

## University of Utah PET Image Analysis Methods

Norman L Foster, Angela Wang  
University of Utah  
Center for Alzheimer's Care, Imaging and Research  
650 Komas Drive, Suite 106A  
Salt Lake City, UT 84108

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### Summary

The focus of The University of Utah component of the PET Imaging Core is on the individual image analysis and processing of molecular imaging data using 3-dimensional stereotactic surface projections (3D-SSP) computed by Neurostat, developed by Satoshi Minoshima [Minoshima et al., 1995].

We submit 6 numeric summary values. We compute the averaged uptake values in 18F-FDG, 18F-AV45 and 11C-PIB images, for regions that are typically relevant to Alzheimer's Disease: the frontal and association cortices. We also convey information on the spatial extent and magnitude of abnormal changes by pixel-wise computation of Z-scores of subjects in standard space compared to a control group. For FDG scans, we submit the number of pixels significantly hypometabolic compared to a group of elderly normal subjects. For amyloid scans, we submit the number of pixels with significant increased uptake compared to a group of amyloid negative subjects. We include a measure of the severity of the deviations with the spatial extent, by reporting the summation of significant Z-scores. For FDG scans, we sum the pixels with significant hypometabolism, and for amyloid scans, we sum pixels with significant increases in tracer uptake.

### Methods

Our methods are based on the Neurostat suite of functions for coregistration, warping into standard Talairach atlas space, ROI determination, Z-score calculation and visualization using Stereotactic Surface Projections (3D-SSP). Control databases are also created using Neurostat.

#### *General Neurostat 3-D SSP analysis*

PET scans are downloaded from LONI using the post-processed group 4 images, i.e. coregistered and averaged frames, standardized image orientation and voxel size, and uniform resolution smoothed to 8mm. Neurostat aligns the brain images along the AC-PC line and non-linearly warps the image into standard Talairach space. Longitudinal scans, for each subject, are co-registered to the baseline scan and a multi-step normalization is used to create a mean template



that reduces the variability between the subject visits. A peak pixel template is created from the mean template and applied to intra-subject serial scans to produce surface projection maps, SSPs. Neurostat pre-defined brain regions in Talairach space are used to calculate the ROI regional values based on the SSP maps. Statistical Z-scores are calculated pixel-wise from a reference set of control subjects to create individual SSP Z-score maps showing the statistical significance of the subject pixel values.

### *FDG-PET analysis*

FDG-PET scans are downloaded and processed as described above. The control subjects used for comparison are a group of cognitively normal elderly subjects (N=27, age=69.6 ± 7.7 yrs) we routinely use in our clinical analysis. Regional values of glucose uptake are computed and normalized to the average pons value.

### *AV45 and PIB PET analysis*

Amyloid PET scans are downloaded as described above. Control subjects are selected from the group of normal subjects at their initial amyloid imaging visit. Subjects that convert on subsequent visits are removed. In order to standardize the selection of amyloid negative subjects, we use an iterative outlier removal procedure (2). Outliers are eliminated based on individual regions consisting of: lateral and medial frontal, lateral and medial parietal, lateral and medial temporal, posterior cingulate, anterior cingulate, and occipital regions. Those that pass the selection process in all regions are used to form the core group of amyloid-negative control subjects.

Amyloid scans are co-registered to the FDG scan at the visit closest in time to the amyloid visit. The warping transformation into standard space is obtained from the FDG and is applied to the amyloid image to get it into Talairach space. Templates from the FDG analysis for selecting cortical and sub-cortical peak pixels are applied to the amyloid image in standard space. Thus, there is a direct correspondence between the pixels used to construct the surface maps and the pixels used to define regions for both FDG and amyloid scans.

In our investigative analysis of PIB scans we performed a cross-sectional processing. Selection of peak pixels for the PIB scan is based on the FDG template created at that visit. A PIB-negative control group (N=11, age=76.9 ± 6.0 yrs) was defined and used for comparison. We normalize to the cerebellar regional value.

AV45 images are normalized using both cerebellar and white matter values. Neurostat automatically defines the averaged cerebellar value. We create an amyloid-negative control group using cerebellar normalization (N=117, age=75.9±11.7 yrs). White matter values are determined by sampling pixels from the amyloid image, in Talairach-space, starting at a much greater depth, thus bypassing the cortical ribbon. We use the Neurostat generated global value for the whole brain white matter value. We define a second amyloid-negative control group using white matter normalization (N=128, age=75.1±13.1 yrs).

### *Numeric summary values*

The numeric summary values we submit are:

- i) AVEREF average regional value of the reference region used for normalization. Neurostat automatically generates averaged values to 20 (right and left hemispheres) regional values, along with pons, global and cerebral cortex values. These regions are

- determined from the Talairach atlas. For FDG we normalized to the pons reference region. For PIB analysis, we normalized to the cerebellar region. For AV45 analysis, we are investigating the effects of using different target regions for normalization and we report both the cerebellar region and white matter normalization results.
- ii) AVEASSOC average regional association cortex value, consisting of both lateral and medial surfaces from frontal, temporal and parietal cortices
  - iii) AVEFRONT average regional frontal cortex calculated from lateral and medial frontal value
  - iv) X2SDSIGPXL number of pixels with Z-scores greater than or equal to 2 standard deviations and less than 3 standard deviations from control mean. For FDG scans these are the number of hypo-metabolic pixels, or the pixels with decreased CMRglc uptake compared with our control group. For the amyloid scans, this is the number of pixels with increased amyloid tracer SUV<sub>r</sub>, compared to the control group.
  - v) X3SDSIGPXL number of pixels with Z-scores greater than or equal to 3 standard deviations from control mean. For FDG scans this is the number of hypo-metabolic pixels, and for the amyloid scans, this is the number of pixels with increased amyloid uptake.
  - vi) SUMZ2 sum of pixel Z-scores greater than or equal to 2 standard deviations. For FDG scans these are derived from the hypo-metabolic pixels, and for the amyloid scans, these are from pixels with increased amyloid uptake.
  - vii) SUMZ3 sum of pixel Z-scores greater than or equal to 3 standard deviations. For FDG scans these are from the hypo-metabolic pixels, and for the amyloid scans, these are from pixels with increased amyloid uptake.

### *Names and versions of software*

#### **Neurostat** functions used:

averageimage - AVERAGING MULTIPLE IMAGE SETS WITH / WITHOUT NORMALIZATION (Version 3.0)  
 cnvtiff - TIFF FILE GENERATOR (Version 3.1)  
 cnvtc6bi - CONVERT CTI6 TO BINARY (Version 2.4)  
 coreg - THREE-DIMENSIONAL IMAGE COREGISTRATION (Version 5.0)  
 coregimg - 3D IMAGE TRANSFORMATION USING COREGISTRATION LIBRARY (Version 3.5)  
 mcoreg - COREGISTRATION PET/SPECT MULTIPLE IMAGE SETS (Version 4.1)  
 mnorm - WITHIN-SUBJECT MULTIPLE IMAGE NORMALIZATION (Version 4.0)  
 mstereo - STEREOTACTIC REGISTRATION WITH MULTIPLE WITHIN-SUBJECT SCANS (Version 6.2)  
 sagicoro - IMAGE MATRIX RESLICING (TRANSVERSE TO SAGITTAL AND CORONAL) (Version 4.0)  
 sspcomp - 3D-SSP DATABASE COMPARISON (Version 8.4)  
 sspdisp - DISPLAY 3D-SSP DATA (Version 4.4)  
 ssploc - PEAK CORTICAL PIXEL DETECTION (Version 2.4)  
 ssplocsub - SUBCORTICAL PIXEL LOCALIZATION (Version 3.0)  
 sspsmpl - PEAK CORTICAL PIXEL SAMPLING (Version 2.5)  
 sspvoiclassic - 3D-SSP VOI SAMPLING USING PREDEFINED LOCATION FILES (Version 4.0)  
 stereo - STEREOTACTIC IMAGE REGISTRATION (Version 7.1)  
 stereo - STEREOTACTIC IMAGE REGISTRATION (Version 8.0)  
 swarpreg - 3D STEREOTACTIC IMAGE WARPING (Version 5.5)

#### **C** functions used:



XCode version 3.0

SumZ – v Feb 27-2012

CountZScores – v Feb 27-2012

Statistical packages used:

R version 2.15.2 (2012-10-26) -- "Trick or Treat"

removeOutliersFile.r – v Feb13-2013

IDL Version 6.2, Mac OS X (darwin ppc m32). (c) 2005

## **Version Information**

This document supersedes our previous uploaded documents: ADNI\_UUCACIR\_Methods.docx, ADNI\_UUCACIR\_NumericSummaries-3-5-2012.csv, and ADNI\_UUCACIR\_Datadict-3-5-2012.csv dated 3-5-2012. Specific changes in our methods are summarized in this section.

We have added statistical Zscores to the amyloid PET processing and updated our numeric summary values to reflect this additional information. The changes are:

- i) The numeric summary AVEPONS has been changed to AVEREF to reflect the target region used for normalization in both FDG and amyloid PET images. The average value of the right and left hemispheric reference regions used for normalization is recorded here.
- ii) The REFREGION field states the reference region used for normalization, recorded in AVEREF. It includes CBL = cerebellum, PNS = pons, WM = white matter.
- iii) We created new control groups for comparison for AV45 and PIB scans. The REFCTRLPOP options are: NORMHR27SM4\_4, 117CORE\_AV45\_cbl, 128CORE\_AV45\_wm, 11CORE\_PIB\_cbl

## **Dataset Information**

This methods document applies to the following dataset(s) available from the ADNI repository:

<b>Dataset Name</b>	<b>Date Submitted</b>
UUtah-PET Analysis	March 2013

## **References**

1. Minoshima S, Frey KA, Koeppe RA, Foster NL, Kuhl DE. A diagnostic approach in Alzheimer's disease using three-dimensional stereotactic surface projections of fluorine-18-FDG PET. J Nucl Med 1995; 36:1238-48.
2. Aizenstein HJ, Nebes RD, Saxton JA, Price JC, Mathis CA, Tsopelas ND, Ziolkko SK, James JA, Snitz BE, Houck PR, Bi W, Cohen AD, Lopresti BJ, DeKosky ST, Halligan EM, Klunk WE.





Frequent amyloid deposition without significant cognitive impairment among the elderly. Arch Neurol. 2008 Nov; 65(11): 1509-17

### **About the Authors**

This document was prepared by Angela Wang, University of Utah, Center for Alzheimer's Care, Imaging and Research. For more information please contact Angela Wang at 801-585-9350 or by email at [angela.y.wang@hsc.utah.edu](mailto:angela.y.wang@hsc.utah.edu).

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