

University of Utah PET Image Analysis Methods

Description of Numeric Summary Values

(Aug 10, 2015)

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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 for each of the PET modalities, 18F-FDG and 18F-AV45. Two of the summary values derive from the normalized average uptake value, for regions that are typically relevant to Alzheimer's Disease: the frontal and association cortices. The other summary values provide information on the spatial extent and magnitude of abnormal changes by pixel-wise computation of Z-scores of subjects 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 florbetapir scans, we submit the number of pixels with significant increased uptake compared to a group of normal subjects. We include a measure of the severity of the deviations by reporting the summation of significant Z-scores. For FDG scans, we sum the pixels with significant hypometabolism, and for florbetapir 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.

Florbetapir (AV45) PET analysis

[Please note that analysis conducted prior to Aug 2015 was processed with a slightly different protocol. Previous data and documentation are available in the LONI archives: [Download/Study Data/ Archive \(8/13/15\)](#)].

Florbetapir PET scans are downloaded from LONI as described above. Control subjects are selected from the group of normal subjects at their initial florbetapir image 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.

Florbetapir scans are coregistered to the baseline FDG scan, as FDG scans are not available at all visits for each subject. The warping transformation into standard space is obtained from the FDG and is applied to the florbetapir image to get it into Talairach space. Templates from the FDG analysis for selecting cortical and sub-cortical peak pixels are applied to the florbetapir 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 florbetapir scans. Selection of peak pixels for amyloid scans is based on the longitudinal FDG template created from each visit for the subject.

Florbetapir images are normalized using both cerebellar and white matter values. We create a florbetapir control group, from the clinically stable normal subjects, using cerebellar normalization (N=165, age = 74.5 ± 6.9 yrs). We define a second amyloid-negative control group using white matter normalization (N=178, age = 74.8 ± 6.9 yrs). White matter values are determined by sampling pixels from the amyloid image at a much greater depth, bypassing the cortical ribbon. We use the Neurostat generated global value for the whole brain white matter value.



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 florbetapir analysis, we normalize to both the cerebellar region and global white matter.
- 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 florbetapir scans, this is the number of pixels with increased tracer SUV_r, 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 florbetapir scans, this is the number of pixels with increased 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 florbetapir scans, these are from pixels with increased 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 florbetapir scans, these are from pixels with increased 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 7.0)
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 3.0)
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 8.0)



swarpreg - 3D STEREOTACTIC IMAGE WARPING (Version 6.0)

C functions used:

XCode version 6.4 (6E35b)

SumGlobalZ – v 8/6/15

CountGlobalZScores – v 7/30/15

Statistical packages used:

R version 3.2.1 (2015-06-18) -- "World-Famous Astronaut"

removeOutliersFile.r – v 2/27/15

Run on machine:

Mac Pro (mid 2012) MacOS Version 10.10.4

Version Information

Aug 10, 2015 – This document version describes our analysis of all FDG and florbetapir PET images downloaded from LONI January and June 2015. As FDG PET images are no longer conducted concurrently with florbetapir PET images, we modified our analysis protocol, as describe above.

- i) New control populations consisting of stable subjects with normal PET images were created. These reference control populations are for statistical comparison of florbetapir images normalized to the cerebellum: 165NL_AV45_cbl, and normalized to global white matter: 178NL_AV45_white.
- ii) We will maintain previously processed biomarker data derived from PET images on LONI for historical reference. However, from 2015 forward, our protocol is to coregister all amyloid images to the baseline FDG-PET image and derive numeric summary values from these images in Talairach atlas space.

May 13, 2013 -- This document supersedes our previous uploaded documents from March 2013. We have included longitudinal analysis of AV45 and PIB PET scans.

- i) With the addition of serial visits, we created new control groups for AV45 and PIB scans. The REFCTRLPOP options are: NORMHR27SM4_4, AV45_168NL_cbl, AV45_173NL_wm, PIB_11NL_cbl, and PIB_11NL_wm.

March 2013 -- 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:

- ii) 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.



- iii) The REFREGION field states the reference region used for normalization, recorded in AVEREF. It includes CBL = cerebellum, PNS = pons, WM = white matter.
- iv) 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:

Dataset Name	Date Submitted
UUCACIR 08 10 15	Aug 13, 2015
UUCACIR 03 17 15	Mar 17, 2015
UUCACIR 08 21 15	Aug 21, 2014
UUCACIR 01 31 14	Jan 31, 2014
UUtah-PET Numeric Summaries.csv	May 13, 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, Ziolkowski 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

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