PMOD Alzheimer's Discrimination Tool (PALZ)

USER MANUAL
Version 4.4

PMOD is a software
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1 PMOD Alzheimer's Discrimination Tool Introduction

The PMOD Alzheimer's Discrimination Tool (PALZ) supports the fully automatic analysis of FDG brain PET scans acquired from subjects with clinical symptoms of Alzheimer's Dementia (AD). It is based on the data of a large multi-center trial and implements the proven discrimination methodology developed by Prof. K. Herholz et al. [1].

Methodology

It is a prerequisite for the applicability of the analysis that the test subject suffers from clinical symptoms of AD. Assuming that this is the case, the PALZ tool performs the following processing steps with a loaded FDG brain PET scan:

- The image is first stereotactically normalized using the methodology and the anatomical PET template of SPM99 [2].
- The resulting image is then smoothed by a 12 mm Gaussian filter to minimize side-effects of varying scanner resolutions.
- The image voxel values are divided by the voxel mean value, averaged within a mask representing voxels with AD-preserved activity. This operation results in normalized voxel values which are comparable across subjects.
- In each image voxel the activity expected at the subject's age is calculated using voxel-wise age regression parameters.
- The difference between the measured and the expected voxel values are transformed into t-values, resulting in a t-map [3].
- The t-values of all abnormal voxels within an predefined AD-mask are summed, yielding a criterion related to AD-severity called *AD t-sum*. The AD mask represents all voxels that had shown a close correlation (at $p<0.01$ uncorrected) with the Mini Mental Status Examination (MMSE) in subjects with probable AD (see [1], Fig. 1). It includes major parts of the temporal and parietal association cortices (including the precuneus and posterior cingulate), as well as some lateral prefrontal areas.
- The AD t-sum is compared with the 95% prediction limit (11089) established in the NEST-DD multi-center trial, and tested for significance of abnormality. The result of this test is the main outcome of the present AD discrimination.
- The *PET Score* is calculated from the AD t-sum by reference to the upper normal limit and log transformation to approach a normal distribution: PET Score = $\log_{2(}$(AD t-sum/11089 +1) [4].
- For interactive reviewing, the t-maps can be displayed and fused with the normalized subject images. They can also be saved for use in an external analysis.
- Additionally, a cluster analysis is performed for grouping of voxels with significantly reduced uptake [1]. Clusters of at least 216 contiguous voxels with $p<0.05$ (not corrected for multiple comparisons) are determined, ordered by their size in a table, and also made available as images.

For a thorough understanding of the discrimination analysis please refer to the *NeuroImage* article which exactly describes how the method was derived and validated [1].

Results

AD t-sum [1]: The discrimination analysis described above provides the basis for a statistical test with null hypothesis *"The AD t-sum is normal"*. As the distribution of the AD t-sum has been assessed in the control group, a 95% prediction limit and error probabilities were calculated. In the evaluation, the AD t-sum was shown to be a highly sensitive indicator of scan abnormality [1]. Therefore, if the AD t-sum is within the normal range it is unlikely that a tested subject has AD. Otherwise, if the AD t-sum is outside the 95% prediction limit, the null hypothesis is rejected (*"AD t-sum within AD regions is abnormal"*), and the error probability is stated (eg. *"Error probability* <

0.0001"). Such a finding, always in conjunction with clinical symptoms, supports a classification as AD.

PET Score [4]: The PET Score was shown to be a valid imaging biomarker for monitoring the progression of mild cognitive impairment (MCI) to Alzheimer's disease (AD). Its excellent test-retest reliability and signal strength is expected to allow substantially reducing the number of subjects or shortening of study duration in clinical trials.

Clusters: The outcome of the cluster analysis is not quantitative and solely intended for the visualization of concentrated area of abnormal voxels. Note that even in perfectly normal subjects up to 5% of all voxels may appear abnormal, and the appearance of a few abnormal clusters does not indicate any abnormality.

Validation

In 2009 the performance of the PALZ tool was assessed with a large number of cases from two independent databases (ADNI and NEST-DD) [5]. The databases differ regarding the demographics and the acquisition protocols as summarized below. The data sets were processed with PALZ, and the AD t-sum outcome used to calculate sensitivity and specificity.

	Controls	Mild AD-subjects	Protocol	Results
ADNI	102 controls, age 76±4.9, MMSE 28.9±1.1	89 subjects, age 75.7±7.6 MMSE 23.5±2.1	Eyes open, quiet darkened room, 3D	Sensitivity: 83% Specificity: 78%
NEST-DD	36 controls, age 62±45; MMSE 29.6±0.7	237 subjects, age 70.8±8, MMSE 20.9±4.4	Eyes closed	Sensitivity: 78% Specificity: 94%

The main outcome of the study is the confirmation of the high accuracy of FDG PET with PALZ for the discrimination between AD subjects and normal controls. Furthermore it was demonstrated that although the eyes open condition results in higher occipital glucose consumption, there is no relevant effect on the AD t-sum. Therefore, PALZ can be equally applied to studies with eyes open or closed during the uptake phase. Only 7 out of 464 images had to be excluded from the analysis due to a failure of the normalization procedure.

Applicability

The PALZ tool may only be used to analyze FDG brain scans of subjects with suspected AD. Note that the following guidelines must be observed to avoid invalid results:

- A subject must not be younger than 49 years. For such subjects, the linear age regression might result in a (most probably too) high expected uptake in the frontal cortex. The consequence of such a situation would be a false positive finding.
- PET images must be reconstructed with attenuation and scatter correction.
- The stereotactic normalization may fail. In that case the subsequent discrimination calculations will be invalid. Therefore, the user is required to verify the outcome of stereotactic normalization. Failure of normalization has been observed in the presence of severe brain atrophy. There are two indications of such a situation:
  1. A shell-like distribution of the abnormal voxels along the boundary cortex/external liquor space.
  2. Concentration of the abnormal voxels in the cingulate gyrus and the basal ganglia as a consequence of the severe widening of the inner liquor space.

Limitation

The PALZ tool is not a general brain FDG analysis tool and thus not suited to search for non AD-related defects in FDG brain scans. Any other disease that also affects the association brain areas, which are abnormal in AD, may also lead to a significantly abnormal result. Scientific evidence is not yet sufficient for the interpretation of an abnormal AD t-sum in subjects without clinical symptoms of AD.

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2 PALZ Operation Modes and Configuration

The PALZ tool can has two modes of operation:

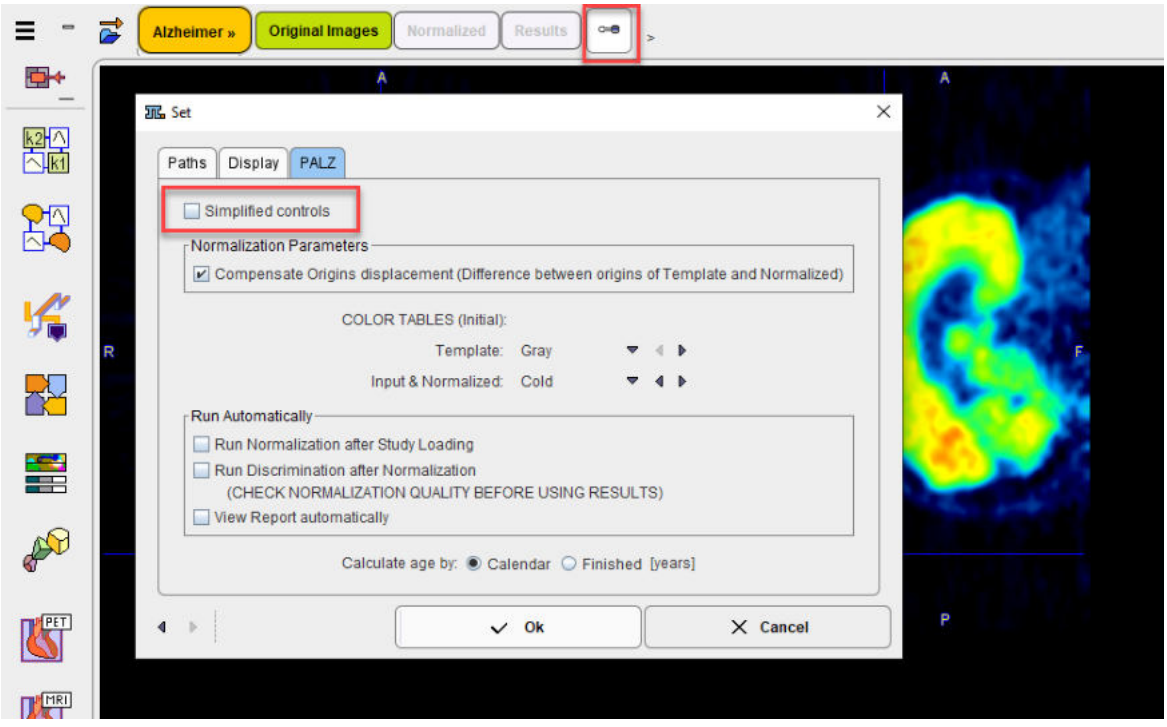
- **Simplified mode:** In this mode the user interface elements are reduced to the essential minimum for minimizing user interaction and avoiding errors. This mode should normally be used.
- **Extended mode:** This mode provides all user interface elements available in PMOD, as well as additional features dedicated to the PALZ analysis. For instance, the original subject images can be viewed, and the t-maps can be saved. This operation mode is recommended for experienced PMOD users.

2.1 Configuration

The PALZ configuration panel can be shown by activating the button in the left part of the status line. The contents of the **PALZ** panel differs on the mode the program is operating in.

Configuration Panel in Simplified Mode

In this mode the configuration panel only contains the elements illustrated below.



Simplified controls allows switching between the two processing modes. In the **COLOR TABLES** section the default color tables of the stereotactic **Template** and the subject images (**Input & Normalized**) can be defined. If the **View Report automatically** box is checked, the report viewer will be started each time a discrimination analysis is completed.

The subject age can be calculated based on birthday and PET study date (**Finished [years]**) or based only on the calendar year (**Calendar**). The options are available for selection in the **Calculate age by** section.

Configuration Panel in Extended Mode

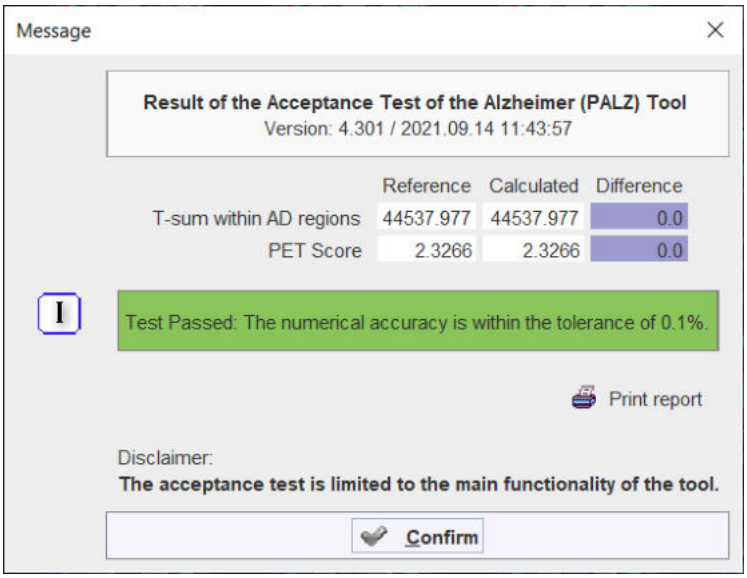
Additional elements are shown on the configuration panel in the extended mode.

Compensate Origins displacement implements a logic to establish a suitable initial situation for the stereotactic normalization. It allows normalizing some cases which would otherwise fail, and therefore should be on per default. The main purpose for switching it off is to maintain exact compatibility with PALZ versions before 3.3.

The Alzheimer's discrimination analysis in the extended mode requires only a few button clicks. However, it is possible to reduce the amount of user interaction further by setting appropriate flags in the **Run Automatically** section. They represent trigger flags, so that for instance after loading the images all processing steps are run sequentially (all checks enabled). However, it is strongly recommended that the normalization result is inspected before trusting the analysis outcome.

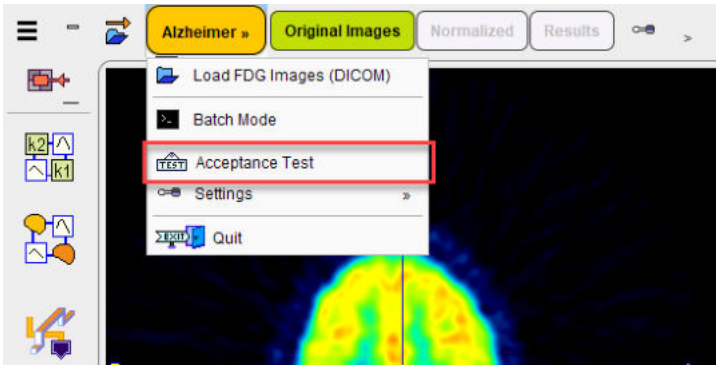
2.2 Acceptance Test

The first time PALZ is started after an installation an **Acceptance Test** is automatically run. It performs all processing steps using a test image and compares the outcome with the stored values. The result is presented as a confirmation dialog window as illustrated below.



If the result is beyond the acceptance criterion of 0.1%, there is a problem with the installation which has to be fixed before proceeding with the analysis of subject data.

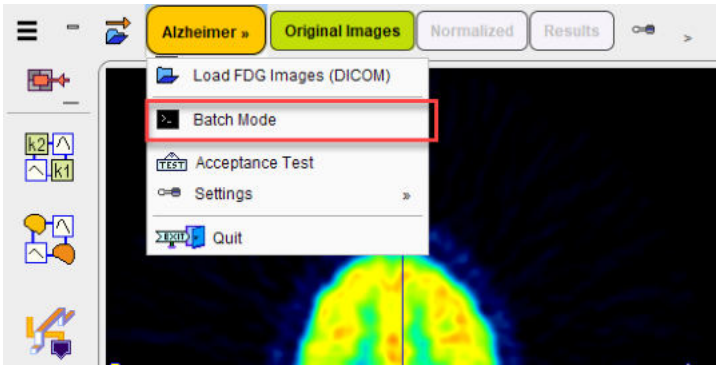
To verify an installation the **Acceptance Test** can be initiated at any time from the **Alzheimer** menu.



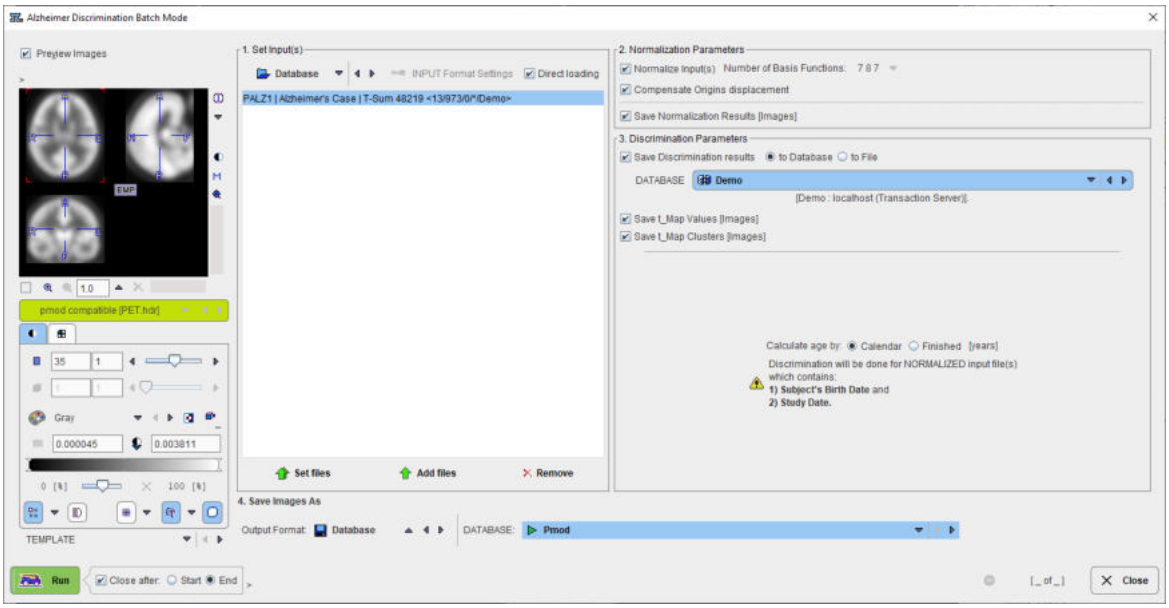
2.3 Batch Mode

The PALZ tool offers a batch facility which is useful when several studies need to be analyzed. The batch mode allows performing the spatial normalization - which is the time-consuming processing step of the whole analysis - for a list of FDG studies and save the normalized images for a later, interactive discrimination analysis. It is also possible to perform the discrimination analysis at the same time and save its results, but this unsupervised mode is *not* recommended due to the potential failure of spatial normalization.

Batch mode is started using the corresponding **Batch Mode** menu entry



and displays the following dialog window.



There are numbered sections in the dialog which must be configured appropriately(example **Database**) and then add the files to the list to be processed using the **Set files** button. Note the button **Input Format Settings** which allows to configure optional pre-processing steps, such as A-P mirroring, smoothing, time-averaging, etc. **Direct loading** disables these options.

1. Set Input(s)	In this section the studies to be normalized are defined. Please first select the data format (in the selection list)
2. Normalization Parameters	The **Normalize Input** check defines whether the input images need to be spatially normalized (this is not necessary if previously normalized images are selected), and the check **Save Normalization Results** whether the resulting images are saved.The number of basis functions used in the elastic part of matching is currently fixed, but may become relevant in future enhancements.

	The **Compensate Origins displacement** implements a logic to establish a suitable initial situation for the stereotactic normalization. It allows normalizing some cases which would otherwise fail, and therefore should be on per default. The main purpose for switching it off is to maintain exact compatibility with PALZ versions before 3.3.
3. Discrimination Parameters	This section is only relevant if the user wants to perform the discrimination analysis in unsupervised mode, which is *not recommended*. All the discrimination results can be saved for post-batch reviewing.
4. Save Images As	If result images have been configured for saving, the format defined in this section will be applied. First select the data format (recommended is the **Database**), then configure additional parameters of that format.

After the configuration is complete, the **5. Run** button can be activated to initiate batch processing.

Note: The **Batch mode** is available only for the Extended mode configuration: the **Simplified controls** check box in the configuration panel has to be disabled.

3 Performing an Alzheimer's Discrimination Analysis with the PALZ Tool

The PALZ tool is started using the

button in the PMOD ToolBox. Depending on the operation mode it organizes the processing steps on three or four pages as explained below.

The explanations assume some familiarity with the PMOD software. If you need more information about the general behavior of the program and in particular image displays, please refer to the *PMOD Base Functionality Guide*.

3.1 Processing in Simplified Mode

3.1.1 Loading the Subject Images

PMOD includes a DICOM database, to which users can directly transfer their images from the PET system. As an alternative, users can load DICOM images from anywhere in the file system or from a CD/DVD.

The DICOM format has the advantage that subject, acquisition and reconstruction related information is included in the image header. Therefore the images can be displayed with consistent orientation (Left/Right, Anterior/Posterior, Inferior/Superior), and the subject's age can be determined which is crucial for the discrimination analysis.

Loading Images from the Database

The **Load Images** page shows all the studies stored in the **Demo** database.

To load the FDG images of a subject with clinical symptoms of AD, first select the subject in the **Subjects** list, then the appropriate image series in the **Series** list. Finally activate the **Open** button.

Loading Images from a CD or from File System

If there is a need to load the FDG images from outside of the database please start the DICOM loader. In the appearing dialog window the contents of the directory from which images were loaded the last time is initially shown. Use the **Change Folder** button to bring up a navigator window which allows changing the current folder.

There are two cases for the path selection: if a **DICOMDIR** file exists such as in the example below, don't navigate to a subdirectory, but activate **Select**. PMOD will read the information in DICOMDIR and list all image series contained in any subdirectory. Select the appropriate FDG series in the list and activate the **Open** button for loading.

If there is no DICOMDIR please navigate into the folder with the image files and **Select**. In this case PMOD will scan all the files in the folder and list the available images series. Proceed by selecting the appropriate FDG series and activate the **Open** button for loading.

Image loading can also be done with the lateral taskbar:

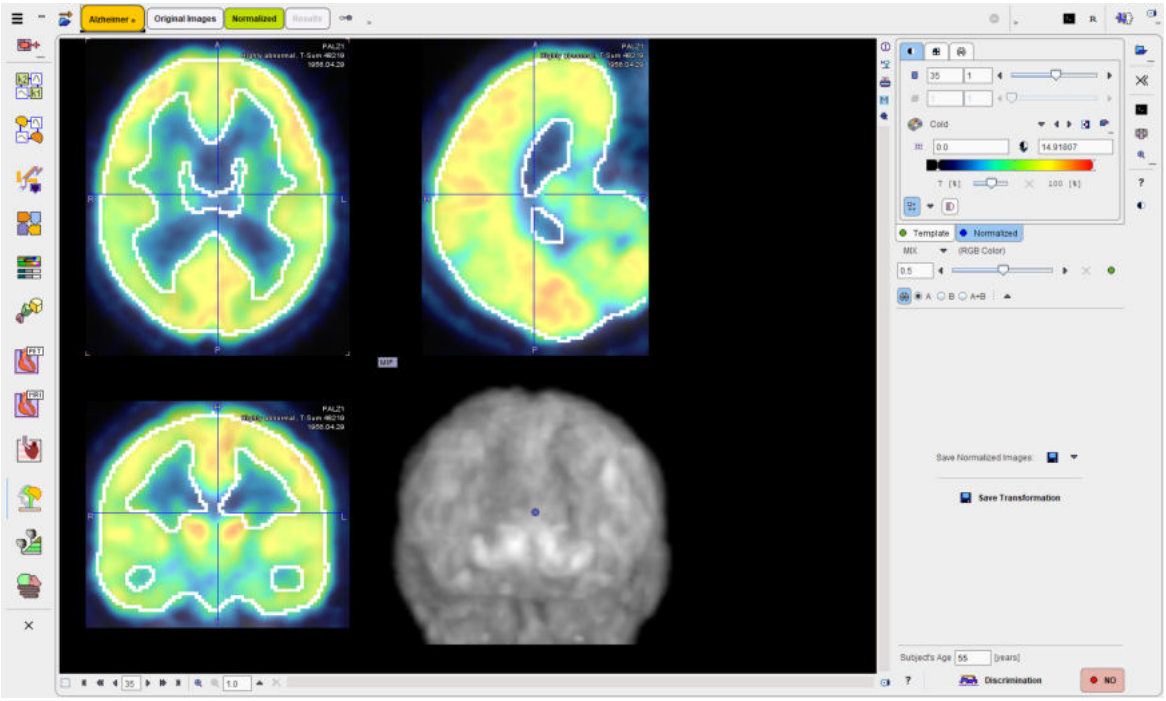
	Load image. The format can be selected with the small down arrow below the button.
	Close all image series in the PALZ tool, including any image results.

Processing of the Loaded Images

After the images have been loaded the stereotactic normalization is immediately started, and the result shown on the **Normalized** page.

3.1.2 Verifying the Normalized Images

The normalization step results in a new image set which represents the subject images in the stereotactic space of the template. This image set has the resolution of the PET template, so that the images can be fused. The fusion result is shown in the large image area.



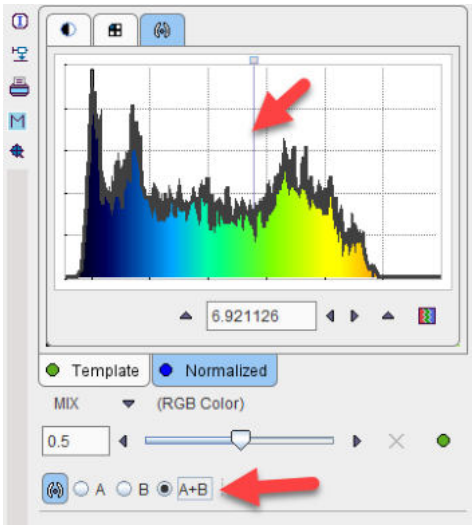
Initially, the color tables are applied which were defined in the configuration 7 panel. To change the color tables or the thresholds please activate either the **Template** or the **Normalized** tab, and adjust the settings according to your preference.

CAUTION: The spatial normalization is expected to succeed in most of the cases. However, the user is strongly recommended to verify that the normalization was accurate by examining the alignment of the resulting brain shape with the template.

Verification of the Normalization Result

There are different features available for checking the normalization result:

- Shift the fusion slider left/right to change the mixing of the two image sets and dynamically visualize the correspondence.
- Display the iso-contours in the images by checking the **A+B** radio box.
  Note that the level of the iso-contouring can be adjusted by selecting the contouring tab of a series (**Template** or **Normalized**) and changing the threshold level.



- Click at different points across the brain to verify the alignment for all relevant anatomical structures.

There are additional fusion options available, which are described in the *PMOD Image Fusion Guide*.

Starting the Discrimination Analysis

The **Subject's Age** is essential for the age regression. If it can be derived from the input data, the age is shown in the number field (and can be edited if required), otherwise the user is prompted to enter the age interactively. If the age is correct and the normalization accuracy has been found to be acceptable, the Alzheimer's discrimination analysis can be started with the **Discrimination** button. Otherwise, processing should be stopped with the **NO** button.

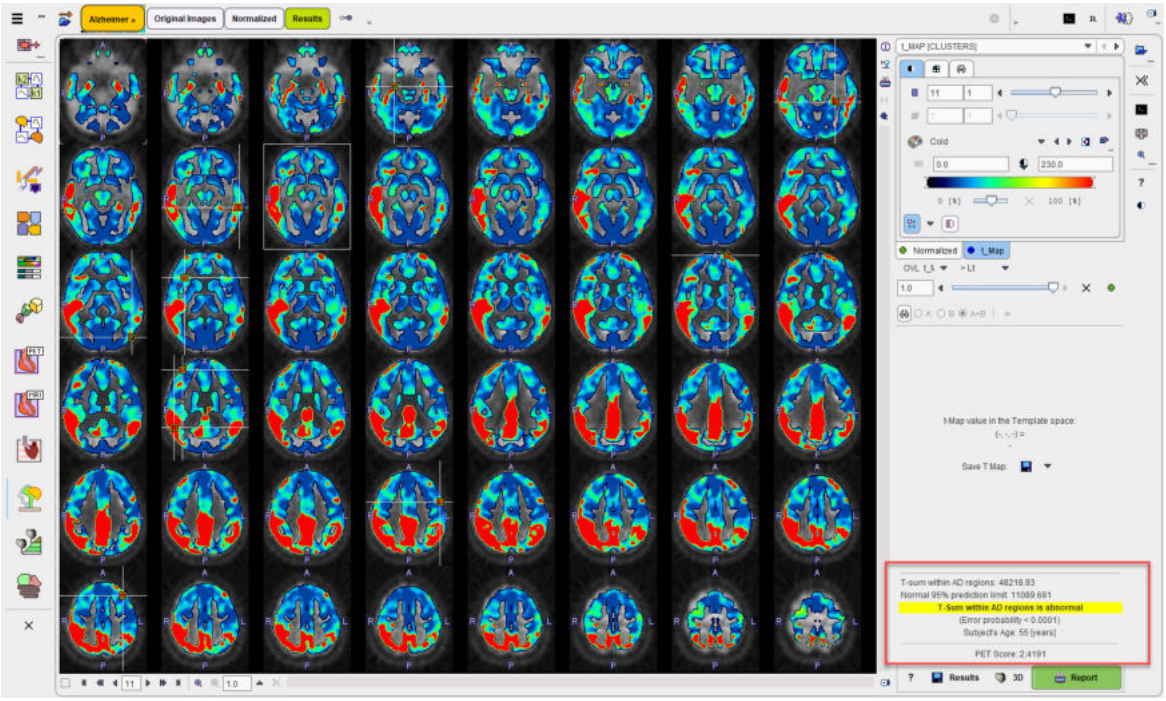
3.1.3 Results of the AD Discrimination Analysis

The outcome of the discrimination analysis is available on the **Results** page.

Result Images

The large image display shows a fusion of the clustered t-maps with the normalized subject images.

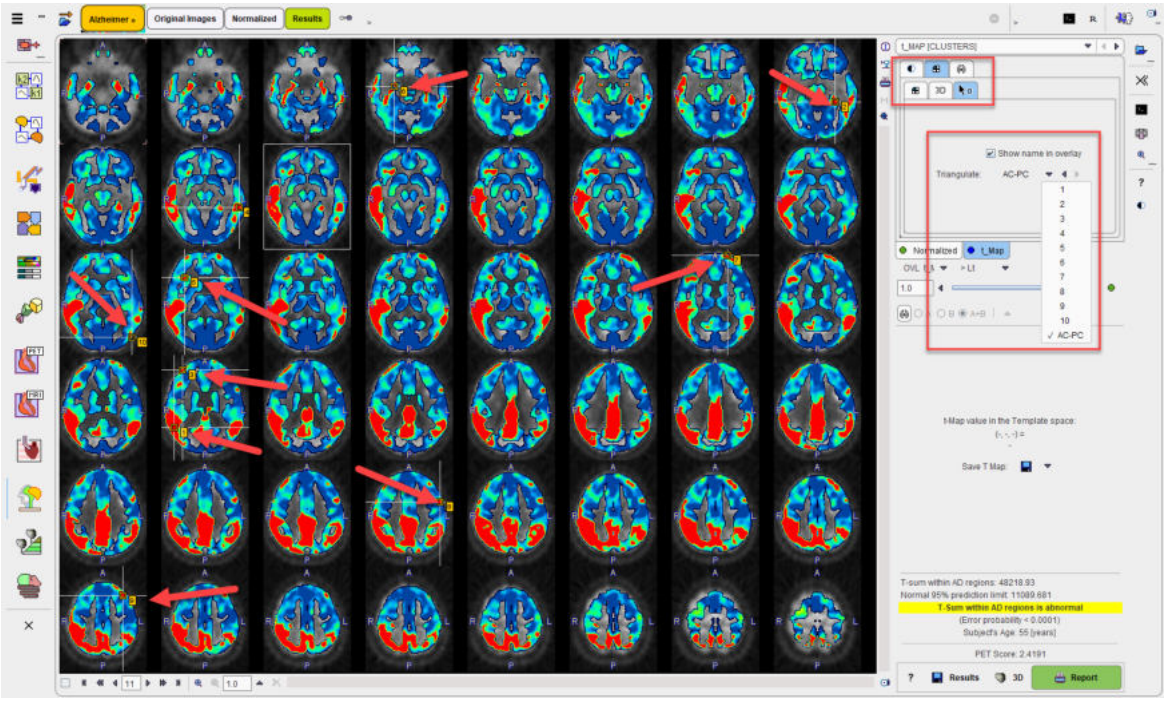
Note: The cluster images are a synthetic compilation of information with values in the range from 0 to 230. The value of 230 corresponds to abnormal voxels and is shown in red using the default color table.



Initially, 2 mm thick slices parallel to the AC-PC line are shown in a 6x8 layout as illustrated above, but the arrangement can be changed as usual using the layout tab.

Using the fusion slider the mixture between the normalized subject images (fully to the left) and the cluster t-maps (fully to the right). There are many other fusion options available to closely examine the data, as described in the *PMOD Image Fusion Guide*.

The image at the AC-PC level is enclosed in a white rectangle. The cluster maxima are indicated in the images by markers and crossing lines. With the **Triangulation** selection button in the markers panel of the **t_Map** it is possible to directly jump to these markers, and also to the **AC-PC** plane.



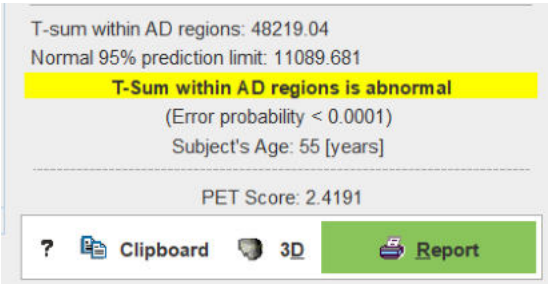
By enabling the **Show marker name in image overlay** box, the cluster numbers can additionally be shown in the image overlay.

The **Template space** section allows localizing the points of interest in the MNI template space. As soon as the cursor is moved over the images, the voxel coordinate is reported together with the t-value.

Note: The MNI template coordinate system is a right-handed subject-oriented system (like the Talairach system). Therefore, the x-coordinate is increasing from the right side of the image (subject left) towards the left side, which might be somewhat unexpected in the beginning.

Statistical Results

The numeric results are summarized in the lower right corner. The **AD t-sum** calculated for the subject (example below: 48219) is shown together with the upper normal limit (always 11089). If it is above 11089 the finding is abnormal, and the error probability is stated (p<0.0001).



The **PET Score** has a value of 1 for an AD t-sum equal to the normal limit, and >1 for abnormal t-sums. It has been shown to be closely related to the stage of AD, providing a measure of cognitive impairment. As it has a high test-retest reliability, it can be used as an imaging biomarker for clinical trials aiming at preventing dementia in MCI subjects.

The results can be saved via the **Clipboard** button, and then pasting into a suitable program such as MS Excel, as illustrated below.

Alzheimer Discrimination Results:

Evaluation Date: 2020.08.31
Evaluation Time: 14:33:51

[SUBJECT INFO]
Subject Name: PALZ1
Birth Date: 1956.04.29
PET Study Date: 2011.09.14
Subject ID : Highly abnormal, T-Sum 48219
Sex: F
Weight: 54.0
Size: 1.65

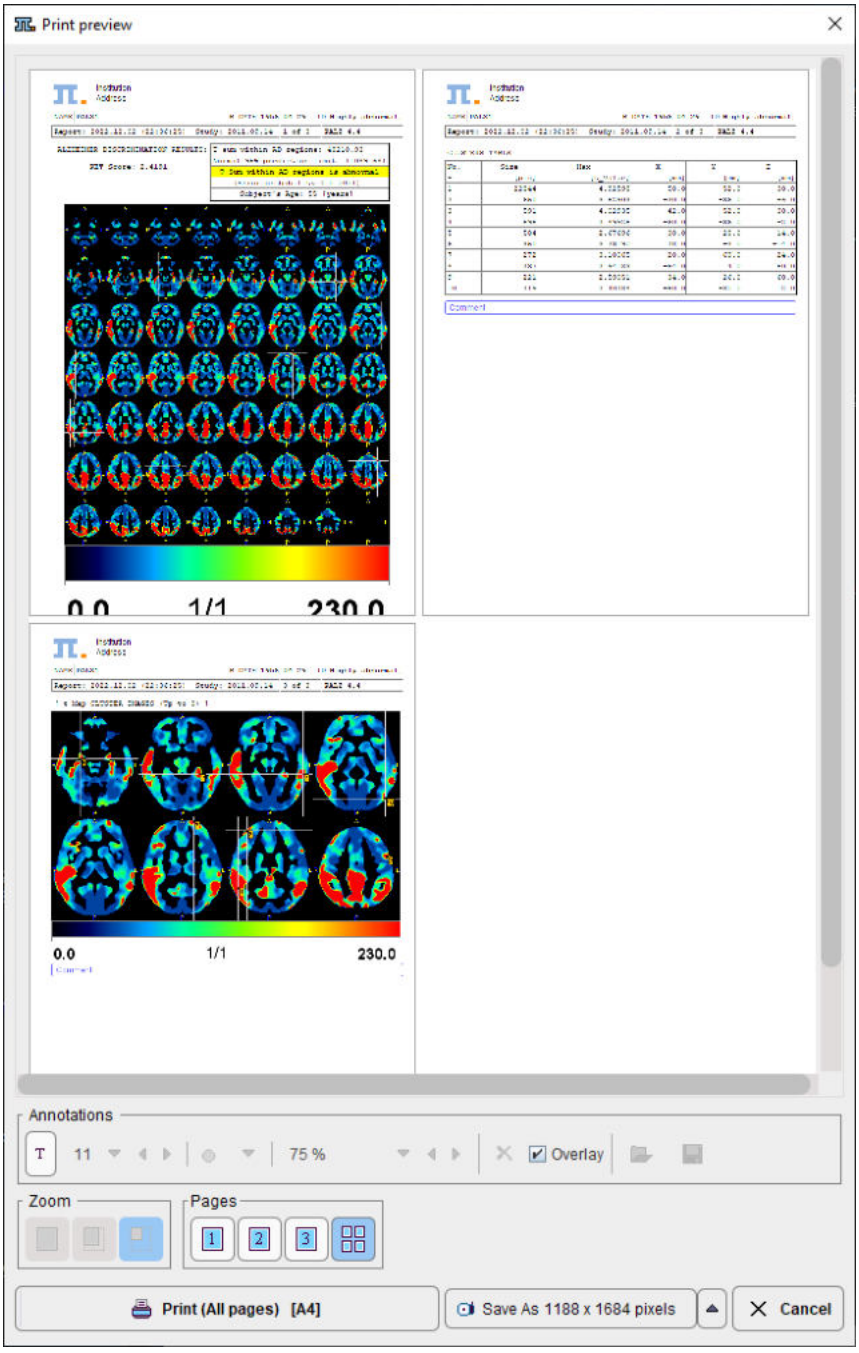
CLUSTERS TABLE:

No.	Size	Max	X	Y	Z
-	[pix]	[t_Value]	[mm]	[mm]	[mm]
1	22844	4.92582	58	-52	30
2	650	3.52901	-30	-36	-6
3	591	4.02966	42	52	30
4	595	2.89921	-60	-36	-2
5	584	2.67745	38	28	14
6	350	3.23179	28	-8	-14
7	272	3.1008	-20	68	24
8	237	2.94186	-54	4	50
9	221	2.59095	-34	26	60
10	219	2.40292	-50	-80	12

ALZHEIMER DISCRIMINATION RESULTS:
T-sum within AD regions: 48219.04
Normal 95% prediction limit: 11089.681
T-Sum within AD regions is abnormal
(Error probability < 0.0001)
Subject's Age: 55 [years]
PET Score: 2.4191

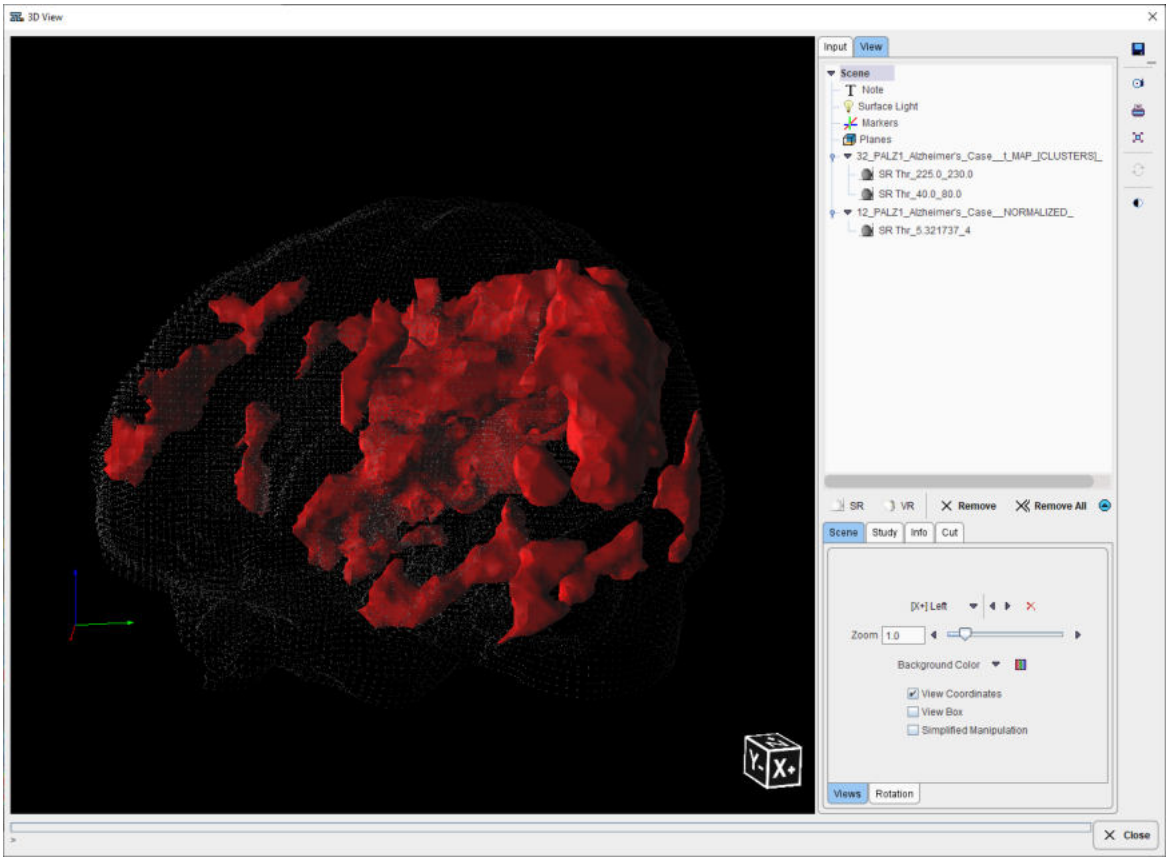
Results Documentation

When the **Report** button is activated a report dialog window appears. It contains the numeric outcome as well as the cluster images from inferior to superior, including markers at the cluster centers. The images are helpful for documenting left/right asymmetries.

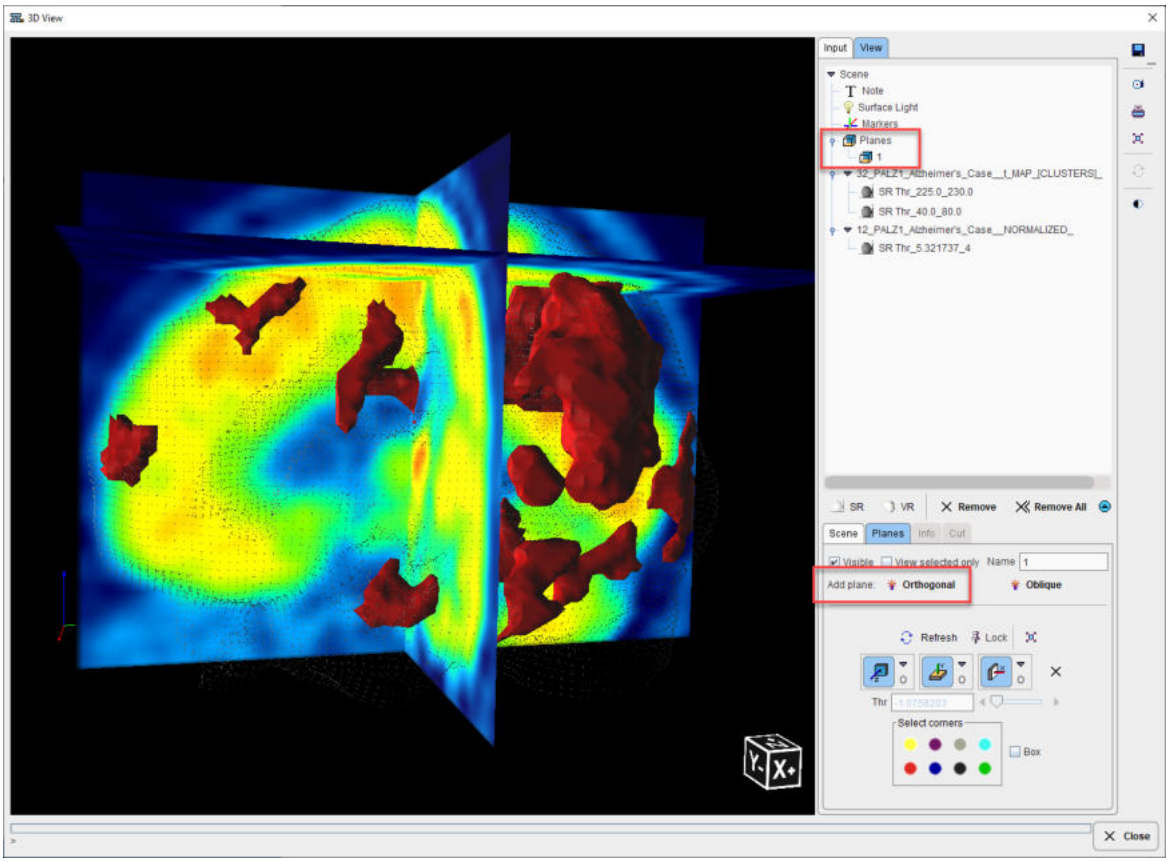


3.1.4 3D Result Rendering (separate Option)

If the PMOD 3D option is included in the PMOD license, the result of the analysis can directly be transferred with the **3D** button and a default rendering will be applied. In the example case the 3D tool will show an image similar to the one shown below.



This scene can interactively be examined and the rendering changed in a multitude of ways.



3.2 Processing in Extended Mode

3.2.1 Reviewing the Original Images

Non-DICOM Images

The **Original Images** page also contains a **Load Images** button for loading images in different formats.

Image Reviewing

The original subject images can be reviewed on this page. Please refer to the *PMOD Base Functionality Guide* to find out how to change layouts, colors, print reports, etc. The example below shows the orthogonal layout, but tiling arrangements are also possible.

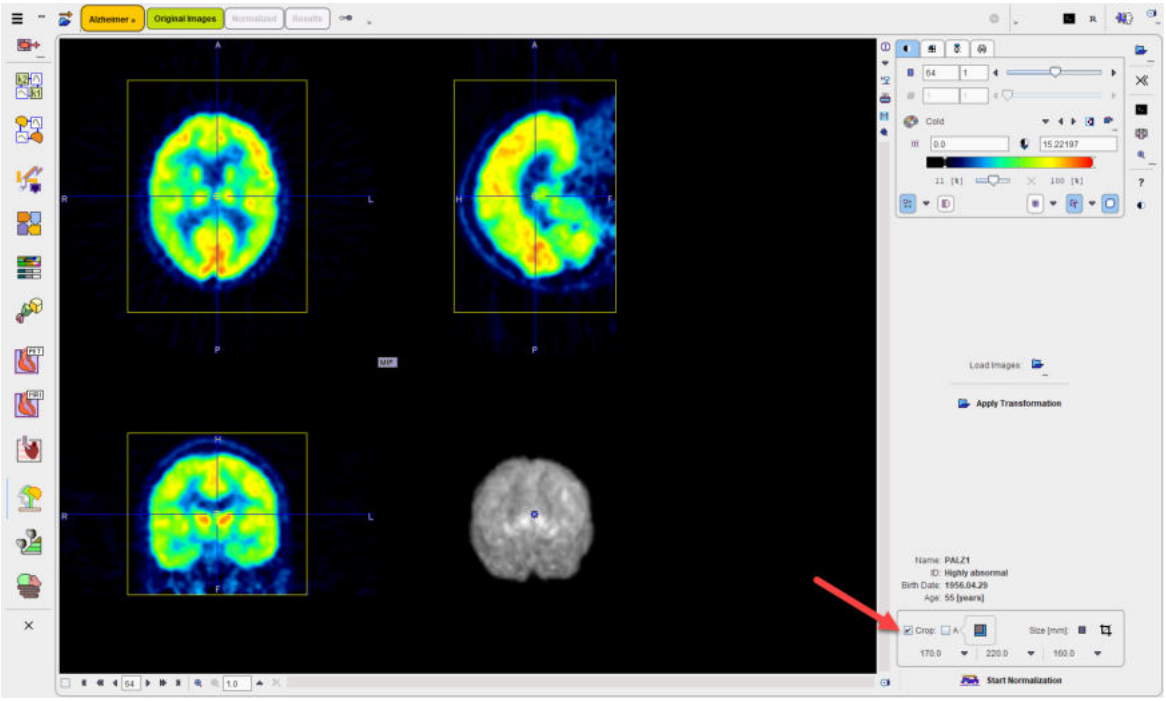
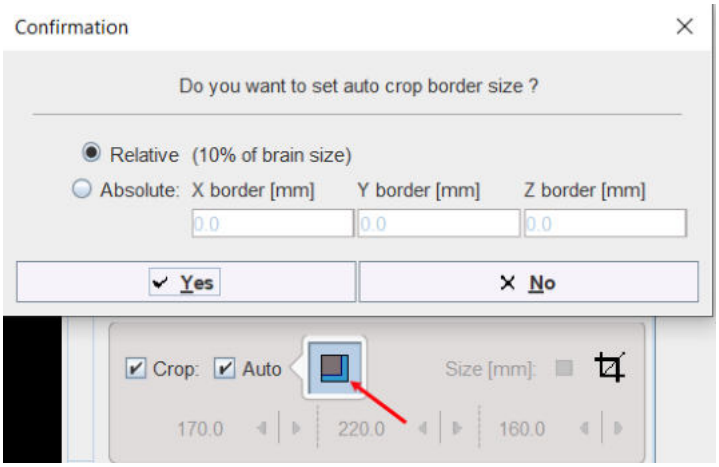


Image Cropping

If the image volume covers much more than the brain, it is advised to crop the data set to the brain. To do so, enable **Crop**. A yellow crop box appears which can be adjusted by clicking at the center of the brain. If the box size needs a change, use the arrow buttons to incrementally increase/decrease the edge length in a certain direction.

If the **Auto** box is enabled, the program tries automatically determining an appropriate cropping volume. In addition, use the button indicated below to specify a **Relative** or an **Absolute** value for the automatic border size:



Cropping can be executed explicitly with the button, but will automatically applied when progressing with **Start Normalization**.

Applying Transformations

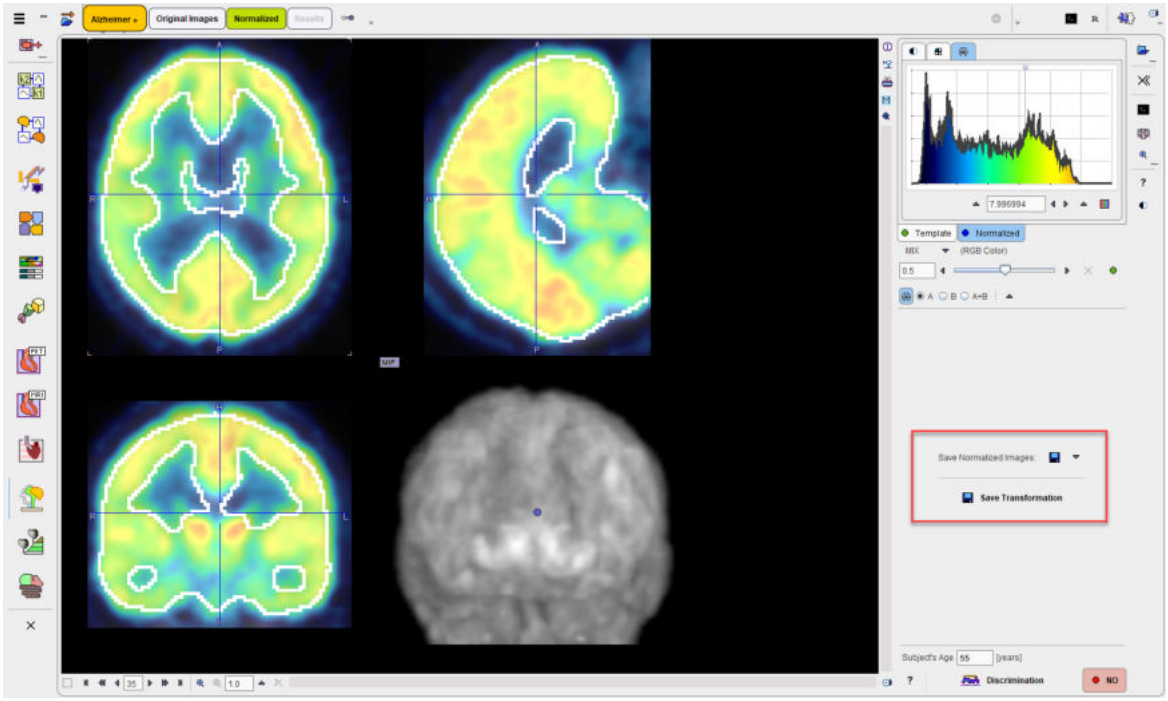
In the extended mode it is possible to save the stereotactic normalization transform (on the **Normalized** page). In case the analysis of the image series needs to be repeated, this transform can be loaded with the **Apply Transformation** button and applied to the image. As soon as the transformation has been retrieved, it is applied to the subject's FDG image and the result shown on the **Normalized** page.

Starting Spatial Normalization

The stereotactic normalization is started with the **Start Normalization** button.

3.2.2 Reviewing the Normalized Images

There are two additional features on the **Normalized** page.



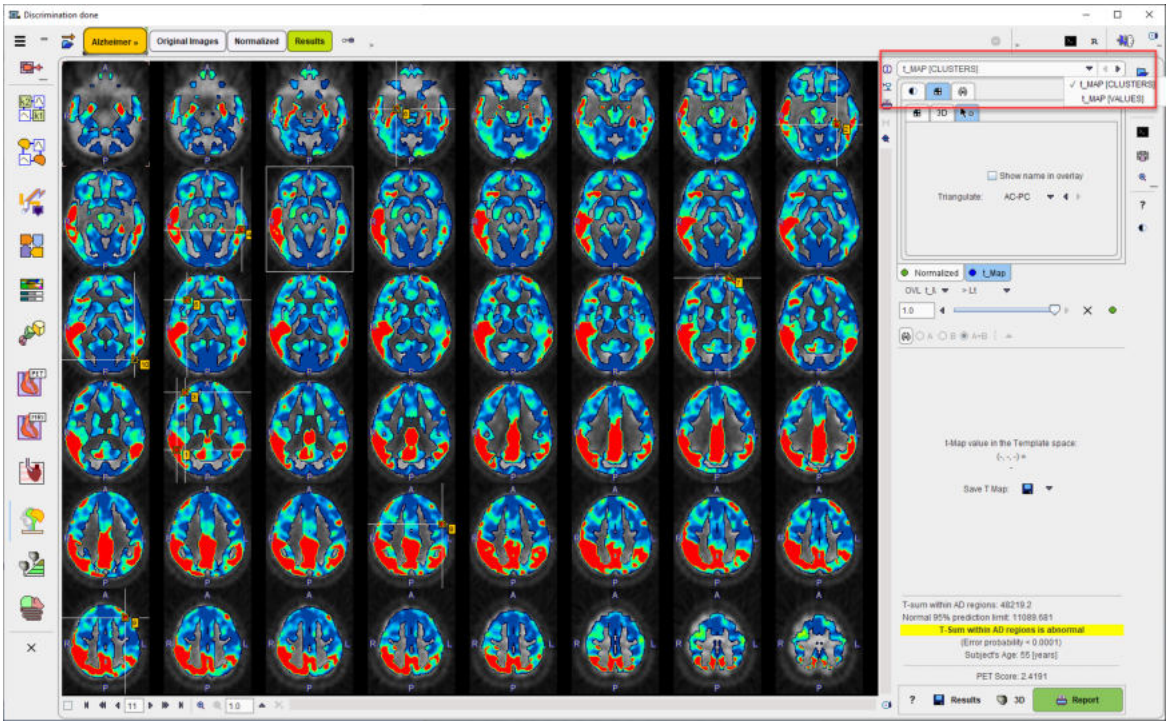
The normalized images can be saved for later referral in the **Save Normalized Images** section. As an indicator that they are the result of a spatial normalization they will contain the term **NORMALIZED** in the series description.

Note: it is important NOT to edit **Series description** for the **NORMALIZED** saved images.

Additionally, the SPM-compliant transformation matrix can also be saved using the **Save Transformation** button. It allows directly recalculating the normalized images from the original images without repeating the normalization calculation.

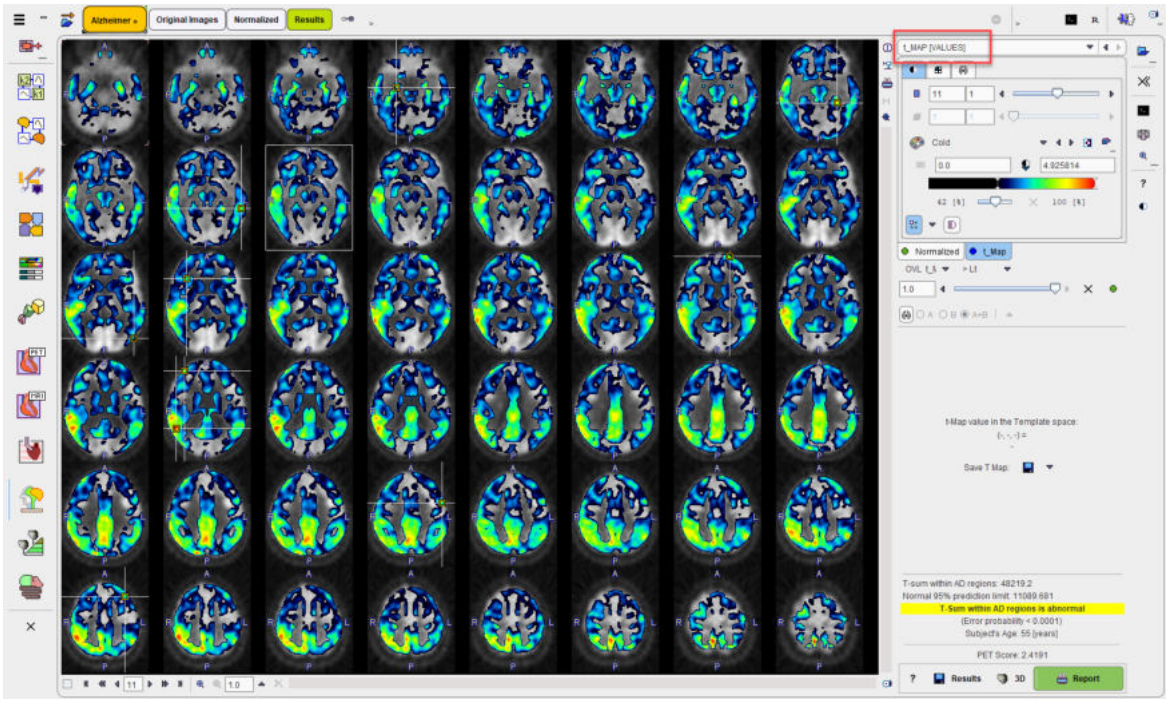
3.2.3 Results of the AD Discrimination Analysis

The extended mode provides additional features on the **Results** page.



Maps Selection

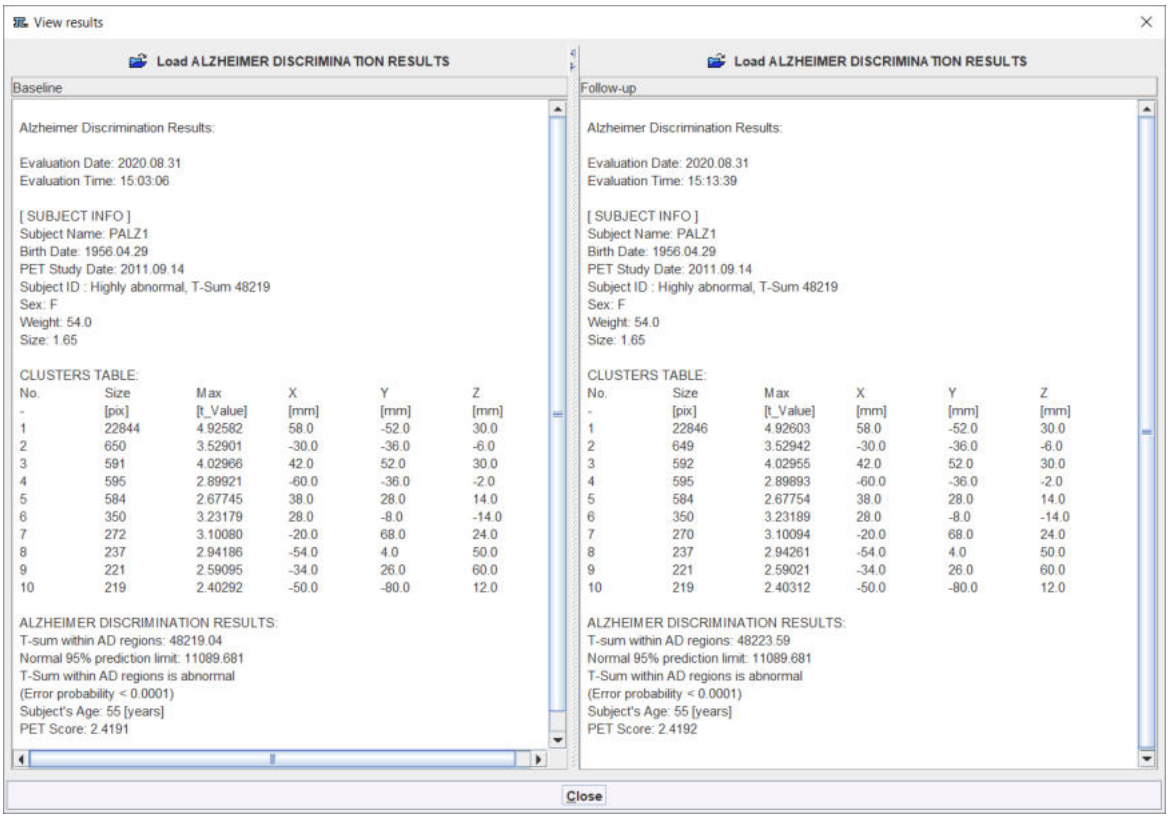
After selecting the **t_Map** panel, the user can select between the clustered t-values (**t_MAP [CLUSTERS]**) which is the default, and the raw t-values (**t_MAP [VALUES]**) as illustrated below. The selected data set can be exported for external processing or visualization using the **Save T Map** button.



Numeric Results Comparison

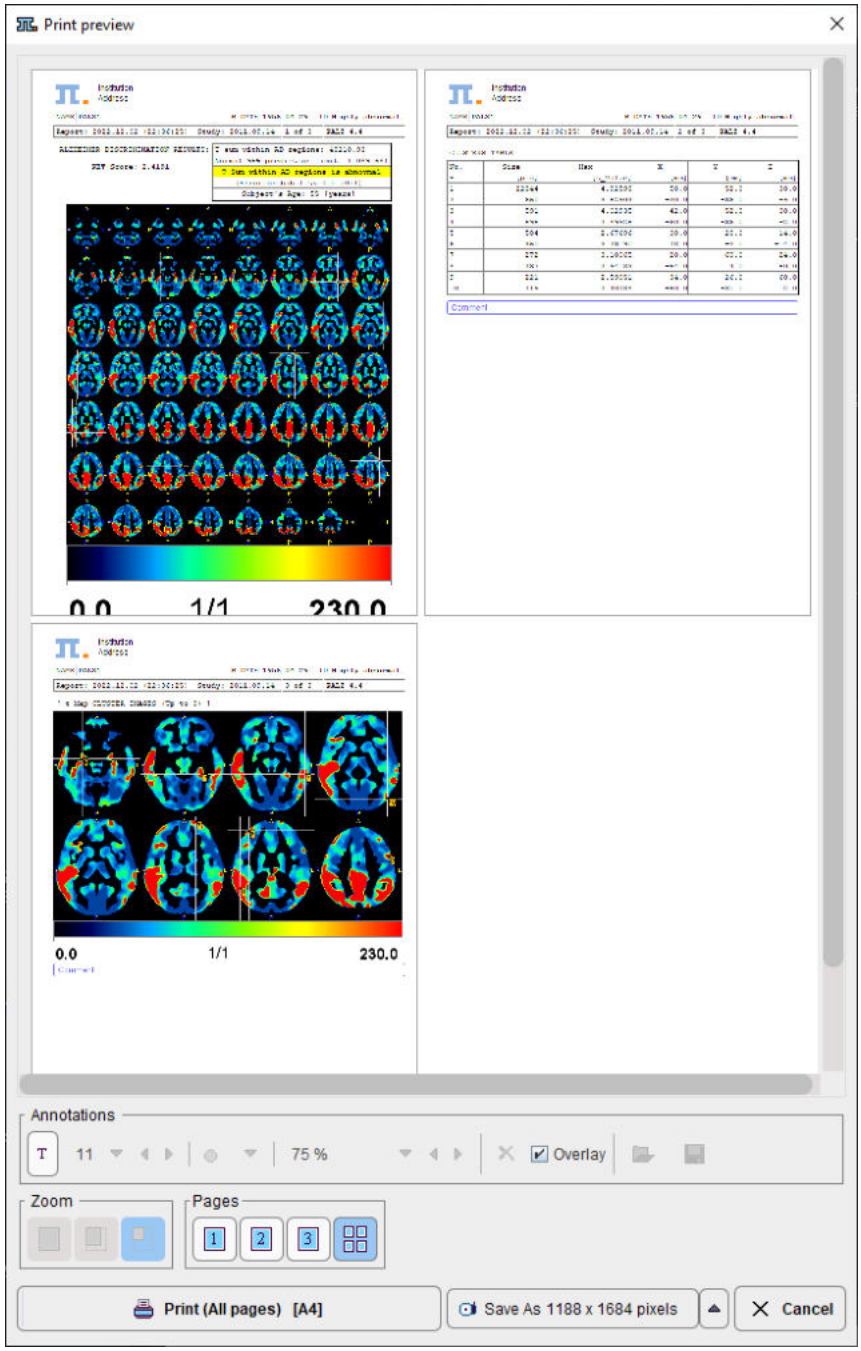
The result of the discrimination analysis is text information, which can be saved using the **Results** button. This file can either be opened in a general editor (eg. Wordpad, Excel), or using the View Results selection in the lateral taskbar of PALZ.

The PALZ result viewer has two windows, into which PALZ results can be loaded and compared side by side as illustrated below.



Report Pages

The illustration below shows the overview of the three available pages. To edit, save or print a page select it in the **Pages** section.



As described above, the first report page contains the discrimination result and slice images of the clustered t-map.

The second report page lists the clusters indicating the cluster size in number of contained pixels, the maximal t-value in the cluster, and the location of the cluster maximum in template coordinates. The list is sorted according to the cluster size.

Institution
Address

NAME PALZ1 B.DATE 1956.04.29 ID Highly abnormal,

Report: 2020.08.31 (22:12:57) Study: 2011.09.14 2 of 3 PALZ 4.2

CLUSTERS TABLE:

No.	Size	Max	X	Y	Z
-	[pix]	[t_Value]	[mm]	[mm]	[mm]
1	22844	4.92582	58.0	-52.0	30.0
2	650	3.52901	-30.0	-36.0	-6.0
3	591	4.02966	42.0	52.0	30.0
4	595	2.89921	-60.0	-36.0	-2.0
5	584	2.67745	38.0	28.0	14.0
6	350	3.23179	28.0	-8.0	-14.0
7	272	3.10080	-20.0	68.0	24.0
8	237	2.94186	-54.0	4.0	50.0
9	221	2.59095	-34.0	26.0	60.0
10	219	2.40292	-60.0	-80.0	12.0

Comment

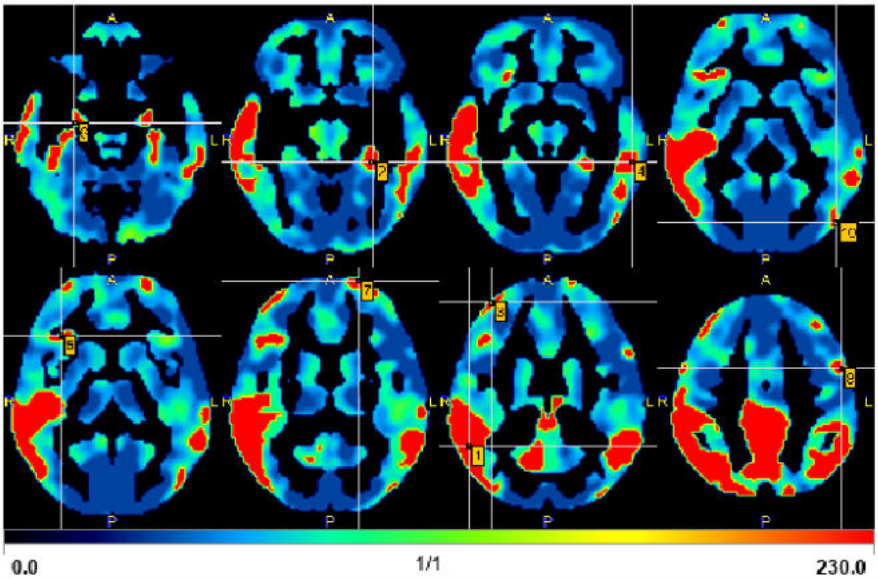
The third report page contains the slice images located at the cluster centers, ordered by slice location.

Institution
Address

NAME PALZ1 B.DATE 1956.04.29 ID Highly abnormal,

Report: 2020.08.31 (22:12:57) Study: 2011.09.14 3 of 3 PALZ 4.2

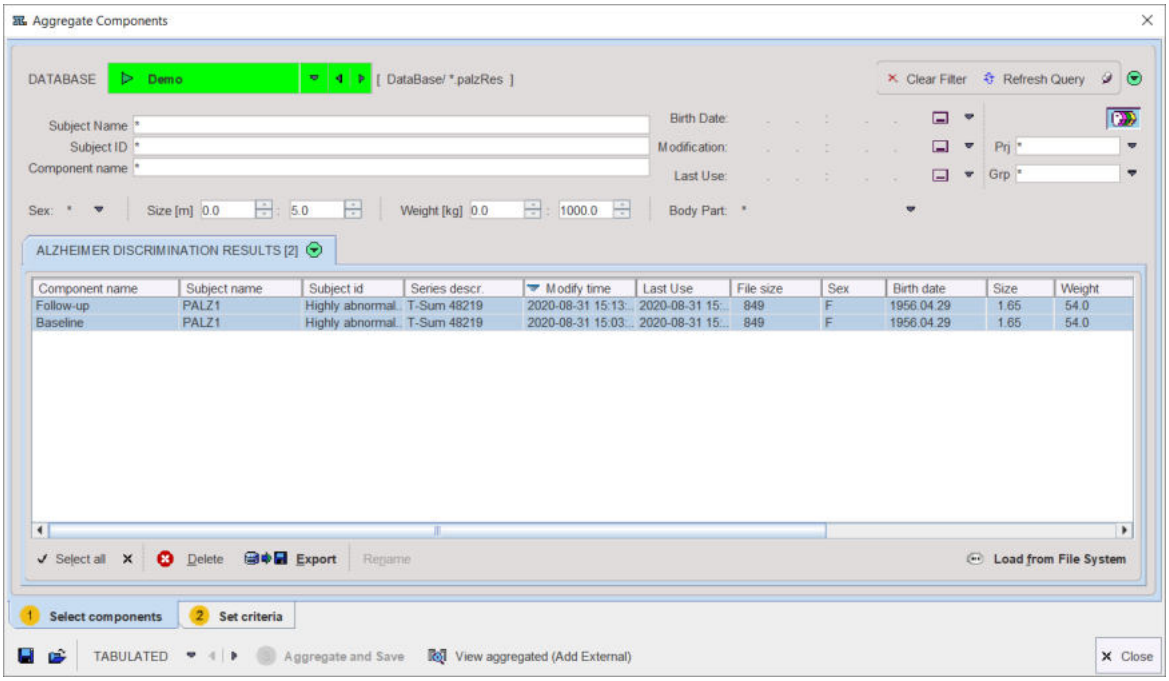
[t_Map CLUSTER IMAGES (Up to 8)]



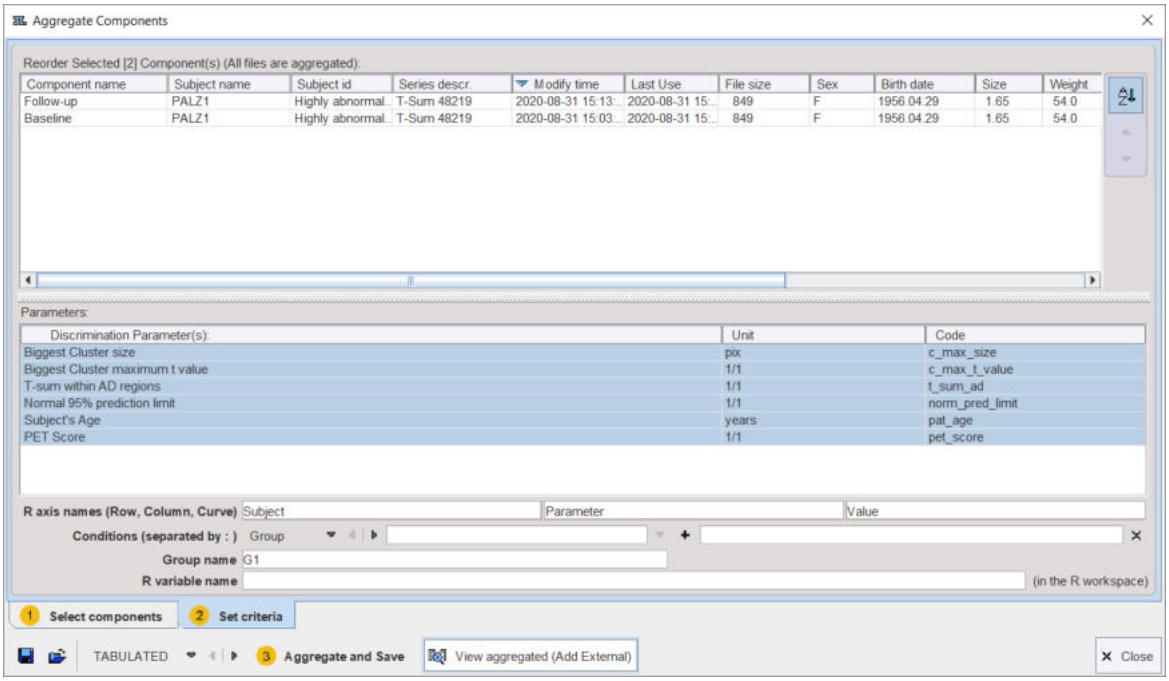
Comment

3.2.4 Results Aggregation

The **PALZ** lateral taskbar contains the shortcut button for the results aggregation. This feature allows concentrating the discrimination results which have been saved in ***.palzRes** text files for statistic analysis. It opens a dialog window with two tabs as illustrated below.



The **Select components** pane allows defining the files from which the results are extracted. The files may be available in a database as in the example, or alternatively using the **Load from File System** button to define the directory were the files reside. All appropriate data sets are listed. Select the entries to be used, and then switch to the **Set criteria** pane.

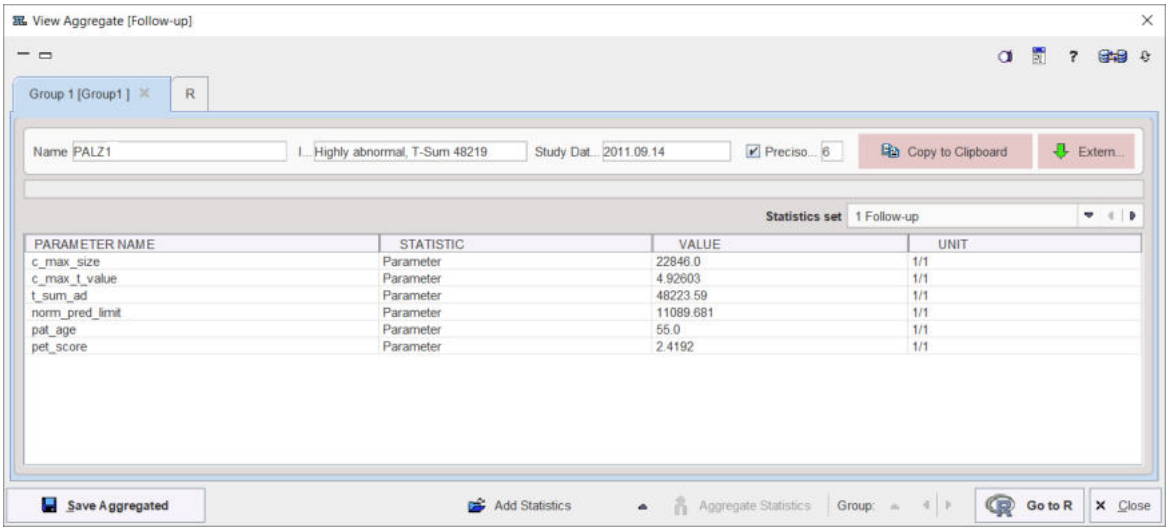


The upper list shows which data sets have been selected. The **Discrimination Parameter(s)** section shows the different parameters which are available in the data sets. Any of these parameters can be selected (CTRL+left mouse click) for defining which parameters shall be extracted from the data.

Finally, data extraction can be initiated with **Aggregate and Save**. This function extracts the parameters and saves them in a file which name has to be specified by the user. There are the file formats **EXCEL (.xls)** and **TABULATED (.dbTab)** available which has to be selected beforehand. Default output is **TABULATED**.

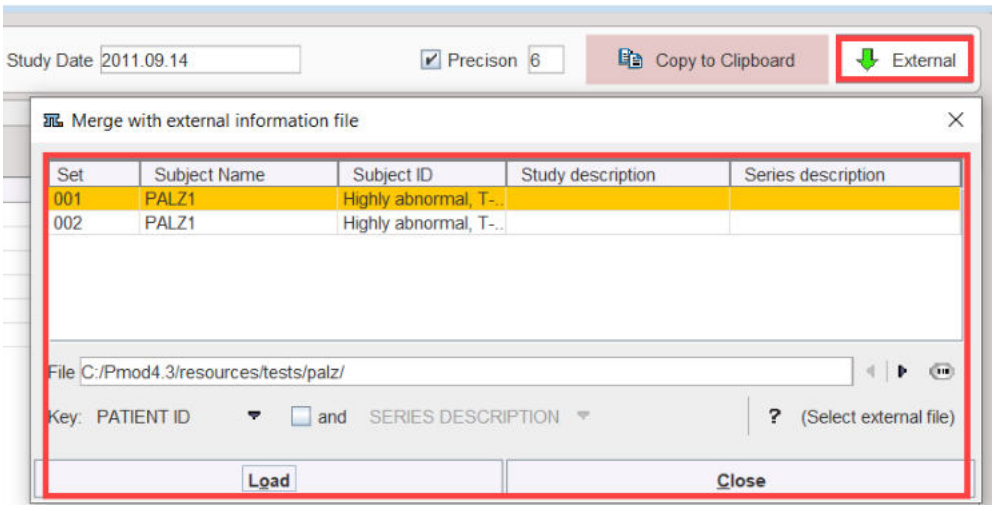
The saved aggregated file can be view with the

button, which is also available on the lateral taskbar. Upon retrieval, a dialog window opens and allows inspecting the aggregation results. The individual PALZ results are available for inspection in the **Statistics set** selection list. The aggregation results can be exported via the **Copy to Clipboard** button. Note that the created aggregate can also be loaded into the PMOD R console for statistical analysis.



Combination with External Data

For the statistical analysis, additional data might be relevant, for instance the blood pressure at scan time, or a mini mental test score. Such data can be included with the aggregate using the **External** button. It shows a dialog window listing the four identifiers **Subject Name**, **Subject ID**, **Study description** and **Series description** of the included data.

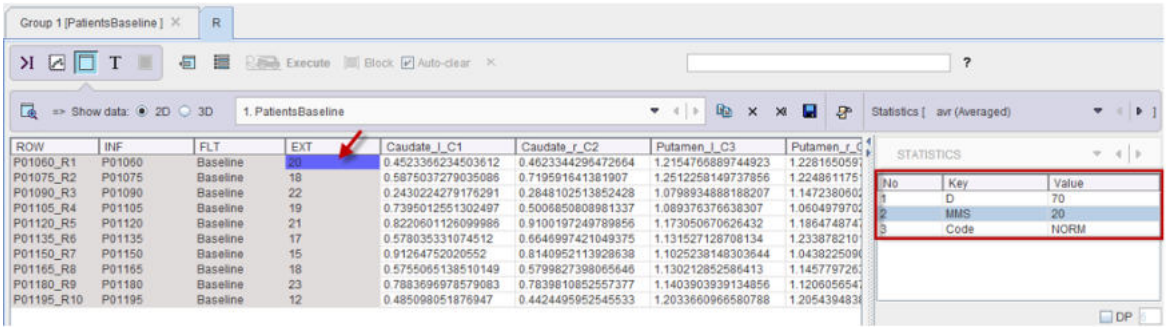


A tab-delimited text **File** with the external data has to be prepared and selected. It has the following structure, which is also summarized by the ? button:

```
# PMOD_EXTERNAL_DATA
# FORMAT[UNI]
# EXTERNAL
// PatientName  D[mmHg]   S[mmHg]   Code[string]
PKIN1           70         120       NORM
PKIN2           80         140       HYPO
```

Patient ID or **Patient Name** can be used as the **Key** for relating the information in the aggregate and in the file, and if this is not unique, it can be combined with **STUDY DESCRIPTION** or **SERIES DESCRIPTION**. Use **Load** to perform to extend the aggregate, and **Save Aggregated** to save the result.

Note that the added external information is not visible in the **Group** window. However, after transferring the information to R using **Go to R**, the external values are encoded in the **EXT** column as illustrated below:



Note: Please note that when numeric **PatientName** or **PatientID** are defined, they have to be converted in "char" format in Excel. This can be easily done forcing the content of the Excell cell to a text representation using the character apostrophe **'** at the beginning of each name/ID definition (eg. **'10**). Otherwise the external data will not be read by Pmod.

4 References

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