NeuroQ™

Quantitative Analysis for Neuroimaging Technology

Display and Analysis Program

Version 2.21

Operator Guide

rev'd February, 2005

NeuroQ™

QUANTITATIVE ANALYSIS FOR NEUROIMAGING TECHNOLOGY

Version 2.21

OVERVIEW

The **NeuroQ™ - PET DP** 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 studies of defined groups having no identified neuropsychiatric disease or symptoms, i.e., asymptomatic controls (AC). The Program provides automated analysis of brain PET 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. This manual describes the display and analysis features of the Program, and their end-user operation.

Program Description

The NeuroQ™ Program is indicated to:

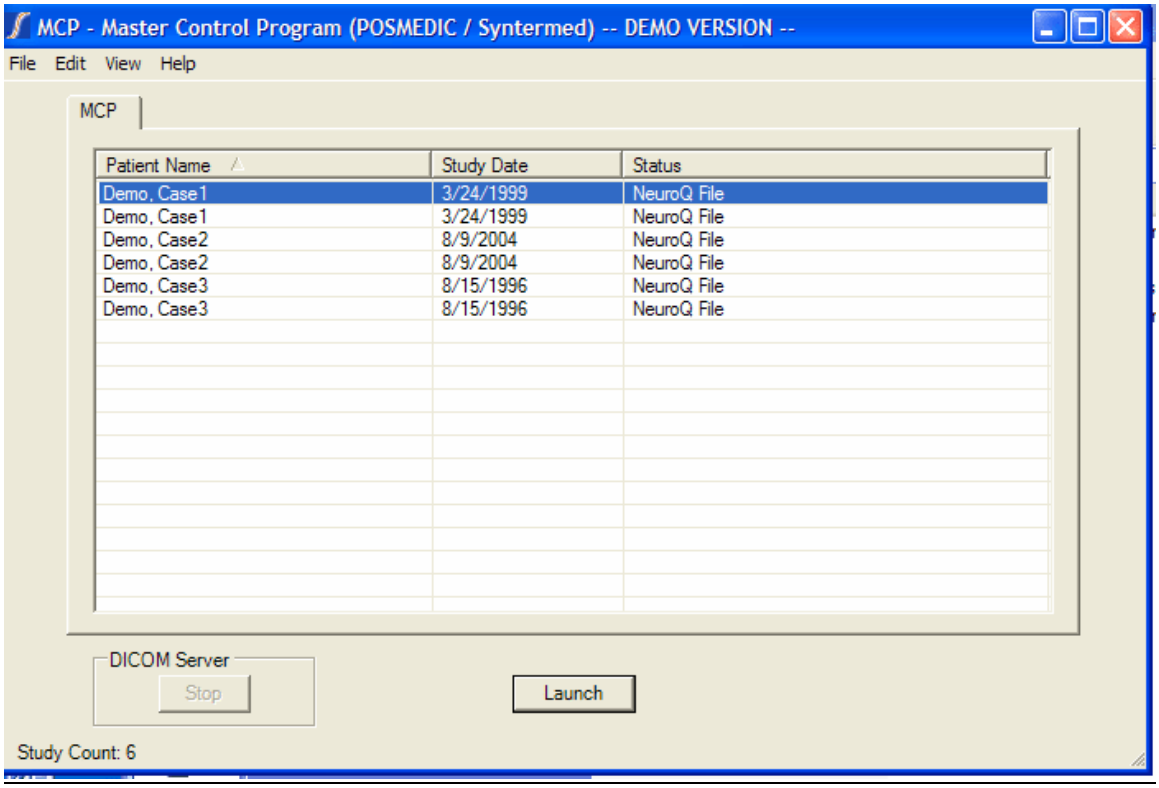
1) assist with regional assessment of human brain scans, through automated quantification of mean pixel values lying within standardized regions of interest (S-ROI's), and
2) assist with comparisons of the activity in brain regions of individual scans relative to normal activity values found for brain regions in FDG-PET scans, through quantitative and statistical comparisons of S-ROI's.

The program requires the operator to select the patient's FDG-Brain scan. Following a number of internal checks on the data (e.g., accurate radiopharmaceutical), the operator has to initiate the 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-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.

LAUNCHING THE PROGRAM

1) After the software applications are loaded onto your computer NeuroQ can be launched by clicking on the MCP Icon on your desktop (shown on the left). Or you can you can go to the C:\Program Files\MCP folder and click on the MCP.exe application.

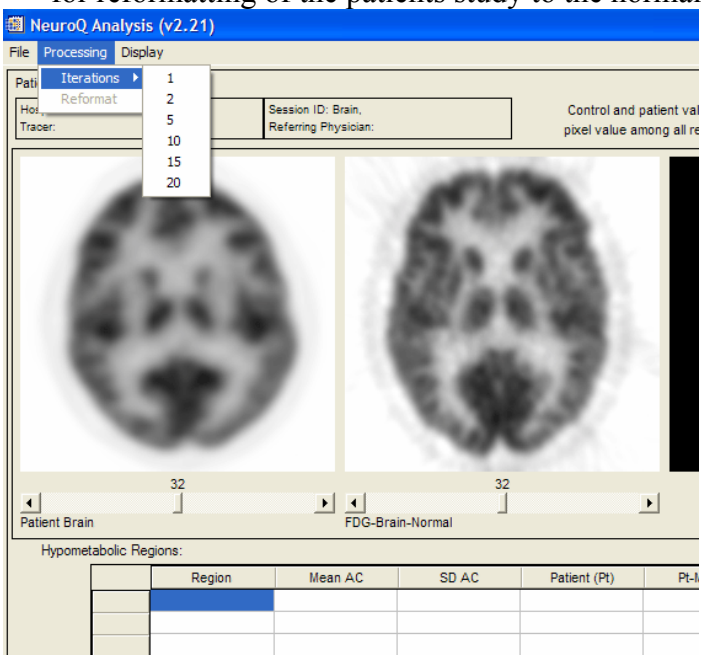
All of the cases that can be run with this demo version are located in the C:\NeuroQ\Demo Cases folder. Once MCP is launched the following screen will be displayed:



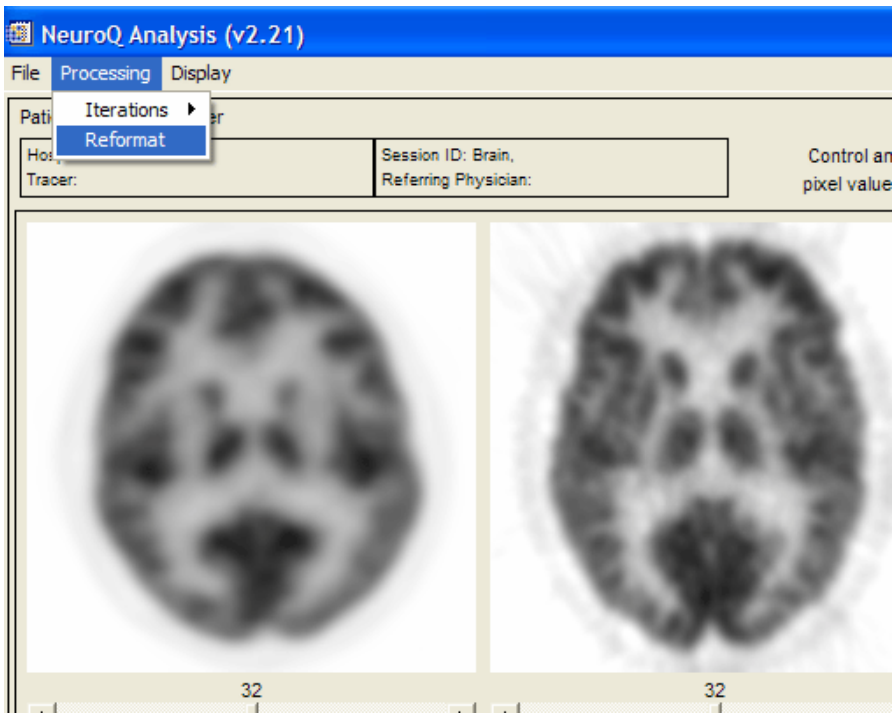
2) There are three demo cases numbered 1-3 and each demo case has two entries. The first entry is the unprocessed study and the 2nd entry is the processed study which was reformatted using 20 iterations. If you want to see how the processing works select the demo case and you can either double click it or hit the Launch button to bring the study into NeuroQ for processing. If you want to skip the processing step then select the second entry for the demo case and either double click or hit the launch button. This will bring the study up already processed.

In order to process the study, do the following:

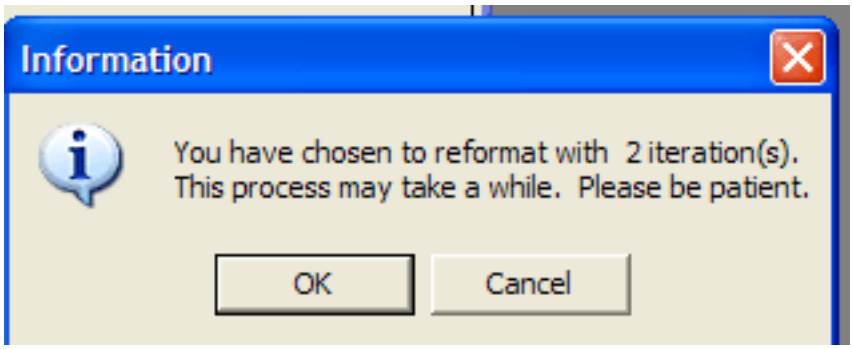
3) From the Processing drop down box select the number of iterations you wish to use for reformatting of the patients study to the normal template as shown below.



4) Once the number of iterations is selected, from the Processing drop down box select Reformat as shown below.



5) An information box will be displayed informing you of the number of iterations you have selected.



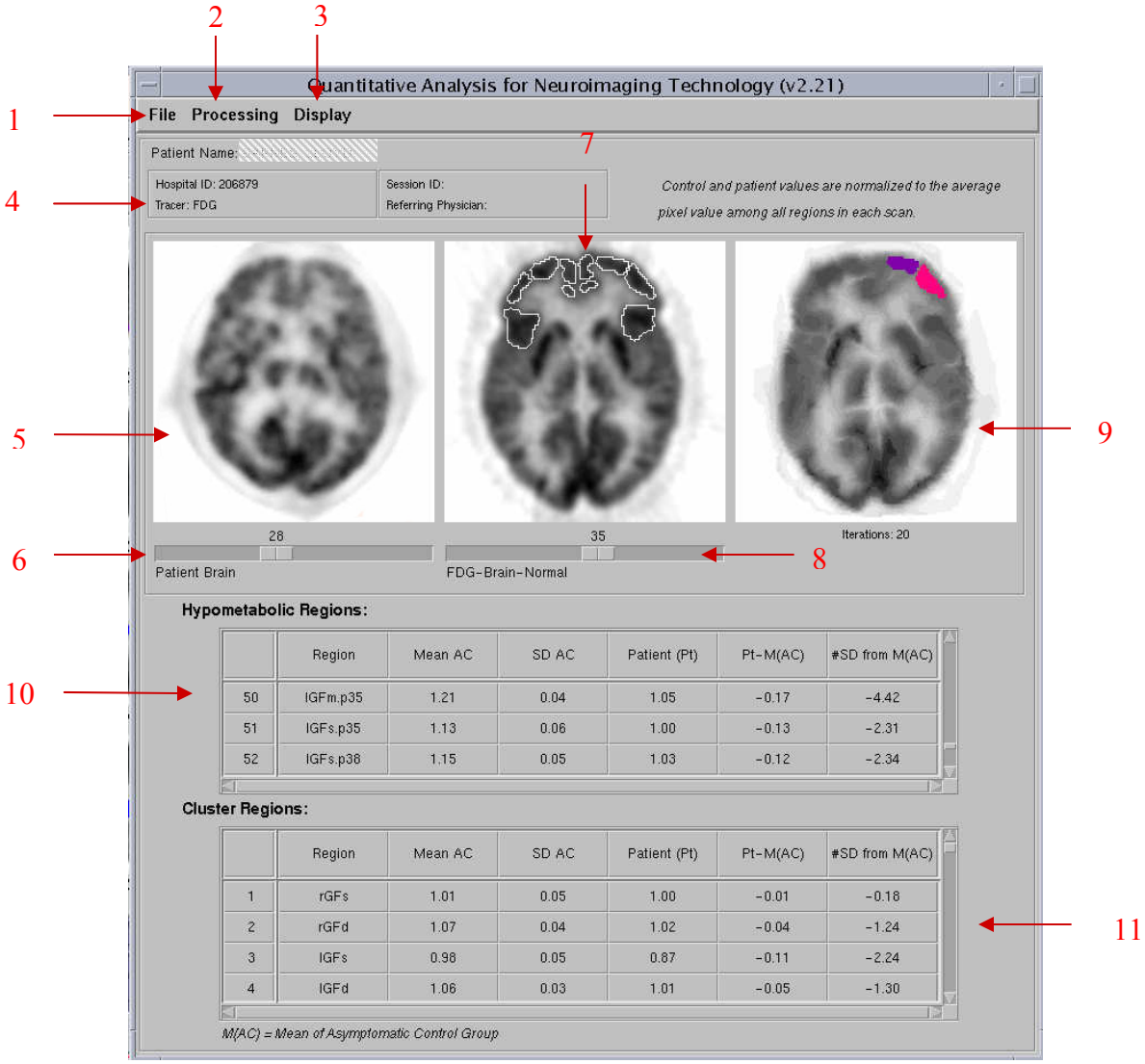
6) Click on the OK button and the patient's study will be reformatted to align with the normal template.

7) Subsequently, the **"NeuroQ™ Analysis (v2.21)"** screen, the **"NeuroQ™ Display (v.2.21)"** screen, and a **textbox** displaying the data for each Region of Interest (ROI) for the patient selected will appear. These displays are defined below.

8) Note: There will be 3 output files created from the process.

a. A file called patientname_it_number.v which contains the processed data for the patient using the indicated number of iterations. When you enter the program the next time you can select just the .v file which will show the results for that patient with the number of iterations selected without having to reformat the patients study again.
b. A file called patientname_ROIdata.dat which contains the information related to the region of interests generated during the processing.
c. A file called patientname_ROImean.dat which contains the mean values generated from the ROI analysis.

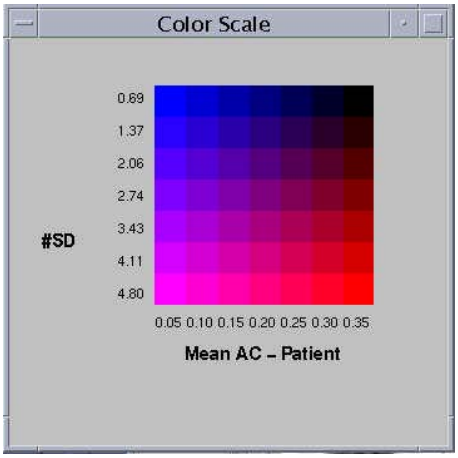
NeuroQ™ ANALYSIS SCREEN



1. File Menu – accesses all the print functions and allows the user to exit, *NOTE: the **"Print in Color"** option has no functionality at this time.*

2. Processing Menu – allows user to reformat the brain, a number of iterations must be selected first before reformatting.

3. Display Menu – **"Hypometabolic"** displays the most hypometabolic regions and performs calculations accordingly, **"Hypermetabolic"** displays the most hypermetabolic regions and performs calculations accordingly, *NOTE: default is "Hypometabolism"*, "**Show Color Scale"** provides legend of the two-dimensional color coding, this tool can be used to check whether the colors are displaying correctly on the monitor system, *NOTE: if colors do not appear correctly in the Brain Plane Displays, proper color coding scheme can still be viewed in saved postscript files.*



4. Patient Information – displays patient information. *NOTE: specific patient information in this display is blacked out for confidentiality purposes.*

5. Patient Brain Display – displays the original patient brain when the loaded file has not been previously reformatted and displays the iterated patient brain when a reformatted file is selected. *NOTE: currently displaying un-reformatted brain.*

6. 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.

7. 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.

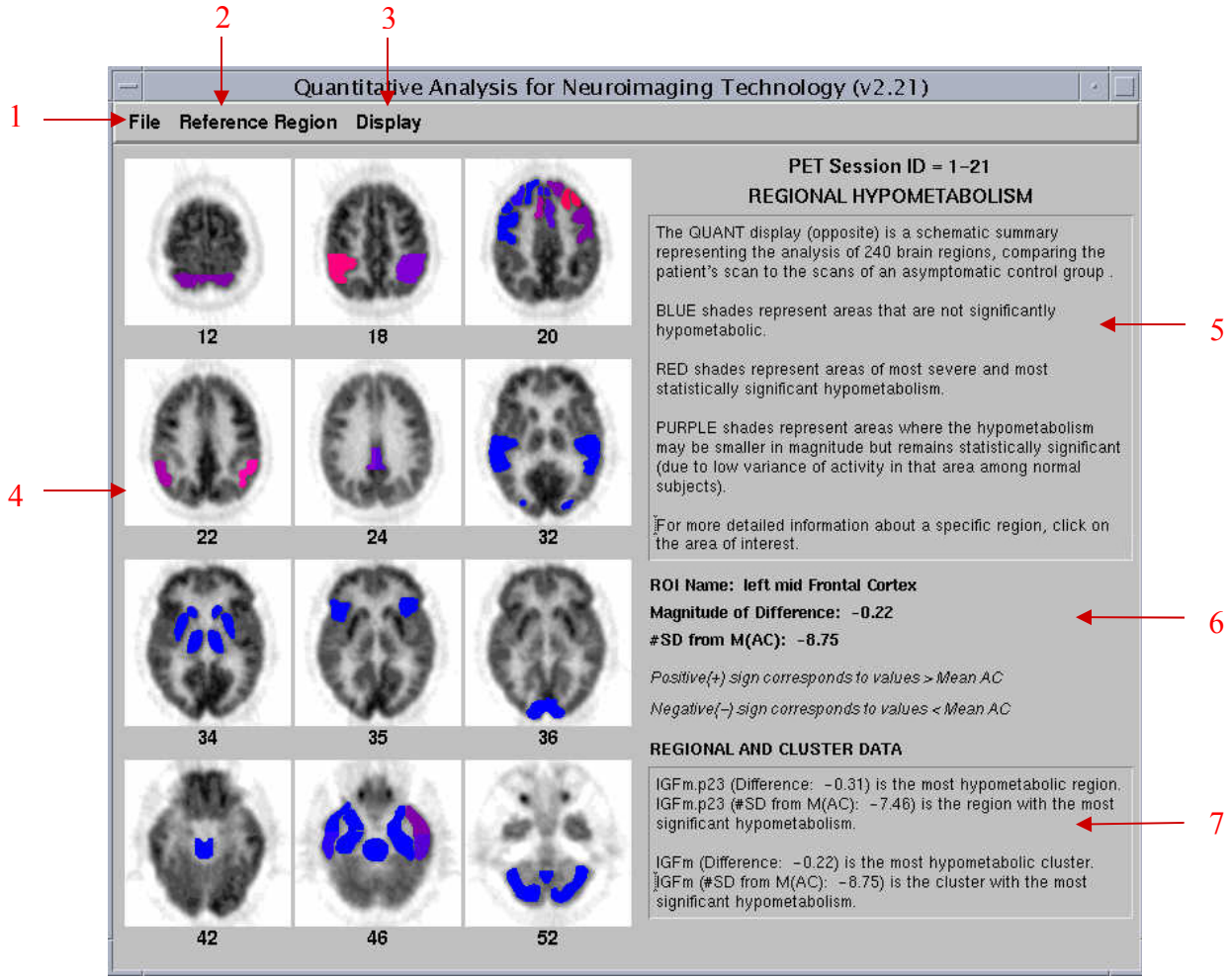
8. Middle Plane Slider - controls the brain plane of the normal brain display and the reformatted patient brain display at right; the current plane number is displayed above the slider, slide to the left or right to access lower or higher planes respectively, simultaneously for both displays.

9. 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, see the NeuroQ™ - PET DP Display Screen for color coding explanation.

10. 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.

11. Table of Cluster Values – the ROI cluster value is based on the average of the represented region across all planes where it is assessed.

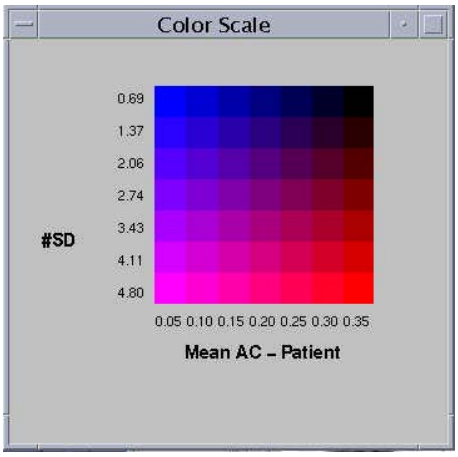
NeuroQ™ - PET DP DISPLAY SCREEN



1. File Menu – user can choose the option to **"Print", "Save As Postscript"** (which saves the display without the frame in a cleaner report format, the postscript file can be opened and saved as a JPEG or other image file), or **"Quit"** *NOTE: user must save all Postscript files with the extension ".ps".*

2. 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.*

3. Display Menu – **"Hypometabolic"** displays the most hypometabolic regions and performs calculations accordingly, **"Hypermetabolic"** displays the most hypermetabolic regions and performs calculations accordingly, *NOTE: default is "Hypometabolism",* "**Show Color Scale"** provides legend of the two-dimensional color coding, this tool can be used to check whether the colors are displaying correctly on the monitor system, *NOTE: If, due to workstation/monitor incompatibility, colors do not appear correctly in the Brain Plane Displays, proper color coding scheme can still be viewed in saved postscript files.*



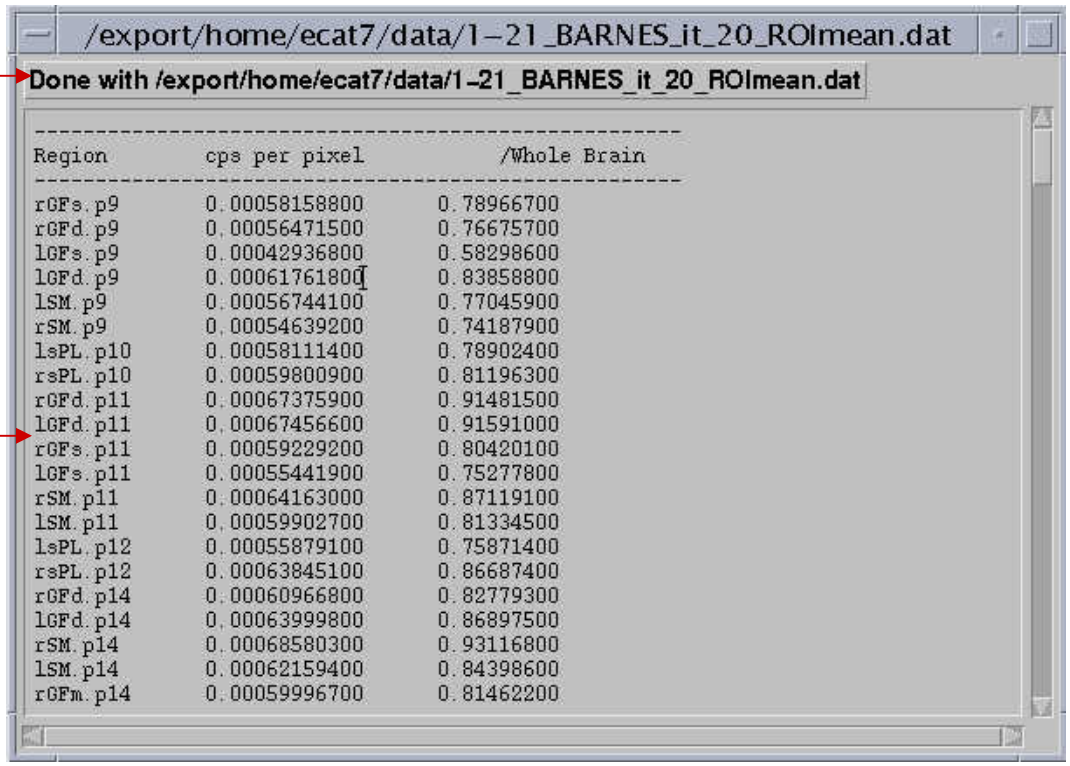
4. Brain Plane Displays – includes schematic display of each of the 47 ROI clusters, shown at the normal template planes numbered below each image. Refer to the "**Show Color Scale"** description for color coding explanation. Clicking on a ROI causes the full name and numerical characterization of that region to appear in the Data Display area (6).

5. Explanation Box – gives brief explanation of the Display Screen and interpretation of two-dimensional color scale.

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

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

TEXT BOX



Region cps per pixel /Whole Brain

Region	cps per pixel	/Whole Brain
rGFs.p9	0.00058158800	0.78966700
rGFd.p9	0.00056471500	0.76675700
lGFs.p9	0.00042936800	0.58298600
lGFd.p9	0.00061761800	0.83858800
lSM.p9	0.00056744100	0.77045900
rSM.p9	0.00054639200	0.74187900
lsPL.p10	0.00058111400	0.78902400
rsPL.p10	0.00059800900	0.81196300
rGFd.p11	0.00067375900	0.91481500
lGFd.p11	0.00067456600	0.91591000
rGFs.p11	0.00059229200	0.80420100
lGFs.p11	0.00055441900	0.75277800
rSM.p11	0.00064163000	0.87119100
lSM.p11	0.00059902700	0.81334500
lsPL.p12	0.00055879100	0.75871400
rsPL.p12	0.00063845100	0.86687400
rGFd.p14	0.00060966800	0.82779300
lGFd.p14	0.00063999800	0.86897500
rSM.p14	0.00068580300	0.93116800
lSM.p14	0.00062159400	0.84398600
rGFm.p14	0.00059996700	0.81462200

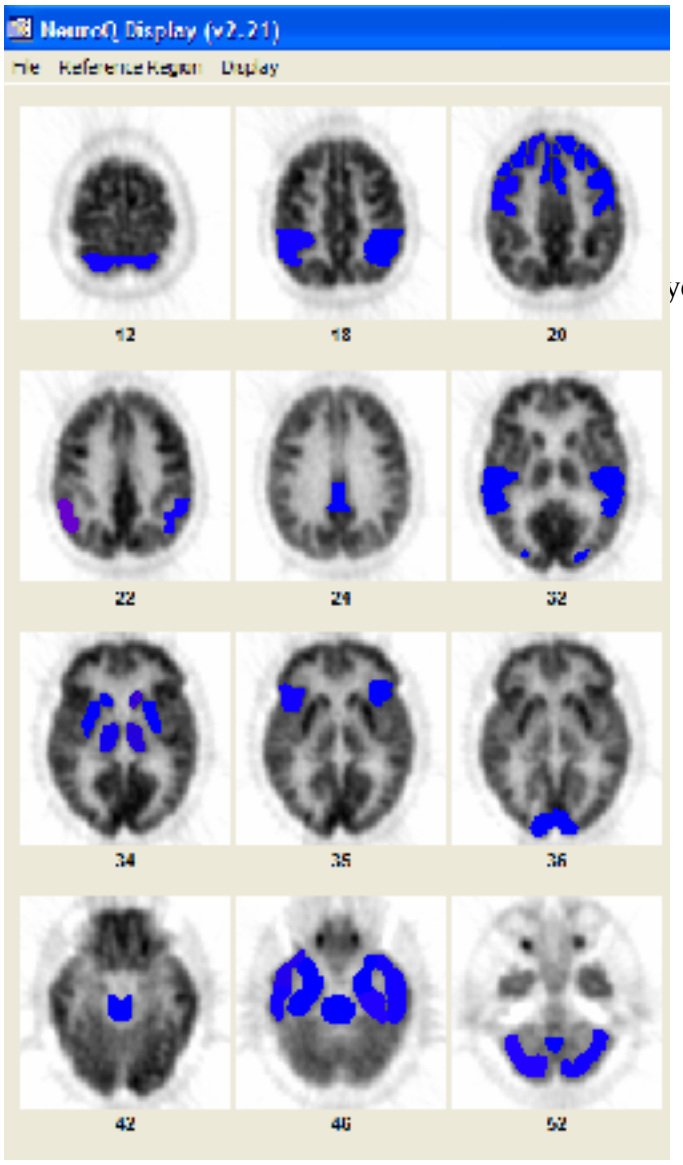
1. Done Bar – shows the directory in which the file is located. Press to close the screen.

2. Data – gives the "mean" (average number of counts per second per pixel in 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).

Description of Example Patient's

1. Demo, Case1 – Normal Case

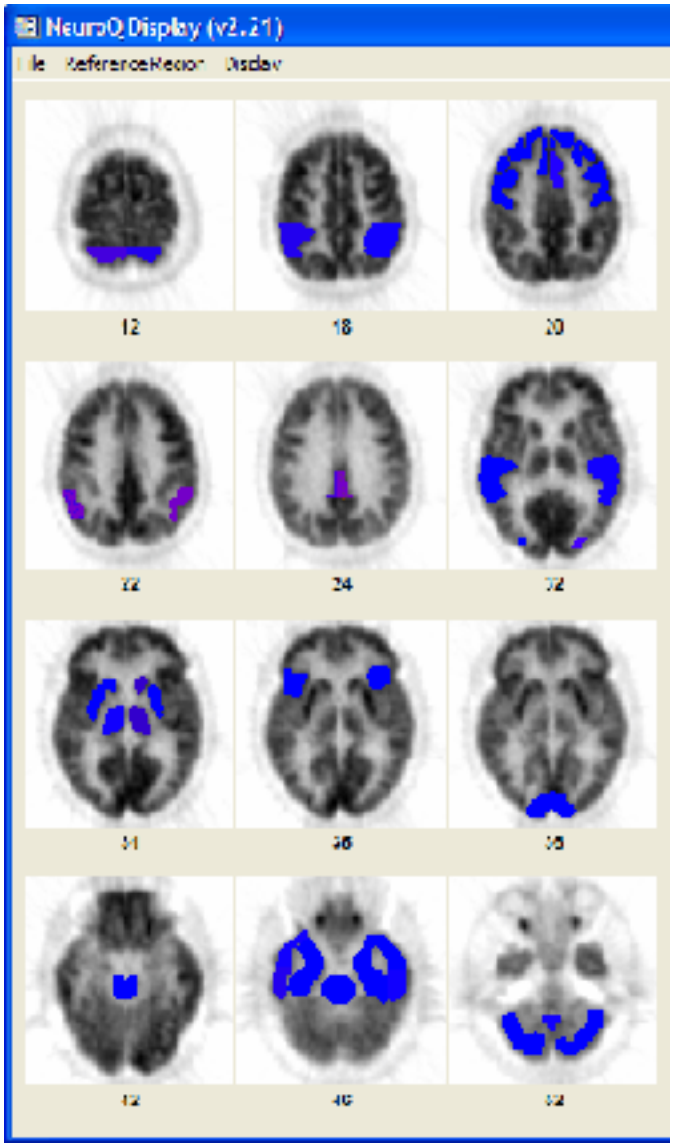
This case demonstrates the quantitative output produced by NeuroQ when it is used to analyze a normal study. The blue areas within the cluster regions indicate that the metabolic uptake was all above the normal limit of 1.65 standard deviation.



years old wh

2. Demo, Case2 – Mildly Abnormal

Patient History



Mr. E was 71 years old when he was first referred to the UCLA Ahmanson Biological Imaging Division in December 2001 with concern for worsening memory. He reported that he always had a poor memory, but that over the preceding seven years, he began to notice his memory getting worse, including forgetting where he put his keys and forgetting names or faces. Mr. E had worked as a physicist for 25 years and taught physics at the University-level for the following 20 years. He reported no psychiatric hospitalizations, illness, or medication use. Mr. E had no significant medical history, including hospitalizations or illness, with the exception of prostate surgery for benign enlargement. He did not use tobacco, alcohol or other drugs and had no history of such use. His physical examination, neurologic exam and blood laboratory values (including TSH, B12, CBC, ALT and Cr) were within normal limits.

Mr. E underwent comprehensive neuropsychologic testing at the time of his first visit in 2001, and was found to be cognitively normal for his age.

Why was a PET scan obtained at this time?

This patient is seeking a diagnosis for his chief complaint, a convincing history of cognitive decline. His symptoms are unexplained by any factors identified in his history, physical or laboratory work-up. Moreover, for patients possessing his apparent high level of pre-morbid intellectual ability and education, it is common for loss of cognitive ability to be experienced, while still being able to perform at levels considered to be within the normal ranges of standard neuropsychological tests.

PET Interpretation

The scans from 2001 and 2004 each reveal mild parietal/temporal hypometabolism, more pronounced on the left (right side of image). NeuroQ™ analysis identifies mild

abnormalities (purple to red shades) in parietal/temporal and posterior cingulate regions, with well-preserved metabolism in other regions (blue shades)… a pattern very suggestive of early Alzheimer's type changes occurring in this patient's brain.

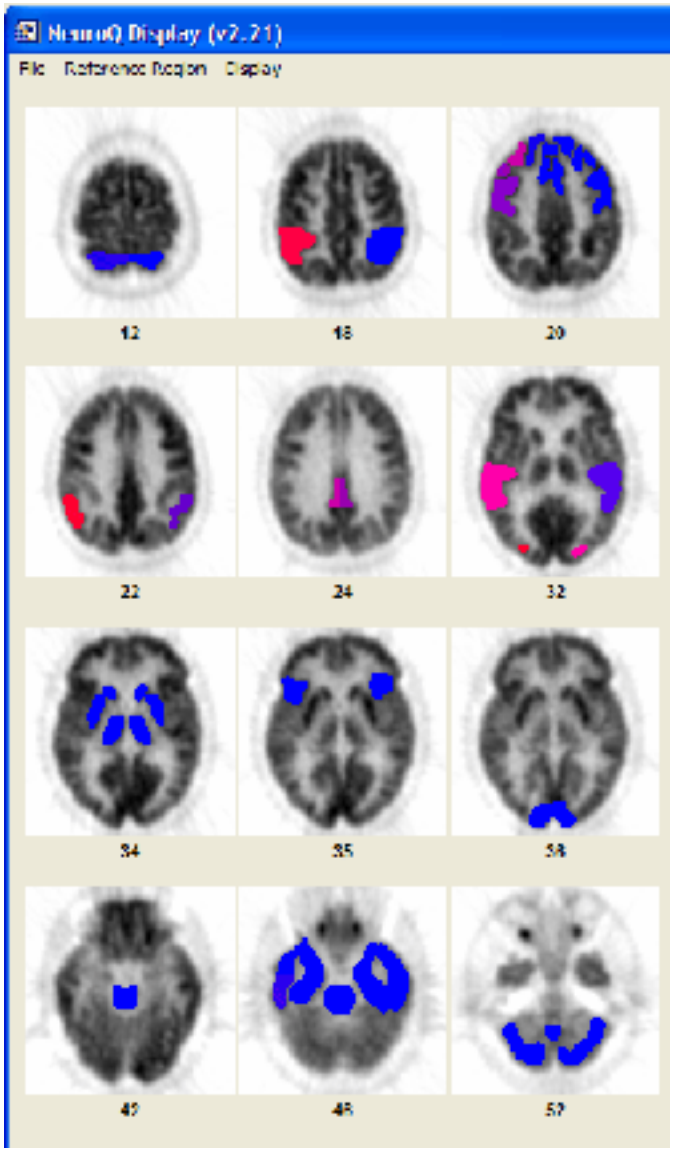
The pattern of cerebral metabolism in 2004 has slightly changed since 2001. Visually, there appears to be slight interim worsening of parietal/temporal hypometabolism. [Show combined figure with arrows, on slide 3, here.] That impression is bolstered by the NeuroQ™ analysis, which shows in its plane 22 image the left parietotemporal cortex advancing to a near-red shade (12% and 4 standard deviations below normal) in 2004, from the purple shade (9% and 3 SD below normal) seen in 2001.

Case Summary

To summarize, at a time when conventional clinical evaluation was not sufficiently sensitive to document cognitive abnormality in this 71 year old physicist reporting memory problems, PET was already documentably (mildly) abnormal, both by visual and quantitative analyses. From 2001 to 2004, neuropsychologic performance with respect to immediate and delayed memory for word associations, contextual information, rote list learning, and complex visual stimuli declined across testing sessions, indicating "significant cognitive deterioration" within those abilities, according to the neuropsychologist. By 2004, Mr. E's performance met criteria for "Mild Cognitive Impairment," performing between one and two standard deviations below the mean established for his same age peers on at least 50% of the memory tasks. The combination of this clinical progression, with the posterior-predominant pattern of hypometabolism affecting especially parietal/temporal cortex is most consistent with the presence of incipient Alzheimer's disease. Armed with the FDG-PET information, his managing physician prescribed an anti-Alzheimer's combination regimen including both donepezil and memantine in advance of the second neuropsychologic testing session. On his current regimen, he continues to achieve 30/30 on the Mini Mental State Examination (MMSE).

3. Demo, Case3 – Severely Abnormal

Patient History



Mr. F was 63 years old when he underwent FDG-PET in August 1996 for symptoms of decreased memory, language and visual skills. The cognitive decline had been noted for at least 2 years, as had been sensory and motor deficits of his left upper extremity. Mr. F's past medical history was positive for pyelonephritis, prostatitis, and prostate surgery for benign enlargement. The patient had a history of heavy alcohol use in the past, but had discontinued drinking, and did not use tobacco or other drugs nor have a history of such use. He was a lawyer, as was his wife, and they had two small children. His physical examination, other than his neurologic exam was normal. His neurologist noted upon exam that the patient got two of three items correct regarding orientation and three of four words remembered correctly at 3 minutes, and that he had marked apraxia of the upper extremities with left worse than right, plus "mild Parkinsonism with a mask face"; cranial nerves were intact and reflexes were normal. Blood laboratory tests obtained one month prior to PET were normal, including CBC, electrolytes, BUN, creatinine, glucose, calcium, cholesterol, and liver enzymes; VDRL and TSH tests obtained the following year were also normal. The neurologist following Mr. F, an internationally recognized expert on dementia and Director of a university-based Alzheimer's Disease Center, diagnosed him with corticobasal degeneration and depression, for which he was treated with the antidepressant sertraline.

Structural Neuroimaging

1992 Brain MRI revealed "mild enlargement of the lateral ventricles… otherwise unremarkable."
1994 Brain MRI with and without contrast revealed "progression of cerebral atrophy."
1995 Brain MRI revealed "moderate generalized cerebral atrophy which is not significantly changed when compared to the scan of 1994. The scan is otherwise within normal limits."
1996 Brain MRI with and without contrast revealed "stable appearance of cerebral cortical atrophy."
1997 Head CT revealed "cerebral atrophy but is otherwise negative."

Why should the patient get a PET scan at this point in his evaluation?

Mr. F has documented cognitive decline and motor symptoms noted on neurologic examination. The symptoms are unexplained by his general history, physical examination, laboratory screen and structural neuroimaging tests, which are largely unremarkable. Although he was evaluated by a prominent dementia expert who did not suspect Alzheimer's disease, there are no tests (short of brain biopsy) documented to be as accurate as FDG-PET in the identification of Alzheimer's disease that the neurologist did, nor could do, to exclude the possibility of that now-treatable condition.

Clinical Follow-up

Mr. F. continued to progressively deteriorate with respect to cognitive and motor symptoms, also developing a seizure disorder before his death that proved resistant to medical therapy. An autopsy was performed in 2000 at the Alzheimer's Disease Center for which the patient's neurologist was Director, and the final diagnosis was "Alzheimer disease, [Braak and Braak Stage VI, CERAD definite]" with abundant neurofibrillary tangles in the hippocampus, entorhinal cortex and neocortex, as well as amyloid-beta(1-42)-staining plaques prominent throughout all areas of hippocampus, entorhinal cortex and neocortex. (Synuclein staining to check for the presence of Lewy bodies was not performed.)

Case Summary

To summarize, by the time of this PET scan, Mr. F. had undergone extensive evaluation of his cognitive and motor symptoms, including history and physical examinations by his internist, neurologic examination by a dementia expert, laboratory screening, as well as multiple brain MRI studies, two of them including contrast, and subsequently a head CT. The clinical examination led to diagnoses of corticobasal degeneration and depression, the laboratory screen was negative, and the structural imaging studies demonstrated only atrophy.

None of the above studies pointed to the presence of Alzheimer's disease, and the patient correspondingly received no treatment specific to that diagnosis. The presence of Alzheimer's disease, however, was clearly evident on both PET and autopsy examinations. PET also revealed profound hypometabolism of associative visual cortex (quantified by NeuroQ™ as falling as much as 12 standard deviations below normal

metabolic levels) suggesting Lewy body involvement, which could also help to explain the prominence of the patient's central motor symptoms.

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