NeuroQ User Manual

NeuroQ™

Quantitative Analysis for Neuroimaging Technology

Display and Analysis Program
Version 3.8

Operator Guide

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Disclaimer: *The quantitative analysis provided by NeuroQ is intended to assist a trained physician to analyze PET or SPECT brain images. It was not meant to replace or eliminate the standard visual analysis of the PET or SPECT brain study. The physician should integrate all of the patients' clinical and diagnostic information, i.e. patients' history, quality control images, visual interpretation of the brain images, and quantitative results, prior to making his /her final interpretation. The final responsibility for interpretation of the study lies with the physician.*

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NeuroQ General Statement

Indication	The NeuroQ™ 3.5 – 3.8 program is used to regionally quantify activity in brain PET and SPECT scans using a ROI count method. It displays co-registered PET, SPECT and CT images, along with output from quantification of activities reflecting regional concentrations of FDG, amyloid imaging agents, SPECT perfusion and dopamine transporter radiotracers, relative to activities in any of several user-selected reference regions or whole brain. It provides for displaying and quantifying the regional differences between two PET or SPECT brain studies for the same patient, or the levels of amyloid imaging agents retained in specified brain regions of a patient, and for assisting the user in the examination of brain scans acquired for assessing differential diagnosis of neurodegenerative processes underlying symptoms of cognitive and movement disorders by comparing regional activity values to each other and to those in brain scans acquired for asymptomatic control subjects. These neurodegenerative

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	processes can be Alzheimer's disease, Lewy body dementia, Parkinson's disease with dementia, vascular dementia, and frontotemporal dementia.
Warning	The product is intended for use by trained nuclear technicians and nuclear medicine physicians. The clinician remains ultimately responsible for the final interpretation and diagnosis based on standard practices and visual interpretation of all SPECT and PET data. This program serves merely as a display and processing program to aid in the diagnostic interpretation of a patient's study. It was not meant to replace or eliminate the standard visual analysis of the PET brain scan. The physician should integrate all of the patients' clinical and diagnostic information, i.e. patients' history, quality control images, visual interpretation of the PET brain scan, and quantitative results, prior to making his final interpretation. This comprehensive processing technique (as with all diagnostic imaging) is not perfect, and will be associated with some false positive and false negative results. This program has no direct adverse effect on health since the results represent only a part of the information, which the physician will utilize for his final interpretation. The final responsibility for interpretation of the study lies with the physician.
Accuracy	The sensitivity and specificity associated with this medical device and this accuracy is published in peer review medical journals. The program is used as an adjunct or additional tool that the physician can use to integrate the output into his clinical interpretation of the study. The initial validation used 44 patients, 26 were documented by clinical longitudinal follow-up to have progressive dementia and 18 were documented by clinical longitudinal follow-up to have a non-progressive course. In this study which compared expert visual interpretation to NeuroQ the sensitivity was 80% for visual and 81% for NeuroQ (1). The specificity was 89% for visual and 93% for NeuroQ. In another study comparing visual to NeuroQ in a separate set of 68 patients the sensitivity was 84% and specificity 94% for NeuroQ with an accuracy of 87% (1). It is our contention that this accuracy will not be changed significantly in the current populations. We continue to perform validation through our testing method by insuring that the output values obtained in a subset of patients used in our testing remain within 1% of the original results which insures that we would obtain the same accuracy in the clinical population that was used previously.
Help/About	The version number and Global Unique Device Identification Database (GUDID) information can be located within the NeuroQ application by going to the Help/About section in the program.
Installation	The installation instructions can be found on our website: https://www.syntermed.com/client password: Client123. Click on the NeuroQ link and open up the NeuroQ Installation Guide document for the instructions. Syntermed will also assist in installation and training remotely via the web. Syntermed can be reached at 888-263-4446 ext. 1.
Rx Statement	Caution: Federal law restricts this device to sale by or on the order of a physician. The NeuroQ application is to be used for the analysis of PET and SPECT brain images produced from brain imaging radiopharmaceuticals. There are no contraindications or adverse reactions associated with this device. Warnings and precautions for the use of this device are described in this user manual.
Hardware Specifications	Minimum: MS Windows 7 SP1 (32 or 64 bit), core i3/i5, 4Gb of RAM and a 24" 1080p monitor

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	Recommended: MS Windows 7 SP1 (64 bit), core i7, SSD, 8Gb of RAM and a 24" 1920x1200 monitor. NeuroQ requires a horizontal resolution of at least 1280 (i.e. 1920x1200 monitor used in portrait mode is not recommended). Note: While systems not meeting the minimum requirements may run, your experience will be better when meeting or exceeding the recommended list.
Cybersecurity	The risks associated with cybersecurity and the NeuroQ™ medical device have been assessed and resolved to a satisfactory level. The risks are associated with the files or images being corrupted by a security breach. There are methods in place to prevent this corruption through MD5 checksums, encryption, multiple patient labels on output screens to allow for patient authentication by users, and using methods for compiling of code and interfaces that substantially reduce or eliminate the ability to corrupt the code. In addition, it is the responsibility of the local information technology personnel at the institution to implement the necessary security methods and procedures to restrict access to the computers and data stored on these systems. Some of these methods include limiting access to trusted users through user ID and passwords, implementing timed methods to terminate sessions, and using strengthen password protection methods. They should also ensure trusted content and implement methods for detection of security compromises and for retention and recovery. New software versions as well as patches are compiled and moved to a known clean computer and are checked there for viruses and malware. Software is then packaged together into an installer which is signed with a key to ensure the installer remains intact throughout testing and on to distribution. Validated software updates and patches are provided at least annually and whenever a cybersecurity risk is identified. Notification of availability of these patches is made through the software itself. These updates are delivered as signed installers that present signature information to the user to confirm validity of the source of the patch. It is always recommended that the installation environment have adequate, updated anti-virus and anti-malware scanners in place. It is also recommended that a firewall, by default, deny all inbound and outbound traffic on the network. At installation time, a list of ports and destinations for firewall exceptions is provided specific to each installation.
Authorized Representative	Medical Device Safety Service GmbH (MDSS) Schiffgraben 41, 30175 Hannover, Germany
Application Backup	The customer is responsible for backing up the application data. The folder to be backed up is the C:\ProgramData\Syntermed folder (on Windows 7 and above). We recommend backing up this data at least once/week. If the customer wants data encryption "at rest" then this folder or the entire drive it resides on should be encrypted by the user (we recommend BitLocker as it is built into Windows).

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Quantitative Analysis for Neuroimaging Technology
Version 3.8

Overview

The **NeuroQ™** Display and Analysis Program has been developed to aid in the assessment of human brain scans through quantification of mean pixel values lying within standardized regions of interest, and to provide quantified comparisons with brain scans derived from FDG-PET or HMPAO SPECT studies of defined groups having no identified neuropsychiatric disease or symptoms, i.e., asymptomatic controls (AC). The Program provides automated analysis of brain PET and SPECT scans, with output that includes quantification of relative activity in 240 different brain regions, as well as measures of the magnitude and statistical significance with which activity in each region differs from mean activity values of brain regions in the AC database. In addition, the program includes NeuroQ™ Quality Control Screen, PET/CT display screen, patient study comparison analysis, amyloid analysis and EQuAL™ a tool for evaluating temporal lobe Epilepsy, PET/MR display screen, saving the cluster screen, remembering display settings, auto processing, and ability for the user to generate their own normal limit and use within the NeuroQ™ application. The new features of version 3.8 include a quantitative analysis of basal ganglia analysis. This manual describes the display and analysis features of the program, and their end-user operation.

Program Description

The NeuroQ™ Program is indicated to:

1) Assist with regional assessment of human brain scans, through automated quantification of mean pixel values lying within standardized regions of interest (S-ROI's).
2) Assist with comparisons of the activity in brain regions of individual scans relative to normal activity values found for brain regions in FDG-PET scans, through quantitative and statistical comparisons of S-ROI's.
3) Compare activity in brain regions of individual scans between two studies from the same patient.
4) Compare activity between symmetric regions of interest within the brain PET study.
5) Perform an image fusion of the patients PET and CT data.
6) Provide analysis of amyloid uptake levels in the brain.
7) Provide analysis of basal ganglia analysis.

The program requires the operator to select the patient's FDG or HMPAO SPECT Brain scan. Following a number of internal checks on the data (e.g., accurate radiopharmaceutical), for FDG, the operator has to initiate the quality control sequence which includes setting the reference line over the brain, perform a scalp correction on the data, subject the data to rigid registration to correct for brain tilt, and perform elastic spatial reformatting or normalization of the patient's scan into a standardized volumetric space. Following this step, the program determines the uptake in 240 ROIs, normalized to the uptake in the subject's sensorimotor cortical region (S-

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ROI). The uptake in the ROIs is then compared to a normal data base of uptakes, based upon uptake in the corresponding S-ROIs determined in 50 normal subjects without identified neuropsychiatric disease. Any region with an uptake below 1.65 S.D of the mean, established from the normal data base is considered abnormal as defined by falling within the lowest 5% of a normal distribution, with respect to regionally quantified control data*.

* (or the highest 5% of a normal distribution, for those cases in which NeuroQ is being used to identify hyper- rather than hypo- activity of radiotracer).

![Syntermed logo — Software solutions for medical imaging]

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Processing

The FDG PET or HMPAO SPECT files in DICOM format need to be selected and imported into the NeuroQ™ program. Once this is done the initial NeuroQ™ Quality Control Screen will be displayed.

1) Note: when the study is first launched the Database in use should list the appropriate database for the patient selected. If the database is incorrect then go to the Control Database menu item and select the proper normal limit database before proceeding to the processing section.
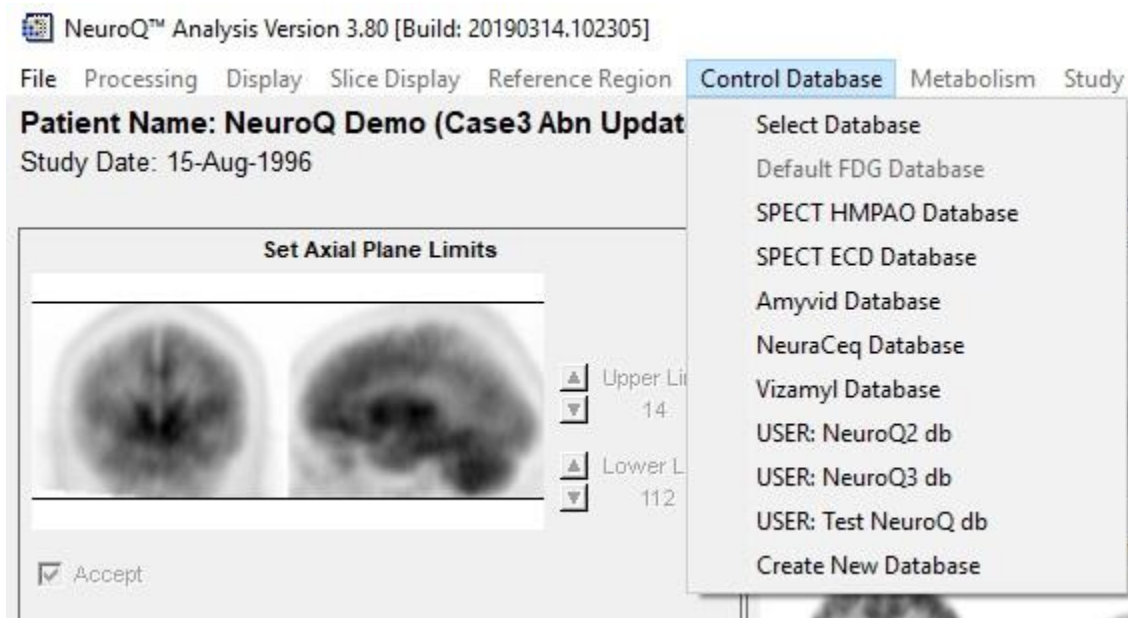
2) The processing for the study is automatically performed by NeuroQ and these steps include: setting axial limits, performing scalp correction, and performing rigid registration. These processing steps are described below.

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NeuroQ™ Quality Control Screen

The Quality Control Screen is comprised of three sections: Set Axial Plane Limits, Removal of Scalp Activity, and Rigid Registration. As mentioned above, these steps will automatically be performed and each of the check boxes will be checked when the processing is completed as shown above.

Set Axial Plane Limits

![Syntermed logo]

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This feature allows the user to set the upper and lower limits for reconstruction by clicking the up and down arrows to move the lines. The limits can also be set by moving the cursor to a point on the image and click left to set the limit. The limits should be set so that only the brain images are included in the reconstruction. When the limits are set to the proper location check the Accept box.

Removal of Scalp Activity
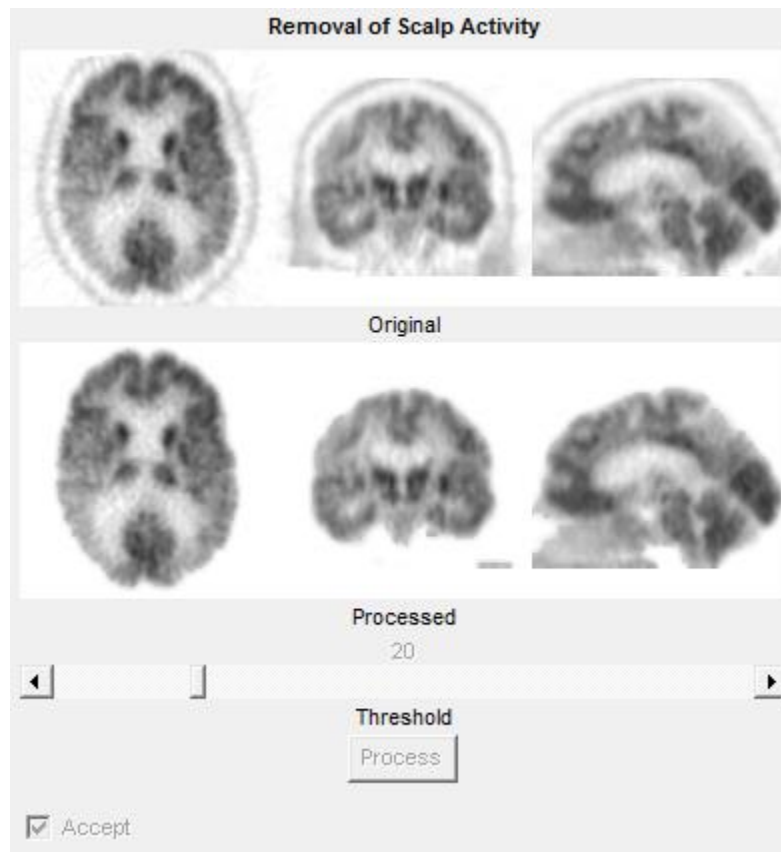
This feature allows for the removal of the scalp activity around the brain. In some cases there is excessive scalp activity which can interfere with the reformatting of the patients study to match the normal template. Move the slider bar to the desired threshold and then click on the Process button. It is recommended that the scalp correction be applied to every study and use 20 as the setting. The processed images are shown in the bottom row. Triangulation is enabled on these images by clicking left on any image and it will show you the plane for that location on the other two images. When the images are processed for scalp correction the Accept box will be checked.

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Rigid Registration
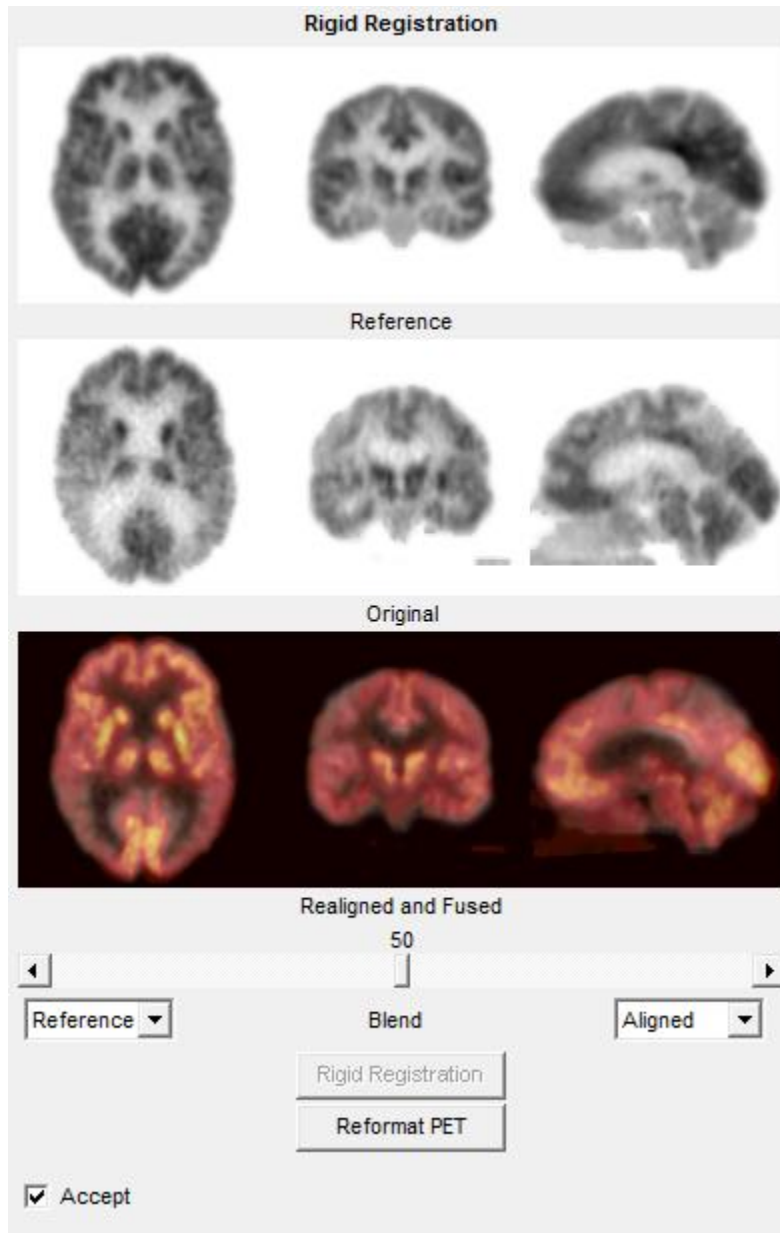
The Rigid Registration allows for applying additional registration prior to the reformatting process used in NeuroQ™. This additional registration is helpful in cases where the patients head has excessive tilt. It is recommended that rigid registration be applied to all studies prior to reformatting. The top row shows the normal template as the reference image the middle row are the patients images and the bottom row are the fused reference and patient images after realignment. Triangulation is enabled on these images by clicking left on any image and it will show you the plane for that location on the other two images. When the images are processed

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the Accept check box will be checked. The user should review each of the QC images once processing is completed and agree that the processing is acceptable before proceeding. If all of these QC steps are performed properly then click on the Reformat button and the study will automatically be reformatted with 10 iterations which is the recommended number of iterations for the reformatting of the study.

3) The next step involves reformatting the patient's transaxial slices to fit the normal template transaxial slices. This is performed by selecting the Reformat PET (or SPECT) button. The registration algorithm used for reformatting of the patient's data is a robust spatial transformation method published by Henry Huang and Ed Hoffman, along with their collaborators. It was originally described in IEEE (Tai et al., *IEEE Trans. Nucl. Sci. NS-44* 1997; **4**: 1606-1612.)
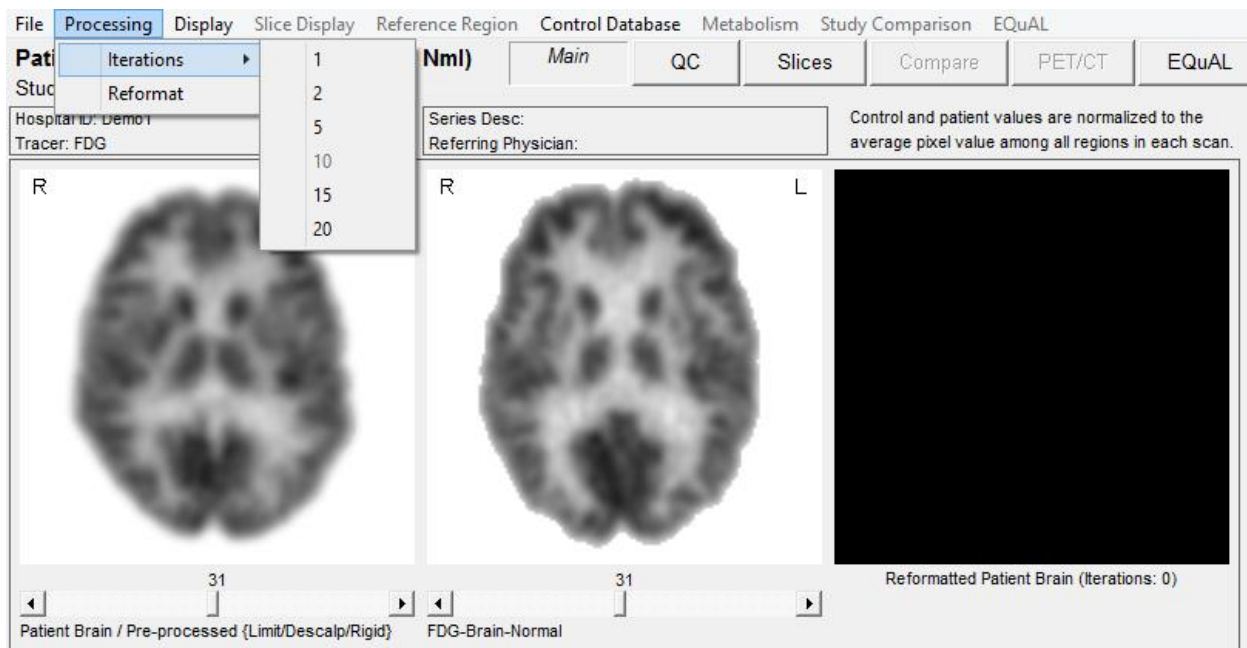
Note: in some cases the user may want to use a different number of iterations. This is performed from the Processing menu item and select Reformat from the drop down box as shown above.

4) For the most standard use of the Program (i.e., comparing an individual scan from the end-user's site to NeuroQ™ 's built-in database), if all of the QC processing is performed as described in the previous section then it is recommended to use 10 iterations, and this is the only option that normally will ever need to be selected. The other choices in the Iterations pull-down menu (1, 2, 5, 15 and 20) have been retained in order to allow flexibility to use the tool in other ways: for example, 1) rapid testing of software operability by selecting a small number of iterations, 2) processing a batch of scans acquired at the end-user's site to create a new database with whatever number of iterations is desired, 3) sequential use of the reiteration routine, such as adding another 5 iterations to a scan that had already been re-

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iterated 20 times in order to obtain a closer spatial fit in a case where the individual's original scan is structurally very different from the normal template scan, 4) various research applications, etc.

5) Once the Reformat button has been selected, an information box will be displayed informing you of the number of iterations you have selected.
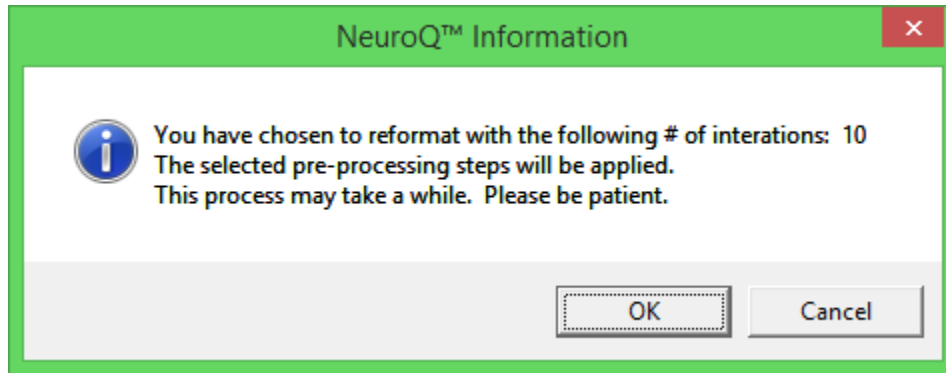
6) Click on the OK button and the patient's study will be reformatted to align with the normal template. On a current processor (core i7) the reformatting will take approximately 1 minute.

7) Once the study is reformatted the final quantitative analysis output will be displayed which is shown below.

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The left side of the window contains the **"NeuroQ™ Analysis"** screen and the right side contains the **"NeuroQ™ Display"** screen. These displays are defined below.

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NeuroQ™ Analysis Screen (Left Side)

1. **File Menu** – this allows the user to print the current screen, save the current screen in various formats, save just the cluster screen in the same various formats, pop-out a new window that displays a table of the abnormal clusters along with the cluster screen, set preferences for the default language and the default database, access the data screen, access the help screen and quit from the application. The Options for the save screen formats are shown below. Note: The DICOM Screen Capture allows the data to be saved in a format acceptable by PACS systems.

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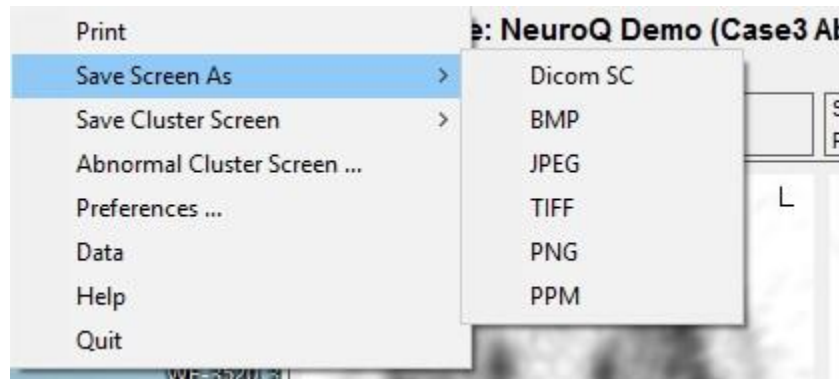
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a. Example of the new pop-out window displaying the abnormal clusters along with the cluster screen. There are options to print and save this screen under the File menu.
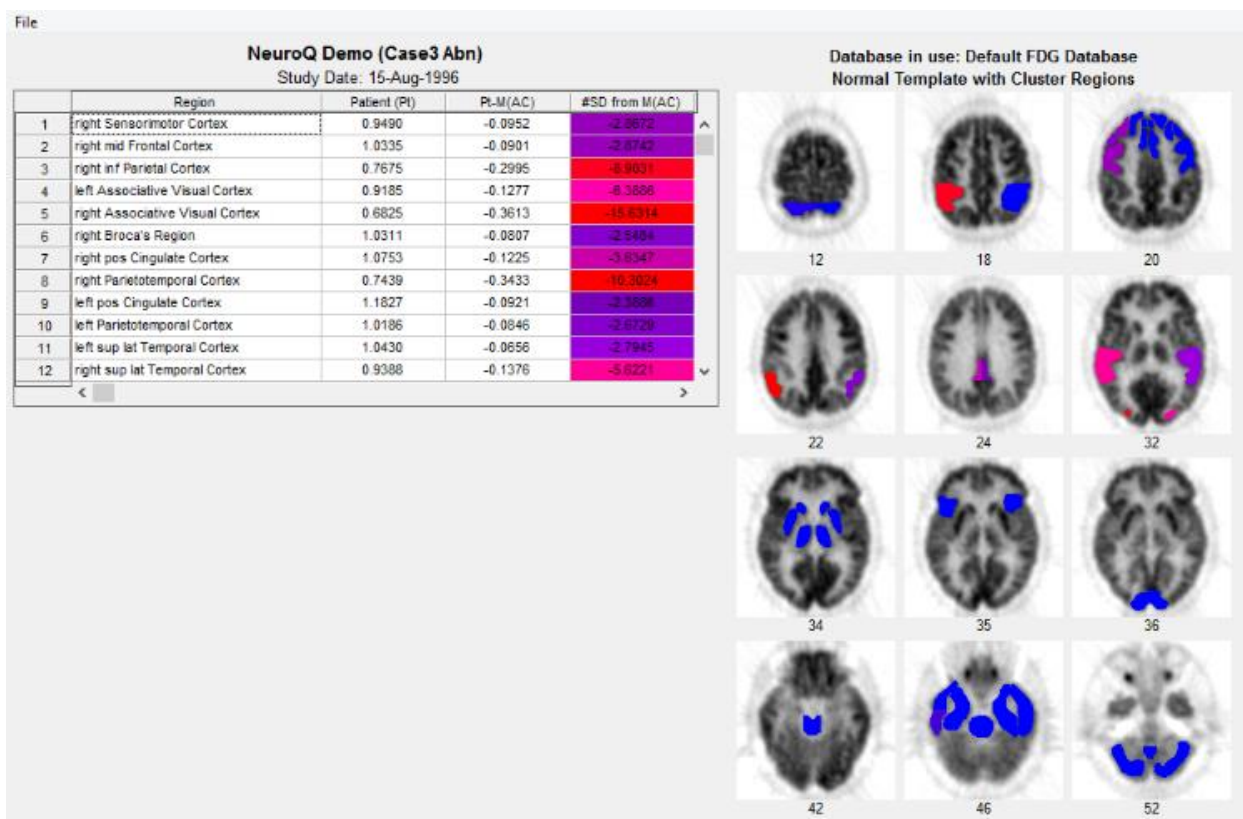
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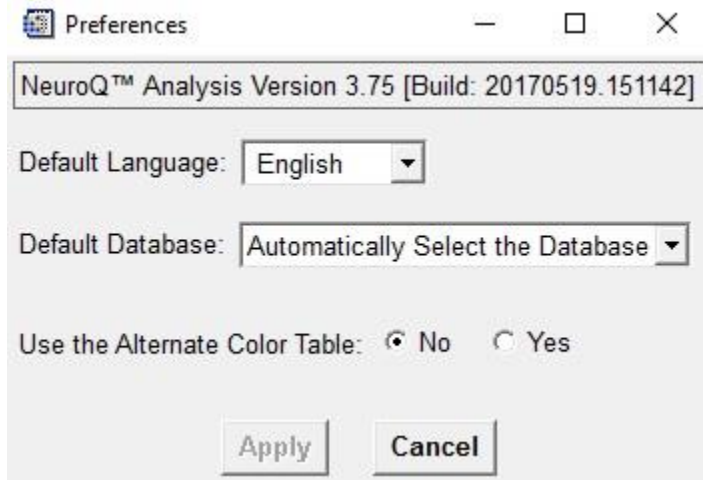
b. Preferences Screen for setting the default language, the default database, and an option for using an alternate color table for the cluster screen colors (blue -> yellow instead of blue -> red) that may be useful for users with Blue/Red color blindness.

c.   Data – The data button will display the data screen which gives the "mean" (average number of counts per second per pixel in each ROI) for each of the 240 ROIs of the patient; "norm" refers to the "mean" normalized to the average of all pixels in all ROI's (default). This screen is shown below. This data can be saved and then imported into another application like Excel for further analysis. You have the option to "Save Tables", which are the tables presented on the Main screen for regions and clusters; "Save Raw Regions", which saves the raw information for the ROIs; or "Save All", which saves all of the available information.

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NeuroQ™ Help — □ ✕

NeuroQ™ Analysis Version 3.80 [Build: 20191113.115039]

NeuroQ Version 3.x
Neurological Application Software

UDI: *+B133NEUROQ300/$$+73.80.201911132*

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The NeuroQ™ Quantitative display (right) is a schematic summary representing the analysis of 240 brain regions, comparing the patient's scan to the scans of an asymptomatic control group.

BLUE shades represent areas that are not significantly tracer hyper-retentive.

RED shades represent areas of most severe and most statistically significant tracer hyper-retention.

PURPLE shades represent areas where the tracer hyper-retention may be smaller in magnitude but remains statistically significant (due to low variance of activity in that area among normal subjects).

For more detailed information about a specific region, click on the area of interest.

Display Manual

d. Help – this option will display the version number of NeuroQ™ and also shows the Unique Device Identifier (UDI) information for NeuroQ. The NeuroQ™ User's Manual can also be displayed in PDF format by clicking the Display Manual button.

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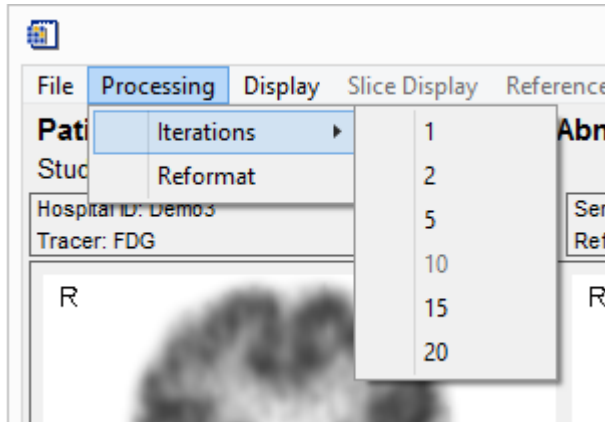
2. Processing Menu – allows user to reformat the brain, the default number of iterations is 10 and that value will be used if the Reformat option is selected from the Processing drop down list. This processing step is described above in the Processing section.
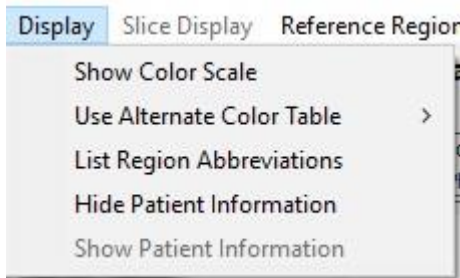
3. Display Menu – the display menu allows you to display the Color Scale, display a list of region abbreviations, and hide/show patient information. The options are shown below.
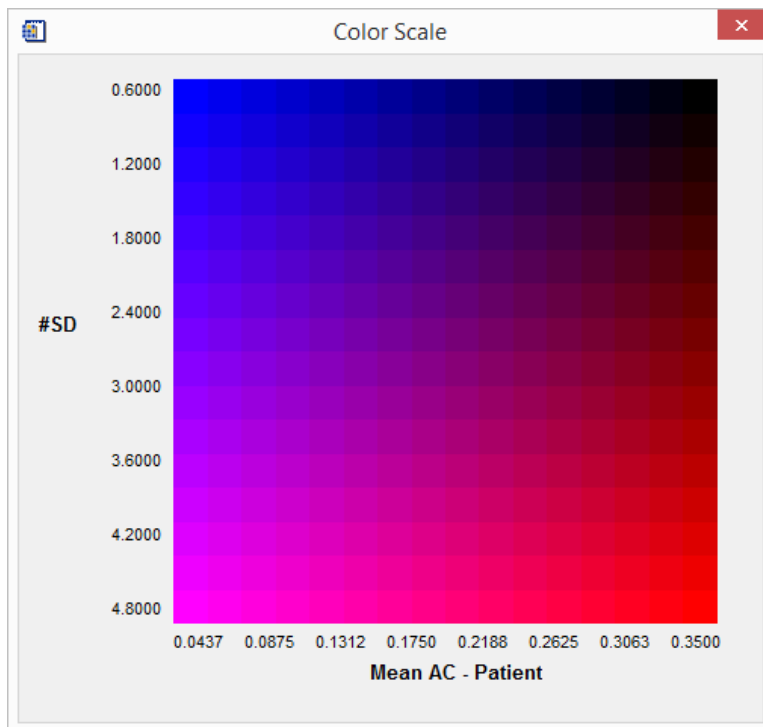
a. "Show Color Scale" provides a legend of the two-dimensional color coding. The # of Standard deviations is listed on the Y axis and the % below the mean normal value is listed on the X axis.

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    b. "List Region Abbreviations" will list the various abbreviations used in the application along with their meaning, i.e. rAVC = right Associative Visual Cortex.

    c. "Hide Patient Information" will remove the patient identifiers from the screen (ie blank out the Patient Name, Hospital ID and Referring Physician).

    d. "Show Patient Information" will re-display the patient identifiers blanked out with "Hide Patient Information".

4. QC – The Quality Control screen allows the user to apply some preprocessing steps including setting axial planes limits, removing scalp activity, and performing a rigid registration. See Quality Control section above for a further description.

5. Slices – When the Slices button is selected it will bring up a new display window which initially will display the patients transaxial slices. From the Slice Display menu item you can also select to display the sagittal or coronal slices. This display is shown below.
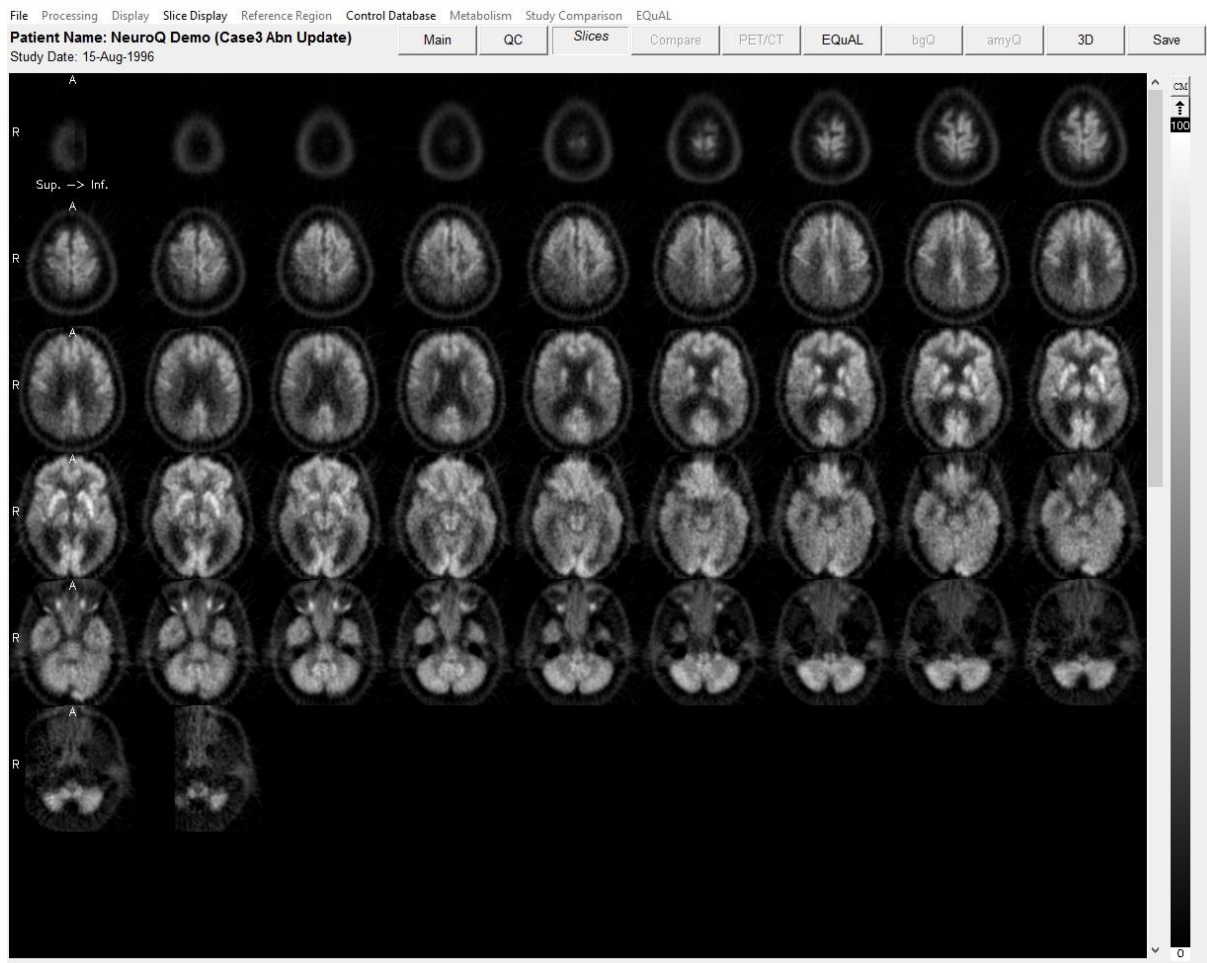
The initial display will show the patients slices in inverted grey scale. An option is provided to display other translation tables by clicking on the CM (Color Map) button located above the color translation bar.

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A table of color translation options will be displayed shown in table to the left. You can select any of these color tables and the display will change to reflect this color.

Changing up/low contrast – At the top of the color bar on the slices page is a value of 100 and at the bottom a value of 0. If you position your cursor over one of these numbers, click left, hold down, and move the value up or down you can adjust the contrast in the image. The upper value (100) when moved down will lower the upper value producing a brighter image. The lower value (0) when moved up will increase the lower value resulting in reducing counts in the image at the low end of the scale or darken the image.

You can display either the original images or images that have undergone registration from the Volume to Display drop down list. Note: to go back to the previous screen click on the Main button.

6. Compare – The compare screen allows the user to compare two studies from the same patient performed at different times. This analysis provides a Difference Image between the two studies showing which regions showed a change in hypo or hyper metabolic activity between the two studies. See the description of the Compare feature below.

7. PET/CT – The PET/CT screen allows the user to display both the PET and CT studies for the same patient – and fuse those two data sets using scroll bars. See the description of the PET/CT feature below.

8. EQuAL – The EQuAL analysis module is an optional feature that is helpful for evaluating temporal metabolic asymmetry. See the description of the EQuAL feature below for more information.

9. bgQ – This is an analysis for DatScan.

10. 3D – This is a surface rendered 3D display that shows a template 3D brain along with the superimposed 47 brain clusters. The display consists of 12 static views of the brain and when one is selected it can be manually rotated. The cluster names can be displayed by rolling over the cluster with the mouse.

11. Save – this option when selected will save all of the reformatted data and analysis into a single file called the NeuroQ™ Review File. This file can then be selected and the previous reformatted data and analysis will be displayed. This avoids having to reformat the data if it needs to be displayed at another time.

12. Patient Information – displays patient information.

13. Patient Brain Display – displays the original patient brain transaxial slices.

14. Left Plane Slider – controls the brain plane of the above patient brain display, the current plane number is displayed above the slider, slide to the left or right to access lower or higher planes respectively.

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15. Normal Template Brain – based on an archetypal normal brain with no clinical or metabolic signs of neurodegenerative disease; ROI values for each plane are drawn in with a white outline.

16. Middle Plane Slider - controls the brain plane of the normal brain display and the reformatted patient brain display at right; the current plane number is displayed above the slider, slide to the left or right to access lower or higher planes respectively, simultaneously for both displays.

17. Reformatted Patient Brain – brain is based on specified number of reiterations of the original patient brain scan; this display only appears after reiteration of brain images. All abnormal regions will be displayed in a two-dimensional coded color scale, click on the Help button for color coding explanation.

18. Table of Abnormal Regions – displays all regions having internally normalized region of interest (ROI) radiotracer uptake values falling more than 1.65 standard deviations below the mean value (in the Hypometabolic operation) and more than 1.65 standard deviations above the mean value (in the Hypermetabolic operation) for a symptomatic control group; regions are displayed in abbreviated form with the plane number after the ".p"; the last row of the table gives a total of the "Pt-M(AC)" and "#SD from M(AC)" columns. By clicking on a hypometabolic region in the reformatted patient brain image, the name of the region will be displayed above the region table and the rwo of the region that was selected will be highlighted in the region table.

19. Table of Cluster Values – the ROI cluster value is based on the average of the represented region across all planes where it is assessed. By clicking on one of the 47 cluster regions in the cluster screen, the name of the region will be displayed in the table below the cluster screen and the row of the region that was selected will be highlighted in the cluster table.

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NeuroQ™ Display Screen (Right Side)

1   2   3

Reference Region   Control Database   Metabolism   Study Comparison   EQuAL

**Database in use: Default FDG Database
Normal Template with Cluster Regions**

12   18   20

22   24   32   ← 4

34   35   36

42   46   52

Regional Hypometabolism

ROI Name:
Magnitude of Difference:
#SD from M(AC): ← 5

Positive(+) sign corresponds to values > Mean AC
Negative(-) sign corresponds to values < Mean AC

REGIONAL AND CLUSTER DATA

rAVC.p20 (Difference: -0.4912) is the most hypometabolic region.
rAVC.p30 (#SD from M(AC): -12.9412) is the region with the most significant hypometabolism. ← 6

rPTC (Difference: -0.4327) is the most hypometabolic cluster.
rAVC (#SD from M(AC): -15.4367) is the cluster with the most significant hypometabolism.

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1. Reference Region Menu – user can select which cluster (among "Pons", "Cerebellum", "Sensorimotor", "Thalamus", or "Whole Brain") to base the normalization of the regions on. NOTE: the default normalization is based on the whole brain.
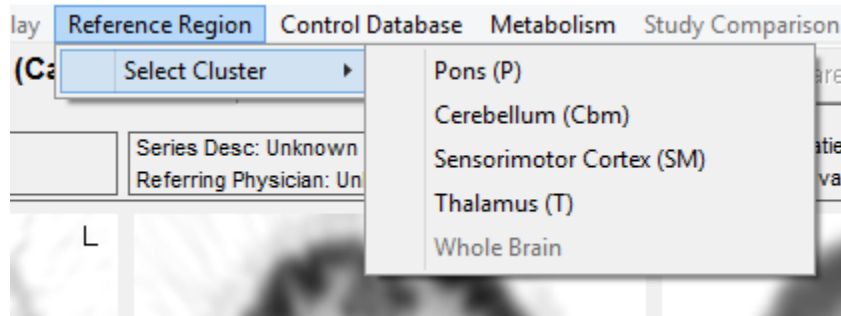
2. Control Database – user can use this feature to create their own database to use within the NeuroQ™ application. See description of this feature below.
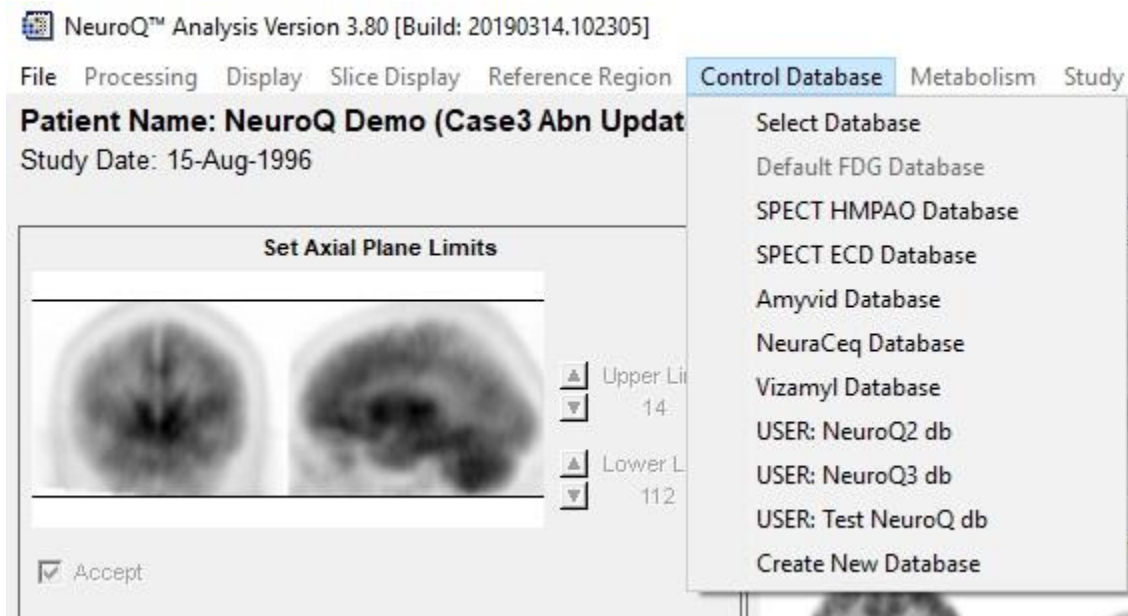
3. Metabolism Menu – "Hypometabolism" displays the most hypometabolic regions and performs calculations accordingly, "Hypermetabolism" displays the most hypermetabolic regions and performs calculations accordingly, NOTE: default is "Hypometabolism".

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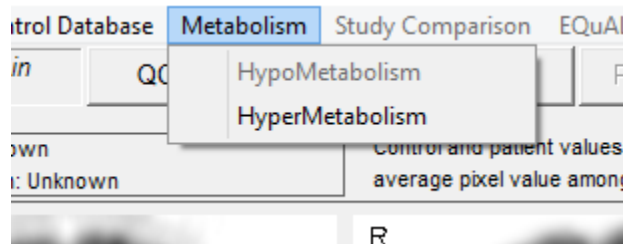
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4. Brain Plane Displays – includes schematic display of each of the 47 ROI clusters, shown at the normal template planes numbered below each image. Refer to the "Show Color Scale" description for color coding explanation. Clicking on a ROI causes the full name and numerical characterization of that region to appear in the Data Display area.

5. Data Display – displays information based on the last ROI cluster the user clicked on.

6. Regional and Cluster Data – gives the most hypometabolic or hypermetabolic and most significant regions and clusters.

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NeuroQ™ Compare Display Screen

Difference Regions:

Region	Mean AC	SD AC	Baseline (B)	Act\Cur (A)	A - B	%Diff((A-B)/B)
rGFs.p32	0.9708	0.0756	1.2397	1.2017	-0.0381	-3.0717
lGFm.p32	1.0079	0.0458	1.2355	1.1843	-0.0512	-4.1436
lGFs.p32	1.2465	0.0444	1.1425	1.1168	-0.0257	-2.2530
lGFd.p32	1.1184	0.0582	1.1354	1.0899	-0.0455	-4.0078
rGFi.p32	1.1303	0.0314	1.1220	1.0946	-0.0274	-2.4391
rGCa.p32	1.0321	0.0419	1.0205	0.9945	-0.0260	-2.5496
lGCa.p32	0.9995	0.0948	1.1017	1.0502	-0.0515	-4.6753
lsLT.p32	1.0773	0.0392	1.1346	1.0926	-0.0420	-3.7028
lTh.p32	1.1323	0.0529	1.0133	0.9391	-0.0742	-7.3233
rTh.p32	1.0452	0.0348	1.0309	1.0248	-0.0061	-0.5882

Cluster Regions:

Region	Mean AC	SD AC	Baseline (B)	Act\Cur (A)	A - B	%Diff((A-B)/B)
rGFs	1.0094	0.0533	1.0461	1.0720	0.0259	2.4772
rGFd	1.0666	0.0375	1.0925	1.1117	0.0192	1.7595
lGFs	0.9778	0.0481	1.0005	0.9713	-0.0291	-2.9134
lGFd	1.0552	0.0347	1.0586	1.0059	-0.0527	-4.9824
ISM	1.0612	0.0422	1.0699	1.0459	-0.0240	-2.2442
rSM	1.0442	0.0332	1.0590	1.0814	0.0224	2.1163
lsPL	0.9202	0.0472	0.8925	0.8878	-0.0047	-0.5222
rsPL	0.9696	0.0462	0.9138	0.9603	0.0465	5.0923
rGFm	1.1236	0.0313	1.1460	1.1663	0.0203	1.7701
lGFm	1.1230	0.0255	1.1145	1.1130	-0.0015	-0.1341

The NeuroQ™ Compare Screen is enabled by selecting the two studies from the MCP screen and clicking on the launch button. Once NeuroQ™ is launched it will show the most recent study in the main NeuroQ™ screen. Click on the Compare button and the Compare display screen will be shown. The oldest study is displayed in the top row, the most recent in the middle row, and the difference image is displayed in the bottom image to the right. Use the middle slider bar in the middle row to step through the planes. All images with the exception of the patient's images in the left hand column will move when the slider bar is moved left or right. The difference image shows the regions in which there is at least a 1 standard deviation difference between the original and recent study. This analysis is helpful to monitor the progression of dementia over a period of time.

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NeuroQ™ PET/CT Display Screen
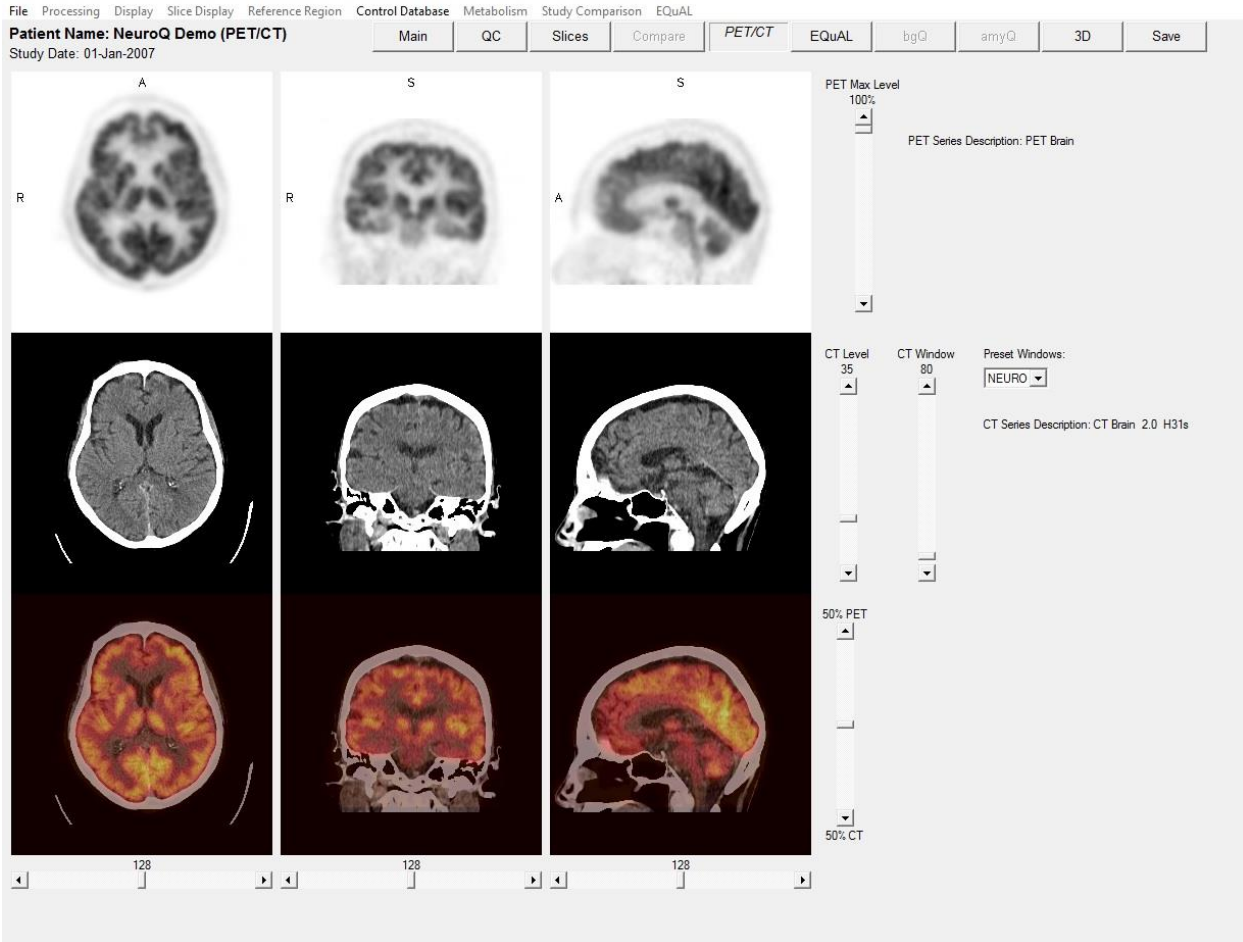
The PET/CT display allows for displaying both the PET and CT brain images from the same patient. The PET brain images are contained in the top row. The PET brain images brightness can be changed by sliding the PET Max Level slider up or down. The CT images are contained in the middle row. The CT brain images window level can be changed by manipulating the sliders for CT Level and CT Window up or down. The user also has the option picking preset windows for Neuro or Bone in the Preset Windows drop down box. The bottom row contains the fused images. The PET/CT slider bar allows the user to display only the PET (slider all the way up), only the CT (slider all the way down), or fused (slider in the middle). Various levels of fusion can be displayed by moving the slider up or down. Triangulation is enabled on the PET, CT and Fused images by clicking left on any image and it will show you the plane for that location on the other two images.

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NeuroQ™ PET/MR Display Screen

The PET/MR display allows for displaying both the PET and MR brain images from the same patient. The tools for displaying and manipulating the images work the same way as described above for the PET/CT display.

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EQuAL™ Analysis
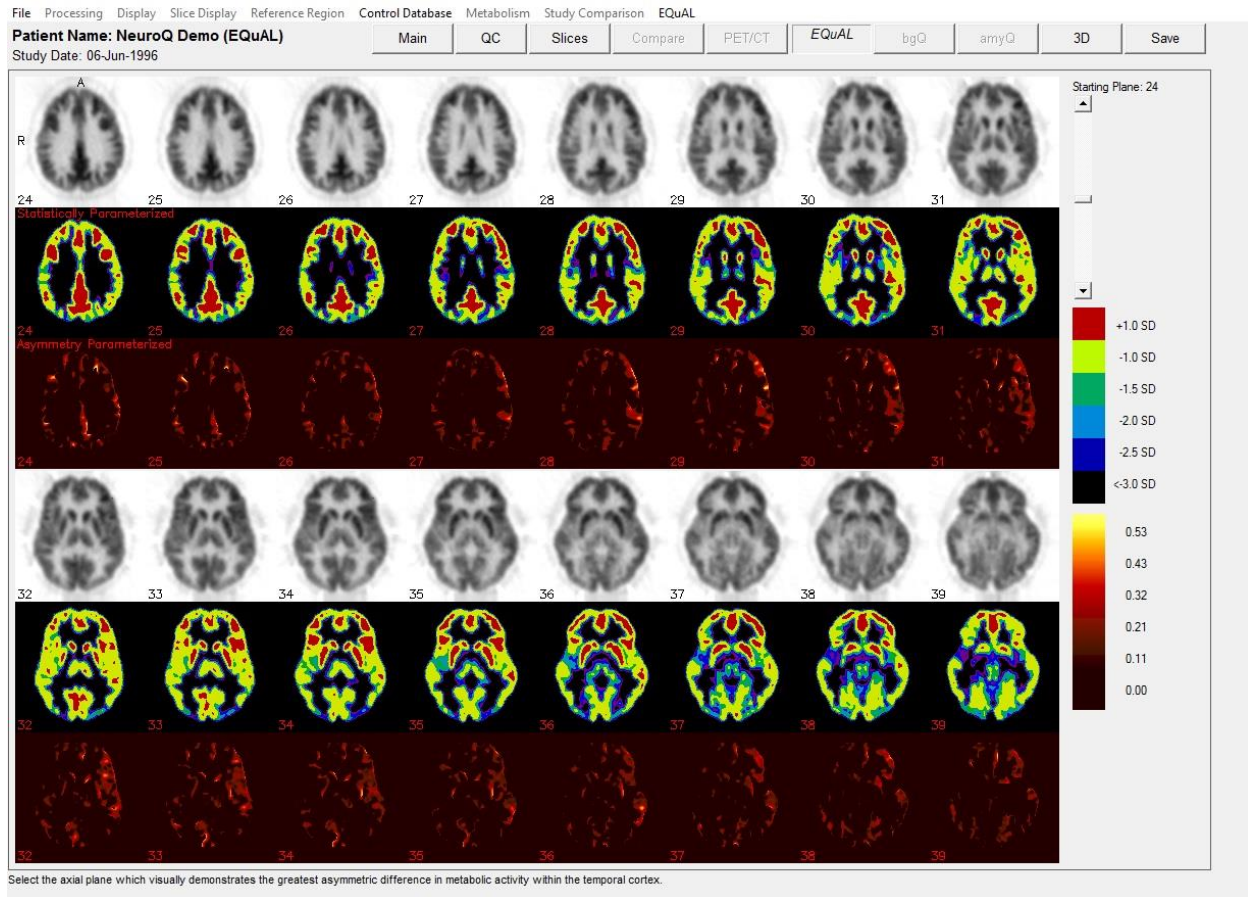
The Extent-Specified Quantified Asymmetry-of-Lobe (EQuAL) Analysis will be included with NeruoQ 3.0. This program is useful for assessing maximal temporal asymmetry over a specified proportion of the temporal lobe which may help to predict whether patients will likely be free of seizures during the years after neurosurgical resection of epileptogenic tissue.

To use EQuAL, select the patient desired and launch NeuroQ™ from MCP. Process the study as you would normally. Once NeuroQ™ is finished reformatting the data, select the EQuAL tab from the top of the screen.   Select the image that the user feels best exemplifies the asymmetrical defect. Use the slider bar on the right hand side of the screen to see all slices. See example above.

Once an image has been selected, the EQuAL ROI screen will appear. Follow the on screen instructions to get the Asymmetry Index (AI).

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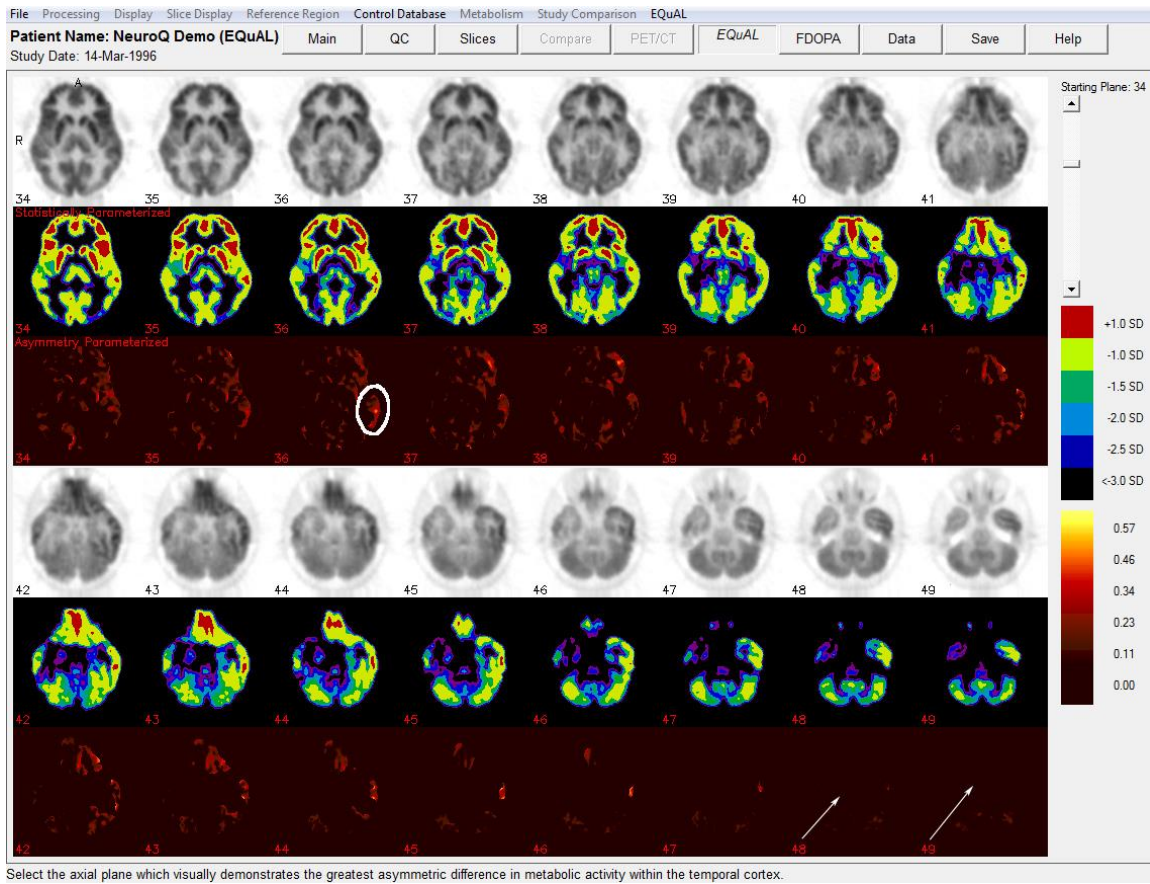
EQuAL Processing – When processing an EQuAL study you are going to select an image from the above display and that is the image where an ROI over the temporal lobe will be drawn, as shown in the display below. When selecting that image you want to use the Assymetry Parameterized (AP) row of images (3rd and 6th row, images displayed in red) to select this image. You must see activity in the AP images in order for this analysis to provide valid data. A proper image would be image 36 shown with the circle drawn over the temporal lobe (remember you will be drawing your ROI on the gray scale images shown below).

If you select images without activity (images 48 or 49 shown with arrows) then the values calculated will be 0. If the EQuAL value is 0, with the default extent specification of 20%, then first insure that there is visually evident bilateral asymmetry in the part of the brain over which the ROI has been drawn, and second, that the ROI has been placed on the side that has higher activity. If these 2 conditions have been met, then a 0 value indicates that fewer than 20% of the pixels in this ROI contribute to the observed asymmetry. To obtain a non-zero EQuAL value, try decreasing the extent specification to less than 20%.

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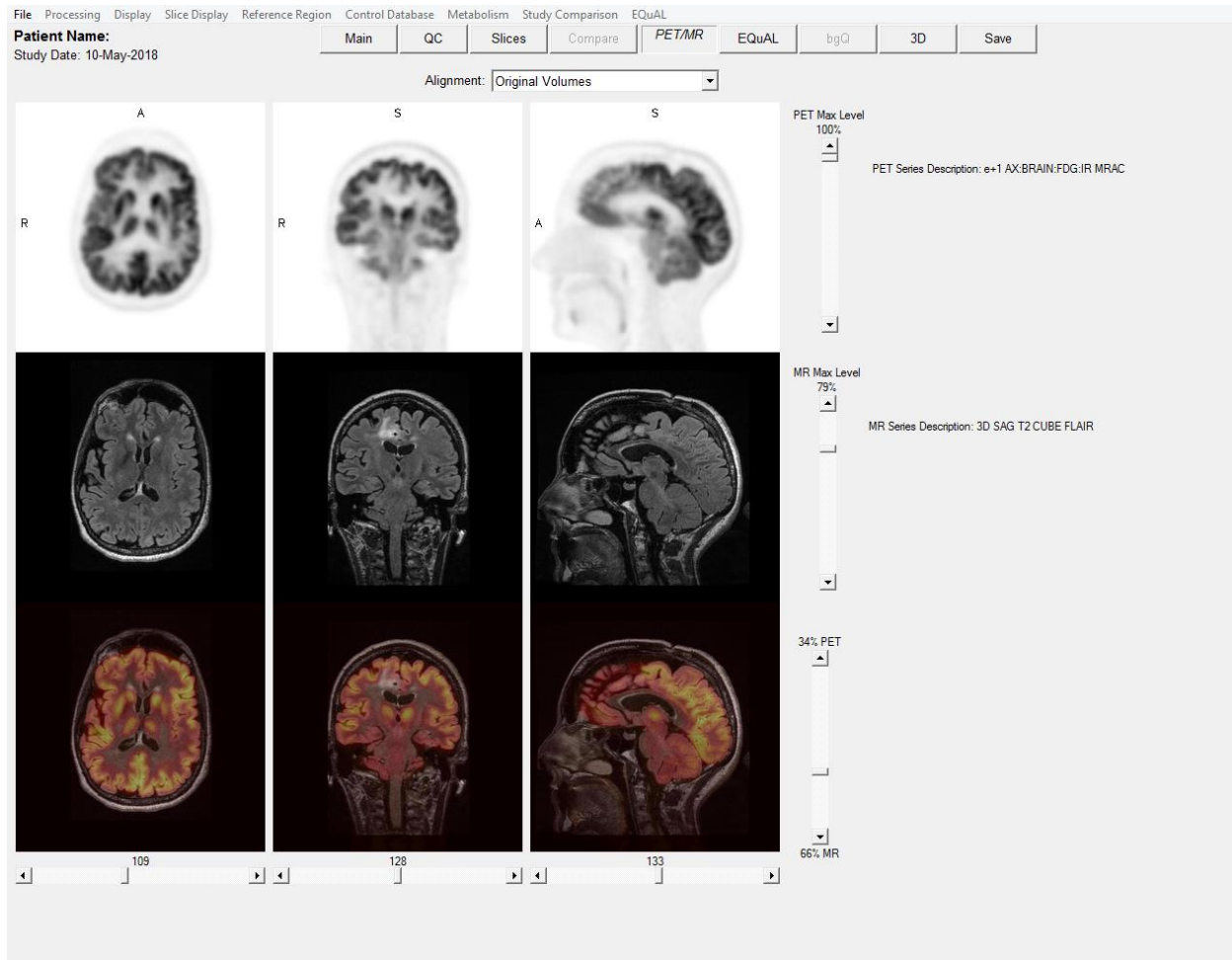
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The results of this study were by Lin et. al from the Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, UCLA Los Angeles was published in the May issue of the Journal of Nuclear Medicine:

> Tina W. Lin, Michelle A. Kung de Aburto, Magnus Dahlbom, Lynn L. Huang, Michael M. Marvi, Michael Tang, Johannes Czernin, Michael E. Phelps, and Daniel H.S. Silverman. Predicting Seizure-Free Status for Temporal Lobe Epilepsy Patients Undergoing Surgery: Prognostic Value of Quantifying Maximal Metabolic Asymmetry Extending over a Specified Proportion of the Temporal Lobe. J Nucl Med. 2007 48(5): 776-782.

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Control Database

NeuroQ™ provides the user with the ability to generate their own normal database to use within the application.
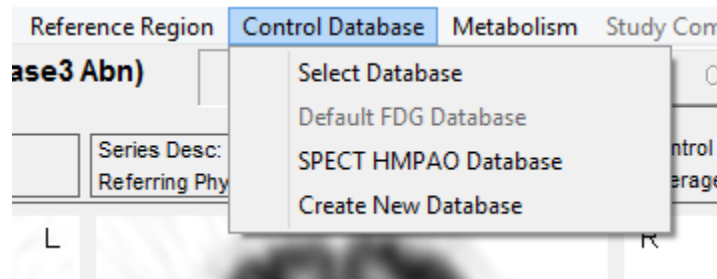
- Select Database – allows the user to select a database that was previously created by the user.

- Default FDG Database – sets the PET FDG database that was created and validated by UCLA.

- SPECT HMPAO Database – sets the SPECT HMPAO database that was created and validated by UCLA.

- Create New Database – This allows the user to create their own normal database. The first step would be to process all of the normal studies through NeuroQ™ and save them as NeuroQ™ review files. These review files will have an extension .nrq. These NeuroQ™ review files then need to be all placed in the same folder on the disk. After selecting Create New Database you will have to browse to the folder containing all of normal NeuroQ™ Review files. After selecting that folder the following dialog screen is displayed.

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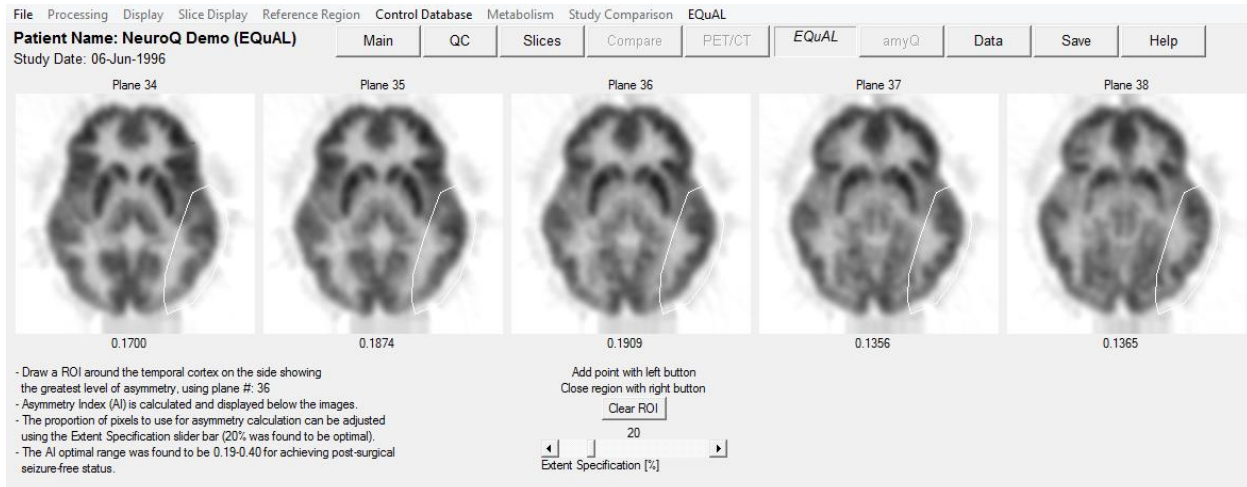
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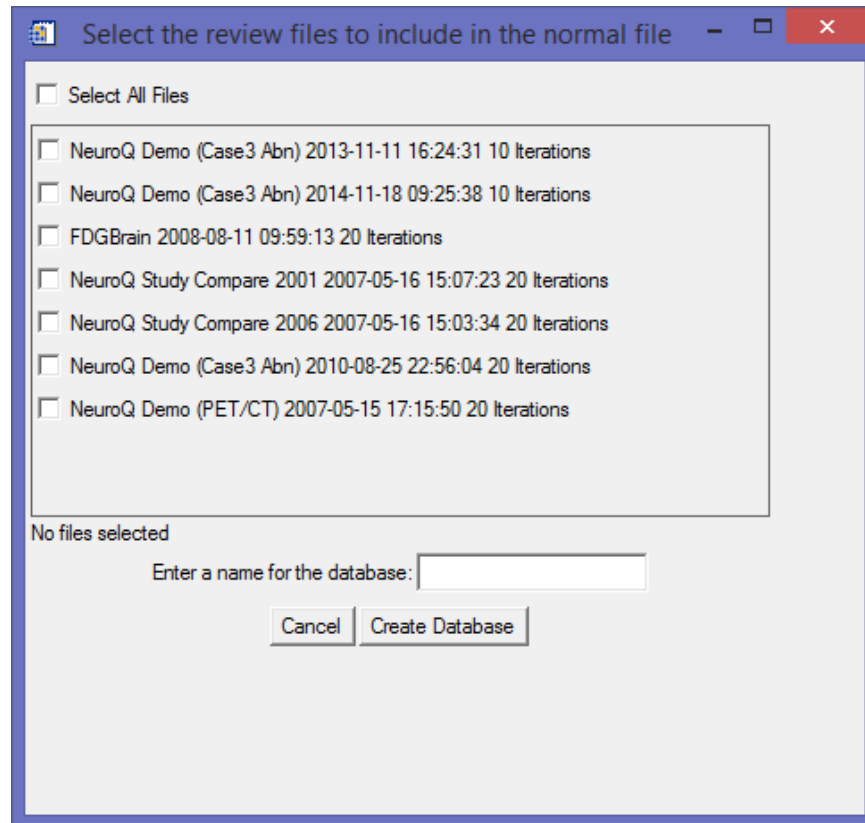
Select all the files you want included in the database, enter the name for the database file in the box, and then click on the Create DB button to generate the normal database. This normal file can then be selected and used as the normal database in NeuroQ™.

IMPORTANT: GENERATION OF A NORMAL DATABASE TO BE USED IN THE NEUROQ™ APPLICATION IS THE SOLE RESPONSIBILITY OF THE USER. SYNTERMED OR UCLA HAVE ONLY VALIDATED THE PET FDG NORMAL DATABASE PROVIDED WITH THE APPLICATION. SYNTERMED AND UCLA HAVE NO RESPONSIBILITY OR ARE LIABLE FOR ANY RESULTS PROVIDED BY NEUROQ™ THAT ARE GENERATED BY ANY OTHER DATABASE GENERATED BY USERS OF THE APPLICATION USING THIS TOOL.

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NeuroQ User Manual

Amyloid Overview, Processing, and Display

Introduction

The FDA approved the florbetapir F18 radiopharmaceutical agent (Trade name Amyvid, Eli Lilly) on April 6, 2012. Florbetapir binds to amyloid aggregates in the brain, and the florbetapir PET image is used to estimate the density of β-amyloid neuritic plaque (17).

Florbetaben, a fluorine-18 (18F)-labeled stilbene derivative, trade name NeuraCeq (Piramal), is a diagnostic radiopharmaceutical developed for routine clinical application to visualize β-amyloid plaques in the brain. The FDA approved NeuraCeq in 2014.

Flutemetamol, a fluorine-18 (18F), is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the brain to estimate β amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other causes of cognitive decline. Trade name Vizamyl and FDA approved in 2013.

Image Registration and Development

The amyloid image registration is performed in two parts. First the subject's brain is aligned to the reference brain using a rigid registration (i.e., translations in x, y and z, and rotations around the three axes). The maximization of the mutual information is the metric used to determine the best registration parameter. The result from the rigid registration is then passed onto a B-spline based deformable image registration algorithm, which also attempts to maximize the mutual information between the two image volumes to determine the best registration. For computational efficiency and faster convergence, the deformable registration is performed in two parts. First, using a coarse grid, which is followed by a registration using a finer and more precise grid.

In addition to the development of the registration software, a template or reference amyloid brain was constructed, which is used when analyzing individual amyloid images. For this, 20 with low uptake of amyloid in PET studies were selected. Each one of these subjects also had anatomical images (i.e., T1 weighted MRI). Using the high-resolution anatomical imaging for registration allows for a more accurate registration compared to a PET-to-PET registration. The subject's PET was first registered to the MRI. Then the MRI was registered to the reference brain template, already defined in NeuroQ for the analysis of FDG brain images. The registration performed was the same as described above (i.e., rigid registration followed by a deformable registration). Once the transformation of the subject's MRI to the reference template was found, the same transformation was applied to the subject's amyloid PET image.

This process was repeated for all 20 low amyloid uptake subjects. Each registered PET study was then normalized to the average uptake in cerebellum.   The amyloid reference brain was finally constructed by taking the average of all 20 registered and normalized brains. In the analysis of a subject's amyloid images, the PET images are first registered to the reference amyloid brain, using the registration method described.

Following the registration, the average uptake in the cortex and in cerebellum is determined. These regions are a subset of the regions already defined in the brain template in NeuroQ. The

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ratio of the average cortex uptake to the average uptake in cerebellum is then calculated. This ratio value has been integrated into the current NeuroQ application (18) and displayed together with a visualization of the regions used in the determination of the uptake in cortex and cerebellum, overlaid on the subjects registered brain. The output for the Amyvid (Lilly) analysis is shown in Figure 1 and NeuraCeq (Piramal) in Figure 2. Vizamyl (GE) shown in Figure 3.

When the initial amyloid study is brought into NeuroQ the QC screen is displayed on the screen (see below).
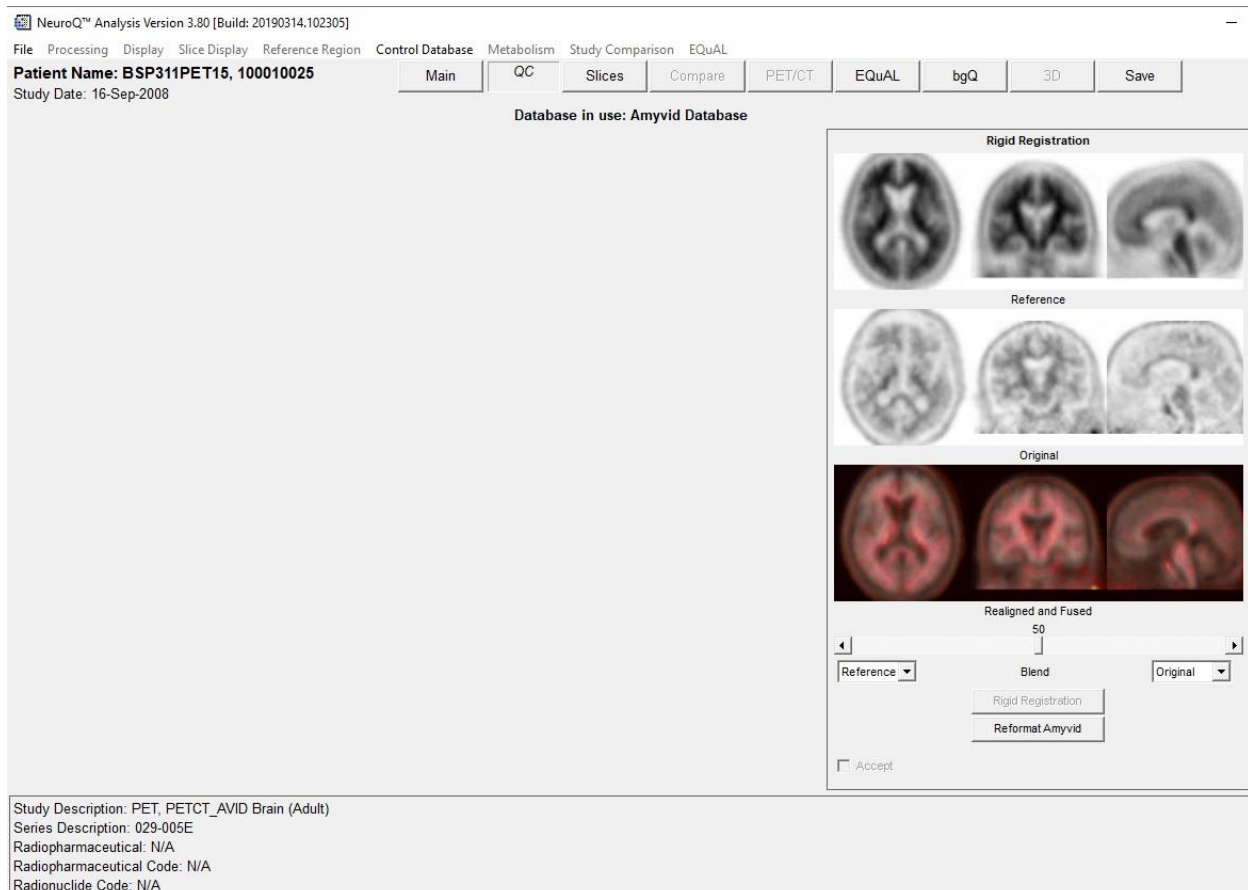
The database in use is shown at the top of the screen along with a description of the study found in the bottom left hand corner. Check the normal database to make sure the correct database is being used. If you need to change the database then go to the "Control Database" menu.

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The "Control Database" screen will then be displayed as shown below (some databases may or may not be available, depending on the users specific NeuroQ license).
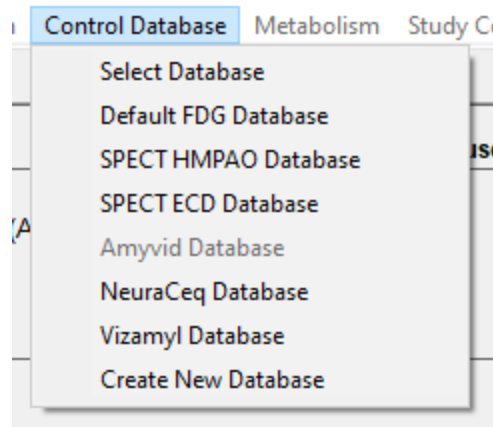
Select the correct Amyloid database for the study (Amyvid, NeuraCeq or Vizamyl), from the available menu items; double-check that the "Database in use" is updated to reflect the newly selected database. See below for the processing steps for the amyloid imaging agents.

Amyloid processing
The steps for processing an amyloid study are listed below.
1. Select the amyloid study from the MCP screen and launch into the NeuroQ application.
2. Click on the "Reformat Amyvid" button (or "Reformat NeuraCeq" or "Reformat Vizamyl", depending on the Amyloid database that has been selected) and the processing will be automatically applied to the data.
3. Once the processing is completed the amyloid analysis window will be displayed showing the patients results (Fig 1/Fig 2/Fig 3).

PLEASE NOTE: The ratios of overall cortex to cerebellum is provided as a general index of the magnitude of cortical tracer retention only for all three amyloid tracers. There are no recognized or intended threshold values for drawing specific conclusions about an individual patient's diagnosis or prognosis.

The relative patterns of distribution of tracer retention within the cortex, as illustrated by the color-coded displays of regional distribution, are intended to be used as an adjunct to visual analysis, which the user can employ for the purpose of indicating specific regions upon which extra attention may be focused in carrying out visual interpretations.

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Amyvid Analysis
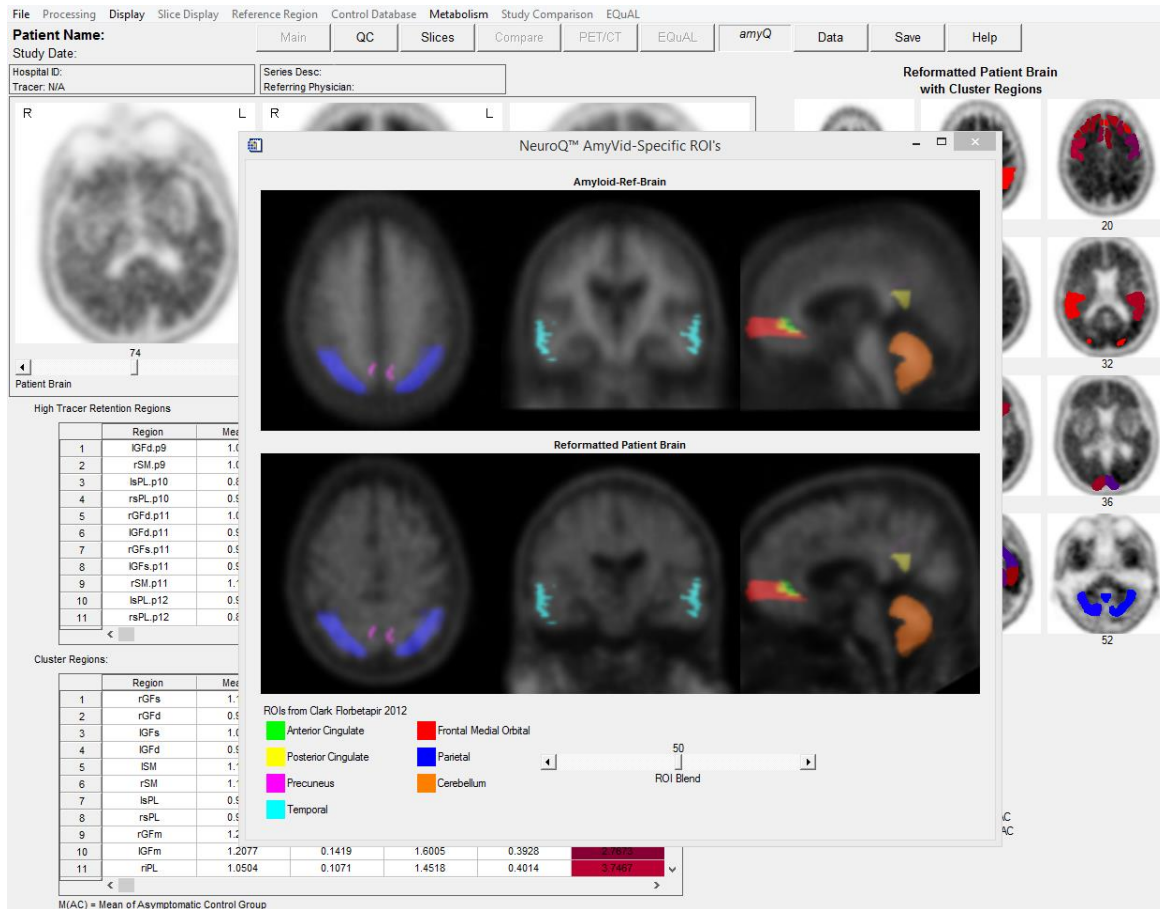
Figure 1 - Amyloid Analysis Display Output. The display output of the amyloid analysis in the NeuroQ application is shown. The regions representing the cortex (white matter) are shown in shades of red/purple and the cerebellum (gray matter) are shown in blue. The ratio between the cortex and cerebellum is calculated and shown on the display output, in this case the ratio was calculated as 1.656. Clicking on the Show ROIs button will bring up a display of the ROIs used in this analysis.

Validation

The results of the Amyvid validation conducted using this technique demonstrated the following with respect to the cortex vs cerebellum average ratio: low amyloid uptake (n=80), mean = 0.988 ± 0.058 and high amyloid uptake (n=39), mean=1.504 ± 0.192. Using a ratio cutoff of 1.10 the results for detecting high levels of amyloid in the high amyloid uptake group was 20/20 and for detecting low levels of amyloid in the low amyloid uptake group was 19/20.

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NeuraCeq Analysis

Figure 2 - NeuraCeq Analysis Display Output. The display output of the amyloid analysis using NeuraCeq in the NeuroQ application is shown. The regions representing the cortex (white matter) are shown in shades of red/purple and the cerebellum (gray matter) are shown in blue. The ratio between the cortex and cerebellum is calculated and shown on the display output, in this case the ratio was calculated as 1.577. Clicking on the Show ROIs button will bring up a display of the ROIs used in this analysis.

Validation

The results of the NeuraCeq validation conducted using this technique demonstrated the following with respect to the cortex vs cerebellum average ratio: low amyloid uptake (n=61), mean = 1.198 ± 0.115 and high amyloid uptake (n=61), mean=1.590 ± 0.243. Using a ratio cutoff of 1.31 the results for detecting high levels of amyloid in the high amyloid uptake group was 55/61 (90%) and for detecting low levels of amyloid in the low amyloid uptake group was 56/61 (92%) .

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Vizamyl Analysis

Figure 3 - Vizamyl Analysis Display Output. The display output of the amyloid analysis using Vizamyl in the NeuroQ application is shown. The regions representing the cortex (white matter) are shown in shades of red/purple and the cerebellum (gray matter) are shown in blue. The ratio between the cortex and cerebellum is calculated and shown on the display output, in this case the ratio was calculated as 1.537. Clicking on the Show ROIs button will bring up a display of the ROIs used in this analysis.
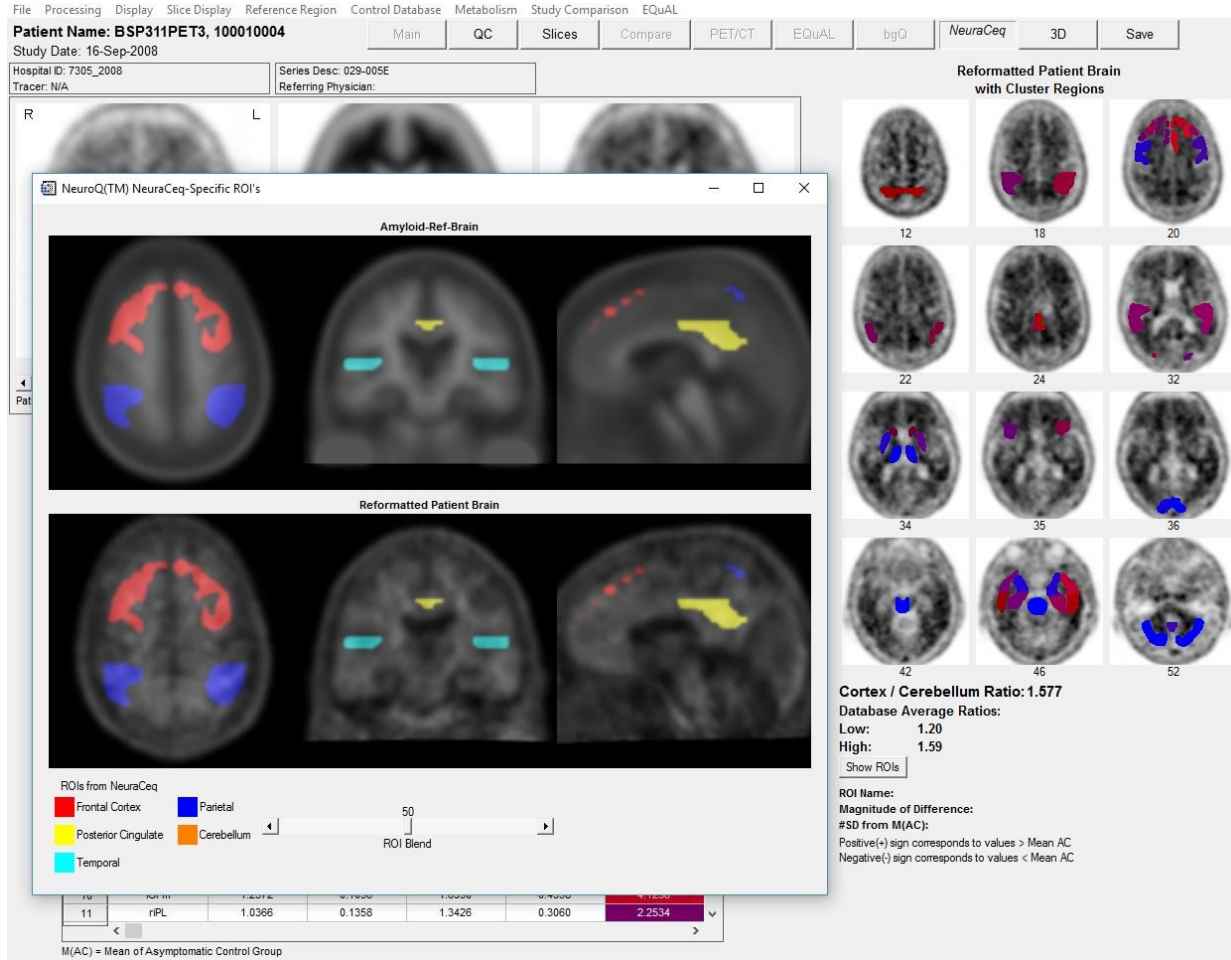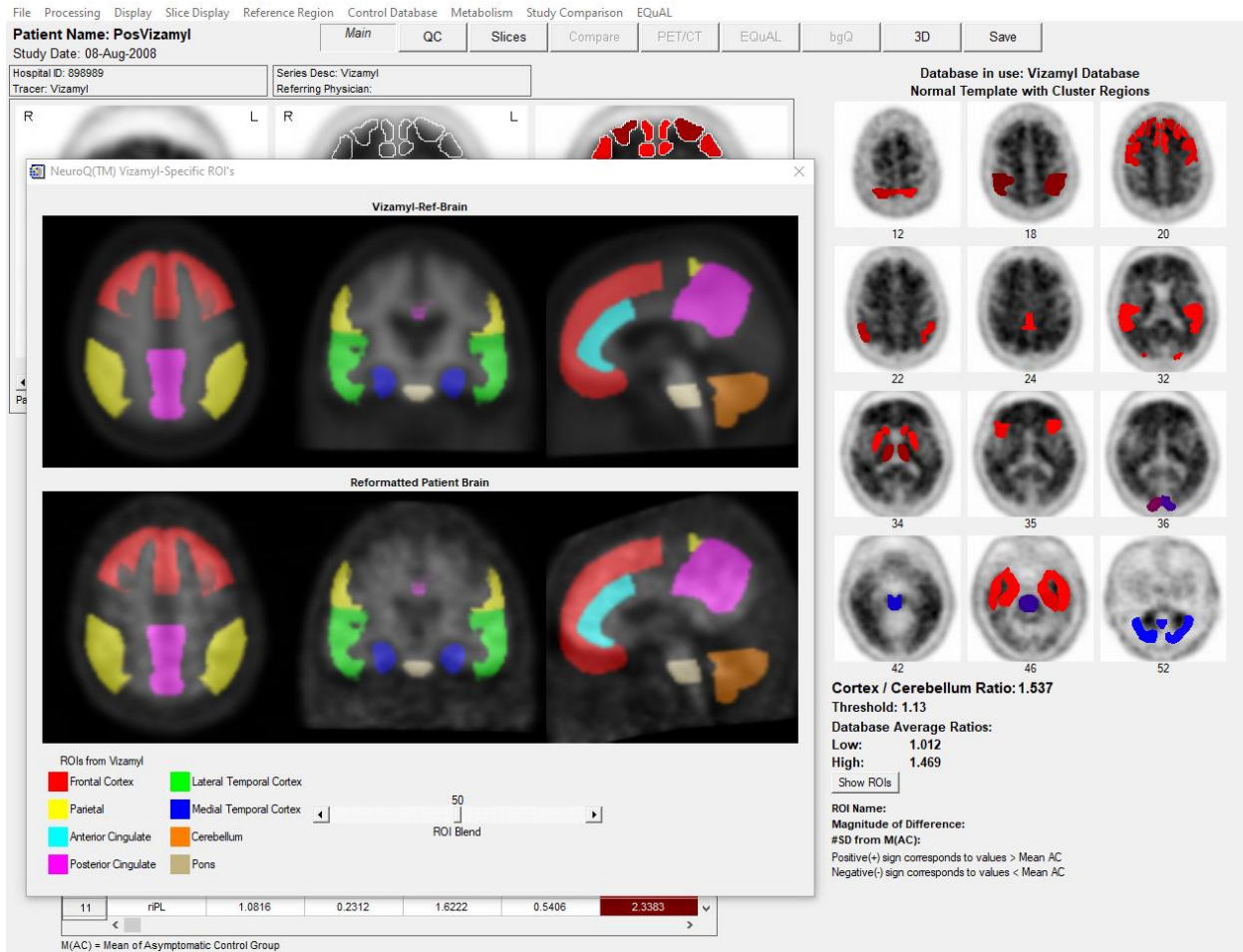
Validation

The results of the Vizamyl validation demonstrated the following with respect to the cortex:cerebellum ratio: low amyloid uptake (n=25), mean = 1.012 ± 0.122 and high amyloid uptake (n=26), mean = 1.469 ± 0.229. Using a ratio threshold of 1.13 the results for detecting high levels of amyloid in the high amyloid uptake group was 23/26 (89%) and for detecting low levels of amyloid in the low amyloid uptake group was 24/25 (96%). Results with respect to the cortex:pons ratio demonstrated the following: low amyloid uptake (n=25), mean = 0.530 ± 0.085 and high amyloid uptake (n=26), mean = 0.799 ± 0.141. Using a ratio threshold of 0.65 the results for detecting high levels of amyloid in the high amyloid uptake group was 23/26 (89%) and for detecting low levels of amyloid in the low amyloid uptake group was 24/25 (96%).

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NeuroQ User Manual

SPECT Overview, Processing and Display

Introduction

The NeuroQ application can also be used to process HMPAO and ECD SPECT brain studies.

When the initial SPECT study is brought into NeuroQ the QC page is displayed on the screen as shown below. The currently selected database is shown at the top of the screen along with a description of the study from select DICOM tags. Check the "Database in use" to make sure the automatically selected database is correct for this study.

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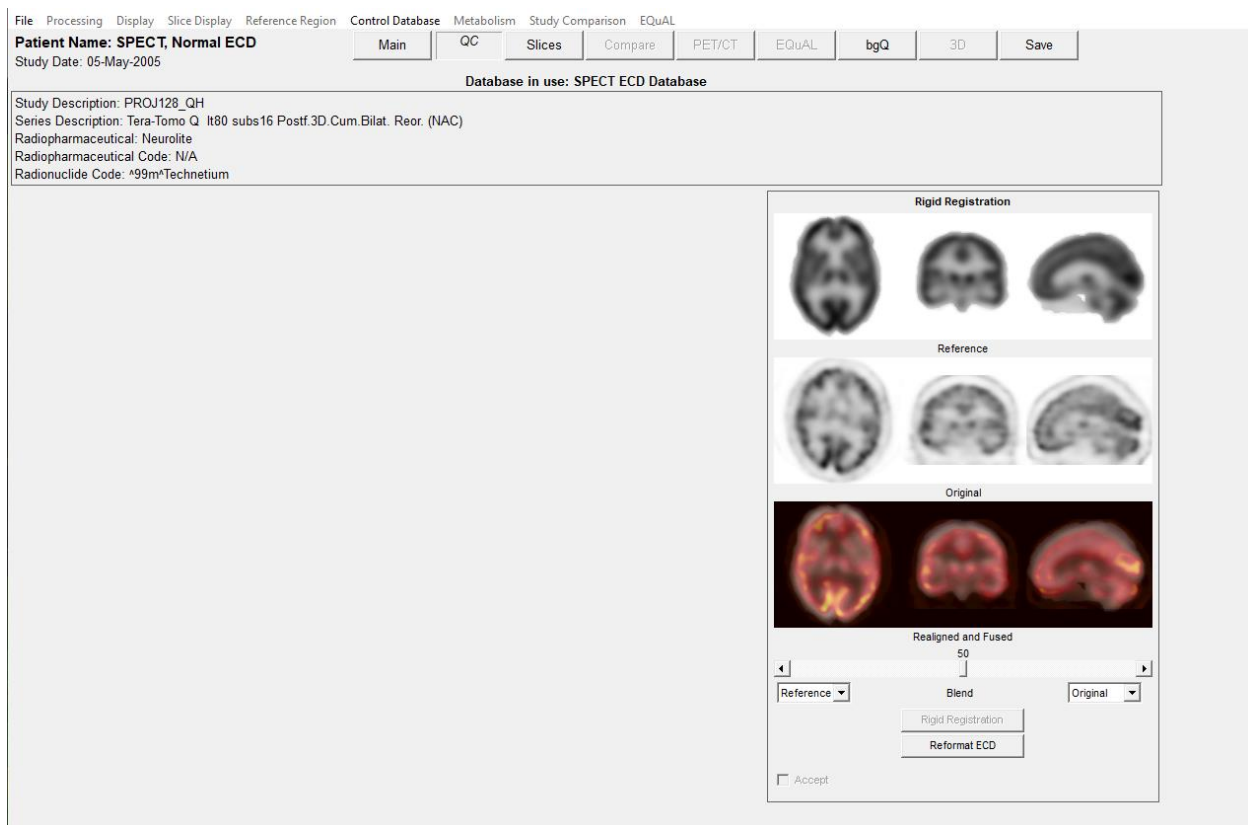
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If you need to change the database then click on the "Control Database" menu item and select the appropriate SPECT database for the study (see below). If the chosen database does not match the automatically determined database, you will receive a warning to confirm your choice.
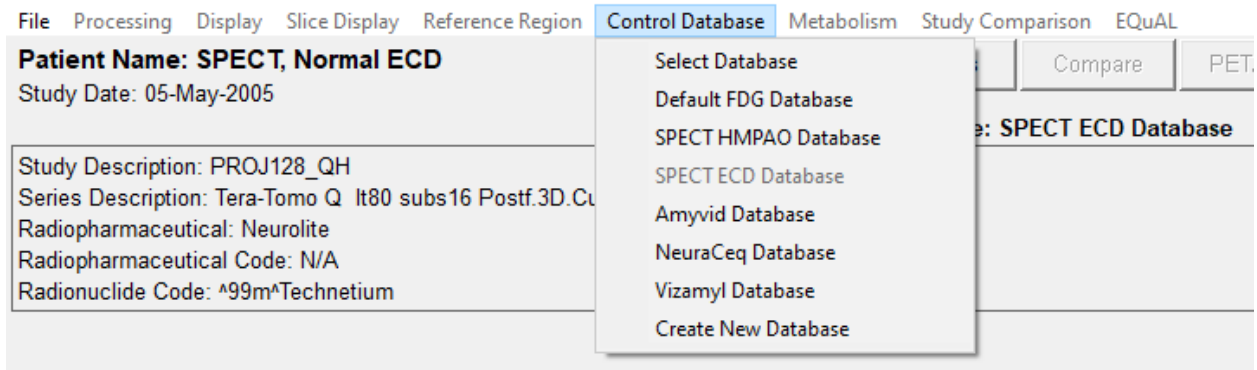
Recommended image acquisition, reconstruction and processing steps for both HMPAO and ECD are listed below.

HMPAO Acquisition and Reconstruction

HMPAO Acquisition Protocol	
Injected Dose	800 MBq
Time between injection and imaging	1-4 hours (the earlier the better the count rate)
Matrix size	128 x 128
Orbit	Circular, 360 degrees
Zoom	1.0
Time per stop	Sec/stop depends on patient count rate

HMPAO Reconstruction Protocol	
Iterative or FBP	Either Iterative or FBP
Attenuation Correction (AC)	Yes, apply either a calculated (Chang) or actual AC with CT

HMPAO Database

> The SPECT HMPAO normal limit development involved initially using a group of normal HMPAO scans from 50 normal subjects that were compiled by the SNM Brain Imaging Council. The database used for analysis of SPECT studies should be the SPECT HMPAO Database.

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ECD Acquisition and Reconstruction Protocol

ECD Acquisition Protocol	
Injected Dose	700 - 840 MBq 99m Tc-ECD
Time between injection and imaging	30 minutes
Matrix size	128 x 128
Orbit	Circular, 360 degrees
Zoom	1.0
Time per stop	Sec/stop depends camera system used

ECD Reconstruction Protocol	
Iterative or FBP	Either Iterative or FBP
Attenuation Correction (AC)	Yes, apply either a calculated (Analytic Chang attn. corr. with 0.08 coefficient) or actual AC with CT

ECD Database

There were 40 normal patients used for the ECD normal database development. The validation was conducted in 52 additional studies with and without dementia. Validation: Sens 31/34 (91%) and spec 16/18 (89%)

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Processing for HMPAO and ECD

Quality Control Screen

The first screen displayed is the Quality Control Screen. The only option is "Reformat HMPAO" or "Reformat ECD" (depending on the selected database); this will automatically perform all of the necessary processing to compare this patient to the appropriate SPECT normal file.
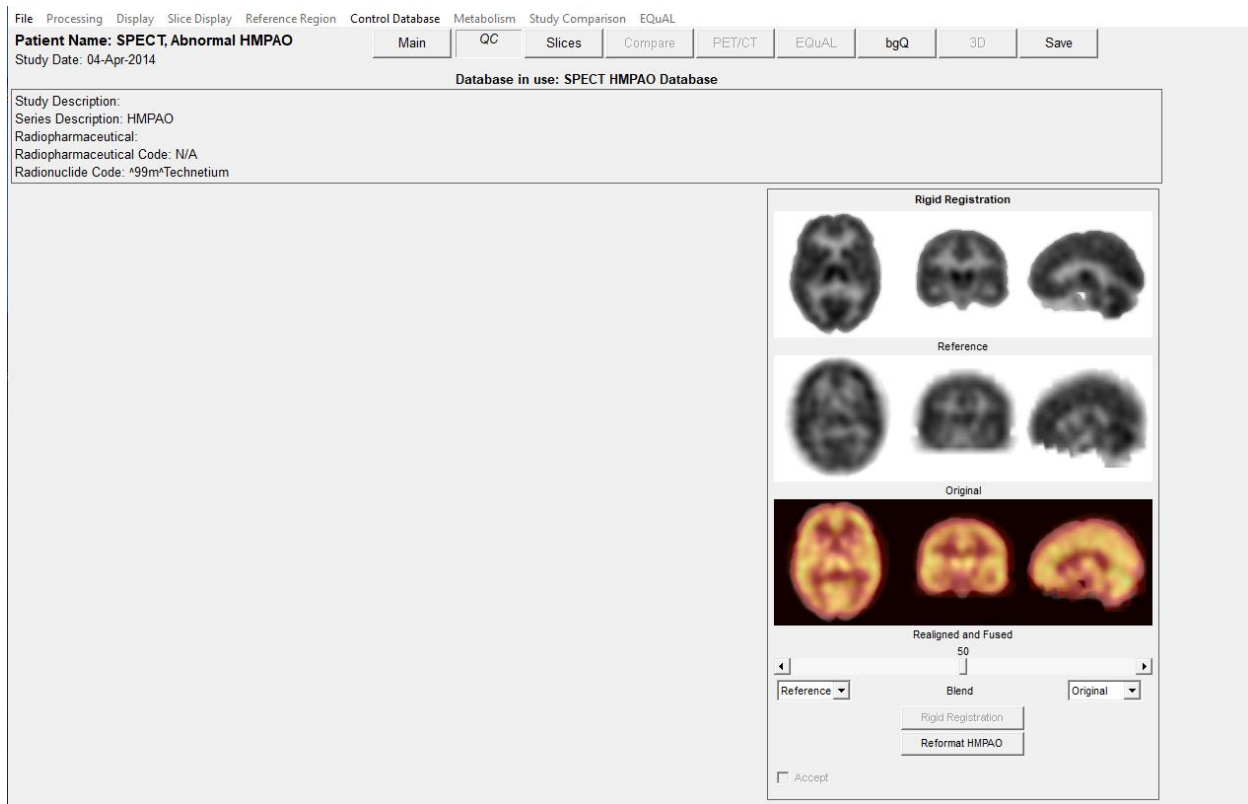
Reformatting

Click on the Reformat HMPAO button (or Reformat ECD button, depending on the selected database); NeuroQ will then display an informational message and automatically start the appropriate SPECT reformatting process.

Further Processing

The remainder of the analysis and display is the same as it is for FDG, this is described above in the section titled NeuroQ Analysis Screen on pages 11 - 17.

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3D Display

Overview

The NeuroQ application can display surface rendered images in 3D with the 47 ROI clusters integrated into the display. Click right on any image and it will be displayed in the center of the image and you will be able to manually rotate the image (click left, hold and move). If you hover the mouse over any of the 47 clusters then the name, Pt-M(AC), and #SD from M(AC) values will be displayed at the bottom left of the image.

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The zoomed image that can be manually rotated is shown below.

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Analysis of Basal Ganglia Structures

Introduction

An algorithm was developed and implemented into NeuroQ to semi-automatically analyze radiotracer uptake data in basal ganglia structures. As seen in Figure 1, the user can choose a plane where the basal ganglia are most pronounced and can overlay a predefined set of ROIs over the right and left sets of regions. The program takes the maximal activity along a line spanning the three outlined structures that comprise the basal ganglia (caudate head, anterior putamen, and posterior putamen). To account for variations in the plane chosen, the average value of the maximal activity on the planes spanning from two below to two above the user's chosen one are calculated relative to the superior occipital cortical activity and output is entered into a table that separates the uptake values by region and cerebral hemisphere.

Validation

Normal limits were established in 35 patients that without reduced dopamine transporter radiotracer (DaTscan™). Validation of this program was performed by running scans of 54 patients referred for evaluation of motor symptoms. Twenty-one of these patients had reduced dopamine transporter radiotracer (DaTscan™), but were considered normal by basal ganglia imaging criteria according to interpretation by the experienced readers and long-term follow up, while 33 were positive with reduced dopamine transporter radiotracer (DaTscan™), by clinical follow up and/or 100% concordance among three to four visual interpreters, at least two separate institutions.

Two tables one reporting the values of right and left caudate head, anterior putamen, posterior putamen, as well as ratios of posterior putamen to anterior putamen, posterior putamen to caudate head, and anterior putamen to caudate head (see Figures 1 and 2), and another listing means and SD's of the values for the normal subjects are provided (Figure 3).

Statistical analysis:

      Mean, standard deviation, and standard error of the mean were calculated for radiotracer uptake in the structures and uptake ratios described above, for normal and PD patient groups for each user. A two-tailed t-test was performed to test for significant differences between users. Inter-rater concordance rates, intra-rater concordance rates for user operating two independent workstations, and sensitivity and specificity values for the automated NeuroQ output versus the conventional scan interpretation were also calculated for the 6 sub regions and 6 corresponding regional ratios.
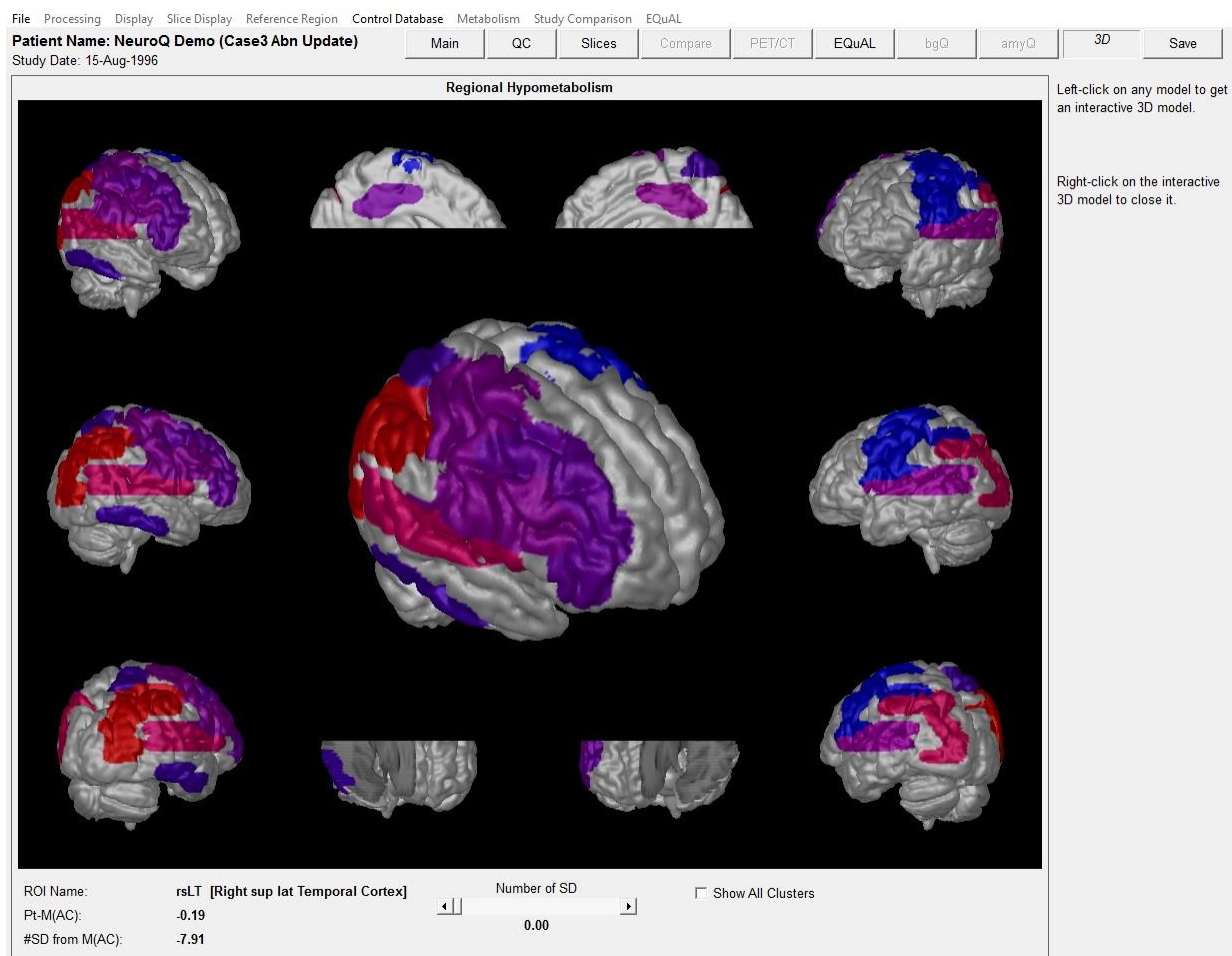
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Results:

Inter-observer reproducibility was highly significant, even between trainee interpreters using the module for quantifying basal ganglia sub regions (e.g., ratios of right posterior putamen to right anterior putamen Pearson coefficient r=0.59, p=0.00002; ratios of left posterior putamen to left anterior putamen r=0.78, p<0.00001)

Guided by the mean ± SD values of the sub regions and ratios of normal scans, it was found that the most diagnostically relevant ratio – activities in posterior putamen to superior occipital cortex - fell below the normal range (at least -2.0 SD lower than normal mean) in 91% of the cases with reduced dopamine transporter radiotracer (DaTscan™), and only in 9.5% of the cases without reduced dopamine transporter radiotracer (DaTscan™)… that is, sensitivity, specificity, and overall accuracy of quantification-based dichotomized interpretations were all at least 90%.
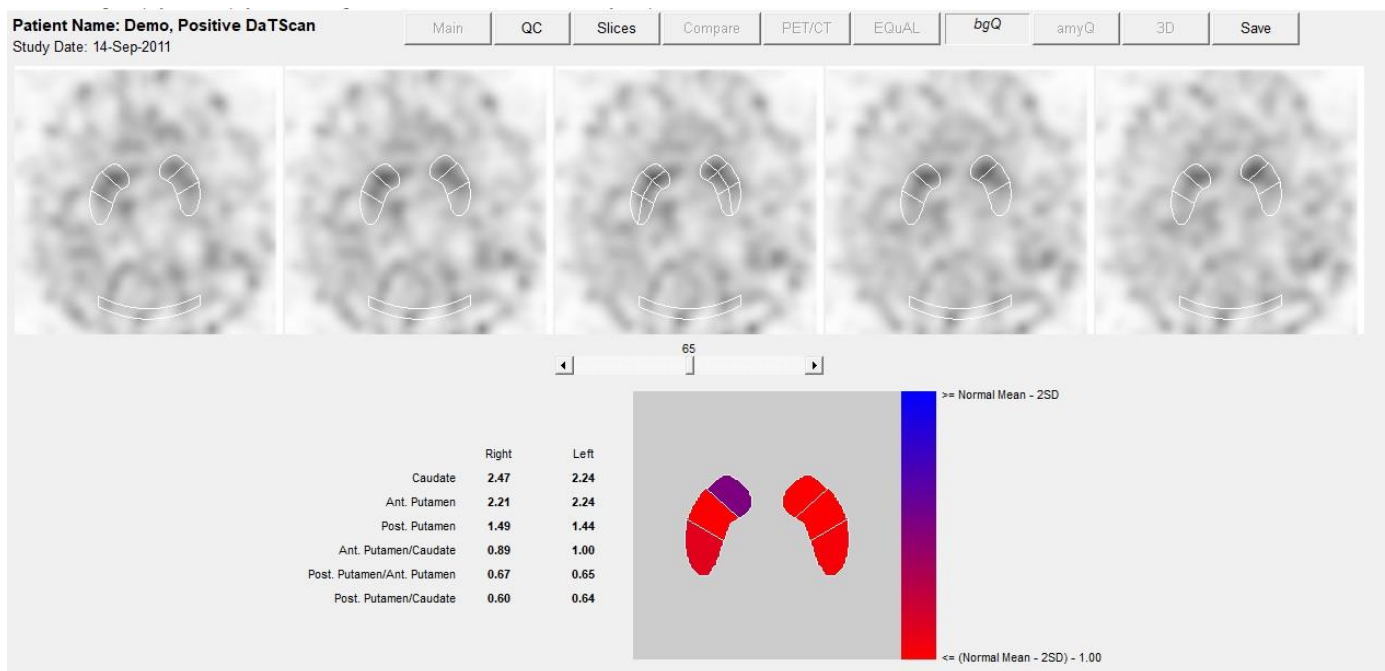
Figure 1: Display output

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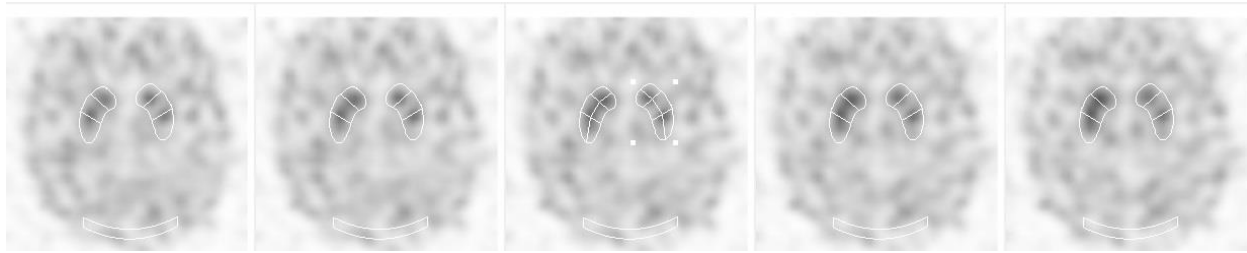
Structure	Right	Left
Caudate	3.32	2.96
Ant. Putamen	3.72	2.70
Post. Putamen	2.60	2.44
Ant. Putamen/Caudate	1.12	0.91
Post. Putamen/Ant. Putamen	0.70	0.90
Post. Putamen/Caudate	0.78	0.82

Figure 2: Positive Patient Study (Pt233, SDx2)
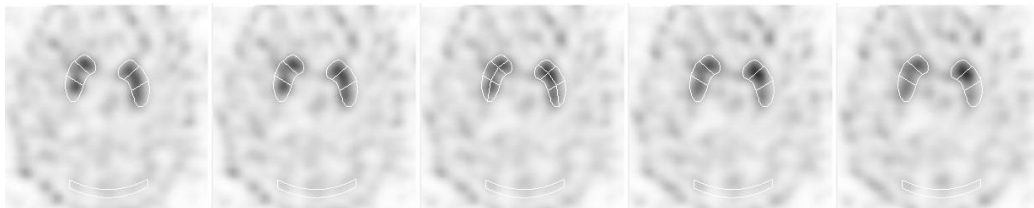
Structure	Right	Left
Caudate	4.46	4.88
Ant. Putamen	3.97	5.25
Post. Putamen	3.72	3.18
Ant. Putamen/Caudate	0.89	1.08
Post. Putamen/Ant. Putamen	0.94	0.61
Post. Putamen/Caudate	0.83	0.65

Figure 3: Negative Patient Study (Pt206, SDx2)

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Regions

Structure	Mean	±1 SD	Lower Limit of Normal (Mean-2SD)
Right Caudate	5.18	±1.11	2.96
Left Caudate	5.41	±1.08	3.26
Right Putamen (Ant)	5.88	±1.23	3.43
Left Putamen (Ant)	5.80	±1.28	3.24
Right Putamen (Post)	4.47	±1.05	2.38
Left Putamen (Post)	4.27	±0.92	2.42

Ratios

Structure	Mean	±1 SD	Lower Limit of Normal (Mean-2SD)
Post/Ant Putamen Right	0.76	±0.10	0.56
Post/Ant Putamen Left	0.74	±0.10	0.55
Post Putamen/Right Caudate	0.87	±0.14	0.60
Post Putamen/Left Caudate	0.80	±0.11	0.58
Ant Putamen/Right Caudate	1.14	±0.10	0.94
Ant Putamen/Left Caudate	1.07	±0.12	0.83

Figure 4: Normal Range for Regions and Ratios

Validation:

E1 unambiguous visual and/or confirming clinical follow up			
	(+)	(-)	
(+)	30	2	PPV = 94%
(-)	3	19	NPV = 86%
	Sensitivity = 91%	Specificity = 90.5%	

Table 1: Sensitivity/Specificity

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Processing the basal ganglia study

1. Select a brain study and launch into the NeuroQ application.
2. Click on the bgQ button
3. The 5 brain slices displaying the basal ganglia are displayed. You can move the slices left or right with the slider bar to select the appropriate slices demonstrating the basal ganglia in all 5 views.
4. The left and right regions can be moved, if not in the correct location and resized, if not the correct size.
5. The program automatically calculates the ROI values and displays them in a table below the images as shown in Figure 1.

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