

Florbetapir processing methods

Susan Landau & William Jagust

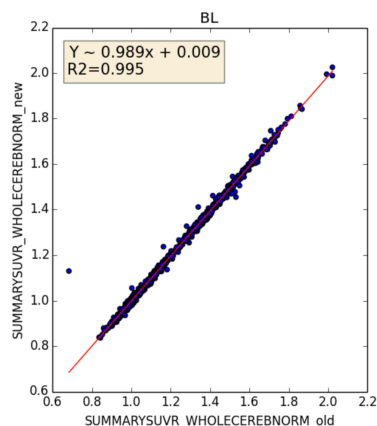
Helen Wills Neuroscience Institute, UC Berkeley and Lawrence Berkeley National Laboratory

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 5.3.0)** 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 calculated 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 and is described below.

Starting in Nov 2015 we have made several changes: (1) we re-analyzed a number of florbetapir scans using a concurrent MPRAGE in cases where the MPRAGE was not concurrent (2) we used Freesurfer 5.3.0, and (3) we have included in our dataset means from all regions defined by the Freesurfer aparc+aseg file, even those not used in the cortical summary region (see below). The correlation between cortical summary values (using the whole cereb reference region) for the previous datasets (dated 06.25.16 and 07.06.15) versus the new (12.03.15) dataset has an $R^2 > 0.99$ and a slope of 0.99 (see figure at left).



Method

Acquisition of florbetapir and MRI image data from LONI

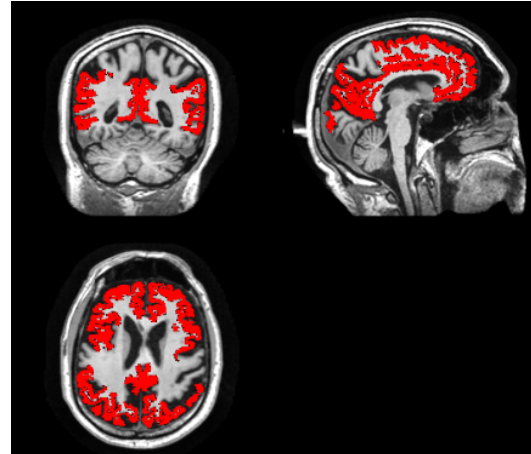
We download florbetapir data from LONI in the most fully pre-processed format (series description in LONI Advanced Search: "AV45 Coreg, Avg, Std Img and Vox Siz, Uniform

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.

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 the figure to the right, subregions listed below). This process has been described in recent publications from our lab [3, 4]. **Subregion and region means and subregion sizes are available in the LONI dataset and are NOT intensity normalized, but can easily be normalized by dividing by one of the reference regions to create an SUVR.**

Available subregions are listed here according to Freesurfer naming convention:



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.

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

Calculation of florbetapir cortical summary values

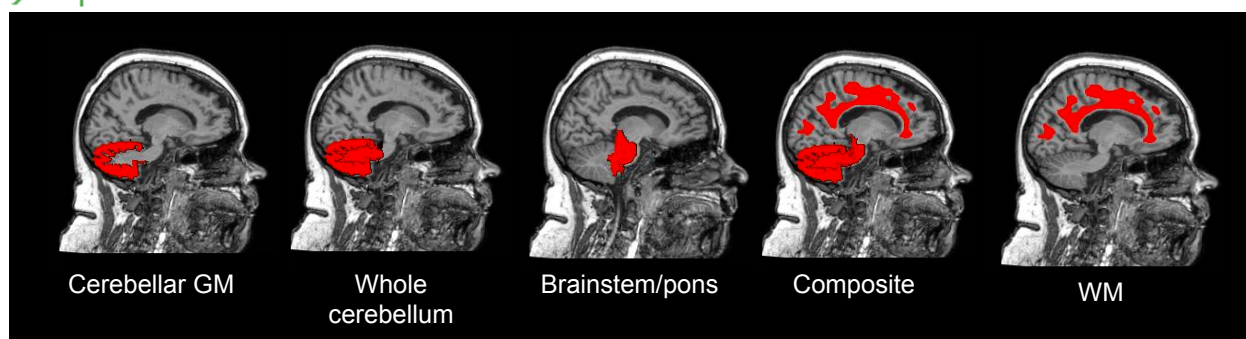
To account for the varying sizes of the subregions listed above, we created weighted means for each of the 4 main cortical regions (frontal, anterior/posterior cingulate, lateral parietal, lateral temporal) using the florbetapir mean and volume of each subregion as follows:

$$\frac{(\text{subregion1_florbetapir_mean} \times \text{subregion1_volume}) + (\text{subregion2_florbetapir_mean} \times \text{subregion2_volume}) + \dots + (\text{subregionN_florbetapir_mean} \times \text{subregionN_volume})}{(\text{subregion1_volume} + \text{subregion2_volume} + \dots + \text{subregionN_volume})}$$

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 [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 8X8X8mm³) 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 included in our dataset are shown. 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

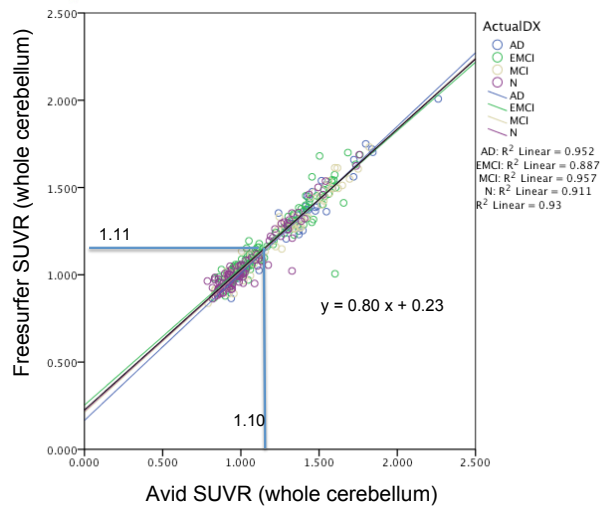
A florbetapir cortical summary measurement (SUVR) can be calculated by creating a conventional (nonweighted) average across the 4 main cortical regions (Figure 1) and dividing by one of the five reference regions (see figure above).

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, recent work by Clark and colleagues[9] 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 (see figure below). 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.



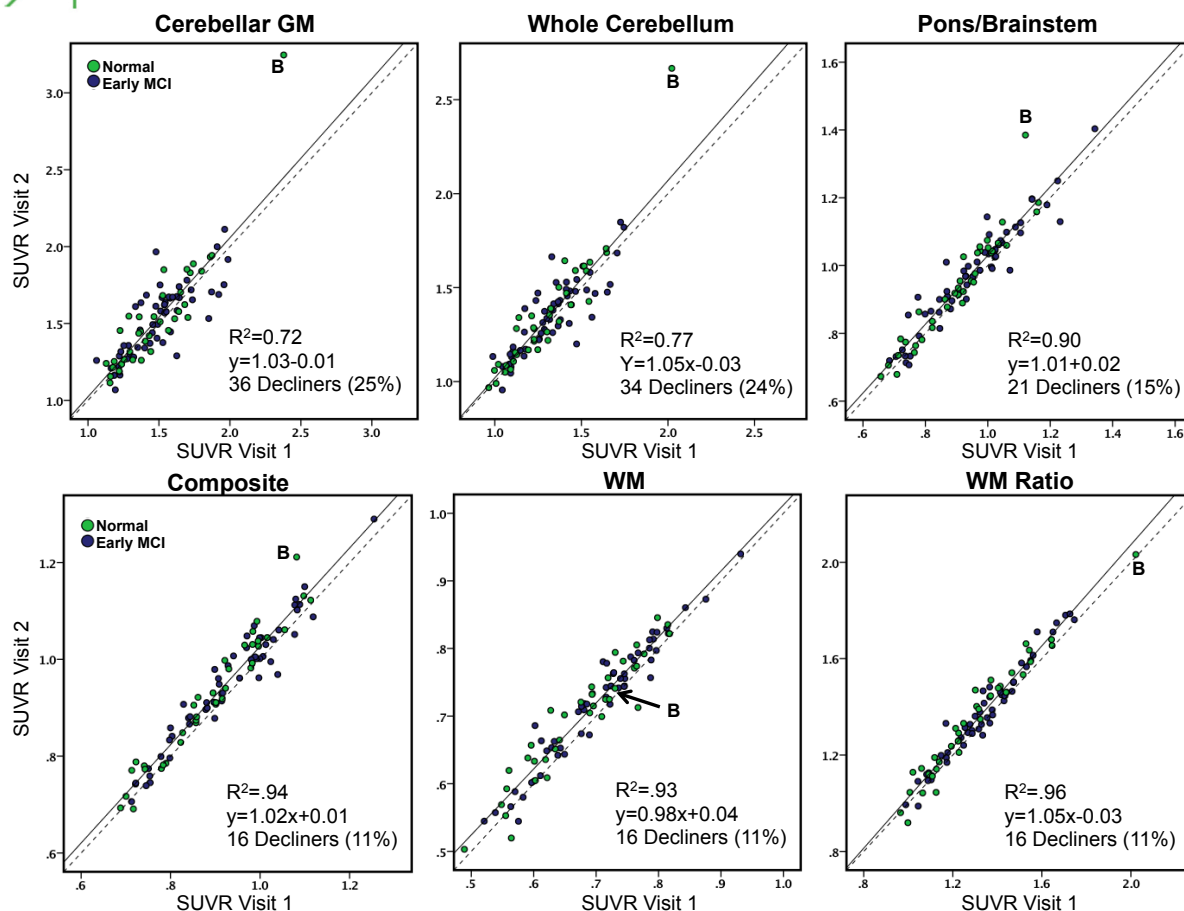
Comparison of 2 florbetapir processing methods: Avid's template-based processing and UC Berkeley's Freesurfer (native space) processing

Plot to the left shows 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

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 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 (see figure below and Landau et al. JNM 2015). 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 0.79**. 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_0.79CUTOFF, respectively.

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.)



Cortical SUVR Visit 1 and Visit 2 measurements using a number of candidate reference regions in a group of normal and EMCI subjects who were expected to increase over time (based on their CSF A β positive status at Visit 1). Use of reference regions containing eroded WM (bottom row) result in cortical SUVR change measurements that were less likely to decline in this group. See Landau et al. 2015 for more detailed information.

References

About the Authors

This document was prepared by Susan Landau, PhD, Helen Wills Neuroscience Institute, UC Berkeley and Lawrence Berkeley National Laboratory. For more information please contact Susan at 510 486 4433 or by email at slandau@berkeley.edu.

Notice: This document is presented by the author(s) as a service to ADNI data users. However, users should be aware that no formal review process has vetted this document and that ADNI cannot guarantee the accuracy or utility of this document.

1. Landau, S.M., et al., Comparing positron emission tomography imaging and cerebrospinal fluid measurements of beta-amyloid. *Ann Neurol*, 2013. 74(6): p. 826-36.

2. Landau, S.M., et al., Amyloid deposition, hypometabolism, and longitudinal cognitive decline. *Ann Neurol*, 2012. doi:10.1002/ana.23650.
3. Mormino, E.C., et al., Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects. *Brain*, 2009. 132(Pt 5): p. 1310-23.
4. Jagust, W.J., et al., Relationships between biomarkers in aging and dementia. *Neurology*, 2009. 73(15): p. 1193-9.
5. Koeppe, R.A., Data analysis for amyloid PET imaging: Longitudinal studies, in *Human Amyloid Imaging*. 2013: Miami, FL.
6. Landau, S.M., et al., Amyloid-beta imaging with Pittsburgh compound B and florbetapir: comparing radiotracers and quantification methods. *J Nucl Med*, 2013. 54(1): p. 70-7.
7. Landau, S.M., et al., Amyloid PET imaging in Alzheimer's disease: a comparison of three radiotracers. *Eur J Nucl Med Mol Imaging*, 2014.
8. Joshi, A.D., et al., Performance characteristics of amyloid PET with florbetapir F 18 in patients with alzheimer's disease and cognitively normal subjects. *J Nucl Med*, 2012. 53(3): p. 378-84.
9. Clark, C.M., et al., Use of florbetapir-PET for imaging beta-amyloid pathology. *JAMA*, 2011. 305(3): p. 275-83.
10. Brendel, M., et al., Improved longitudinal [(18)F]-AV45 amyloid PET by white matter reference and VOI-based partial volume effect correction. *Neuroimage*, 2015. 108: p. 450-9.
11. Chen, K., et al., Improved power for characterizing longitudinal amyloid-beta PET changes and evaluating amyloid-modifying treatments with a cerebral white matter reference region. *J Nucl Med*, 2015. 56(4): p. 560-6.
12. Landau, S.M., et al., Measurement of longitudinal beta-amyloid change with 18F-florbetapir PET and standardized uptake value ratios. *J Nucl Med*, 2015. 56(4): p. 567-74.