ADNI Alzheimer's Disease Neuroimaging Initiative

Florbetaben (FBB) processing methods

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ADNI Florbetaben analysis overview

ADNI Florbetaben PET data have been acquired in ADNI3 starting in Jan 2017. Our florbetaben PET processing and analysis pipeline is nearly identical to our florbetapir PET pipeline (see UC Berkeley AV45 Methods document). Briefly, we use a native-space MRI scan for each subject that is processed 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. We have also defined several candidate reference regions (cerebellar grey matter, whole cerebellum, brainstem/pons, eroded subcortical white matter, and a composite reference region made up of whole cerebellum, brainstem/pons, and eroded subcortical WM). We then coregister each florbetaben scan to the corresponding MRI and calculate the mean amyloid PET uptake within the cortical and reference regions. See UC Berkeley AV45 Methods document for the complete list of Freesurfer cortical summary regions and an example subject's MRI overlaid with regions of interest.

Are the florbetaben data in our dataset already intensity normalized?

Yes. The Stage 3 FBB images as well as the Stage 4, fully pre-processed FBB images ("FBB Coreg, Avg, Std Img and Vox Siz, Uniform Resolution") available for download on LONI are SUVR images that have been intensity normalized using an atlas-space cerebellar cortex region defined by Bob Koeppe during his pre-processing procedures (see Jagust et al. Alz & Dementia 2015 and PET preprocessing info at adni.loni.usc.edu). These procedures include defining an atlas-space cerebellar cortex region using a coregistered FDG or structural MRI scan and reverse normalizing this region back onto the native space florbetaben image. This initial intensity normalization carries with it some noise associated with the region definition and warping, so in our FreeSurfer-based pipeline, we defined native-space reference regions (as well as cortical summary region of interest) more precisely using Freesurfer.

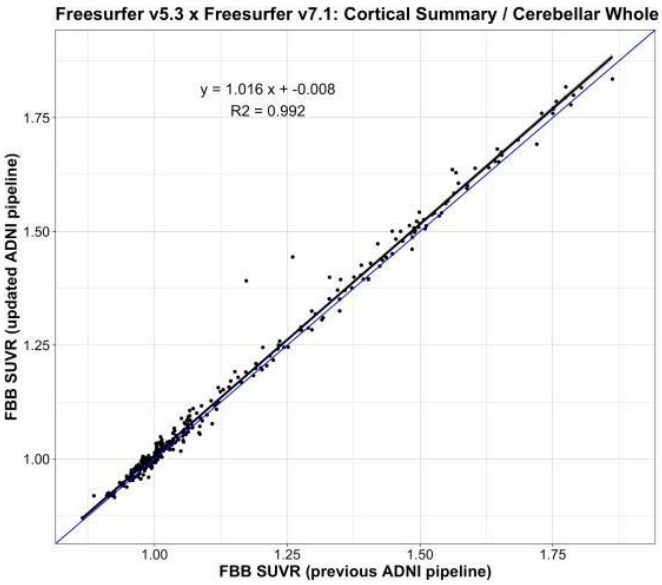
Therefore we recommend re-intensity normalizing the cortical summary SUVRs in our dataset using FreeSurfer-defined reference regions, since the initial intensity normalization applied during pre-processing did not take advantage of these native space, FreeSurfer-defined reference regions.

Two amyloid summary measures in our dataset contain Freesurfer-defined cortical summary SUVRs that have already been divided by Freesurfer-defined reference regions:
SUMMARYSUVR_WHOLECEREBNORM
SUMMARYSUVR_COMPOSITE_REFNORM

Florbetaben cortical summary SUVRs from our dataset can also be generated by taking the volume-weighted average across the cortical composite region (COMPOSITE_SUVR) and dividing this by one of the reference regions.

For cross-sectional analyses, we recommend using the summary SUVR based on the whole cerebellum reference region **(SUMMARYSUVR_WHOLECEREBNORM; cortical composite region already intensity normalized by the FreeSurfer-defined whole cerebellum) with positivity threshold = 1.08, which represents 2SD above the mean of a group of young controls (n=62).** For longitudinal analyses, we recommend using the cortical composite SUVR based on the composite reference region (**SUMMARYSUVR_COMPOSITE_REFNORM; cortical composite region already intensity normalized by the FreeSurfer-defined composite reference region) with positivity threshold = 0.74**, derived with data-driven linear regression. Thresholds are further explained below and described in Royce et al. (submitted).

Jan 2021 data processing update



Starting with the UC Berkeley FBB dataset dated January 2021 we have made several changes:
(1) we re-analyzed all FBB scans using regions defined with Freesurfer v7.1, (2) added the inferior temporal gyrus to the cortical summary ROI, and (3) re-calculated the cortical summary uptake using a volume-weighted average, instead of the previous straight-average across frontal, cingulate, parietal, and lateral temporal regions.

These changes resulted in essentially no systematic changes in SUVRs as shown in the plot to the left. The correlation between the updated FS v7.1 cortical summary SUVRs (whole cerebellum ref region) and comparable SUVRs from the previous dataset (05.12.20) has an $R^2 > 0.99$ and a slope of 1.02 in 295 baseline FBB scans.

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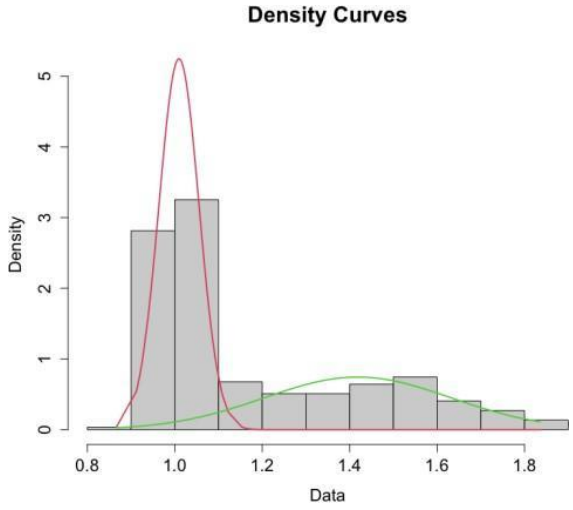
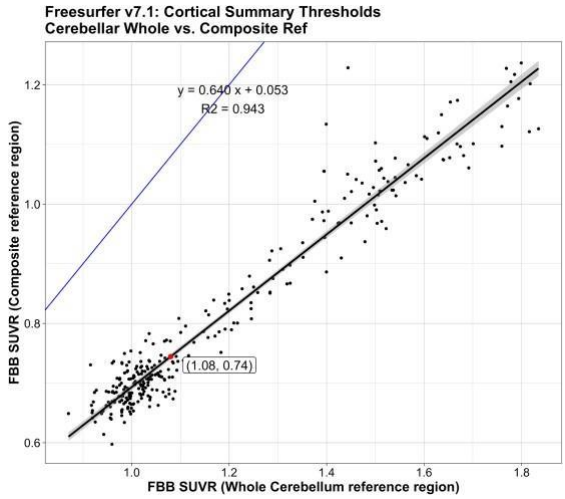
Gaussian Mixture Model approach for derivation of data-driven FBB cortical summary / whole cerebellum reference region threshold



We used a GMM (normalmixEM function from mixtools using R) to identify upper (green) and lower (red) distributions of N=295 baseline cortical summary FBB SUVRs with whole cerebellum normalization (figure at left). 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) (Royce et al submitted).

Linear regression for derivation of data-driven FBB cortical summary / composite reference region threshold



To determine the amyloid-positivity threshold for the cortical summary SUVR normalized to the composite reference region, we used a linear regression model to compare the whole-cerebellum-normalized and composite-reference-region-normalized cortical summary SUVRs of 296 ADNI subjects. The resulting linear equation transformed the 1.08 threshold, recommended for whole cerebellum normalized cortical summary FBB SUVRs, to 0.74, recommended longitudinal threshold for use with cortical summary/composite reference SUVRs.

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Dataset Information

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

Dataset Name	Date Submitted
UC Berkeley – Florbetaben PET	14 January 2021

References

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