ADNI Alzheimer's Disease Neuroimaging Initiative

# Amyloid PET Processing Methods

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## Summary

This methods document describes all amyloid PET data using [18F] florbetaben (FBB), [18F] florbetapir (FBP), (referred to as AV45 in image filenames), and [18F] NAV4694 (NAV), smoothed to a uniform resolution of 6 or 8mm.

The **primary quantitative amyloid PET measurement is tracer uptake in a cortical summary SUVR which captures overall amyloid burden in the brain and can be used to determine amyloid +/- status using previously validated thresholds**. This dataset contains the continuous cortical summary SUVR and Centiloid (CL) values that reflect amyloid PET uptake across the cortical summary region and other individual regions, dichotomous variables that reflect amyloid +/- status, and volumetric measurements for each PET ROI.

**Please note that the 6mm dataset contains SUVrs from multiple amyloid PET tracers. CL values can be compared directly to one another in analyses involving multiple tracers, but SUVrs from multiple tracers are not directly comparable.**

Our native space PET analysis pipeline uses the structural MRI scan that is closest in time to each amyloid PET scan. The MRI is segmented and parcellated with Freesurfer v7.1.1 to define a **cortical summary region that is made up of frontal, anterior/posterior cingulate, lateral parietal, lateral temporal regions** (see complete list in Appendix 1).

We have also defined **five candidate reference regions: cerebellar grey matter, whole cerebellum, brainstem, eroded subcortical white matter, and a composite reference region** (made up of whole cerebellum, brainstem, and eroded subcortical WM).

**To generate the SUVRs in this dataset, we coregistered each amyloid PET scan to the corresponding segmented/parcellated MRI, intensity normalized the PET scan by the whole cerebellum, and calculated the mean uptake (SUVR) within each Freesurfer Desikan-Killiany region (left, right and volume-weighted bilateral), the cortical summary region, and the five reference regions.**

***Are the numerical amyloid data already intensity normalized?***

Yes. The SUVR and CL values reflect data that has been intensity normalized by the whole cerebellum. This can be observed by the whole cerebellum column having an intensity of "1.0" across all scans. **However, since the reference regions are themselves intensity normalized by the whole cerebellum, it is possible to re-intensity normalize regional or summary SUVRs once by dividing by one of the other reference regions in our dataset. This re-normalization divides out the initial whole cerebellum normalization.** For example, to calculate summary SUVRs normalized by the composite reference region you must divide the SUMMARY_SUVR values by COMPOSITE_REF_SUVR values.

**NOTE: The cortical summary CLs cannot be directly transformed to a different intensity normalization. For cross-sectional analyses, we recommend using the summary SUVR (SUMMARY_SUVR) normalized by the whole cerebellum reference region. For longitudinal analyses, we recommend using the summary SUVR normalized by the composite reference region (SUMMARY_SUVR / COMPOSITE_REF_SUVR)**. See "Amyloid Positivity Status" section for the provided binarized SUVR variables and derivation of the positivity thresholds.

## Version Information

This document supersedes our AV45/FBP Methods and FBB Methods documents dated Nov 15 2021. It applies to the FBP 8mm and FBB 8mm datasets published on Feb 17 2023, which include all ADNI FBP and FBB scans acquired through Aug 2022. It also applies to the Amyloid 6mm dataset published since May 25 2023.

Listed below are the changes that from the previous version:

1. **Intensity normalization**: all SUVR columns have been normalized to the cross-sectional reference region (whole cerebellum), making cross-sectional reference region SUVRs equal to 1.000.
2. Addition of **blank rows** for PET that could not be processed due to medical abnormalities or unavailable MRIs.
3. Removal of lobar subregions (frontal, cingulate, temporal, parietal): "FRONTAL_SUVR", "CINGULATE_SUVR", "TEMPORAL_SUVR" and "PARIETAL_SUVR" are no longer provided.
4. Addition of bilateral regional volumetric and SUVR data which are weighted averages of the Freesurfer-defined left/right regions.

Additional changes for the 6mm dataset only:

1. **Merging of tracer**: Multiple tracers (FBP, FBB and NAV) are combined in a single dataset, distinguishable by the "TRACER" column. **Use CL values, not SUVrs to directly compare data from different tracers.**
2. Amyloid positivity variables ("AMYLOID_STATUS" and "AMYLOID_STATUS_COMPOSITE_REF") use different tracer-dependent thresholds.
3. Addition of "**qc_flag**". Please refer to "Pipeline Quality Control Flag" section.

# Methods

## Acquisition of amyloid PET and MRI from LONI

We download amyloid PET images from LONI in the most fully pre-processed format (Step4, frames realigned and averaged, linear transformation to straighten out the head, standardized voxel size and smoothed to 6 or 8mm uniform resolution). LONI image description search terms for each tracer are listed in Table 1. Note that for historical reasons "AV45" is used as a descriptor for FBP on LONI but is referred to as FBP in this document.

**Table 1: LONI image search terms for pre-processed amyloid and original MRI**

| Image Resolution | Modality | LONI Image Description Search Term | Image Type |
|---|---|---|---|
| **8mm** | FBP | AV45 Coreg, Avg, Std Img and Vox Siz, Uniform Resolution | "Pre-processed" |
| | FBB | FBB Coreg, Avg, Std Img and Vox Siz, Uniform Resolution | |
| **6mm** | FBP | AV45 Coreg, Avg, Std Img and Vox Siz, Uniform 6mm Res | |
| | FBB | FBB Coreg, Avg, Std Img and Vox Siz, Uniform 6mm Res | |
| | NAV | NAV Coreg, Avg, Std Img and Vox Siz, Uniform 6mm Res | |
| - | MRI | *Accel* | "Original" |

## FreeSurfer-defined cortical summary and reference regions

The pipeline uses a native-space structural MRI scan that is closest in time to each amyloid PET scan. The MRI is first segmented and parcellated with Freesurfer (FS) v7.1.1, and then coregistered to the amyloid PET image with SPM. The cortical summary region ("SUMMARY_SUVR") is made up of frontal, anterior/posterior cingulate, lateral parietal, lateral temporal regions) [3, 4] defined by the Desikan-Killiany atlas, shown in Figure 1 and listed in Appendix 1 adapted from FreeSurfer naming convention.

There are five candidate FreeSurfer-defined reference regions: cerebellar grey matter, whole cerebellum, brainstem, eroded subcortical white matter, and a composite reference region. We recommend intensity normalization using whole cerebellum for cross-sectional analyses and composite reference region for longitudinal analyses (Figure 2).

The composite reference region is a non-weighted average of whole cerebellum, brainstem/pons, and subcortical WM regions proposed by Koeppe [5]. We eroded the subcortical white matter region away from ventricles and cortical grey matter to reduce spillover from signal in these regions into white matter. To do this, we smoothed a binarized a FreeSurfer-defined bilateral white matter region mask ("Cerebral White Matter" in FS naming convention) to the same resolution as the PET data, and then thresholded it at 0.70, resulting in an eroded subcortical WM region made up of voxels containing at least 70% white matter.

Recent work in our laboratory and others [10, 11] has shown that reference regions containing subcortical eroded WM result in longitudinal FBP measurements that appeared to be less noisy and more accurate [12]. Therefore, **our current recommendation is to use eroded WM or a composite reference region, made up of whole cerebellum, brainstem, and eroded subcortical white matter for longitudinal amyloid PET analyses.**

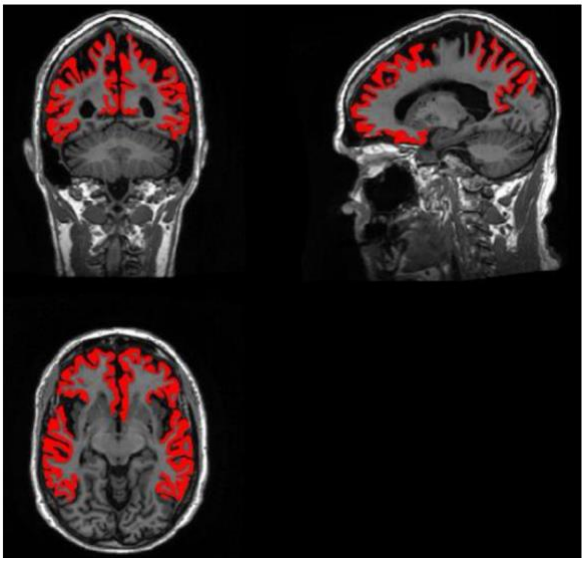

**Figure 1.** All cortical regions used to create the composite summary region ("SUMMARY_SUVR") are shown in red on an example subject's MRI. Freesurfer-defined regions making up this composite region are listed in Appendix 1.

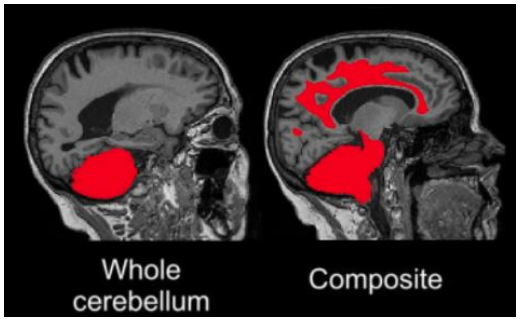


**Figure 2.** Reference regions recommended for cross-sectional (whole cerebellum) and longitudinal (composite reference) analyses. The WM is eroded away from cortex to avoid partial volume effects. The composite reference region is an average of the whole cerebellum, brainstem and eroded WM regions. See [12].

Summary regions and recommended reference regions are summarized in Table 2.

***Table 2***

| | Target region | Recommended Reference regions | |
|---|---|---|---|
| | **Cortical summary region** | **Whole cerebellum (cross-sectional)** | **Composite Ref (longitudinal)** |
| **Native space FS ROIs** | Frontal, temporal, parietal, cingulate regions (see Figure 1 and complete list in Appendix1 ) | Cerebellar GM + WM (see Figure 2) | Whole cerebellum, brainstem, eroded WM (see Figure 2) |

## Centiloids

The "CENTILOIDS" column contains a standardized quantitative amyloid measure called Centiloids (CLs), intended to facilitate comparison across different amyloid PET tracers. The Centiloid scale is tied to a 0 anchor, based on typical young controls, and a 100 anchor, based on typical AD patients, but some values will lie outside of the 0-100 bounds. Equations, derived by Royse et al. [13], for converting tracer-specific cortical summary SUVRs normalized to whole cerebellum (SUMMARY_SUVR variable) to CLs are listed in Table 3. See Klunk et al. [14] for more information on the CL scale. **The equations below were developed for the cortical summary region and are not validated for use in other ROIs.**

**Table 3. Centiloids conversion equations for cortical summary SUVRs normalized by whole cerebellum**

| **Centiloids Conversion Equations for the Cortical Summary Region Normalized by Whole Cerebellum** | |
|---|---|
| **FBP** | **FBB** |
| CL=188.22 × SUMMARY_SUVR − 189.16 | CL= 157.15 × SUMMARY_SUVR − 151.87 |

## Amyloid positivity status

A cutoff for establishing amyloid positivity or negativity is specific to both the radiotracer and the image processing methods used [6, 7]. Selection of an appropriate cutoff depends on the goals of the study or analysis. We have provided amyloid positivity categorizations by the whole cerebellum reference cutoff (for cross-sectional analyses) and the composite reference cutoff (for longitudinal analyses).

For FBP 8mm dataset, the binarized SUVR variables are "SUMMARYSUVR_WHOLECEREBNORM_1.11CUTOFF" and "SUMMARYSUVR_COMPOSITE_REFNORM_0.78CUTOFF".

For FBB 8mm dataset, the binarized SUVR variables are "SUMMARYSUVR_WHOLECEREBNORM_1.08CUTOFF" and "SUMMARYSUVR_COMPOSITE_REFNORM_0.74CUTOFF".

For the Amyloid 6mm dataset (combined of multiple tracers), the tracer-dependent binarized SUVR variables are "AMYLOID_STATUS" (whole cerebellum reference) and "AMYLOID_STATUS_COMPOSITE_REF" (composite reference).

The SUVrs were binarized based on the positivity thresholds listed and described in Table 4. **The thresholds apply to the cortical summary SUVRs normalized by the whole cerebellum reference region or composite reference region ONLY and are NOT applicable to the individual subregions.**

**Table 4. Amyloid Positivity Threshold by Tracer and Reference Region and their derivation method**

| Tracer | **FBP** | | **FBB** | |
|---|---|---|---|---|
| Reference Region | Derivation Method | Threshold | Derivation Method | Threshold |
| **Whole Cerebellum** | Upper 95% CI above mean of Young Controls | **1.11 SUVR** | Mean+2SD of Young Controls | **1.08 SUVR** |
| **Composite Reference** | Linear transformation from whole cerebellum-normalized threshold | **0.78 SUVR** | Linear transformation from whole cerebellum-normalized threshold | **0.74 SUVR** |

For cross-sectional analyses, we derived FBP and FBB positivity thresholds based on the upper limit of cortical uptake in whole cerebellum-normalized SUVRs in young control samples: 1.11 FBP whole cerebellum-normalized SUVR represents the upper 95% confidence interval above the mean of a group of young controls (n=325) [2, 8]; 1.08 FBB whole cerebellum-normalized SUVR represents 2SD above the mean of a group of young controls (n=62) [13].

For longitudinal analyses, we converted whole cerebellum-normalized thresholds to composite reference-normalized SUVR units (FBP: 0.78; FBB: 0.74) based on linear regression of composite reference-normalized SUVRs against whole cerebellum-normalized SUVRs (Figure 4).

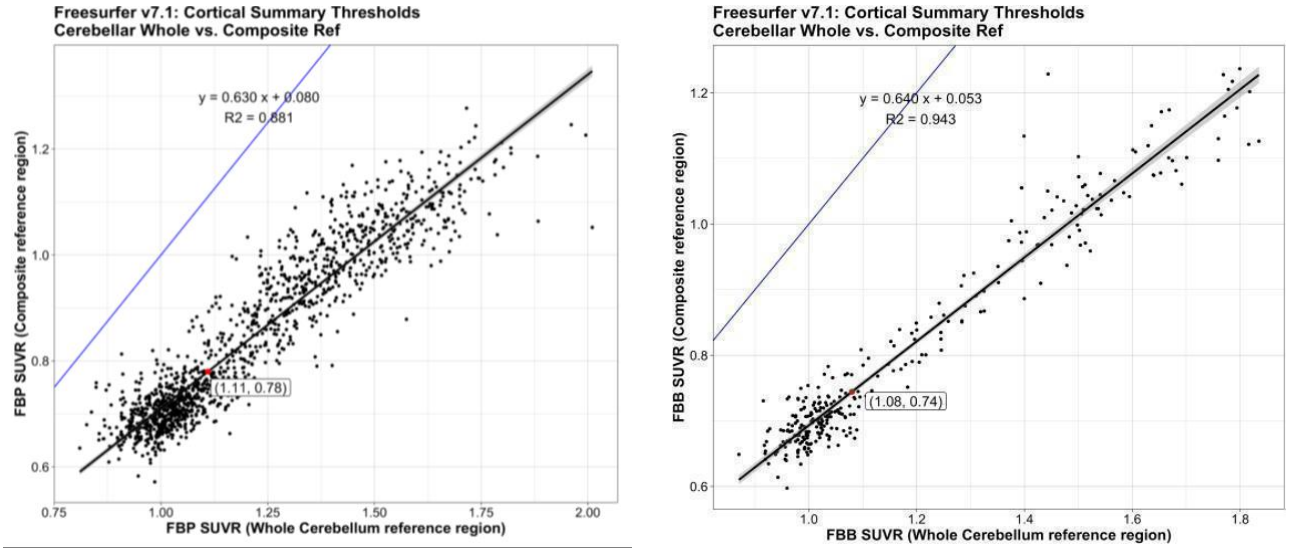


***Figure 4. Linear regressions of FBP (left) and FBB (right) composite reference-normalized SUVRs against whole cerebellum-normalized SUVRs.*** *Transforming the FBP whole cerebellum-normalized threshold of 1.11 into composite reference-normalized units results in a threshold of 0.78 (left). Transforming the FBB whole cerebellum-normalized threshold of 1.08 into composite reference-normalized units results in a threshold of 0.74 (right).*

## FBP and FBB thresholds

Our recommended FBP cross-sectional threshold (1.11 whole cerebellum-normalized SUVR) was based on an upper limit of Avid-acquired young control data [8]. In addition, work by Clark and colleagues [9] showed that no patients with probable Alzheimer's disease at autopsy had a FBP SUVR of greater than 1.10, using Avid's template-based processing method which differs from ours and results in slightly different SUVRs. To determine the relationship between Avid-processed SUVRs and Freesurfer-processed SUVRs (both using a whole cerebellum reference region), we analyzed 325 FBP scans that were analyzed using Avid's SUVR quantification. We used the linear regression equation that resulted from this correlation (y=.80x + 0.23) to convert the Avid cutoff of 1.10 to an almost identical value of 1.11 in the Freesurfer processing based "units".

Our recommended FBB cross-sectional threshold is a whole cerebellum-normalized SUVR of 1.08, which is based on an upper limit of young controls acquired by Life Molecular Imaging, and cross-validated using Gaussian Mixture Model derivation method with ADNI FBB sample (1.10 whole cerebellum-normalized SUVR) as shown in Figure 5 [13].

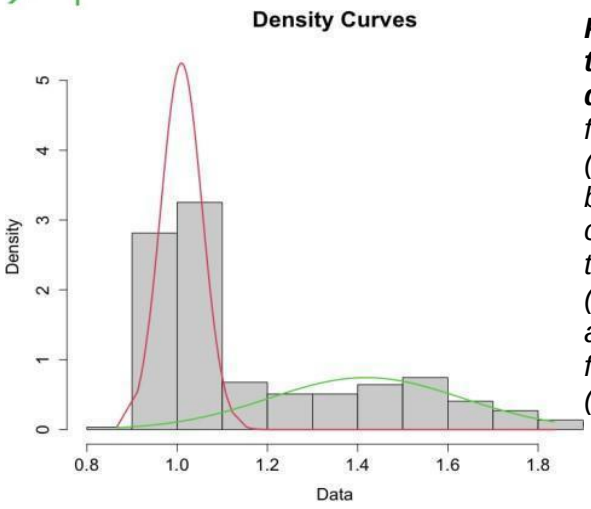


***Figure 5. Validation of FBB cross-sectional threshold with Gaussian Mixture Model derivation method.*** *GMM (normalmixEM function from mixtools using R) was used to identify upper (green) and lower (red) distributions of N=295 baseline cortical summary FBB SUVRs with whole cerebellum normalization 2SDs above the mean of the lower distribution was an SUVR of 1.10 (mean=1.010, SD=0.046, a value that was in agreement with the 1.08 SUVR threshold derived from the mean+2SD of the young control group (mean=1.012, SD=0.033) (Royse et al, 2021).*

## Pipeline Quality Control Flag

Included in the 6mm dataset is a column (qc_flag) for our technicians to flag errors in the pipeline where the data (SUVR or volume) are unavailable or may not be reliable based on visual inspection of the FreeSurfer segmentation and MR/PET registration. Our QC emphasizes accuracy of primary regions of interest (cortical summary and whole cerebellum), so usable images may receive a full pass (qc_flag=2) or partial pass (qc_flag=1) depending on our assessment of the usability of the primary ROIs relative to the other brain regions.

| *qc_flag* | Result | Description |
|---|---|---|
| ***2*** | Pass | Primary ROIs meet the processing requirement and the Freesurfer parcellation follows the T1 cortical ribbon throughout the whole brain. |
| ***1*** | Partial pass | Primary ROIs meet the processing requirement; other ROIs may be incorrect. |
| ***0*** | Fail | A processing related error has a significant effect on the segmentation of the primary ROIs. |
| ***-1*** | Not assessed | The image has not been QC'd. |
| ***-2*** | Cannot be processed | The image cannot be processed or has failed to complete the pipeline despite troubleshooting efforts. |

## Dataset Information

This methods document applies to the following datasets available from the ADNI repository:

| TBLNAME | Dataset Name | Date Submitted |
|---|---|---|
| UCBERKELEYAV45_8MM | UC Berkeley - AV45 8mm Res Analysis | 17 Feb 2023 |
| UCBERKELEYFBB_8MM | UC Berkeley - FBB 8mm Res Analysis | 17 Feb 2023 |
| UCBERKELEY_AMY_6MM | UC Berkeley - Amyloid PET 6mm Res Analysis | 25 May 2023 (*1st version) |

*New data will be uploaded to the 6mm dataset (UCBERKELEY_AMY_6MM) periodically. Users can refer to its "update_stamp" column to check when the dataset is last updated. The "PROCESSDATE" column represents the date when the quantification pipeline was run. If a PET image has been re-processed (e.g., when a new MRI becomes available), its numerical data will be updated along with new PROCESSDATE and update_stamp.

Data dictionaries can be found at Download Study Data > Study Info > Data Dictionary [ADNI1,GO,2,3]. Use TBLNAME column to filter the corresponding data dictionaries from the long spreadsheet.

### References


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## About the Authors

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# Appendix 1 - Cortical Summary ROIs

We include both volumes and SUVrs for right/left (shown) and bilateral versions of the following FreeSurfer regions.

**Frontal regions:**
ctx-lh-caudalmiddlefrontal
ctx-lh-lateralorbitofrontal
ctx-lh-medialorbitofrontal
ctx-lh-parsopercularis
ctx-lh-parsorbitalis
ctx-lh-parstriangularis
ctx-lh-rostralmiddlefrontal
ctx-lh-superiorfrontal
ctx-lh-frontalpole
ctx-rh-caudalmiddlefrontal
ctx-rh-lateralorbitofrontal
ctx-rh-medialorbitofrontal
ctx-rh-parsopercularis
ctx-rh-parsorbitalis
ctx-rh-parstriangularis
ctx-rh-rostralmiddlefrontal
ctx-rh-superiorfrontal
ctx-rh-frontalpole

**Anterior/posterior cingulate regions:**
ctx-lh-caudalanteriorcingulate
ctx-lh-isthmuscingulate
ctx-lh-posteriorcingulate
ctx-lh-rostralanteriorcingulate
ctx-rh-caudalanteriorcingulate
ctx-rh-isthmuscingulate
ctx-rh-posteriorcingulate
ctx-rh-rostralanteriorcingulate

**Lateral parietal regions:**
ctx-lh-inferiorparietal
ctx-lh-precuneus
ctx-lh-superiorparietal
ctx-lh-supramarginal
ctx-rh-inferiorparietal
ctx-rh-precuneus
ctx-rh-superiorparietal
ctx-rh-supramarginal

**Lateral temporal regions:**
ctx-lh-inferiortemporal
ctx-lh-middletemporal
ctx-lh-superiortemporal
ctx-rh-inferiortemporal
ctx-rh-middletemporal
ctx-rh-superiortemporal