ADNI Alzheimer's Disease Neuroimaging Initiative

Florbetaben (FBB) processing methods

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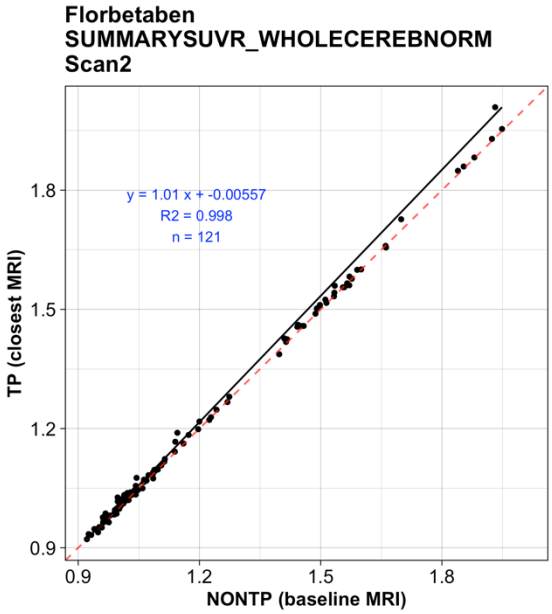
Summary

ADNI Florbetaben PET data have been acquired starting in Jan 2017 with ADNI3. Our florbetaben PET processing and analysis pipeline is nearly identical to our florbetapir PET pipeline (described in UC Berkeley florbetapir methods document). Briefly, we use the native-space MRI scan closest to each PET, which 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. We have also defined five 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 MRI closest in time and calculate the mean florbetaben uptake within the cortical and reference regions. See UC Berkeley florbetapir methods document for the complete list of Freesurfer cortical summary regions and an example subject's MRI overlaid with regions of interest.

Florbetaben SUVRs from our dataset can be created by taking the volume-weighted average across the cortical summary region and dividing this by one of the reference regions. While the reference region selection depends on the goals of the study, we have provided two summary SUVRs in our dataset. **For cross-sectional analyses, we recommend using the summary SUVR based on the whole cerebellum reference region (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 summary SUVR based on the composite reference region (positivity threshold = 0.74)**, derived with data-driven linear regression. Thresholds are further explained below and described in Royse et al. (2021).



Starting with the UC Berkeley florbetaben dataset dated November 2021, we are processing and quantifying longitudinal PET scans the MRI closest in time to each PET scan. This timepoint specific (TP) PET-MRI pairing replaces our previous non-timepoint specific (NONTP) method, which used baseline MRI to quantify regional SUVRs in baseline *and subsequent* PET scans.

The change in MRI selection resulted in very small changes in SUVRs as shown in the plot to the right. Note, baseline SUVRs are unchanged.

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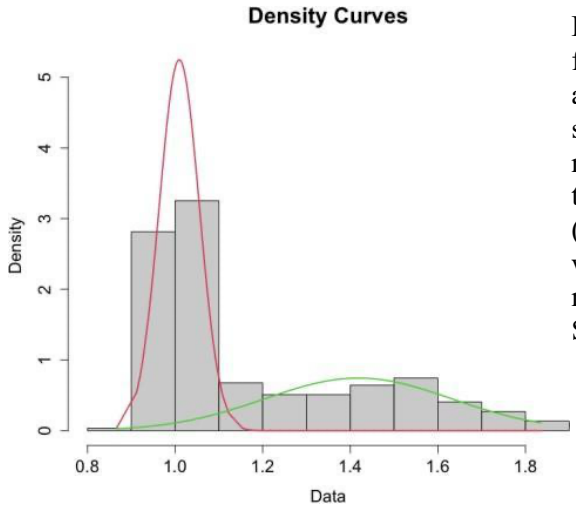
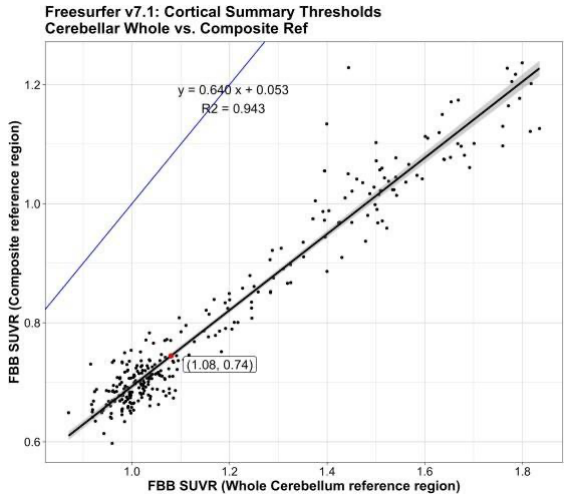
Gaussian Mixture Model approach for derivation of data-driven FBB cortical summary / whole cerebellum reference region threshold



Drs. Landau and Jagust 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) (Royse et al, 2021).

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 composite referenced cortical summary FBB SUVRs.

We have provided amyloid positivity categorizations by the whole cerebellum reference cutoff and the composite reference cutoff in SUMMARYSUVR_WHOLECEREBNORM_1.08CUTOFF and SUMMARYSUVR_COMPOSITE_REFNORM_0.74CUTOFF, respectively.

Are the florbetaben data in our dataset already intensity normalized?

Yes. Regional florbetaben means in our dataset are SUVRs that have already been intensity normalized by Bob Koeppe during the generation of the pre-processed images available for download from LONI. The

Stage 3 florbetaben images as well as the Stage 4, fully pre-processed florbetaben images ("FBB Coreg, Avg, Std Img and Vox Siz, Uniform Resolution") are SUVR images that have been *approximately* 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 warping procedures, so we defined native-space reference regions (as well as regions of interest) more precisely using Freesurfer. We recommend replacing (e.g. dividing out) the initial intensity normalization carried out by Bob Koeppe with a subsequent intensity normalization using our Freesurfer-defined, native space reference regions. **However, we recommend intensity normalizing the regional SUVRs in our dataset using one of the reference regions in our dataset, since the initial intensity normalization applied during pre-processing did not take advantage of FreeSurfer-defined regional information.**

Acknowledgement

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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	25 April 2022

References

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