

## Florbetapir 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 segmented and parcellated with Freesurfer (version 4.5.0) to define cortical grey matter regions of interest (frontal, anterior/posterior cingulate, lateral parietal, lateral temporal) that make up a summary cortical ROI. We have also defined five reference regions (cerebellar grey matter, whole cerebellum, brainstem/pons, eroded subcortical white matter, and a composite reference region). We then coregister each florbetapir scan to the corresponding MRI and calculate the mean florbetapir uptake within the cortical and reference regions.

Florbetapir SUVRs can be created by averaging across the 4 cortical regions and dividing this cortical summary ROI by one of the five reference regions. Selection of a cortical region of interest and reference region depend on the goals of the analysis. We have provided two summary SUVRs in our dataset. The first is the cortical summary ROI divided by the whole cerebellum reference region (SUMMARYSUVR\_WHOLECEREBNORM), which our group [1, 2] and others have used for cross-sectional florbetapir analyses. The second is the cortical summary ROI divided by a composite reference region (SUMMARYSUVR\_COMPOSITE\_REFNORM), which we have evaluated recently for longitudinal florbetapir analyses [3] and is described below.

### 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 SPM5 to that subject's MRI image (series description: ADNI 1 scans \*N3;\* and ADNI GO/2 scans \*N3\*) that was closest in time to the florbetapir scan. We use the MRI scan that is closest in time to the first florbetapir scan, but 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 all subsequent florbetapir scans.

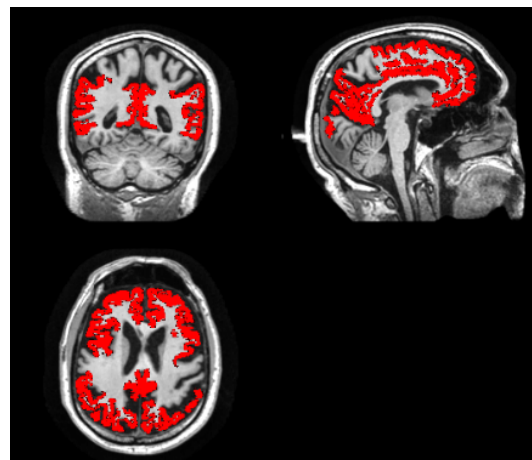


Figure 1: All cortical grey matter-only regions that can be used to create a composite florbetapir index (SUVR) are shown in red on an example subject's MRI. Main regions are frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal cortex. Subregions within each of these main regions are listed to the left.

#### *Freesurfer-defined cortical regions*

We carry out Freesurfer processing to skull-strip, segment, and delineate cortical and subcortical regions in all MRI scans. We then extract florbetapir means from grey matter in

each subregion within 4 large regions (frontal, anterior/posterior cingulate, lateral parietal, lateral temporal – shown in Figure 1, subregions listed below). This process has been described in recent publications from our lab [4, 5]. **Subregion and region means and subregion sizes are available in the LONI dataset and are NOT intensity normalized.** Available subregions are listed here according to Freesurfer naming convention:

**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

**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-middletemporal  
ctx-lh-superiortemporal  
ctx-rh-middletemporal

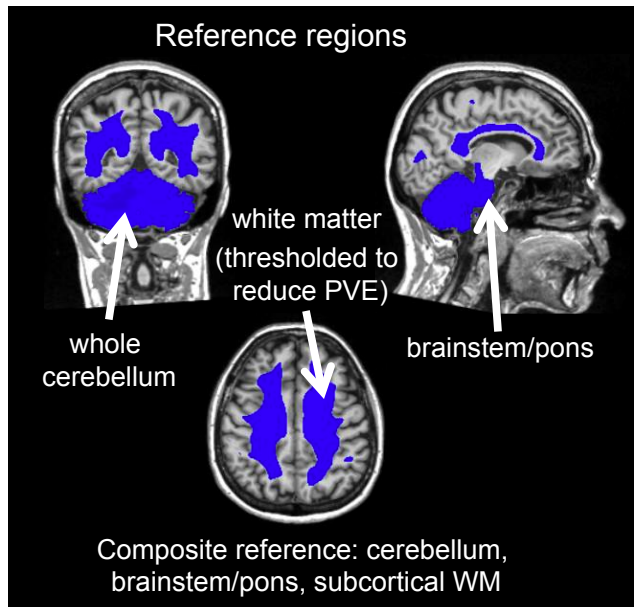


Figure 2: Reference regions included in our dataset are whole cerebellum, cerebellar grey matter (not shown separately), brainstem/pons, eroded subcortical white matter, and a composite reference region (average of the whole cerebellum, brainstem/pons, and subcortical WM regions).

### ***Calculation of florbetapir cortical summary values***

To account for the varying sizes of the subregions listed above, we created weighted means for each of the 4 main cortical regions (frontal, anterior/posterior cingulate, lateral parietal, lateral temporal) using the florbetapir mean and volume of each subregion as follows:

$$\frac{(\text{subregion1\_florbetapir\_mean} \times \text{subregion1\_volume}) + (\text{subregion2\_florbetapir\_mean} \times \text{subregion2\_volume}) + \dots + (\text{subregionN\_florbetapir\_mean} \times \text{subregionN\_volume})}{(\text{subregion1\_volume} + \text{subregion2\_volume} + \dots + \text{subregionN\_volume})}$$

### ***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, as proposed recently by Koeppe [6]. 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<sup>3</sup>) and then thresholded it at 0.70, resulting in an eroded subcortical WM region made up of voxels containing at least 70% white matter.

### ***Calculation of florbetapir SUVR***

A florbetapir cortical summary measurement (SUVR) can be calculated by creating a conventional (nonweighted) average across the 4 main cortical regions (Figure 1) and dividing by one of the five reference regions (Figure 2).

### ***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[7, 8]. 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[9]. In addition, recent work by Clark and colleagues[10] showed that no patients with probable Alzheimer'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 plotted SUVRs in the same group of ADNI subjects (Figure 3). We used the linear regression equation that resulted from this correlation to convert the Avid cutoff of 1.10 to an almost identical value of 1.11 in Freesurfer "units". **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.**

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

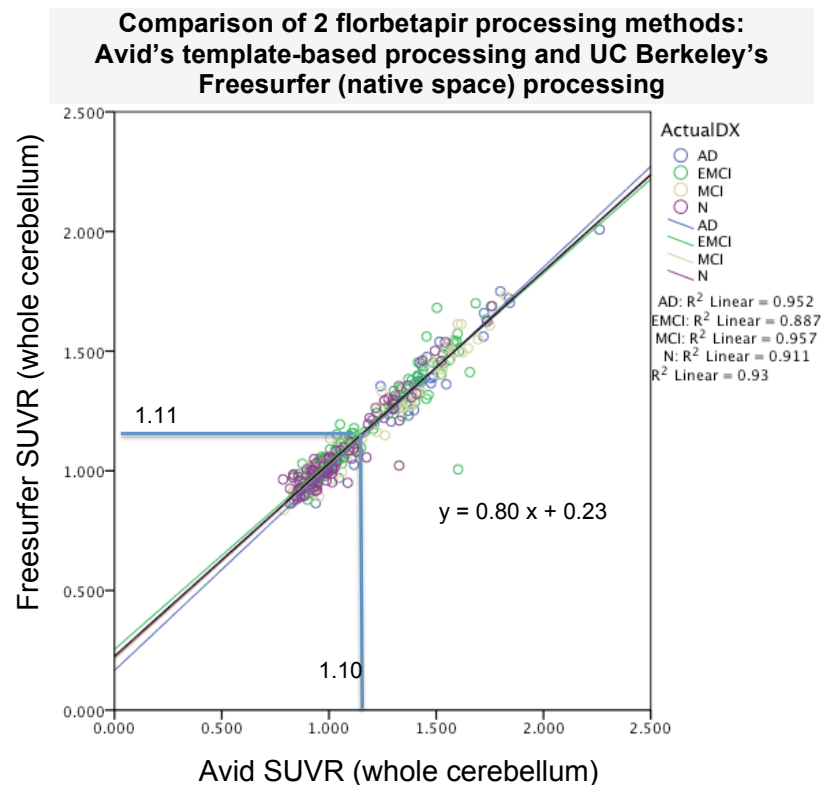


Figure 3: Plot showing cortical AV45 uptake for 325 ADNI subjects analyzed using Avid's template-based processing method and the Freesurfer processing stream outlined here. We used the regression equation for this association to convert Avid's autopsy-validated cutoff of 1.10 from Clark et al. (JAMA 2011) to Freesurfer "units", resulting in a Freesurfer cutoff of 1.11.

### ***Recommendations for longitudinal florbetapir analyses***

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.)

The question of what reference region is optimal for longitudinal amyloid PET analyses is currently unresolved. Based on recent work in our laboratory[3], our current recommendation is to use a **composite reference region, made up of whole cerebellum, brainstem/pons, and eroded subcortical white matter for longitudinal florbetapir analyses**. Use of this region reduces the relationship between cortical SUVR change and white matter (relative to whole cerebellum) Transforming the whole cerebellum cutoff of 1.11 into composite reference region

units using linear regression results in a **cutoff of 0.79**.

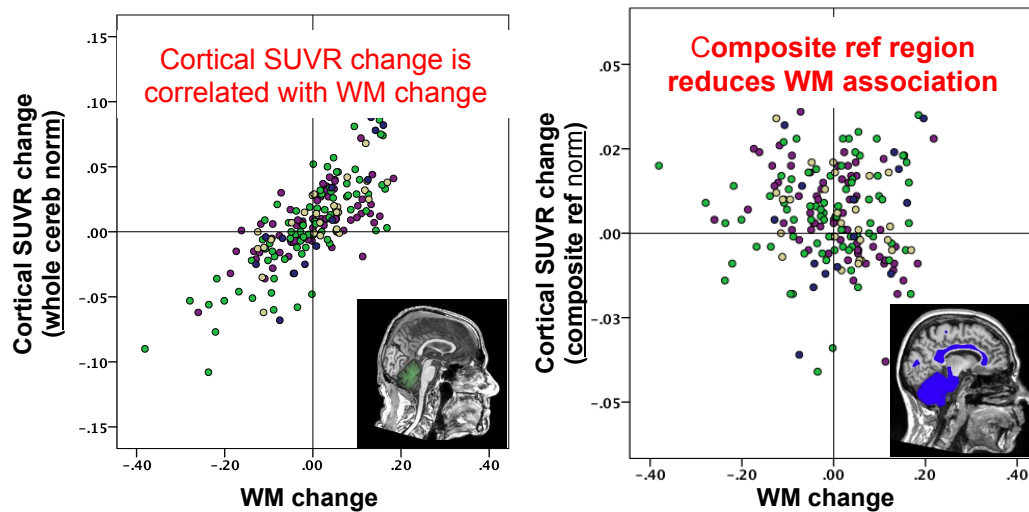


Figure 4: Use of the whole cerebellum reference region for calculation of florbetapir change results in cortical SUVR change measurements (y-axis left) that are positively correlated with white matter change (x-axis left), which is noise. We therefore recommend use of the composite reference region for longitudinal analyses, which reduces correlations between cortical SUVR change (y-axis right) and white matter change (x-axis right).

## References

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