ADNI Alzheimer's Disease Neuroimaging Initiative

Florbetaben processing and positivity threshold derivation

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ADNI Florbetaben analysis overview

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 (see separate UC Berkeley florbetapir methods document). Briefly, we use Freesurfer-defined regions (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 florbetaben scan to the corresponding MRI and calculate the mean florbetapir uptake within the cortical and reference regions.

Florbetaben SUVRs from our dataset can be created by averaging across the 4 cortical regions 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. We recommend using the summary SUVR based on the **whole cerebellum reference region (positivity threshold = 1.08), which represents 2SD above the mean of the lower, "negative" distribution identified in a Gaussian Mixture Model approach**. This was revised from our initial autopsy-based value of 1.20 to a data-driven threshold of 1.08 in April 2019 as explained below.

Motivation for changing the threshold

Our initial FBB threshold was 1.20 (whole cerebellum normalization), which is described below and was based on the Piramal Phase II/III datasets with visual read and autopsy serving as the gold standard. After acquisition of the first ~100 FBB images in ADNI3 and application of the 1.20 threshold, we found that the rate of amyloid positivity (using FBB PET) in cognitively normal individuals in ADNI3 was around 20%, which is lower than the ~30% amyloid positivity we have seen consistently throughout ADNI GO/2 using florbetapir-PET. We also found that some FBB scans that were negative and just below the 1.20 threshold appeared to be positive based on a visual read. These two observations suggested that 1.20 autopsy-based threshold was too high. To determine whether the threshold should be revised, Dr. Koeppe and Drs. Landau/Jagust used separate and independent data-driven strategies (Dr. Koeppe: visual reads, Drs. Landau/Jagust: Gaussian Mixture Model approach) for determining a new threshold and ultimately arrived at the same conclusion, so we decided to change the threshold.

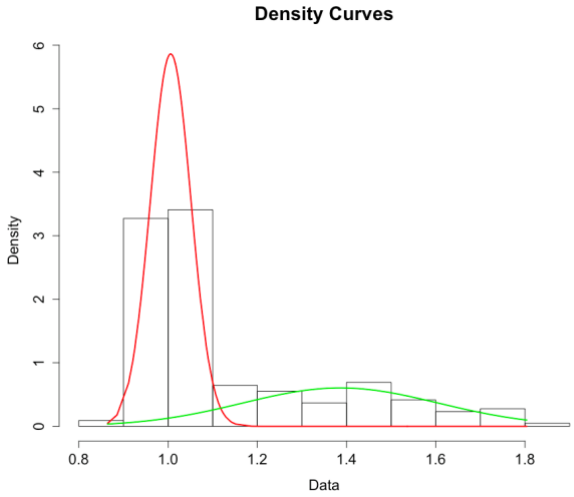
Visual read-based threshold

Dr. Koeppe carried out visual reads of all ADNI3 FBB images of cognitively normal participants, and identified a subset of unambiguously negative scans. He then calculated the mean and SD of cortical summary SUVRs (whole cerebellum intensity normalization) in this group sing a template-based approach, translated it to our Freesurfer-based approach units using

the linear regression equation representing the association between the template-based and Freesurfer-based methods. He determined that an SUVR of 1.08 represented 2SDs above the mean of scans read as unambiguously visually negative.

Gaussian Mixture Model approach for derivation of data-driven FBB threshold

Drs. Landau and Jagust used a GMM (normalmixEM function from mixtools using R) to identify upper (green) and lower (red) distributions of N=189 baseline cortical summary FBB SUVRs with whole cerebellum normalization (figure at left). 2SDs above the mean of the lower distribution was an SUVR of 1.08, a value that was in agreement with Dr. Koeppe's approach using a visual read approach to define the lower distribution.



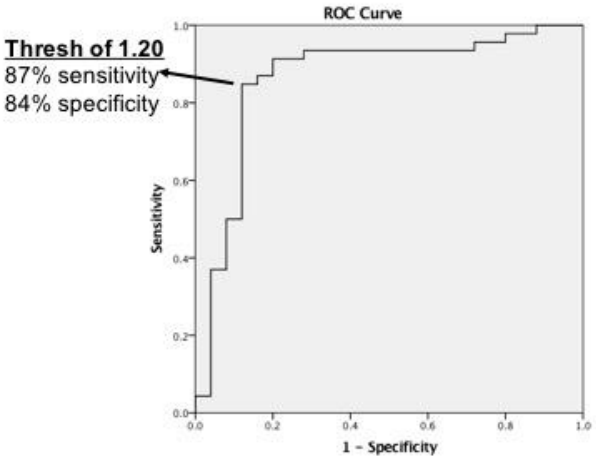
Summary of previous threshold derivation

Our previous threshold approach used Piramal's Phase II/III FBB data to derive an ADNI-independent threshold based on an ROC analysis with visual reads (Phase II) and moderate to frequent plaques at autopsy (Phase III) as the gold standard.

Analysis of Piramal Phase II and III image data using ADNI PET analysis pipeline

A Phase III study of end-of-life patients scanned with florbetaben-PET determined a positivity threshold of 1.478 for florbetaben uptake in cortex relative to a cerebellar grey matter reference region using CERAD scores (no or sparse plaques vs. moderate to frequent plaques) at autopsy as the standard of truth in an ROC analysis [1]. Because this threshold was dependent on image processing methods that differed from our ADNI PET methods, our goal was to determine an equivalent threshold using our pipeline. We worked with Piramal Imaging to acquire previously-reported florbetaben-PET and corresponding T1 images for 142 images with visual reads [2] and for 71 end-of-life patients whose amyloid positivity status was validated with CERAD scores at autopsy [1]. We also acquired the quantitative SUVRs used in these studies that were calculated using processing methods that differed from our Freesurfer-based approach, so the Piramal SUVRs were not directly comparable to our SUVRs.

We analyzed the 142 florbetaben images from the visual read study and the 71 images from the autopsy study using our existing Freesurfer-based pipeline that has been used for quantitative SUVR analysis of florbetapir images in ADNI (see ADNI florbetapir methods description and [3, 4]). Briefly, we used an average of Freesurfer-defined frontal, parietal, cingulate, and temporal regions for the cortical summary SUVR numerator. For the denominator, we examined two candidate reference regions, whole cerebellum and cerebellar grey matter.



Area Under the Curve

Test Result Variable(s): SUMMARYSUVR_WHOLECEREBNORM

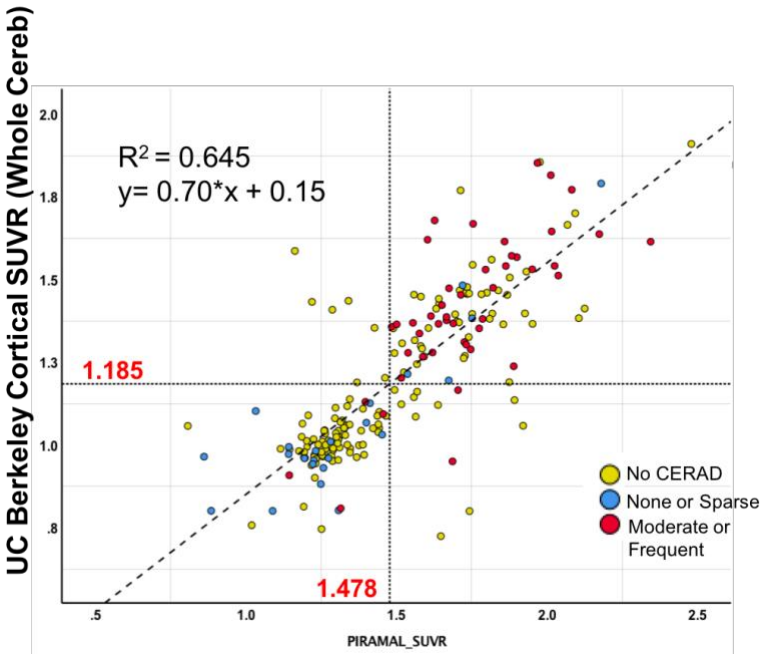
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.864	.052	.000	.762	.966

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Whole cerebellum reference region

We carried out an ROC analysis using whole cerebellum-normalized cortical summary SUVRs for the 71 florbetaben images from the autopsy study only using CERAD scores (no/spase plaques vs. moderate/frequent plaques) as the standard of truth. This analysis resulted in a threshold of 1.20 (AUC=0.864) with 87% sensitivity and 84% specificity (see plot at right). The results of this analysis were reasonably comparable to the results reported in Sabri et al. (2015) with a different florbetaben analysis pipeline and using a cerebellar grey matter reference region (Threshold =1.48, AUC=0.914, 89% sensitivity and 92% specificity).



We also examined the linear relationship between cortical summary SUVRs reported in the visual read and the autopsy studies, cerebellar grey reference and different processing methods and the SUVRs for the same subjects that we calculated using our Freesurfer-based processing method, whole cerebellum reference. We used the best-fit regression line equation to transform the 1.478 cerebellar grey-based threshold from Sabri et al. to a value of 1.185 using our processing methods and whole cerebellum reference. Based on the similarity between 1.185 and the 1.20 threshold from our ROC analysis, we concluded that the thresholds that we calculated using different approaches are

nonetheless consistent with one another and we settled on the more conservative 1.20 threshold value.

Selection of 1.20 whole cerebellum reference-based summary threshold for florbetaben positivity

We repeated the analyses described above using cerebellar grey matter and found that the two reference regions resulted in approximately equivalent performance. We selected the whole cerebellum-based SUVRs and the 1.20 threshold since definition of the whole cerebellum is more forgiving in cases of poor T1 segmentation. In addition, the larger number of voxels making up the whole cerebellum is beneficial due to the possibility of noisy signal at the bottom of the field of view for some scans.

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	3 March 2019

References

1. Sabri O, Sabbagh MN, Seibyl J, et al. Florbetaben PET imaging to detect amyloid beta plaques in Alzheimer's disease: phase 3 study. Alzheimers Dement 2015;11:964-974.
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4. Landau SM, Mintun M, Joshi A, et al. Amyloid deposition, hypometabolism, and longitudinal cognitive decline. Ann Neurol 2012;doi:10.1002/ana.23650.

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