SCAN Amyloid PET MRI-free Processing

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Summary

A goal of SCAN (Standardized Centralized Alzheimer's & Related Dementias Neuroimaging) is to generate PET data that could be merged with other multisite studies, such as ADNI. However, the ADNI PET pipeline[1] requires an MRI, and many SCAN PET images do not have an accompanying MRI. For this reason, we have implemented MRI-free processing for SCAN PET images; all numerical data provided in this dataset has been calculated without the use of an MRI for definition of ROIs. It is important to understand that the MRI-free pipeline does not yield quantitative values that are identical to values produced from an MRI-based pipeline. However, the values are quite similar and linearly related. Further down in this document, we explain how to transform MRI-free data to equivalent MRI-based data.

The MRI-free β-amyloid (Aβ) PET processing pipeline builds on our previously validated MRI-free PET processing methods[2] by employing an approach that can be used across multiple amyloid PET tracers (^{11}C-Pittsburgh Compound B (PiB),^{18}F-florbetapir (FBP), ^{18}F-florbetaben (FBB), and ^{18}F-NAV4694 (NAV)). The pipeline consists of (1) a linear registration of individual PET scans to a MNI152 T1 template, (2) non-linear spatial normalization to a generic amyloid PET template, (3) quantification within cortical regions of interest (ROIs), and (4) intensity normalization to create standardized uptake value ratios (SUVRs) in relation to a reference region.

Methods

Acquisition of amyloid PET data from LONI

We download SCAN PiB, FBP, FBB, and NAV images from LONI in the most fully pre-processed format (Step4, frames realigned and averaged, linear transformation to straighten out the head, standardized voxel size and smoothed to 6mm resolution). In the table below, LONI series descriptions are listed for each tracer and acquisition-time pair. For historical reasons "AV" is used as a descriptor for FBP on LONI but is referred to as FBP in this document. For each tracer, a primary acquisition time window was used to generate numerical quantification data (Table 1).

Table 1. SCAN amyloid PET LONI Series Descriptions. Primary acquisition times are in bold.

Tracer	Acquisition Time	LONI Series Description
PiB	40-60	PIB Coreg, Avg, Rigid Reg to Std Img/Vox Size, 40-60*, 6mm Res
	40-70	PIB Coreg, Avg, Rigid Reg to Std Img/Vox Size, 40-70*, 6mm Res
	50-70	PIB Coreg, Avg, Rigid Reg to Std Img/Vox Size, 50-70*, 6mm Res
FBP	**50-70**	AV Coreg, Avg, Rigid Reg to Std Img/Vox Size, 50-70*, 6mm Res
FBB	**90-110**	FBB Coreg, Avg, Rigid Reg to Std Img/Vox Size, 90-110*, 6mm Res
NAV	**50-70**	NAV Coreg, Avg, Rigid Reg to Std Img/Vox Size, 50-70*, 6mm Res

Generic amyloid PET template

FBP, FBB and PiB scans with MRIs from other studies were used to create the generic amyloid PET template. These were warped to MNI-space using their MRI, averaged together to create the generic amyloid template, and then used for spatial normalization of SCAN amyloid PET scans to template-space in SPM12 as part of the MRI-free processing pipeline. At the time of generic template development NAV scans with MRI from other studies were not available to be included, but this tracer behaves similarly to PiB. First, we made three tracer-specific templates by creating mean images. For both FBP and FBB, we used scans from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Each template consists of 50 Aβ-negative and 50 Aβ-positive males and 50 Aβ-negative and 50 Aβ-positive females, n=200. For PiB, we used scans from the Berkeley Aging Cohort Study (BACS: 25 Aβ-negative and 25 Aβ-positive males and females) and the University of California, San Francisco (UCSF: 50 Aβ-negative and 50 Aβ-positive), n=200. The final generic amyloid template is the mean of the three tracer-specific templates (Figure 1).

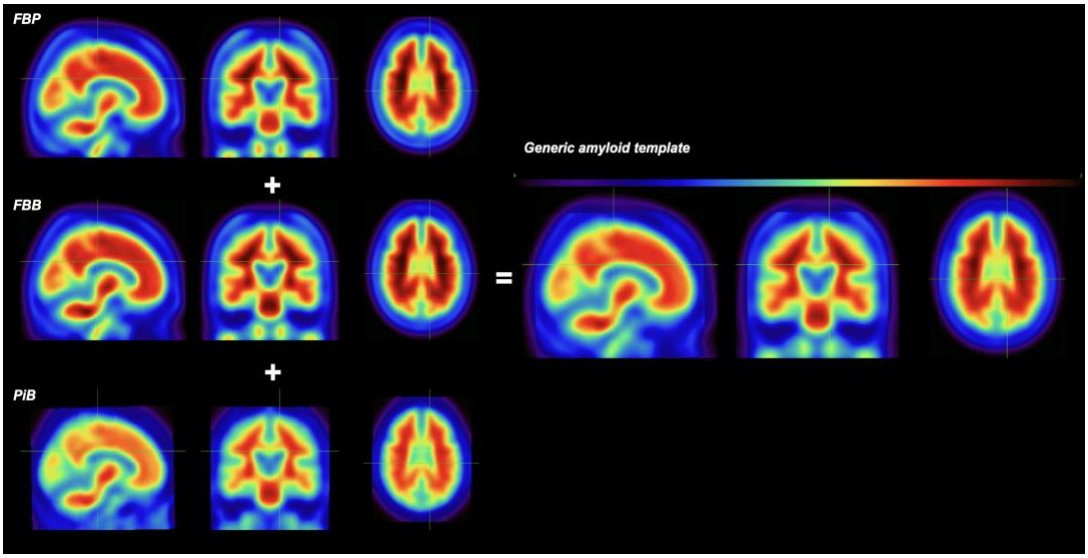

Figure 1. Tracer-specific templates (left) and the resulting generic amyloid template (right). Color bar shows 0-2 SUVR.

Calculation of SUVRs

Once PET images are warped to template space, we sample regional means within template space ROIs. We offer 2 different datasets reflecting SUVRs from two atlases, described below: (1) the Global Alzheimer's Association Interactive Network centiloid regions (GAAIN-based), which was used for our recommended and previously validated[2] cortical summary SUVRs / CLs, and amyloid +/- status, and (2) our own Normalized Probability Desikan-Killiany Atlas (NPDKA), for whole brain, individual regional SUVRs, and an alternative summary measure that mimics the summary measure used in standard MRI-dependent analyses with the native space Desikan-Killiany Atlas. In addition, we provide the regional volumes of the NPDKA in a supplementary spreadsheet. Summary regions and recommended cross-sectional/longitudinal reference regions for the GAAIN-based atlas (A) and the NPDKA (B) are shown in Figure 2. Both atlases produced summary SUVRs that were linearly correlated with our standard MRI-dependent SUVR quantification (Figure 3).

Note, GAAIN-based and NPDKA regional SUVRs are intensity-normalized to their respective whole cerebellum reference regions and can be "re-normalized" *once* by dividing them by one of their other reference region SUVRs, since this cancels out the original intensity normalization. The cortical summary CLs cannot be directly transformed to a different intensity normalization.

Although multiple acquisition time windows are available for some scans, we preferentially provide data for the primary acquisition time window for each tracer (see Table 1). When the primary acquisition is not available, we make a secondary acquisition window available instead. Combining data across acquisition windows is not recommended. Our tracer-specific MRI-free Centiloid conversion equations are derived using primary acquisition window scans, we therefore do not recommend using them for non-primary acquisition window scans and do not provide Centiloids for non-primary acquisition window data.

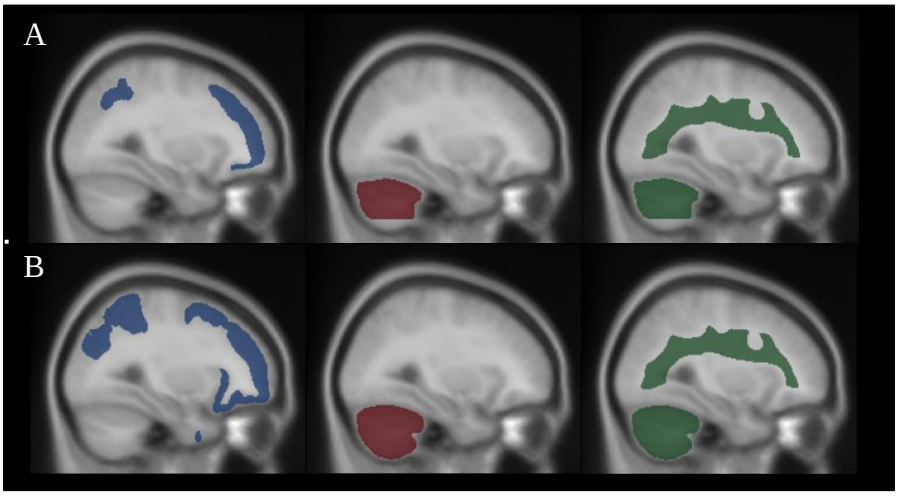

Figure 2. GAAIN-based (A) and NPDKA (B) regions overlaid on the SPM T1 average image (spmdefault_1mm_MNI_avg152T1). The cortical summary ROIs, whole cerebellum reference regions, and composite reference regions are shown in blue, red, and green respectively.

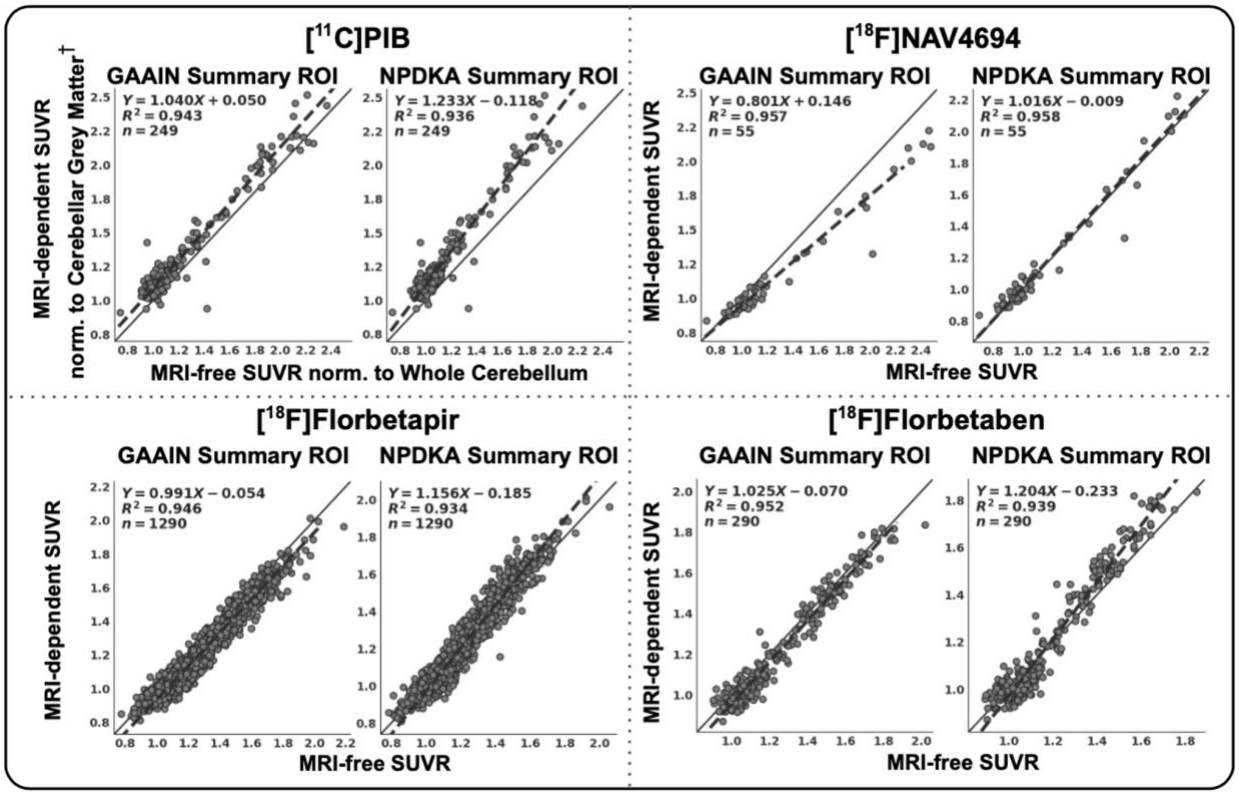

Figure 3. Regressions between MRI-dependent and MRI-free cortical summary SUVRs (normalized to whole cerebellum) using the GAAIN and NPDKA volumes in PiB, FBP, FBB, and NAV. †PiB MRI-dependent SUVRs are normalized to the cerebellar grey matter region, the recommended reference region for PiB MRI-dependent processing[4].

GAAIN-based Summary SUVRs

We used the GAAIN cortical summary ROI and whole cerebellum reference region that are available on the GAAIN website. The SUVRs reported in the GAAIN-based dataset are intensity normalized to the GAAIN whole cerebellum (note the "1" value for the GAAIN whole cerebellum column), and this reference region is recommended for cross-sectional analyses. Several other reference regions are provided that can be used to re-intensity normalize the GAAIN cortical summary region: composite reference (recommended for longitudinal analyses; made up of the GAAIN whole cerebellum and brainstem regions, and the NPDKA-defined eroded subcortical white matter), eroded subcortical WM alone, and cerebellar grey matter.

The GAAIN summary ROI outperformed the NPDKA summary ROI with respect to its agreement with our gold standard, the MRI-dependent DK cortical summary SUVR (Figure 3).

NPDKA Summary and Regional SUVRs

The purpose of the NPDKA was to provide template-space SUVRs for the 111 Freesurfer-defined ROIs used in our MRI-dependent, native space pipeline[1]. **Use of this dataset is recommended for region-wise analyses that go beyond the use of a binary Aβ status or single cortical summary SUVR value.** The NPDKA cortical summary and regional SUVRs reported in the dataset are intensity normalized to the NPDKA whole cerebellum (note the "1" value for the NPDKA whole cerebellum column), and this reference region is recommended for cross-sectional analyses. Other NPDKA-defined reference regions provided include composite reference (recommended for longitudinal analyses; made up of the whole cerebellum, brainstem, and eroded subcortical white matter), eroded subcortical WM alone, and cerebellar grey matter. Like our MRI-dependent pipeline[1], the NPDKA cortical summary region is made up of frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal regions. The NPDKA subcortical white matter mask was eroded through smoothing with an $8mm^3$ Gaussian kernel and thresholding at 0.90.

The NPDKA (Figure 4) was derived from Freesurfer v7.1 Desikan-Killiany segmentations of 200 cognitively normal, Aβ-negative ADNI participants. Template-space probability maps were created for each region first by (1) warping each segmentation to MNI-152 space using the parameters from the T1 (SPM12 normalize), (2) lightly smoothing each ROI mask with a 1.5mm FWHM gaussian kernel to clean the edges, (3) averaging the ROI masks across the 200 subjects, and (4) normalizing each ROI between 0 and 1 by dividing out the highest voxel probability. ROI probability maps were combined into a single whole brain atlas by assigning each voxel to the ROI whose probability map was the highest for that voxel. We used ADNI FBP and FBB scans to compare NPDKA SUVRs with our MRI-dependent DK SUVRs and found concordance of 94% and 92% respectively for each tracer's primary outcome positivity threshold (Table 3).

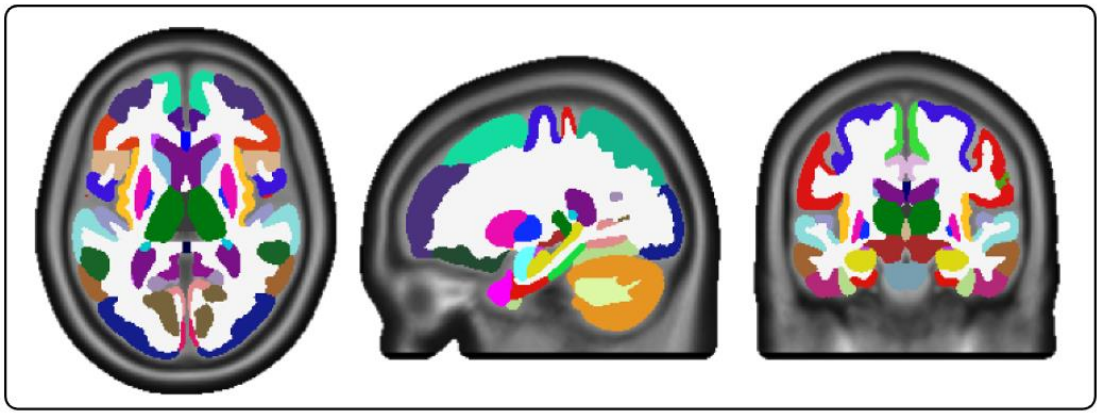

Figure 4. Normalized Probability Desikan-Killiany Atlas (NPDKA)

Centiloids

The "CENTILOIDS" column contains a standardized quantitative amyloid measure called centiloids (CLs), a linear transform of the MRI-free GAAIN cortical summary SUVRs normalized to whole cerebellum. The centiloid scale is tied to a 0 anchor, based on typical young controls, and a 100 anchor, based on typical AD patients, but some values will lie outside of the 0-100 bounds. Equations for converting tracer-specific SUVRs to generic amyloid centiloids are listed in Table 2. These equations are based on data acquired using the primary acquisition time for each tracer (Table 1). We derived each of these equations through the level 2 GAAIN centiloid analysis method[3]. For FBP, FBB, and NAV, we used datasets consisting of subjects scanned with both PiB and the other tracer to find the relationship between the standard PiB processing and the generic amyloid MRI-free processing of the tracer. For PiB, we used the level 1 PiB data to find the relationship between the standard PiB processing and our MRI-free PiB processing. We then scaled the MRI-free SUVRs to standard PiB SUVRs, using the regression equation, and scaled these units to centiloids, using the anchor points. This analysis method is described further in Klunk, et al[3].

Transformation Between MRI-free and MRI-dependent Pipeline Results

The MRI-free GAAIN cortical summary SUVRs can be transformed to be compatible with the MRI-dependent cortical summary SUVRs (generated by our ADNI pipeline) using the MRI-dep SUVR ←→ MRI-free SUVR transformation equations listed in Table 2. These reversible equations are based on the MRI-free to MRI-dependent total least squares regression shown in Figure 3. Users may convert to MRI-dependent or MRI-free units depending on their specific projects. Note that these transformation equations apply to MRI-free and MRI-dependent data that is intensity normalized by the whole cerebellum- except for PiB, where whole cerebellum-normalized MRI-free PiB SUVRs are transformed to be compatible with cerebellar grey matter-normalized MRI-dependent PiB SUVRs[4].

*Table 2. MRI-free centiloid conversion equations and relationships between MRI-dependent and MRI-free GAAIN cortical summary SUVrs, normalized to the whole cerebellum reference region. *Note: FBP and FBB centiloid equations were calculated for our tracer-specific template MRI-free processing method, but these equations can be applied to generic amyloid template MRI-free SUVrs due to the high correlation between SUVrs from these methods (R^2≥0.998).*

Tracer	MRI-dep SUVR ←→ MRI-free SUVR	MRI-free SUVR ← → MRI-free CL
PiB	(PiB MRI-dep SUVR/CerebGray)=1.040(PiB MRI-free SUVR/WC)+0.05	(PiB MRI-free CL)=92.08(MRI-free PiB SUVR)-95.83
FBP	(FBP MRI-dep SUVR)=0.991(FBP MRI-free SUVR)-0.054	(FBP MRI-free CL)=192.40(MRI-free FBP SUVR)-207.27 *
FBB	(FBB MRI-dep SUVR)=1.025(FBB MRI-free SUVR)-0.07	(FBB MRI-free CL)=164.60(MRI-free FBB SUVR)-171.97 *
NAV	(NAV MRI-dep SUVR)=0.801(NAV MRI-free SUVR)+0.146	(NAV MRI-free CL)=88.86(MRI-free NAV SUVR)-91.71

Amyloid Status

Categorizing a participant as amyloid +/- is fairly complex and may be done in several different ways for SCAN. One recommended approach is to use the "AMYLOID_STATUS" column, provided only in the GAAIN-based dataset, which contains a binary conversion of the MRI-free GAAIN cortical summary SUVRs normalized to whole cerebellum. SUVRs were binarized based on the positivity thresholds listed and described in Table 3. For each tracer, we derived positivity thresholds using two methods: (1) converting an established MRI-dependent threshold to MRI-free SUVRs and (2) calculating two standard deviations above the mean SUVR of a young control group processed with the MRI-free method. For FBP and FBB, both approaches yielded identical thresholds. For NAV, we did not have an established MRI-dependent threshold to convert to MRI-free SUVRs, so we only calculated a threshold equal to two standard deviations above the mean of a group of young controls and used this threshold. For PiB the threshold resulting from the two methods were slightly different (1.12 SUVR and 1.15 SUVR) so we took an average to determine the PiB threshold for SCAN.

Table 3. The SCAN amyloid positivity thresholds, shown on the right, are based on GAAIN cortical summary SUVRs normalized to the whole cerebellum.

Tracer	MRI-dependent Threshold	Threshold Approach 1: Converted (to MRI-free) MRI-dependent Threshold	Threshold Approach 2: Mean+2SD of MRI-free Young Controls	SCAN MRI-free Aβ Positivity Threshold
PiB	1.21 SUVR[4]	1.12 SUVR	1.15 SUVR	**1.14 SUVR**
FBP	1.11 SUVR[5]	1.17 SUVR	1.17 SUVR	**1.17 SUVR**
FBB	1.08 SUVR[5]	1.12 SUVR	1.12 SUVR	**1.12 SUVR**
NAV	NA	NA	1.14 SUVR	**1.14 SUVR**

Another reasonable approach to determining amyloid+/- status for participants using the MRI-free pipeline is to use the continuous centiloid values provided. In this case, we recommend categorizing subjects as amyloid-negative for CL<10, amyloid-positive for CL>20, or 'ambiguous' for 10≤CL≤20. In addition, both centiloids and SUVRs can be used continuously. It is important to recognize that these different approaches to classification will not entirely agree with one another, especially for participants with values near the thresholds.

FAQs

1. How do I find amyloid status info for SCAN individuals?

The "AMYLOID_STATUS" column categorizes individuals as amyloid-positive ("1") or amyloid-negative ("0"), based on thresholds for the GAAIN cortical summary SUVR normalized to the whole cerebellum. More below in the "Amyloid Status" section.

2. Are the SUVRs in these datasets already intensity normalized?

Yes. The GAAIN cortical summary and NPDKA regional SUVRs are already normalized by their respective whole cerebellum reference regions.

3. Can I intensity normalize the SUVRs using a different region?

To use a different reference region, re-normalize once with the provided values (divide original SUVRs by new reference region mean). For more information, see the "Calculation of SUVRs" section above.

4. Can I merge SCAN data with ADNI data?

Yes, but ADNI SUVRs were generated using a different pipeline that depends on the use of an MRI, so it is important to ensure the SUVRs being merged are on the same numerical scale. To merge MRI-free SCAN data with MRI-dependent ADNI data, transform the SCAN MRI-free SUVRs to their MRI-dependent equivalents using the MRI-free vs. MRI-dependent regression equations listed in Table 2 and plotted in Figure 3.

5. Can I merge SCAN data with PET data from other studies?

SCAN data can be merged with PET data from other studies that have been analyzed using an MRI-dependent pipeline identical to that used at UC Berkeley to process ADNI and POINTER PET data, using the strategy described above. To merge SCAN data with PET data from other studies using other another method, there are several options: (1) the SCAN images can be analyzed using the other study's analysis methods in order to calculate a linear transformation equation that describes the relationship between SCAN SUVRs and the other study's SUVRs for the same individuals, and this relationship can be used to convert SCAN data SUVRs to be compatible with the other study's SUVRs, (2) process the other study's PET data using SCAN's MRI-free approach, or (3) simply use the standardized amyloid burden unit, centiloids, and no conversion is needed across studies.

Version Information

This is our fourth amyloid PET MRI-free processing methods document for SCAN.

Dataset Information

This methods document applies to the following datasets available from the SCAN repository:

DATASET DESCRIPTION
UC Berkeley - Amyloid MRI-free GAAIN Analysis
UC Berkeley - Amyloid MRI-free NPDKA Analysis
UC Berkeley - MRI-free NPDKA Appendix

References

1. Landau, SM, Murphy, A, Lee, JQ, et al. Florbetapir (AV45) processing methods. *LONI ADNI*. 2022; 1-7.
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