SCAN MRI-free Tau PET Processing

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Summary

A goal of SCAN 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 available. 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 tau PET processing pipeline builds on our previously validated MRI-free PET processing methods[2] by employing an approach that can be used across multiple tau PET tracers (^{18}F-Flortaucipir (FTP), ^{18}F-MK-6240). *The tau PET tracer ^{18}F-PI-2620 will also be processed as part of SCAN and the MRI-free pipeline is currently being validated*. Our MRI-free pipelines consist of (1) a linear registration of individual PET scans to a MNI152 T1 template, (2) non-linear spatial normalization to a tracer-dependent PET template, (3) mean intensity quantification within regions of interest (ROIs), and (4) intensity normalization to create standardized uptake value ratios (SUVRs) in relation to a reference region.

Methods

Acquisition of tau PET data from LONI

We download SCAN FTP and MK-6240 images from LONI in the most fully pre-processed format (Step 4; 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 each tracer, a primary acquisition time window was used to generate numerical quantification data (Table 1).

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

Tracer	Acquisition Time	LONI Series Description
FTP	**80-100**	T80 Coreg, Avg, Rigid Reg to Std Img/Vox Size, 80-100*, 6mm Res
MK-6240	70-90	M62 Coreg, Avg, Rigid Reg to Std Img/Vox Size, 70-90*, 6mm Res
	70-110	M62 Coreg, Avg, Rigid Reg to Std Img/Vox Size, 70-110*, 6mm Res
	90-110	M62 Coreg, Avg, Rigid Reg to Std Img/Vox Size, 90-110*, 6mm Res

Tau PET templates

FTP and MK-6240 scans with MRIs from other studies were used to create the tau PET templates. A set of n=200 of images for each tracer were transformed to MNI-152 space using subject matched MRIs. Samples between tracers were matched for a similar distribution of sex, age, diagnosis, and amyloid status as best as possible for the cohorts we had available to us (Table 2). The FTP template is a subset of Alzheimer's Disease Neuroimaging Initiative (ADNI: 50 Aβ-negative and 50 Aβ-positive unimpaired; 50 Aβ-negative and 50 Aβ-positive impaired males and females). For MK-6240, we used scans from the Alzheimer's Association U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (U.S. POINTER: 50 Aβ-negative and 50 Aβ-positive) for unimpaired subjects and scans from Cerveau Technologies (Cerveau: 41 Aβ-negative and 59 Aβ-positive) for impaired subjects with MCI or AD. Each set of images were preprocessed by the University of Michigan and downloaded at "Step 4" images through LONI in the same method as SCAN images. Template space PET scans were intensity normalized and averaged together for each tracer to create tau PET templates (Figure 1). These templates are used for spatial normalization of SCAN tau PET images as part of the MRI-free processing pipeline.

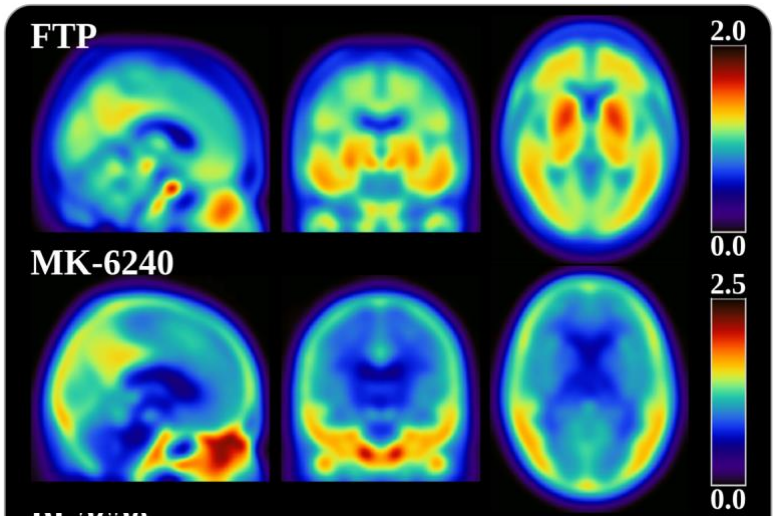

Figure 1. Tau PET templates used for spatial normalization to MNI-152 space.

Table 2. Distribution of total subjects, age, and sex by diagnosis and amyloid status for FTP and MK-6240 Tau PET templates. CN: Cognitively Normal, CI: Cognitively Impaired.

Tracer		CN / Aβ+	CI / Aβ+	CN / Aβ-	CI / Aβ-
FTP	n	50	50	50	50
	Age	73.8 (7.2)	75.4 (6.4)	71.6 (6.6)	73.9 (7.0)
	Sex (M)	40%	52%	40%	62%
MK-6240	n	50	59	50	41
	Age	69.7 (4.8)	73.3 (7.9)	67.7 (4.9)	71.6 (8.8)
	Sex (M)	50%	49%	50%	44%

Calculation of SUVRs

Once images are warped to their respective PET template, we sample regional means within template space ROIs. A whole brain atlas was developed to sample template space Desikan-Killiany ROIs equivalent to those produced by Freesurfer in native space (Figure 2; for more information see NPDKA section below). This was done to reduce differences between our MRI-free and MRI-dependent pipelines so that datasets could more easily be compared. From this atlas, two primary ROIs (meta-temporal, entorhinal cortex) and two reference regions (inferior cerebellar gray matter, eroded hemispheric white matter) are provided at the front of the dataset. **The tau PET dataset is intensity normalized by the inferior cerebellum, visible as a column of 1's. Any SUVR can be renormalized once by dividing the region by another. We recommend using the inferior cerebellum as a reference region for cross-sectional analyses and the eroded hemispheric white matter as the reference region for longitudinal analyses.**

Although multiple acquisition time windows are available for some scans, we currently provide data only for the primary acquisition time window for each tracer (see Table 1). Scans acquired using a different acquisition time are not currently being quantified using our pipeline, but the preprocessed scans are available for download on LONI.

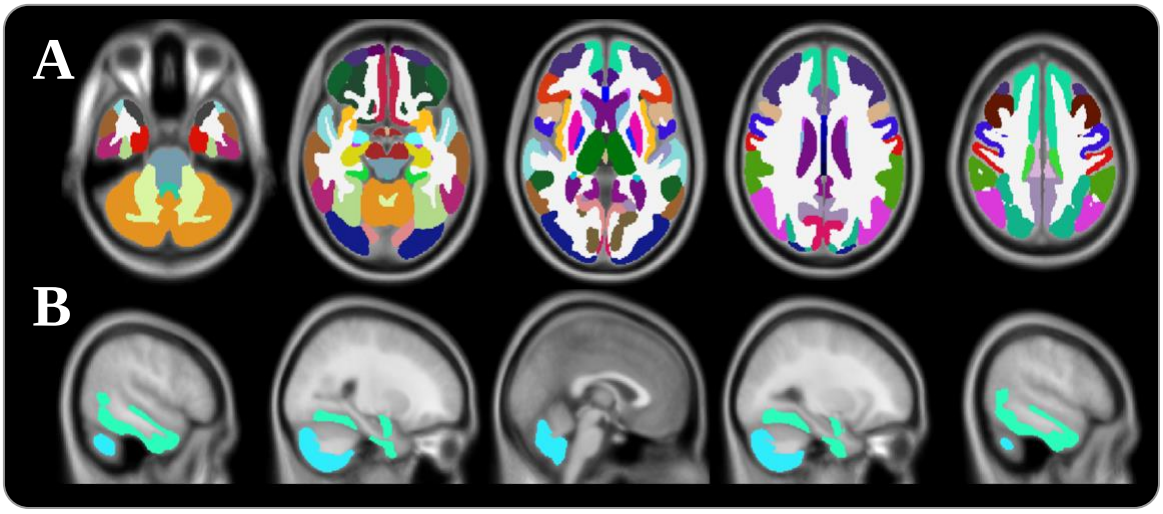

Figure 2. (A) Normalized Probability Desikan-Killiany atlas (NPDKA) based on the Desikan-Killiany atlas and derived from an average of 200 Freesurfer 7.1 segmentations. (B) Inferior cerebellar grey matter and meta-temporal masks. These masks exist in MNI-152 space and are used to sample SUVRs from SCAN tau PET images after MRI-free spatial normalization.

NPDKA Summary and Regional SUVRs

The purpose of the normalized probability Desikan-Killiany atlas (NPDKA) was to provide template-space SUVRs for the 111 Freesurfer-defined ROIs used in our MRI-dependent, native space pipeline[1]. The NPDKA meta-temporal, and regional SUVRs reported in the dataset are intensity normalized to a template space inferior cerebellum mask created from a subset of voxels in the Desikan-Killiany cerebellar gray matter, detailed methods described in Baker, et al (2017)[3]. The inferior cerebellum is recommended for cross-sectional analyses. The eroded hemispheric white matter is another common reference region provided in our dataset and was created from the hemispheric white matter mask in the NPDKA atlas by smoothing the binary mask with an $8mm^3$ Gaussian kernel and threshold at 0.9 units. We recommend using the eroded hemispheric white matter as a reference region for longitudinal analyses.

The NPDKA (Figure 2) 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 FTP data from ADNI and MK-6240 data from POINTER (unimpaired) and Cerveau (impaired) cohorts to compare MRI-free and MRI-dependent SUVRs to evaluate the correspondence of the MRI-free atlas and normalization (see Table 3 and Figure 3).

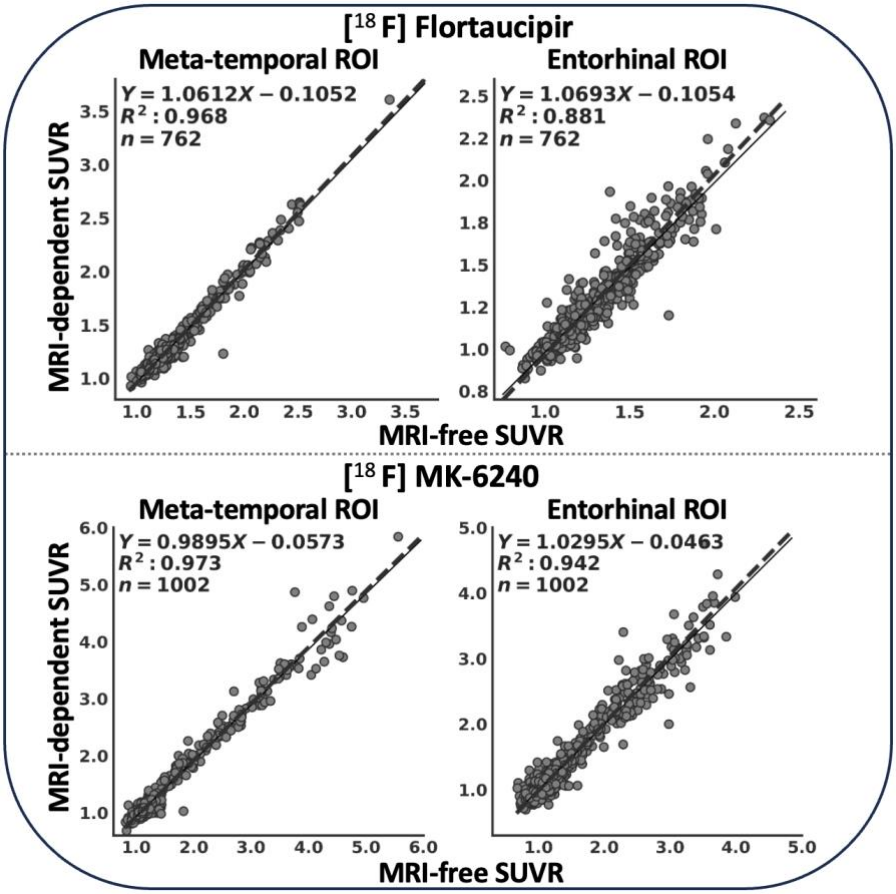

Figure 3. Regressions between MRI-dependent and MRI-free Meta-temporal and Entorhinal ROI SUVRs (normalized to inferior cerebellum) using the NPDKA volumes in FTP and MK-6240.

Transformation Between MRI-free and MRI-dependent Pipeline Results

The MRI-free meta-temporal SUVRs can be transformed to be compatible with the MRI-dependent meta-temporal SUVRs (generated by our MRI-dependent 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 inferior cerebellum.

Table 3. Relationships between MRI-dependent and MRI-free NPDKA Meta-temporal and Entorhinal ROI SUVrs, normalized to the inferior cerebellum reference region.

Tracer	MRI-dep SUVR ←→ MRI-free SUVR Meta-temporal ROI	MRI-dep SUVR ←→ MRI-free SUVR Entorhinal ROI
FTP	(FTP MRI-dep SUVR)=1.0612(FTP MRI-free SUVR)-0.1052	(FTP MRI-dep SUVR)=1.0693(FTP MRI-free SUVR)-0.1054
MK-6240	(MK-6240 MRI-dep SUVR)=0.9895(MK-6240 MRI-free SUVR)-0.0573	(MK-6240 MRI-dep SUVR)=1.029 (MK-6240 MRI-free SUVR)-0.0463

FAQs

1. ***Are the SUVRs in these datasets already intensity normalized?***
Yes. The SUVRs are already normalized by the inferior cerebellum. This is observable as a 1.000 SUVR in the column "INFERIORCEREBELLUM_SUVR".

2. ***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.

3. ***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.

4. ***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 two 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 methods.

Version Information

This is our first tau PET MRI-free processing methods document for SCAN.

Dataset Information

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

Dataset Name
UC Berkeley – Tau 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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3. Baker, S. L., Maass, A., & Jagust, W. J. (2017). Considerations and code for partial volume correcting [^{18}F]-AV-1451 tau PET data. *Data in brief*, *15*, 648–657.

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