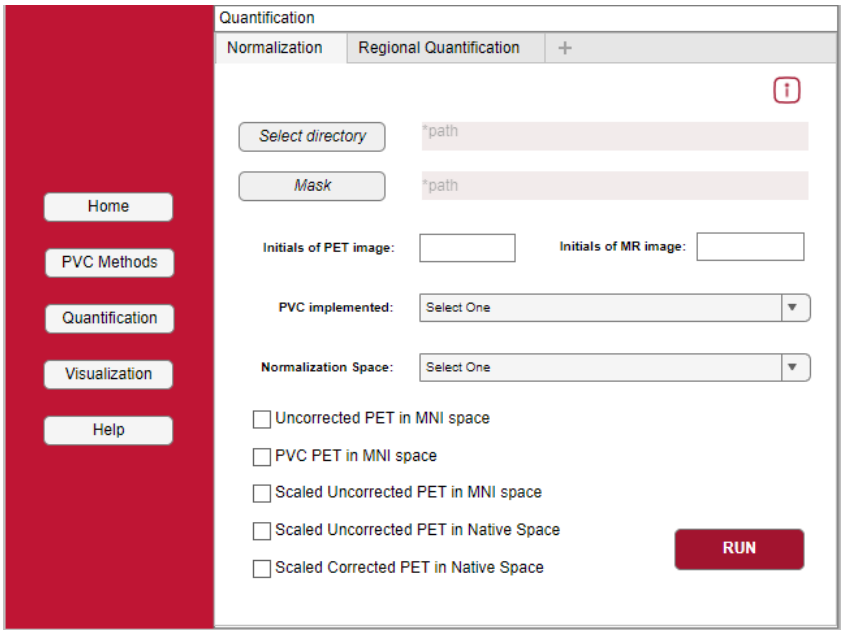
So for using the toolbox, you need just click on Partial Volume Correction Toolbox icon in Apps bar, and following window will appear:



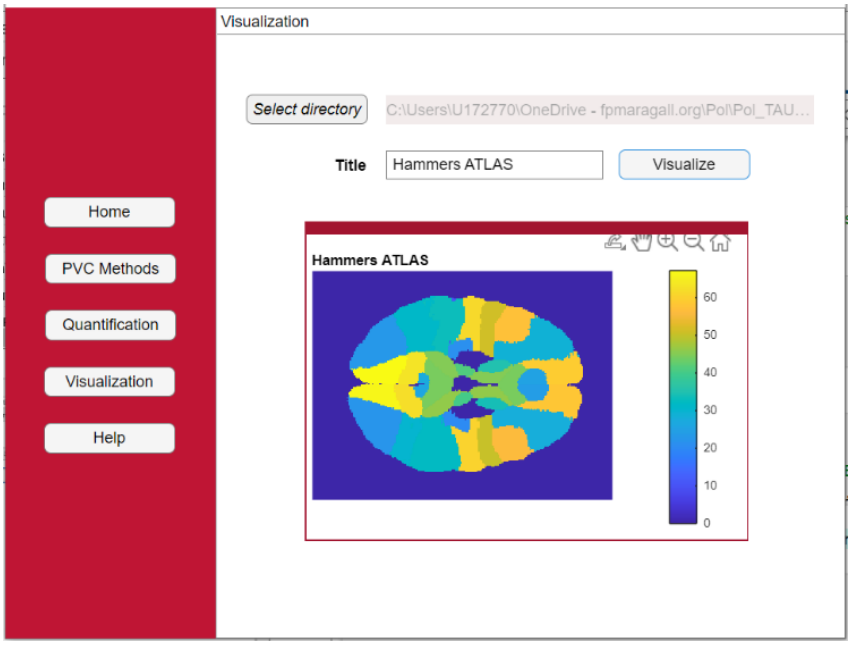
The toolbox is structured in 5 different screens. When we open the application, ‘Home’ opens. To see the PVC methods and apply them, select the 'PVC Methods' button:



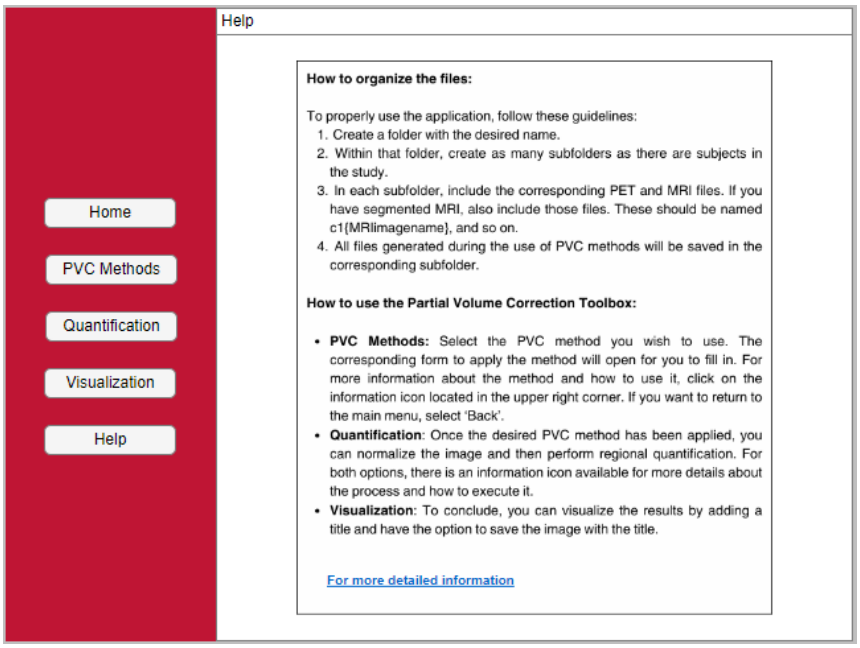
By clicking the button ‘Quantification’:



By clicking the 'Visualization button:



And finally, a Help section:



Below the document you will find the necessary information for each toolbox functionality.

2.3 Muller Gartner

Muller Gartner partial volume correction method is the default PVC method used in U1077, and it is the same method used in PMOD platform as "PVCorrection1".

This method is based on considering brain as three regions including grey matter, white matter, and CSF. To extract each region, using SPM12 segment function, 3 tissue probability maps for grey matter, and white matter will be created from a high resolution T1-wighted MRI. In the next step, a binary mask will be created by apply a threshold to grey matter and white matter tissue probability maps. Then high resolution binary mask will be move to PET space (Figure 7).

Figure 9. Preprocessing MRI image for implementing Muller Gartner method

Finally compensating spill out and spill in for GM and WM segments will be done by applying following equation:

Equation 1

$$Corrected_{PET} = \frac{Uncorrected_{PET} - (WM_{Uptake} \times rWM) \otimes PSF}{rGM \otimes PSF}$$

Where PSF is point spread function of the scanner, rWM and rGM are binary masks in the PET space, and also $\otimes$ refers to convolution operator. WMuptake refers to average activity in the regions with pure white matter, and is estimated by averaging activity in regions are pure white matter and are not affected by grey matter spill over and signal contamination.

How to use Muller Gartner PVC

After arranging data in a way explained in the part "3.Arranging Data" and clicking on the Muller Gartner (Figure 8) following steps should be taken:

1. Click on "Select Directory" to choose the folder, containing your arranged data. For example, here "Alcool Group" is chosen as the main directory of subjects.
2. To determine the PET and MRI file within the pipeline, it is mandatory to write at least 3 initials of the PET and MRI name, which are defined based on protocol here. For example, as for AlcoolGroup patients, all PET data start with "1H_" and all MRI data start with "alco", these initials passed to the specified fields for PET and MR initials.
3. Type scanner resolution for x, y, and z direction respectively. If the PET images acquired on the Cyceron PET scanner, 3.76, 3.76, 4.9 mm3 should be

allocated to x (mm), y (mm), and z (mm) respectively, otherwise scanner point spread function in x, y, and z axis should be considered. PSF of each scanner can be find in the white papers provided by manufacturers.

4. “Binarizing Threshold” is used for creating binary mask and should be between 0 and 1. For example if you choose a threshold of 0.1, all the voxels in grey matter (c1) which are greater than 0.1 will be allocated to grey matter, substituted by 1, and the rest will be 0.
5. “Regression Threshold”, used for estimating white matter uptake, should be a value between 0.9 and 0.99.

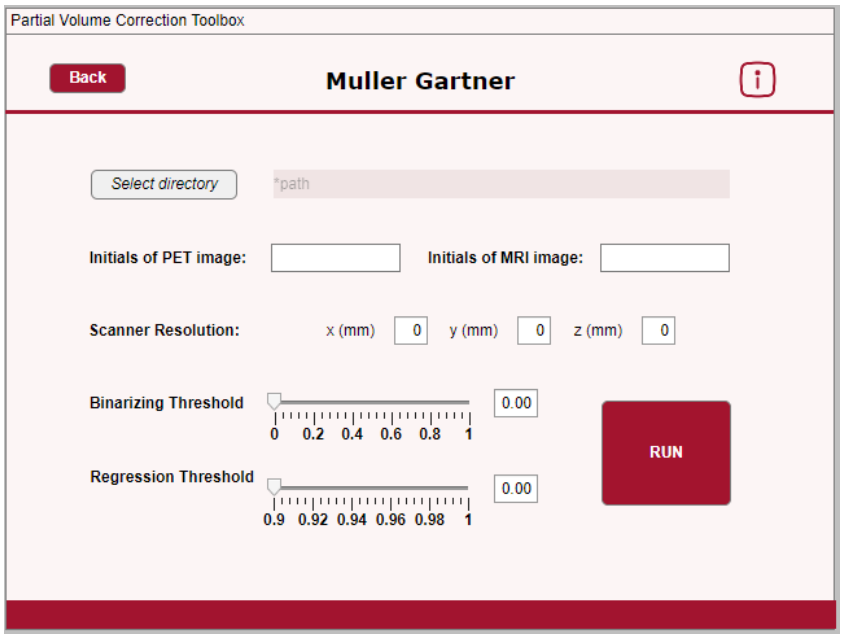


Figure 10. Passed inputs for Muller Gartner PVC

6. Now, click on RUN for initiating Muller Gartner PVC.
7. After finishing partial volume correction, there will be a text file in the main directory, named as “MPVCParameters.txt”, containing name of the directory and all the parameters you applied for partial volume correction.

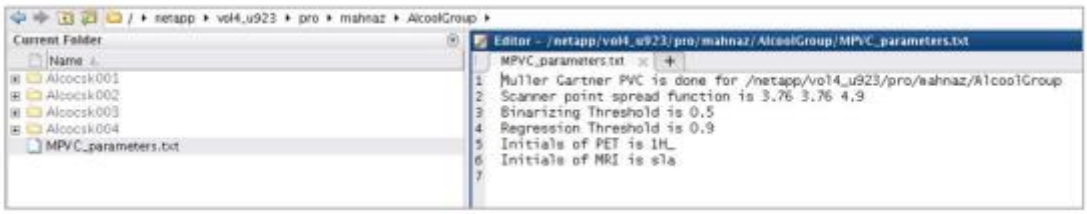


Figure 11. Text file saved in the main directory, showing parameters applied by user

8. After finishing Muller Gartner PVC, each subfolder contains files shown in Figure 10.

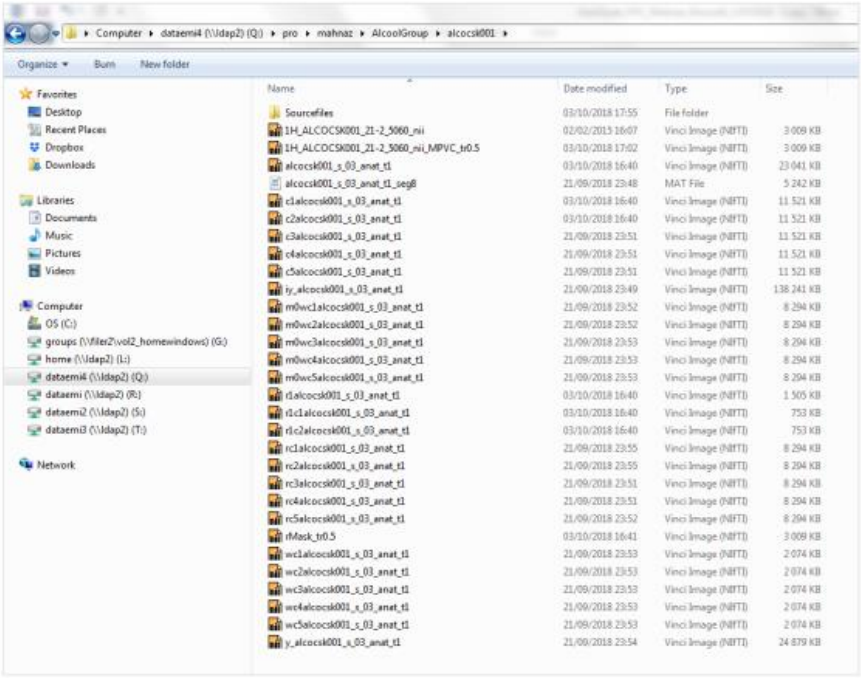


Figure 12. Files created for each subject by Muller Gartner method

- Source files: this subfolder contains primary files of PET and MR images.

- Segmented MRI files: Segmentation parameters are defined in a way to create c1, c2, c3, c4, c5, y, and iy. It also creates the normalized and resliced tissue probability maps (wc1, wc2, wc3, wc4, wc5, rc1, rc2, rc3, rc4, rc5).

- r1c1 and r1c2 respectively are representing resliced grey matter and white matter with the same dimension of the PET image.

- PV corrected PET image with a suffix of "_MPVC_tr0.1"

- File named as "rMask_tr0.1" is the brain binary mask of the subject, defined based on binarizing threshold and it has the same dimensions as the PET image. The figure 0.1 in the mask name refers to the value user applied for creating binary mask.

9. Figure 11 displays uncorrected and corrected PET images by Muller Gartner method for visual comparison, and also brain mask used for PVC for the subject.

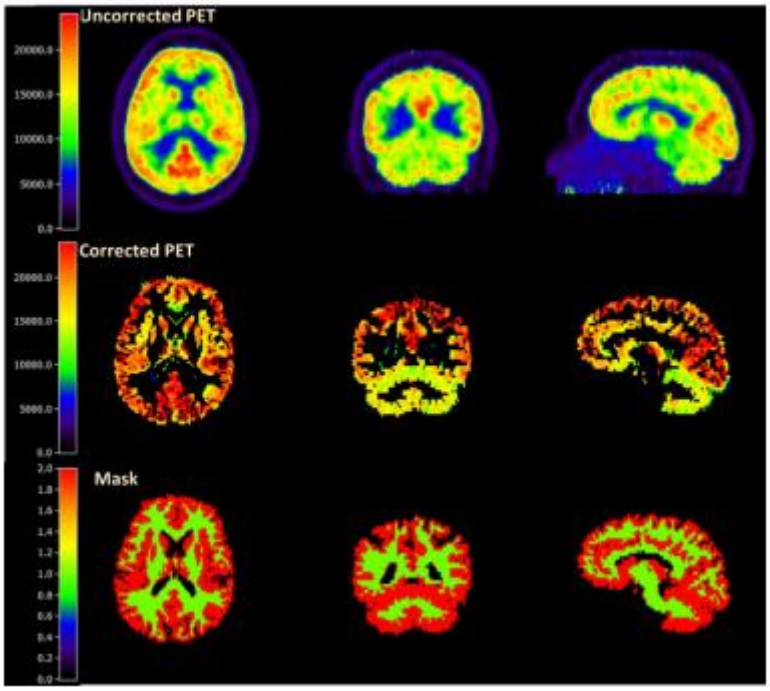


Figure 13. PET images in transverse, coronal and sagittal view. First row shows uncorrected PET image, second row is PVC image by Muller Gartner method, and third row is binary mask of grey matter and white matter for the subject

2.4 Rousset

Rousset method uses the high resolution MR images to extract brain's segments for PVC. This method performs regional partial volume correction by modeling the interaction between PET scanner and each region.

As PET imaging system considered as linear system, resulted PET image can be modeled as the weighted integration of the activity distribution f(r) present in the field of view (FOV), by the response function of the PET system in terms of its PSF h(r):

Equation 2

$$g(r) = \int_{FOV} f(r')h(r,r')dr'$$

Where r, r' are three dimensional vectors in object and image space respectively. Assuming that object consists of N different tissues with uniform uptake (Ti), image can be considered as below:

Equation 3

$$g(r) = \sum_{i=1}^{N} T_i \int_{D_i} h(r,r')dr'$$

As T_i is a constant value for each region, integration of system's point spread function h(r) over each region D_i, called as regional spread function (RSF_i), should be calculated.

RSF for each region is calculated by smoothing the corresponding mask of region i with scanner PSF, and then contribution of region i on the other regions will be calculated for correcting spill over. Mathematically, it can be written as:

Equation 4

$$RSF_i(r) = \int_{D_i} h(r, r')dr'$$

Equation 5

$$t_j = \frac{1}{n_{pix_j}} \sum_{i=1}^{N} T_i \int_{ROI_j} RSF_i(r)dr$$

Where t_j is the average activity in region j (ROI_j) resulted from RSF_i. In other word, above equation calculates the activity spill out form region i to other regions as well as computing preserved activity in region i. It means that if image were segmented to N regions, there are N weighting factors for each region, as below:

Equation 6

$$w_{ij} = \frac{1}{n_{pix_j}} \int_{ROI_j} RSF_i(r)dr$$

By accounting weighting factor in each region, average activity can be calculate as:

Equation 7

$$\begin{bmatrix} t_1 \\ t_2 \\ . \\ . \\ . \\ t_N \end{bmatrix} = \begin{bmatrix} w_{11} & \cdots & w_{1N} \\ \vdots & \ddots & \vdots \\ w_{N1} & \cdots & w_{NN} \end{bmatrix} \begin{bmatrix} T_1 \\ T_2 \\ . \\ . \\ . \\ T_N \end{bmatrix}$$

Considering both weighting matrix and average value for each region (tj) are known, corrected regional activity (Ti) can be computed by solving above linear equation.

How to use Rousset PVC

Rousset method, as mentioned in previous section, is a regional based method and corrects PET activity within each predefined region.

In the proposed function for Rousset PVC, all regions would be extracted based on the predefined regions in the atlas chosen by user. Also, it is capable of considering white matter as a homogeneous region, which has a uniform uptake, or heterogeneous regions whit different uptake for each region. It means that for the subjects that part of white matter is damaged or there is the possibility of malfunctioning, user can take advantage of choosing "Heterogeneous 11 white

matter" to minimize the bias in corrected activity. Figure 12 displays the process of extracting regions from GM, WM, and CSF segments based on an atlas chosen by user.

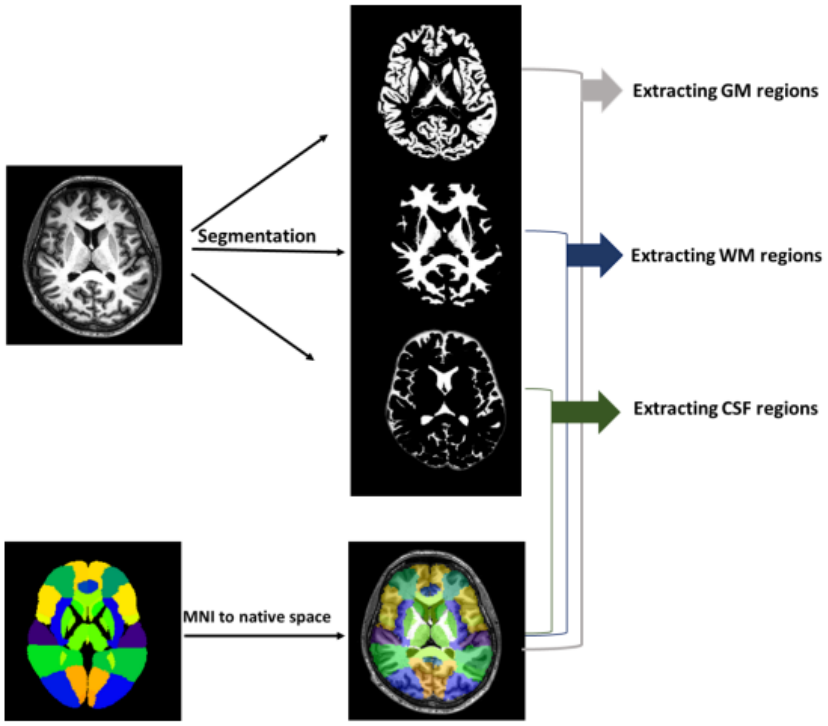


Figure 14. Schematic of extracting brain regions according to MR image segmentation and Hammer atlas regions

After arranging data in a way explained in the part "3.Arranging Data" and choosing "Rousset" following steps should be taken for passing inputs (Figure 13):

1. Click on "Select Directory" to choose the folder, containing your subjects.
2. By clicking on "Atlas", user can choose the brain atlas that wants to be used for extracting each regions.
   If not, user can check the box 'Own Subject Specific Mask' and write at least 3 initials of the mask in the 'Initials of Subject Specific mask'. This option allow user to use their own generated masks with the corresponding regions defined.
   On the other hand, whether an atlas has been entered or the subject specific mask has been defined, there is the option to include the meninges and the skull in the case of containing them. To do so, it is necessary to select the corresponding box either Meninges, Skull or both. In the case of selecting Meninges, it is mandatory to have in the subfolders the mask with the name starting as "Meninges_". In the case of selecting Skull, the mask file must start with "Skull_".
3. To determine the PET and MRI file within the pipeline, it is mandatory to write at least 3 initials of the PET and MRI name, which are defined based on protocol here. For example, as for AlcoolGroup patients, all PET data start

with “1H_” and all MRI data start with “alco”, these initials passed to the specified fields for PET and MR initials.

4. Type scanner resolution for x, y, and z direction respectively. For the Cyceron PET scanner, it is 3.76, 3.76, 4.9 mm3 , otherwise PSF provided by manufacturer should be passed in the fields corresponding to “Scanner Resolution”.
5. “Binarizing Threshold” is a value between 0 and 1. For example if user selects 0.1 for binarizing threshold, all the voxels in grey matter which are greater the 0.1 will be substituted by 1, and the rest will be 0. It means that all the voxels with the possibility greater that 10% will be allocated to grey matter.
6. Depending on the subject and the aim of study, user can choose “Uniform White Matter” or “Heterogeneous White Matter”. It should be considered that while using an atlas like “AAL2”, user should just choose ”Uniform White Matter” while for “Hammer” you can choose either “Uniform WM” or “Heterogeneous White Matter”.

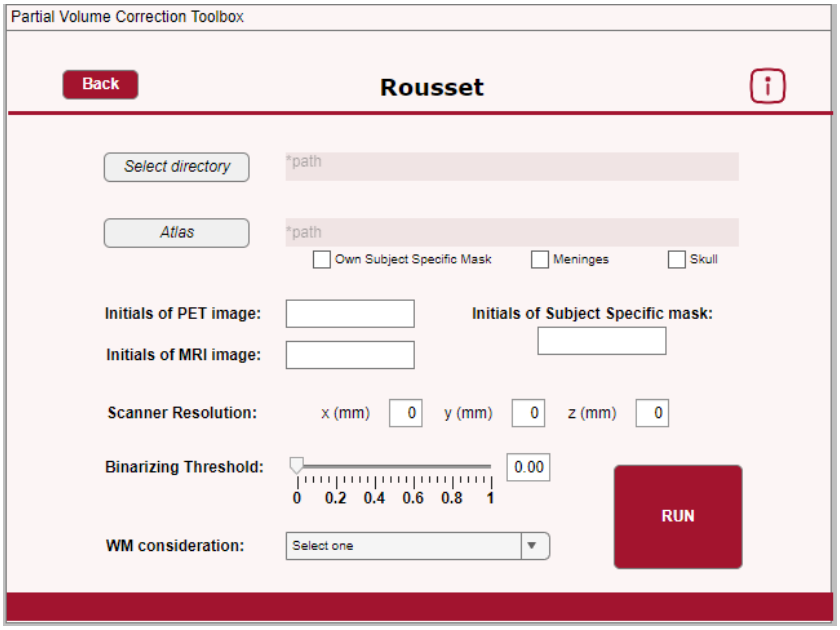


Figure 15. Rousset method and required inputs

7. Last step is just clicking on “RUN” button.
8. While PVC is done, there is a text file named as “Rousset_parameters.txt” containing all the inputs passed for Rousset partial volume correction, in the main directory.

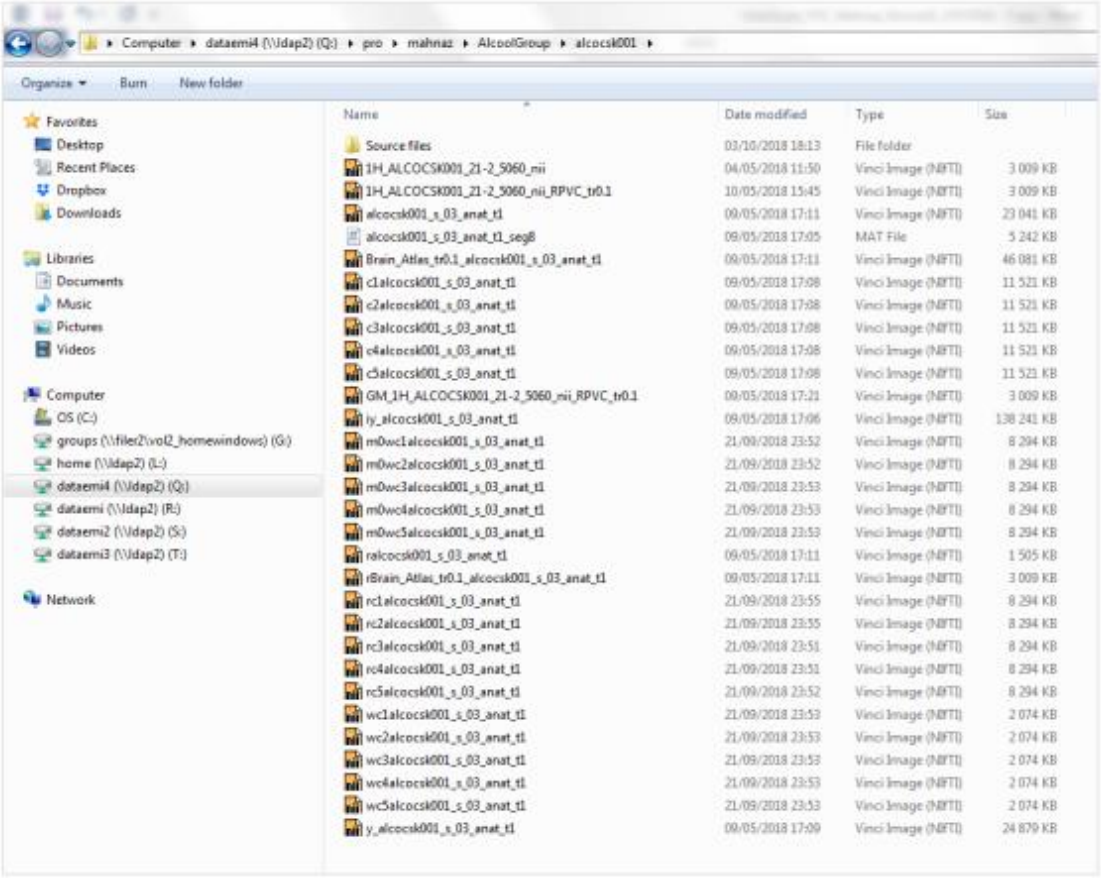


Figure 16. Resultant files after performing Rousset PVC for each subject

- Source files: this subfolder contains primary files of your PET and MR images.

- Segmented MRI files: Segmentation parameters are defined in a way to create c1, c2, c3, c4, c5, y, and iy. It also creates the normalized and resliced tissue probability maps (wc1, wc2, wc3, wc4, wc5, rc1, rc2, rc3, rc4, rc5).

- High resolution brain atlas of the subject, file with the “Brain_Atlas_” prefix. This atlas has the same dimension of MR image.

- Resliced MRI, "ralco", with the same dimension of PET image.

- Resliced brain atlas, which has the dimension of PET image, “rBrain_Atlas_”, used for defining brain segments in PET image.

- PV corrected PET image with a suffix of “_RPVC_tr“. The number after "_RPVC_tr" is the value assigned by user for creating grey matter binary mask.

- PV corrected grey matter with the prefix of “GM_”

9. Main outputs of Rousset PVC, implementing two different atlas, are shown in Figure 15. First row is corrected image by Rousset method while applying Hammer atlas for extracting regions and white matter is considered as

heterogeneous (84 sub regions for grey matter & 84 sub regions for white matter). Second row displays PET image corrected by choosing AAL2 atlas for extracting grey matter regions (121 regions) and white matter was considered

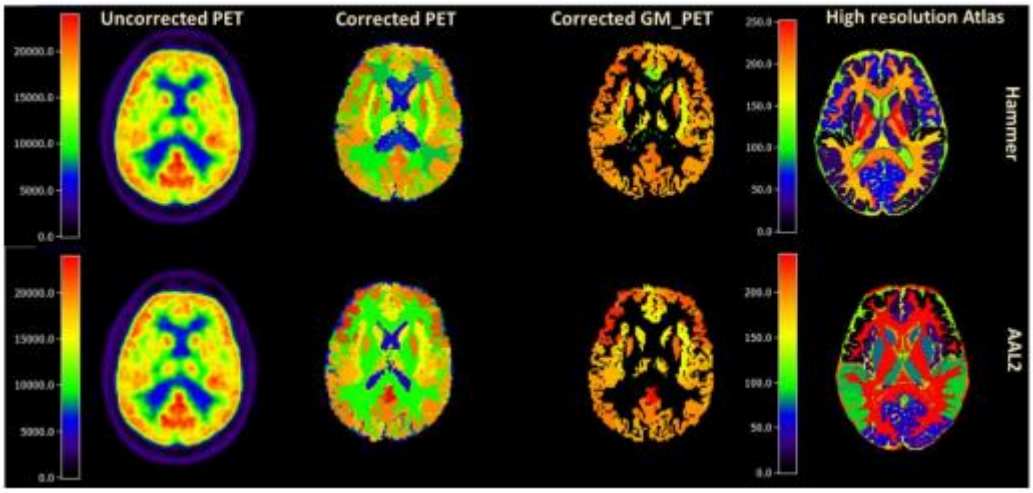


Figure 17. Results of partial volume effect corrected PET images and corresponding subject's atlas. First row displays uncorrected and corrected PETs for heterogeneous white matter and Hammer atlas. Second row is uncorrected and corrected PETs for uniform white matter and AAL2 atlas.

as one region with uniform uptake.

2.5 Lucy Richardson

Lucy Richardson method is a conventional deconvolution method, derived from Bayes's theorem. This is a voxel-wise correction method compensating the partial volume effect voxel by voxel. As each voxel is treated like a region, there is no need to do the segmentation for defining region while implementing Lucy Richardson algorithm. This method can be presented as:

Equation 8

$$f^{k+1} = \frac{f^k}{h^T 1_{N_{IJK}}} h^T \frac{g}{h f^k}$$

h: Scanner PSF — g: uncorrected PET image

h^T: Transpose of h — f: Primary estimate

k: Number of iteration — 1_{NIJK}: Matrix of ones with the dimension of PET

In Equation 8, partial volume corrected image f is iteratively estimated and corrected from uncorrected PET image (g) by increasing iteration from k to k+1.

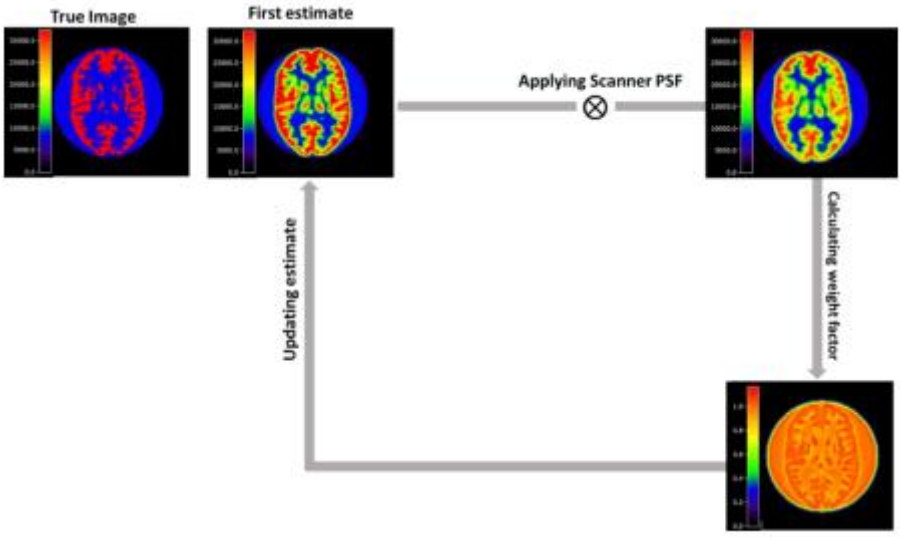


Figure 18. Updating corrected image by Luccy Richardson iterative deconvolution

Figure 16 shows the process of updating each estimation. As it is shown, the primary estimate will be smooth by scanner point spread function, and then weight matrix will be calculated by convolving the ratio between observed image and smooth image. To update the primary estimate (from k to k+1) , weight matrix will be multiplied element wise by primary estimate matrix.

How to use Lucy Richardson PVC

After arranging data, detailed in section 3, and clicking on “Lucy Richardson”, windows for passing inputs comes up (Figure 17).

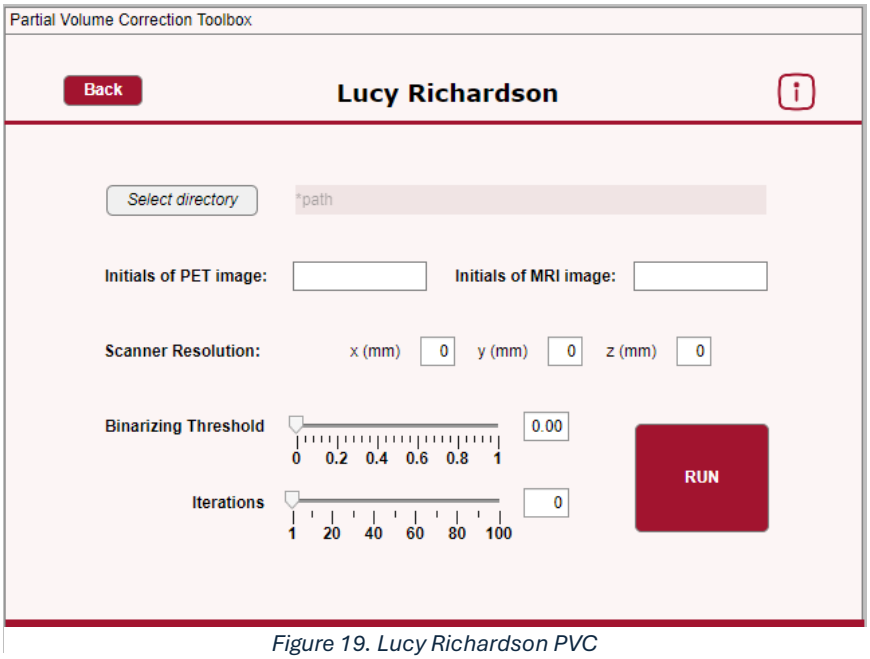


Figure 19. Lucy Richardson PVC

1. Click on “Select Directory” to choose the folder, containing your subjects.
2. To determine the PET and MRI file within the pipeline, it is mandatory to write at least 3 initials of the PET and MRI name, which are defined based on protocol here. For example, as for AlcoolGroup patients, all PET data start with "1H_" and all MRI data start with "alco", these initials passed to the specified fields for PET and MR initials.
    - As it was mentioned before, Lucy Richardson method corrects the PET image voxel by voxel and there is no need to define regions as well. Here, MR image is used just for creating grey matter segment and extract corrected grey matter for further voxel wise analysis, and also the result of segmentation is used for “Quantitative Normalization” as well.
3. Type scanner resolution for x, y, and z direction respectively. For the Cyceron PET scanner, it is 3.76, 3.76, and 4.9 mm3 , otherwise scanner resolution provided by manufacturer should be entered for the corresponding fields.
4. For Iteration number, user should enter a positive integer. Choosing suitable iteration number could help to reduce computing power as well as time for correcting each image. Figure 18 shows a transverse section of a simulated PET image quality phantom, smooth with an isotropic Gaussian filter (FWHM=6.8 mm). Simulated image corrected for partial volume effect by implementing Luccy Richardson method. Plot shows the rate of convergence for corrected activity in the biggest insert by increasing iteration number up to 100. As it can be seen, after about 20 iteration the plot is saturated, meaning that increasing iteration number will not lead to improving correction process significantly. Regarding the dot plot, 50 iteration can be considered as suggested value, which is not premature like 5 iterations and also it can be assured that applying an iteration number higher than 50 leads no significant value in the quantification.

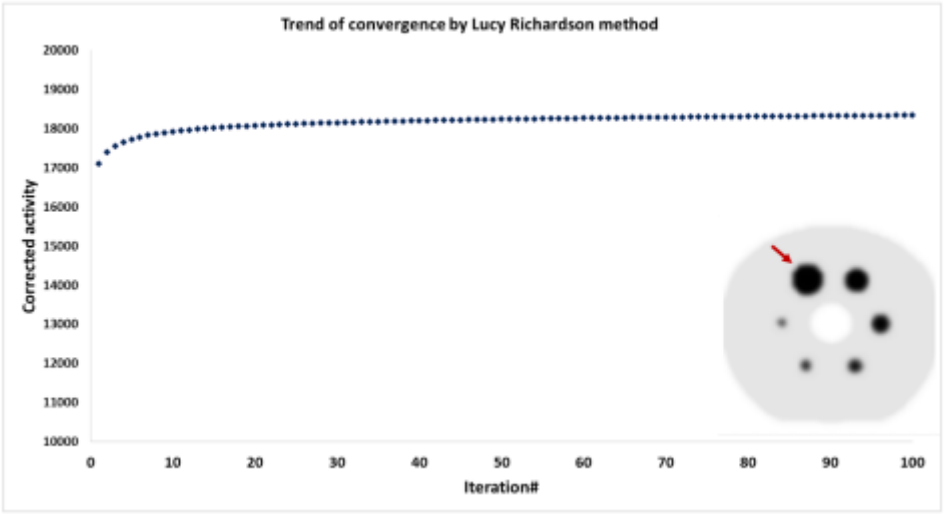


Figure 20. Rate of convergence for a spherical insert with 37mm in diameter (red arrow)

5. After defining all inputs, choose “RUN” for initiating correction of PET data.
6. By completing PVC, there is a text file named as “LRPVC_parameters.txt” in the directory, indicating parameters defined by user.
7. When Lucy Richardson is done, there resulted outputs are as below:

- Source files: this subfolder contains primary files of your PET and MR images.

- Segmented MRI files: Segmentation parameters are defined in a way to create c1, c2, c3, c4, c5, y, and iy. It also creates the normalized and resliced tissue probability maps (wc1, wc2, wc3, wc4, wc5, rc1, rc2, rc3, rc4, rc5).

- PV corrected PET image with a suffix of "_LRPVC_Itr". It should be noted that to avoid confusion, the number of iteration selected by user will be saved in the corrected image name as well. For example, if the PET image has been corrected by 50 iteration the suffix would be "_LRPVC_Itr50" .

- PV corrected grey matter with the prefix of "GM_" .

- File named as "Mask_tr0.1" is the brain binary mask of the subject, defined based on binarizing threshold and it has the same dimensions as the MR image. The figure 0.1 in the mask name refers to the value user applied for creating binary mask. File named as "rMask_tr0.1" is the brain binary mask of the subject in the PET space. Corrected grey matter extracted using “rMask_tr”

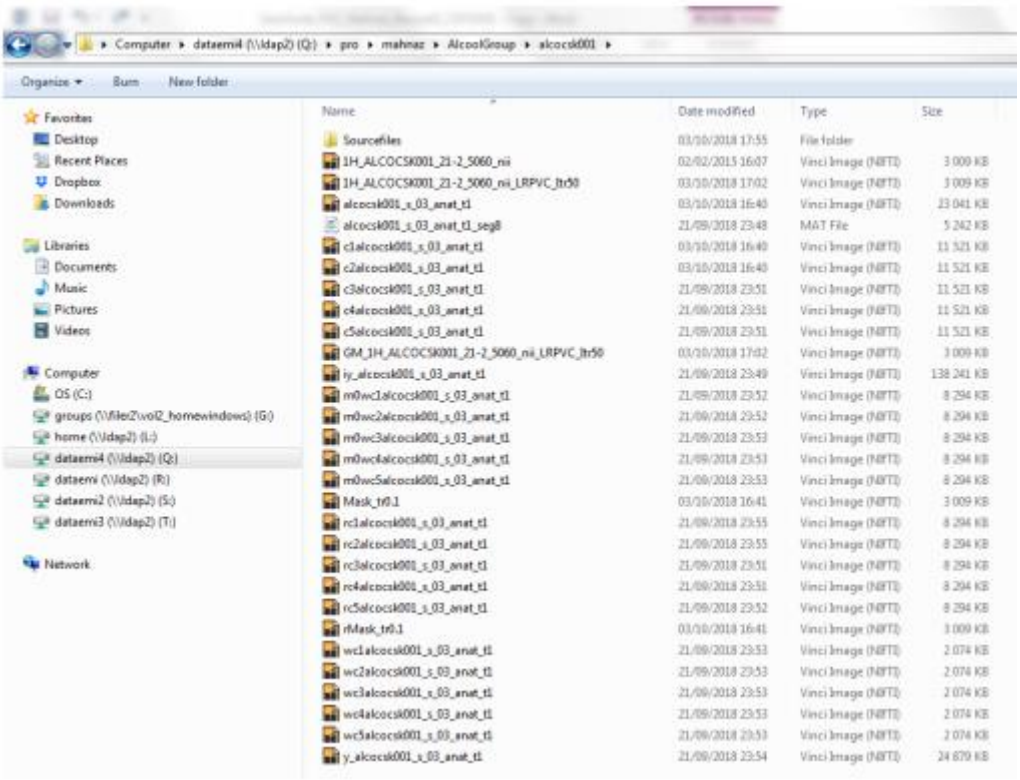


Figure 21. Outputs of Lucy Richardson method with the suffix of _LRPVC_Itr50

8. Uncorrected PET image and resultant corrected images by Lucy Richardson algorithm are shown in Figure 20.

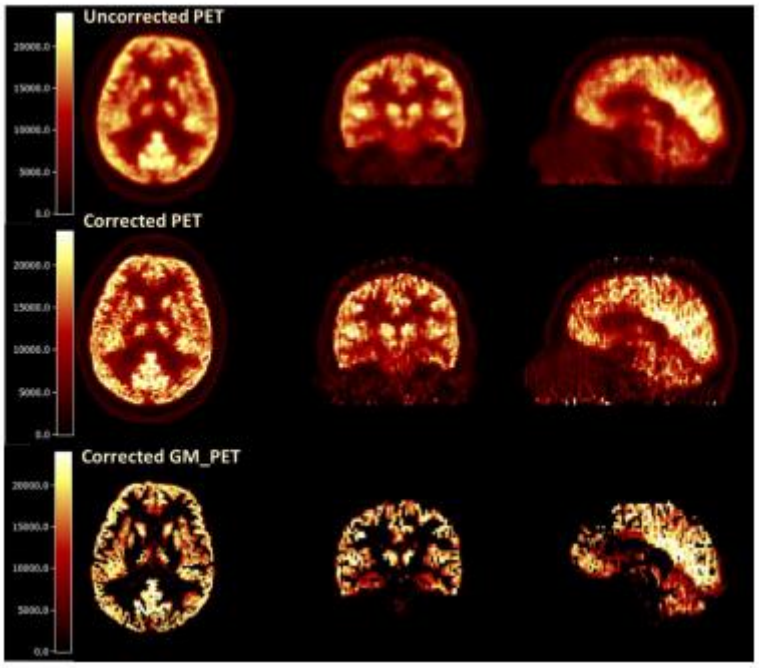


Figure 22. Transverse, axial, and sagittal views of uncorrected (First row), corrected PET image (Second row), and corrected grey matter PET by Lucy Richardson method

2.6 PARSLR

Partially Segmented Lucy Richardson (PARSLR) is a hybrid iterative method implementing both voxel wise and regional quantification as well. This algorithm uses region based partial volume correction for segmentable regions and also benefits from voxel wise Lucy Richardson deconvolution for the voxels not included in the regions. So, by implementing this method whole image volume will be corrected for partial volume effect, leading to more accurate quantification. PARSLR is presented in Equation 9.

Equation 9

$$\theta^{k+1} = \frac{\theta^k}{B^T h^T 1_{N_{IJK}}} B^T h^T \frac{g}{hB\theta^k}$$

h: Scanner PSF	g: uncorrected PET image
h^T: Transpose of h	Θ: Primary estimate of activity vector
B: Map of brain regions	B^T: Transpose of B
k: Number of iteration	1_{NIJK}: Matrix of ones with the dimension of PET

This method is an iterative method, correcting spill over by applying weight vector coefficients to update activity vector (Θ) from k^{th} to $k + 1^{th}$iteration.

How to use PARSLR PVC

By choosing PARSLR method, following window pops out with the fields for passing different inputs (Figure 22).

1. Click on “Select Directory” to choose the folder, containing your subjects.
2. By clicking on "Atlas", user can choose the brain atlas that wants to be used for extracting each regions.
   If not, user can check the box ‘Own Subject Specific Mask’ and write at least 3 initials of the mask in the ‘Initials of Subject Specific mask’. This option allow user to use their own generated masks with the corresponding regions defined.
   On the other hand, whether an atlas has been entered or the subject specific mask has been defined, there is the option to include the meninges and the skull in the case of containing them. To do so, it is necessary to select the corresponding box either Meninges, Skull or both. In the case of selecting Meninges, it is mandatory to have in the subfolders the mask with the name starting as “Meninges_”. In the case of selecting Skull, the mask file must start with “Skull_”.
3. To determine the PET and MRI file within the pipeline, it is mandatory to write at least 3 initials of the PET and MRI name, which are defined based on

protocol here. For example, as for AlcoolGroup patients, all PET data start with "1H_" and all MRI data start with "alco", these initials passed to the specified fields for PET and MR initials.

4. Type scanner resolution for x, y, and z direction respectively. For the Cyceron PET scanner, it is 3.76, 3.76, 4.9 mm3 , otherwise PSF provided by manufacturer should be entered as scanner resolution in x, y, and z direction.
5. “Binarizing Threshold” can be a value between 0 and 1. This value is used to extract grey matter voxels and create binary masks. So if user choose a value equal to 0.3, it means that all the voxels with the chance of 30% and more in the probability tissue map of grey matter, c1, will be considered as grey matter.
6. For Iteration number, user should enter a positive integer. As PARSLR is an iterative method like Lucy Richardson, it is better to have a trade of between corrected activity and iteration number for getting the best acceptable performance. There is no limitation in iteration number applied by user, but it should be noted that the more iteration number the more time for computation. To find the impact of iteration number, a group of 19 brain PET images corrected by PARSLR for 50 and 100 iteration, and paired t-test showed that difference between two groups are not statistically significant (p=0.76). Figure 21 is a Bland Altman plot for comparing corrected value in each region for 50 and 100 iterations. This plot shows majority of dots, displaying differences, distributed around the line of equality. This result confirms that 50 iterations could be a suitable value for iteration, preserving the quantitative correction accuracy.

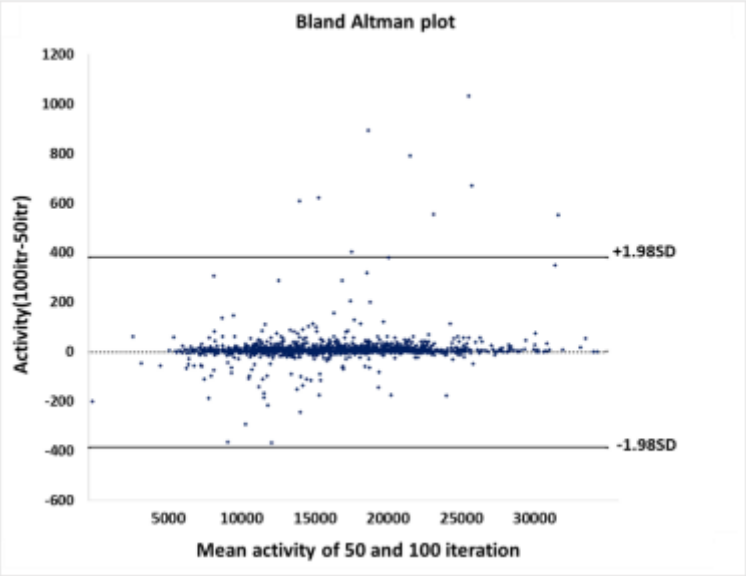


Figure 23. Bland Altman plot for comparing the effect of increasing iteration in corrected activity

7. For PARSLR, just like Rousset method, user can consider whole white matter as one region with uniform uptake, or different regions. So regarding subject and the aim of study, user can choose "Uniform White Matter" or "Heterogeneous White Matter". It should be considered that while using an atlas like "AAL2", user should just choose "Uniform White Matter" while for "Hammer" you can choose either "Uniform WM" or "Heterogeneous White Matter".
8. After passing all required inputs, PVC can be starting by selecting “RUN” button.

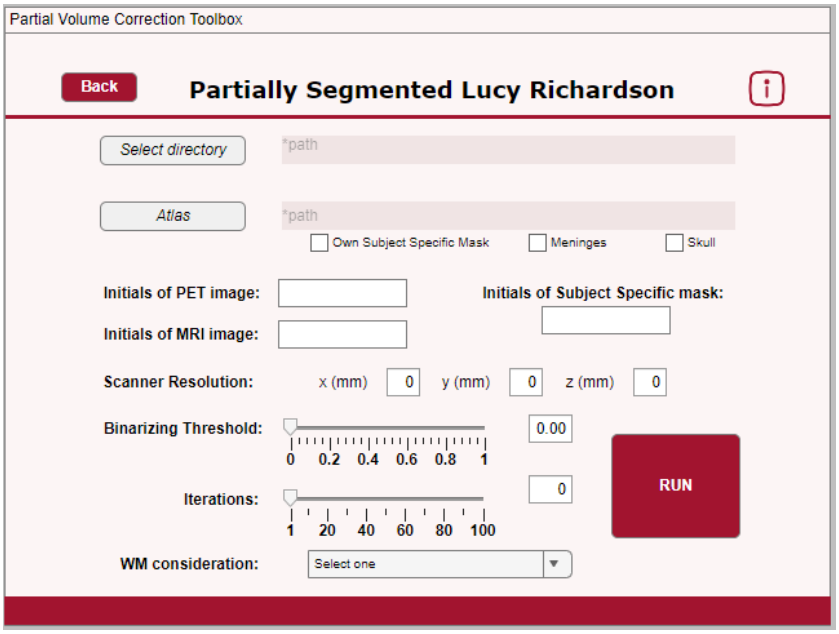


Figure 24. Fields for performing PARSLR method

9. By finishing the partial volume correction for all subjects, a text file, named as “PARSLRPVC_parameters.txt”, will be saved in the main directory, showing all passed inputs by user.
10. When PARLSR is done, there resulted outputs are as below:

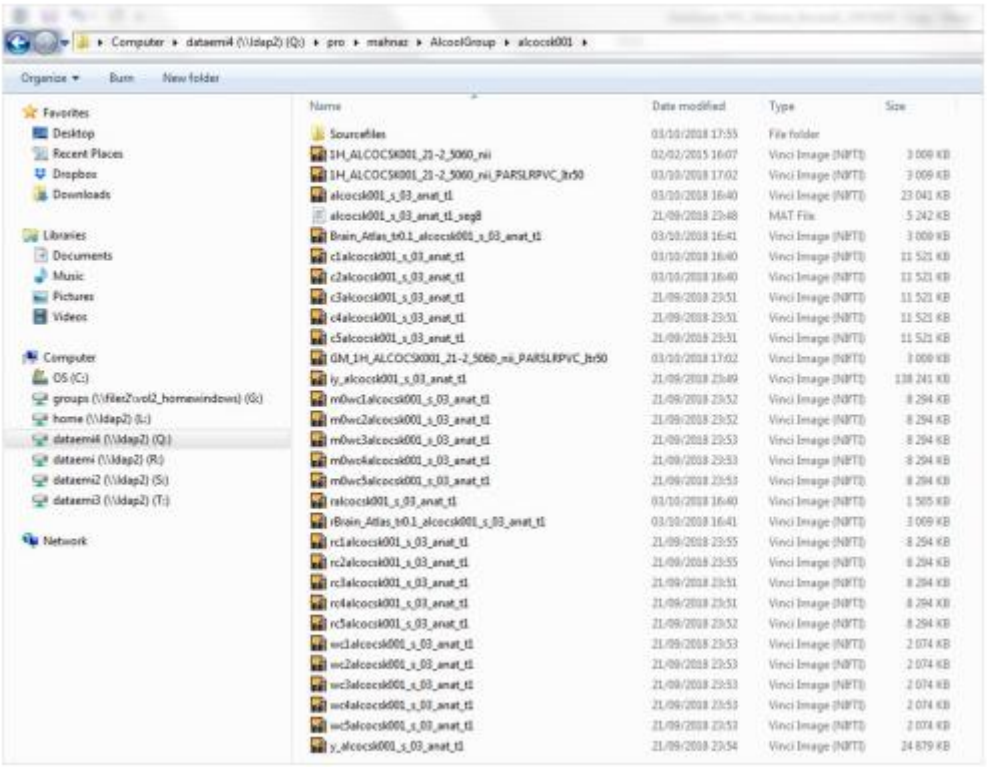


Figure 25. Resultant outputs of PARSLR method for a subject

11. Figure 24 displays transverse view of uncorrected and corrected PET images by PARSLR method, under 2 different condition (uniform and heterogeneous
12. WM) while implementing two different atlases.

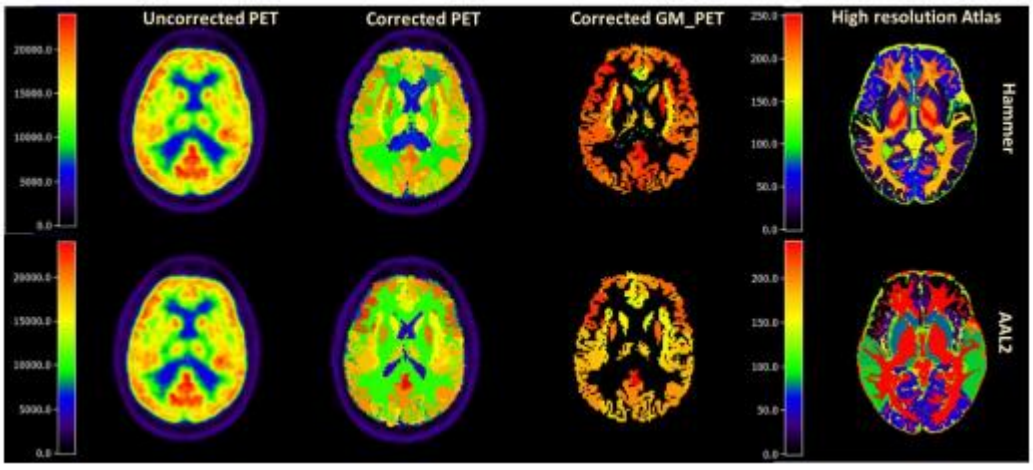


Figure 26. Transverse view of uncorrected and corrected PET images by PARSLR method. First row brain mapped on Hammer atlas and white matter considered as heterogeneous, second row brain mapped on AAL2 atlas and white mater considered as a uniform region

2.7 Quantitative Normalization

Due to the importance of reducing inter-subject variability in PET quantification, it is necessary to apply quantitative normalization on all PV corrected PET images. Quantitative normalization refers to scaling the corrected PET image by dividing activity in each voxel to average activity in a reference region.

How to use Quantitave Normalization

After completing partial volume correction on the PET data, select “Quantitative Normalization” and define required fields as explained below (Figure 25).

1. “Select Directory” is for loading the main directory of PVC subjects.
2. By “Select Mask” user should pass the suitable mask for the subjects, such as cerebellum mask, for quantitative scaling.
3. To determine the PET and MRI file within the pipeline, it is mandatory to write at least 3 initials of the PET and MRI name, which are defined based on protocol here. For example, as for AlcoolGroup patients, all PET data start with "1H_" and all MRI data start with "alco", these initials passed to the specified fields for PET and MR initials.
4. In the first choice box, regardless of PVC method user can select to have scaled image in “MNI Space”, “Native Space Conventional” or “Native Space New”. Considering the method used for partial volume correction, it is suggested to choose “MNI” space for Muller Gartner for further voxel based analysis and “Native” space for “Rouuset” and “PARSLR” PVC for regional analysis.

   *** In the “Native Space Conventional”, quantitative mask is directly map to PET images, but for the "Native Space New", quantitative mask will be mapped on grey matter first to extract the voxels covering the grey matter. "Native Space New" is more accurate and also is practical when your mask for quantitative normalization is pure grey matter.

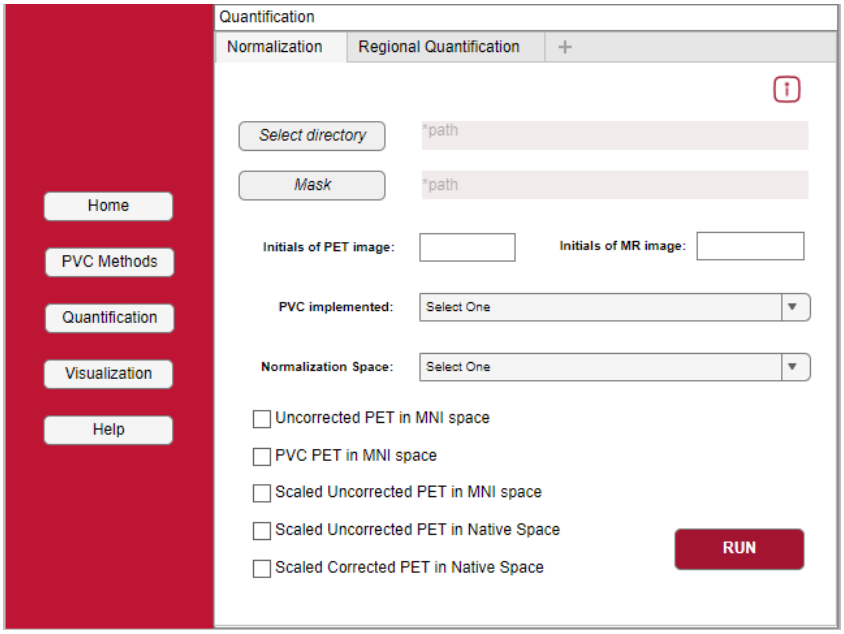


Figure 27. Inputs for Quantitave Normalization

5. There are also 6 different check box. Each box will create an specific output as bellow:

- Uncorrected PET in MNI: It will move uncorrected PET to MNI space, and you can choose this option just when you have chosen to do the quantitative normalization in MNI space. This file is named as w+PET file name. For example, here it is named as “w1H_ALCOCSK001_21-2_5060_nii.nii”.
- PVC PET in MNI: This check box give you the ability to move your partial volume corrected PET to MNI space. Select this checkbox only if the quantitative normalization in MNI space is desired. This file is named as w+PVCPET file name. For example, here it is named as "w1H_ALCOCSK001_21-2_5060_nii_MPVC_tr0.5.nii".
- Scaled uncorrected PET in MNI space: User can select this item for both MNI and Native space. For MNI space, this file is named as “MScaled_rw1H_ALCOCSK001_21- 2_5060_nii.nii” while for Native space it is called as “wNScaled_1H_ALCOCSK001_21- 2_5060_nii.nii”.
- Scaled corrected and uncorrected PET in Native space: It can be selected while user has chosen Native space. NScaled_1H_ALCOCSK001_21-2_5060_nii.nii and NScaled_1H_ALCOCSK001_21-2_5060_nii_MPVC_tr0.5.nii correspond to scaled uncorrected and corrected PET in native space respectively.

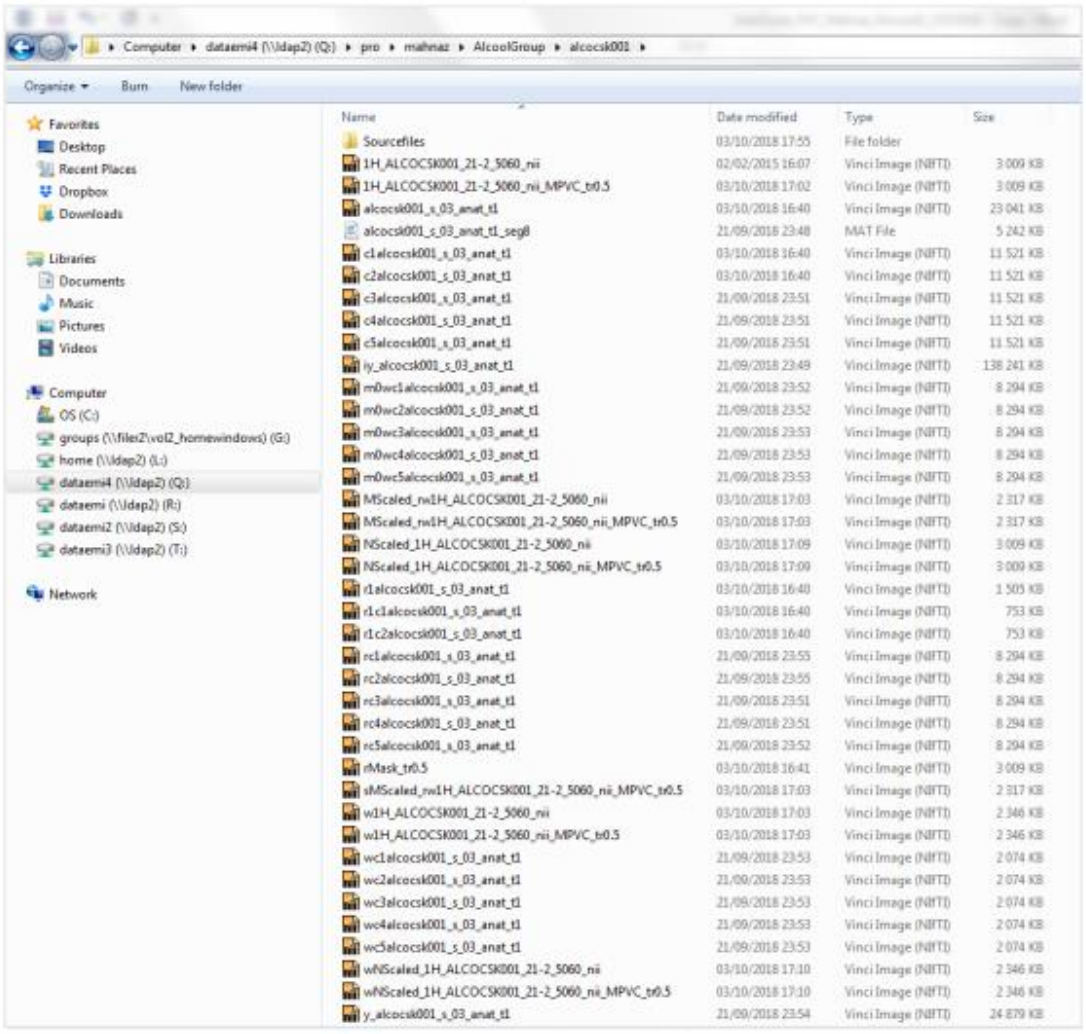


Figure 28. Outputs files for quantitave normalization on both MNI and Native space

6. For the second choice box, implemented method for correcting partial volume effect should be specified. By completing running the function, there would be a scaled PET image with the prefix of "MScaled_" for MNI space and "NScaled_" native space for each subject. Figure 27 displays quantitative normalize PET images for two different MNI and native spaces.

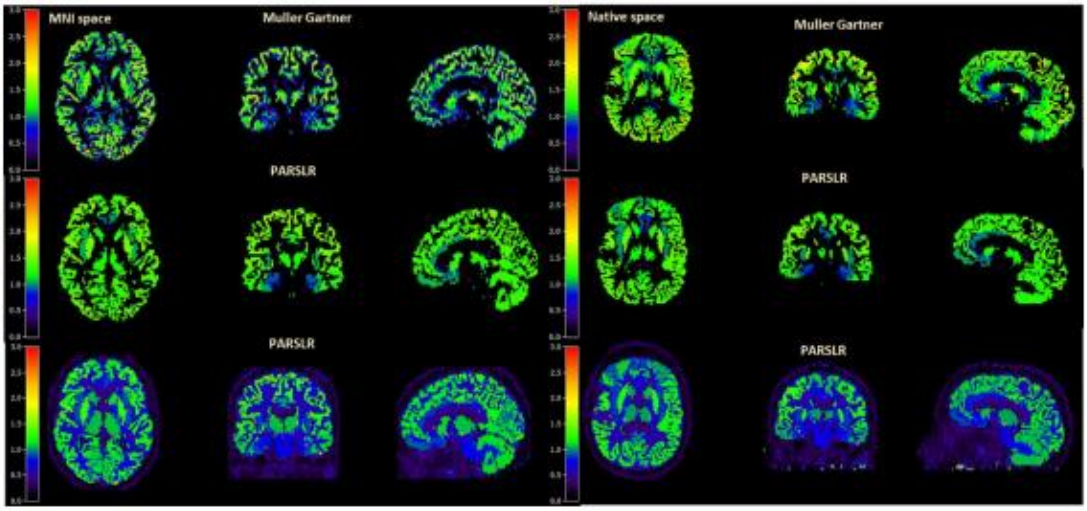


Figure 29. Scaled PET images corrected by "Muller Gartner" (first row) and "PARSLR" (second row) in MNI and native space

It should be noted that if PET data has been corrected by Muller Gartner or Lucy Richardson method, and user selects "MNI" space, in addition to scaled PET image, there will be a smooth image with a prefix of "sMScaled_" for performing furthermore voxel wise analysis (Figure 28). This image has been created by smoothing scaled image with an isotropic Gaussian filter with FWHM of 8 mm.

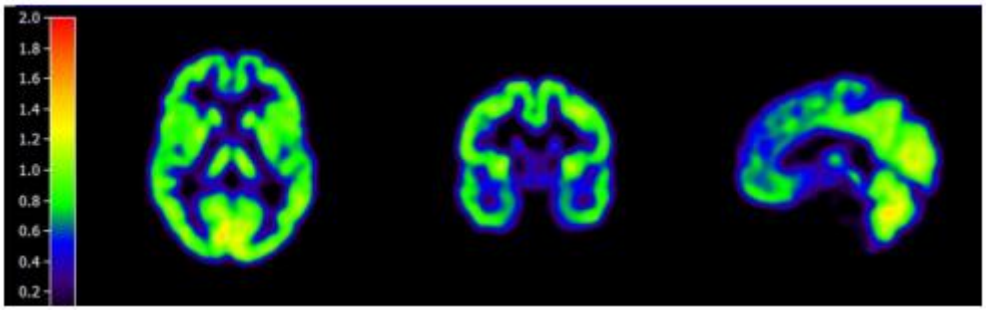


Figure 30. Smoothed scaled PET image corrected by Muller Gartner method

2.8 Regional Quantification

This item is designed to export the average activity concentration of scaled regions as an excel file for each subject. To implement this option, user should take following steps:

How to use Regional Quantification

1. Click on the "Select Directory" and choose the main directory of subjects.
2. If PET data has been corrected by Muller Gartner or Lucy Richardson, click on "Atlas" and choose your desired atlas for defining brain regions, otherwise just go to step 3.
3. To determine the PET and MRI file within the pipeline, it is mandatory to write at least 3 fixed initials of the PET and MRI name, which are defined based on protocol here. For example, as for 26 AlcoolGroup patients, all PET data start

with "1H_" and all MRI data start with "alco", these initials passed to the specified fields for PET and MR initials.

4. For "choose box", the method used for PVC should be selected.
5. It should be noted that for all PVC methods, all PET images should have been scaled in native space.
6. By choosing check box named as "Regional quantification for uncorrected PET image", regional quantification will be calculated for both uncorrected and corrected PET images. Output of this function is an excel file, including two columns for each subject, first one displays region's index specified by brain atlas and the second one is average activity concentration in the region corresponding to the index. Excel file for regional quantification of corrected PET images, saved in the path folder, is called "Corrected_Regional_values" and the file named as "Uncorrected_Regional_values" corresponds to regional value for uncorrected PET images.

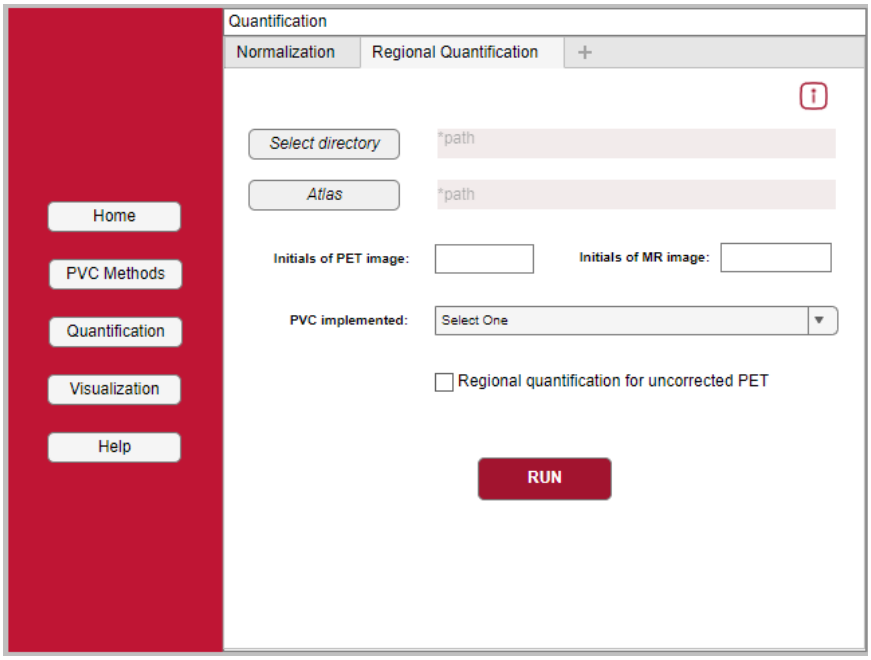


Figure 31. Inputs of Regional Quantification

References

Segobin, S., La Joie, R., Ritz, L., Beaunieux, H., Desgranges, B., Chételat, G., ... & Eustache, F. (2015). FDG-PET contributions to the pathophysiology of memory impairment. Neuropsychology review, 25(3), 326-355