ADNI Alzheimer's Disease Neuroimaging Initiative

Florbetapir (AV45) processing methods

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Summary

ADNI Florbetapir summary data are updated regularly and uploaded to LONI by our group. 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 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 florbetapir scan to the MRI closest in time.

Are the florbetapir data in our dataset already intensity normalized?

Yes. The Stage 3 AV45 images as well as the Stage 4, fully pre-processed AV45 images ("AV45 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 florbetapir 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.

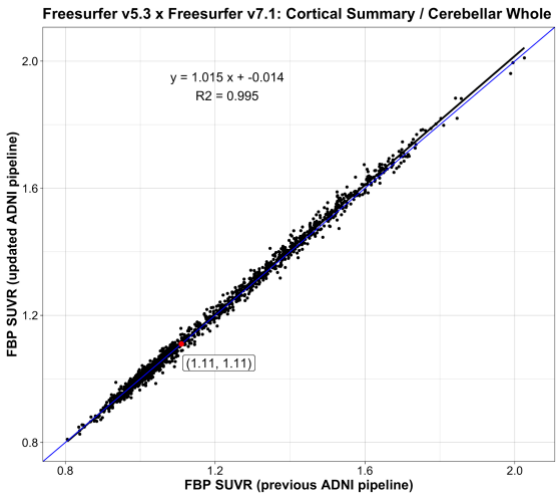
Two amyloid summary measures in our dataset contain Freesurfer-defined cortical summary SUVRs that have already been divided by Freesurfer-defined reference regions:
SUMMARYSUVR_WHOLECEREBNORM
SUMMARYSUVR_COMPOSITE_REFNORM

Florbetapir SUVRs can be also be calculated by dividing the cortical summary region (COMPOSITE_SUVR) by one of the reference regions. Selection of a cortical region of interest and reference region depend on the goals of the analysis.

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) region**

already intensity normalized by the FreeSurfer-defined whole cerebellum) with a threshold of 1.11 [1, 2]. 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 a threshold of 0.78 (see below for validation)**, which we and others have validated for use in longitudinal florbetapir analyses.

Jan 2021 data processing update



Starting with the UC Berkeley AV45 dataset dated January 2021 we have made several changes: (1) we re-analyzed all AV45 scans using regions defined with Freesurfer v7.1.1, (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 conventional average across frontal, cingulate, parietal, and lateral temporal regions.

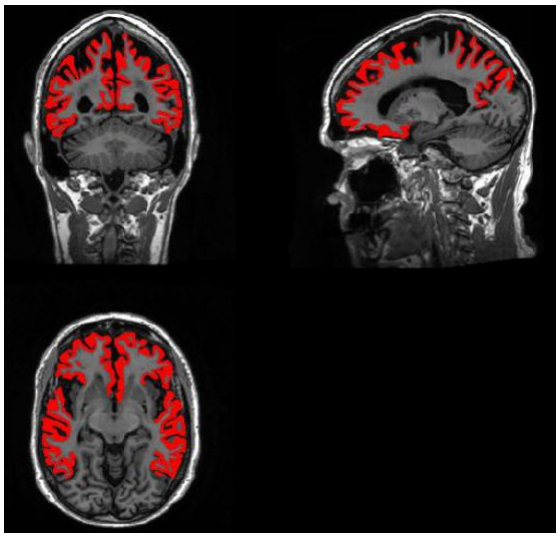
The correlation between the updated cortical summary SUVRs (whole cerebellum reference region) and comparable SUVRs from the previous dataset (05.12.20) has an $R^2 > 0.99$ and a slope of 1.02 in 1290 baseline AV45 scans (see figure above). Our previously defined 1.11 threshold using this reference region is unchanged in the updated dataset.

Method

Acquisition of florbetapir and MRI image data from LONI

We download florbetapir data from LONI in the most fully pre-processed format (series description in LONI Advanced Search: "AV45 Coreg, Avg, Std Img and Vox Siz, Uniform Resolution"). Each subject's first florbetapir image is coregistered using SPM8 to that subject's MRI image that was closest in time to the florbetapir scan (LONI image search series description: ADNI 1 search "*N3;*" in "Image Description" with "pre-processed" box checked, ADNI GO/2 search "*N3m*" with "pre-processed" box checked, ADNI 3 search "*Accel*" with "original" box checked). We use the MRI scan that is closest in time to the first florbetapir scan; note that not all subjects have a concurrent MRI available on LONI so in some cases we use an MRI scan acquired at another visit. The baseline MRI is used to define regions for the baseline and subsequent florbetapir scans.

Freesurfer-defined cortical regions



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

We carry out Freesurfer processing to skull-strip, segment, and delineate cortical and subcortical regions in all MRI scans. We then extract volume-weighted florbetapir means from a cortical summary region that includes frontal, anterior/posterior cingulate, lateral parietal, lateral temporal regions [3, 4] shown in the figure to the right and listed below according to their Freesurfer naming convention. In our dataset, SUVRs are provided for the subregions listed below ("FRONTAL_SUVR" etc) and for the cortical summary region alone ("COMPOSITE_SUVR"). In order to maximize flexibility of this dataset, these are "implicitly" intensity normalized by cerebellar grey matter defined during Bob Koeppe's preprocessing, but they have not yet been intensity normalized by the Freesurfer-defined reference region means included in our dataset. Only the two cortical summary variables described above ("SUMMARYSUVR_WHOLECEREBNORM"**, "**SUMMARYSUVR_COMPOSITE_REFNORM") have been intensity normalized using the Freesurfer-defined reference 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

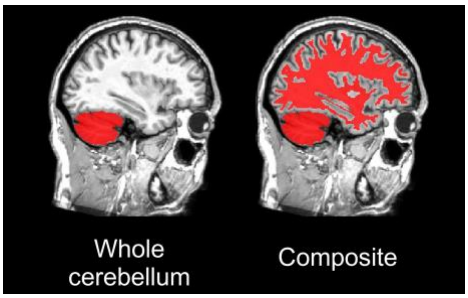
Lateral temporal regions:
ctx-lh-inferiortemporal
ctx-lh-middletemporal
ctx-lh-superiortemporal
ctx-rh-inferiortemporal
ctx-rh-middletemporal
ctx-rh-superiortemporal

Calculation of florbetapir cortical summary values

We created a single binary cortical summary region composed of the subregions listed above and calculated the mean uptake across that region ("COMPOSITE_SUVR").

Freesurfer-defined reference regions

We calculate means for five Freesurfer-defined reference regions (cerebellar grey matter, whole cerebellum, brainstem/pons, eroded subcortical white matter, and a composite reference region) that can be used to intensity normalize the cortical summary ROI or individual cortical regions. The composite reference region is a conventional (nonweighted) average of whole cerebellum, brainstem/pons, and subcortical WM regions proposed recently by Koeppe [5]. The only modification we have made to the Freesurfer delineation of these reference regions is that we eroded the subcortical white matter region away from cerebrospinal fluid and cortical grey matter in order to reduce spillover from signal in these regions into white matter.
To do this, we smoothed a binarized a Freesurfer-defined white matter region mask to the same resolution as the PET data (effective 8X8X8mm^3) and then thresholded it at 0.70, resulting in an eroded subcortical WM region made up of voxels containing at least 70% white matter.



Reference regions recommended for our dataset are shown above. The WM is eroded away from cortex to avoid partial volume effects. The composite reference region is an average of the whole cerebellum, brainstem/pons, and eroded WM regions. See Landau et al. JNM 2015.

Calculation of florbetapir SUVR

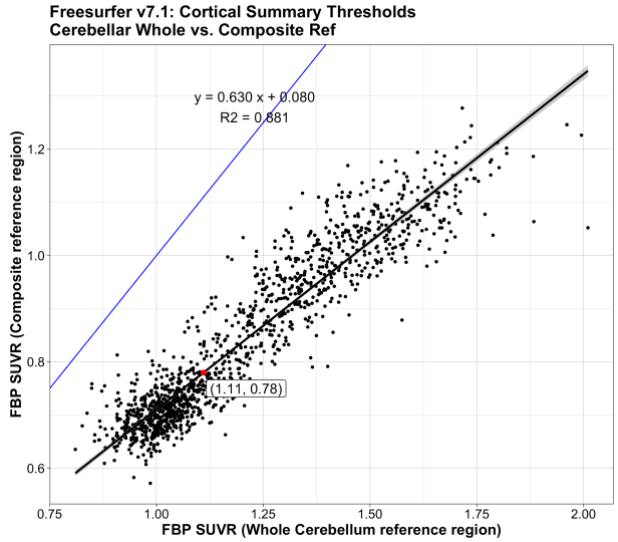
A florbetapir cortical summary SUVR can be calculated by dividing "COMPOSITE_SUVR" by one of the reference regions ("CEREBELLUMGREYMATTER_SUVR", "WHOLECEREBELLUM_SUVR", "BRAINSTEM_SUVR", "COMPOSITE_REF_SUVR", "ERODED_SUBCORTICALWM_SUVR"). The recommended reference regions for cross-sectional and longitudinal analyses are shown in the figure above.

Calculation of florbetapir cutoff for cross-sectional analyses

A cutoff for establishing amyloid positivity or negativity is specific to both the radiotracer and the image processing methods used[6, 7]. Even for a specific tracer and processing method, selection of an appropriate cutoff depends on the goals of the study or analysis.

For this dataset, our current recommendation for cross-sectional florbetapir analyses is a **florbetapir cutoff of 1.11 using the whole cerebellum reference region,** which is equivalent to the upper 95% confidence interval above the mean of a group of young normal controls[8]. In addition, work by Clark and colleagues[9] showed that no patients with probable Alzheiemer's disease at autopsy had a florbetapir SUVR of greater than 1.10, based on Avid's template-based processing method. To determine the relationship between Avid-processed SUVRs and Freesurfer-processed SUVRs (both using a whole cerebellum reference region) for 325 ADNI florbetapir scans, we previously analyzed 325 AV45 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 Freesurfer "units". This value was unchanged by the updates made to our processing pipeline in the January 2021 dataset. **The cutoff of 1.11 applies to the SUVR normalized by the whole cerebellum reference region ONLY and is NOT applicable to the individual subregions or the SUVR normalized by the composite reference region.**

Recommendations for longitudinal florbetapir analyses



Recent work in our laboratory and others[10, 11] has shown that reference regions containing subcortical eroded WM result in longitudinal florbetapir measurements that appeared to be less noisy and more accurate[12]. Specifically, reference regions containing WM result in longitudinal florbetapir measurements that are less likely to decrease in a group of subjects who are expected to increase. Therefore, our current recommendation is to use eroded WM or a **composite reference region, made up of whole cerebellum, brainstem/pons, and eroded subcortical white matter for longitudinal florbetapir analyses**.

Transforming the whole cerebellum cutoff of 1.11 into composite reference region units using linear regression results in a **cutoff of 0.78, as shown in the plot above.** We have provided amyloid positivity categorizations by the whole cerebellum reference cutoff and the composite reference cutoff in SUMMARYSUVR_WHOLECEREBNORM_1.11CUTOFF and SUMMARYSUVR_COMPOSITE_REFNORM_0.78CUTOFF, respectively.

ADNI subjects can be categorized as amyloid positive or negative by applying the cutoffs to the florbetapir composite SUVR values described above.

Note that the Freesurfer analysis that defines regions used for florbetapir SUVRs is carried out on the baseline MRI scan only. (When an MRI scan was not available at the same timepoint as the florbetapir scan, we used the MRI that was closest in time to the florbetapir scan.)

Dataset Information

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

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

References

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