FHS PET Processing Details

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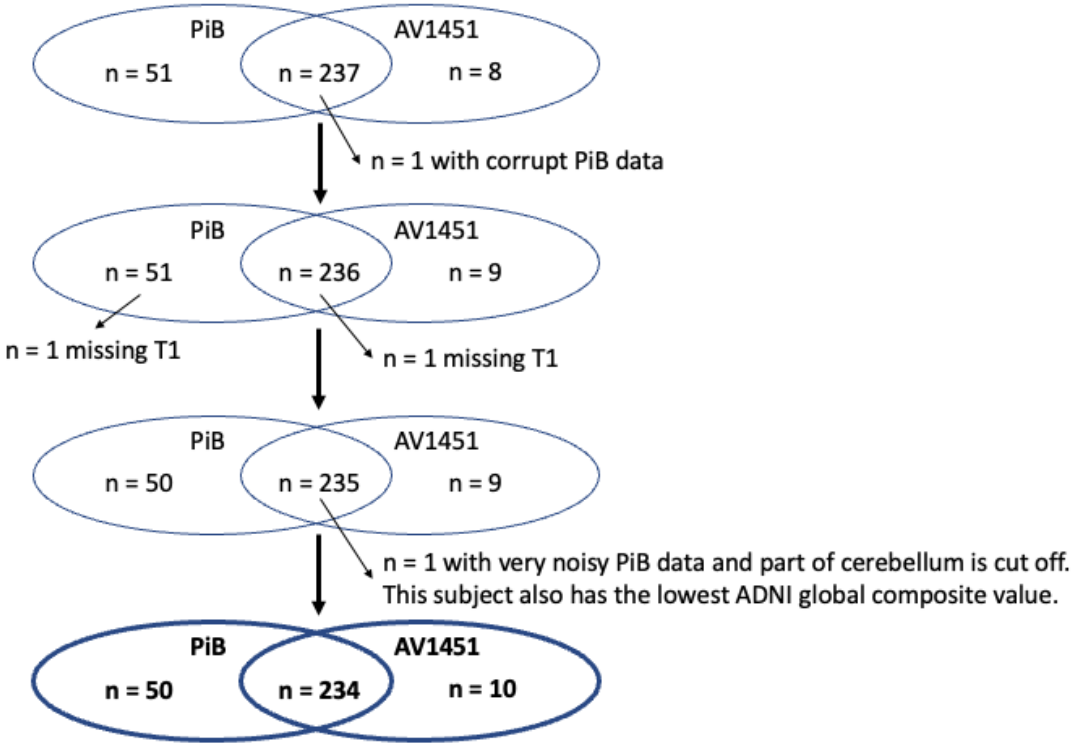
MRI, amyloid PET, and tau PET data were processed on the FHS remote desktop. This document describes amyloid DVRs in FHS_amyloidDVR_ref-bicerebellumcortex_volweighted_20220415.csv and tau SUVRs in FHS_tauSUVR_ref-bicerebellumcortex_volweighted_20220415.csv.

A description of the PET data acquisition and pre-processing steps was adapted from Sanchez et al.[1] and Gonzales et al.[2]:

^{11}C-Pittsburgh Compound B (PiB) and ^{18}F-Flortaucipir (AV1451) were acquired using either a Siemens/CTI (Knoxville, TN) ECAT HR+ scanner (n=203) or a GE scanner (n=91). PiB PET were acquired after a bolus injection (mCi range to be determined; Sanchez references Johnson et al.[3], which reported a 8.5 to 15 mCi bolus injection whereas Gonzales et al.[2] reported 10 to 15 mCi bolus injection) followed immediately by a 60-minute dynamic acquisition in 39 frames (timing of frames to be determined). AV1451 were acquired after a 9.0 to 11.0 mCi bolus injection with presumably 5-minute frames (timing and number of frames to be determined; Sanchez et al.[1] and Gonzales et al.[2] reported 80-100 minutes with 4 x 5-minute frames but the raw data have 6 frames and an email from Cody and Justin Sanchez states 6 frames from 75-105 minutes). PET data were reconstructed and attenuation corrected and each frame was evaluated to verify adequate statistics and absence of head motion. PiB and AV1451 dates were collected on the same date for everyone except for 13 participants. MRI was performed on a 3T Tim Trio (Siemens) and included an MPRAGE processed with FreeSurfer to identify gray-white and pial surfaces and to allow for ROI parcellation.

PiB PET data were expressed as the distribution volume ratio (DVR) by Logan (40-60 min) and AV1451 PET data were expressed as the standardized uptake value ratio (SUVR; time frame to be determined); both metrics use cerebellar gray as the reference region and do not use partial volume correction. Each participant's PiB DVR and AV1451 SUVR data were coregistered to their closest MRI scan and MRI data along with the aparc+aseg FreeSurfer labels were coregistered to PET space. PiB DVR and AV1451 SUVR values were extracted from each aparc+aseg region and volume-weighted DVR and SUVR values were calculated for each bilateral region.

Figure 1. Participant flow.



The processing steps were as follows:

1. Organize data
    a. PIB
        i. If a subject directory existed in /encryptedfs/data/pet_data/2021_06_15/pet_scans/20200219/neuro_pet_scans/fhs_ids/GE/PIB/DVR or /encryptedfs/data/pet_data/2021_06_15/pet_scans/20200219/neuro_pet_scans/fhs_ids/HR+/PIB/DVR, their *PIB_DVR.nii file was brought into a single directory /encryptedfs/christina/subjects
    b. AV1451
        i. If a subject directory existed in /encryptedfs/data/pet_data/2021_06_15/pet_scans/20200219/neuro_pet_scans/fhs_ids/GE/TAU/SUVR or /encryptedfs/data/pet_data/2021_06_15/pet_scans/20200219/neuro_pet_scans/fhs_ids/HR+/TAU/SUVR, their *TAU_SUVR.nii file was brought into a single directory /encryptedfs/christina/subjects
    c. MRI
        i. Multiple MRI files from the 1990s onward existed per subject. Since all the PIB and AV1451 scans occurred between 2015 and 2019, the most recent MRI was used. Note that the MRI occurred years (amyloid: mean (SD) = 6.28 (1.54), range = 3.05 – 12.49; tau: mean (SD) = 6.36 (1.45), 2.61 – 9.78 years) before the PET scan (Figure 2). PiB and AV1451 dates were on the same date for everyone except for 13 participants.

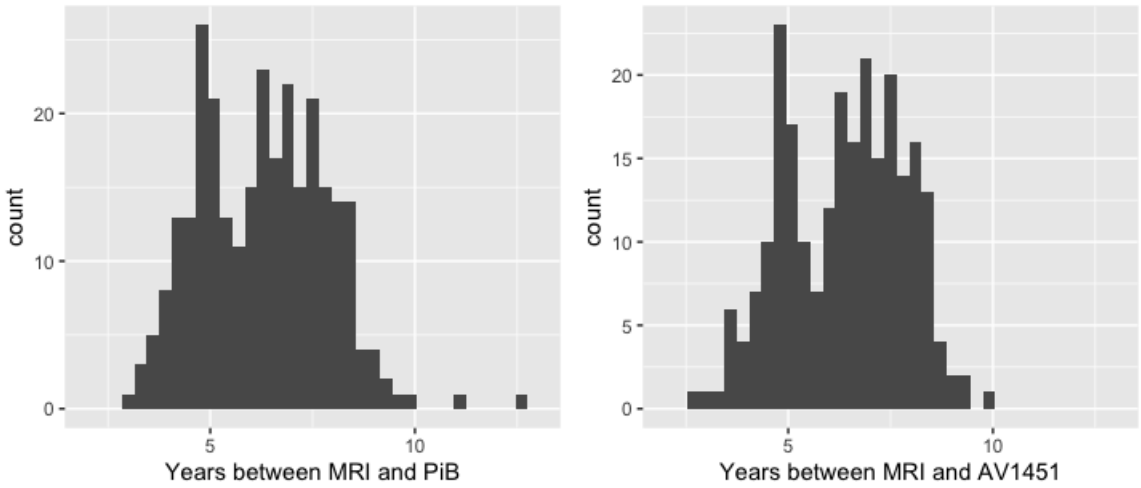


Figure 2. Histogram of years between MRI and PET scans.

        ii. MRI files were pulled from /encryptedfs/data/mri_data/pet_pts/2021_06_17/*/*/t1_mpr_sag.nii.gz.
2. Reconstruction and segmentations
    a. Reconstruction to create 2D surfaces and segmentations were run on all the T1 data using Freesurfer's recon-all command. The important output were nu.mgz and aparc+aseg.mgz files.
3. PET and T1 coregistration
    a. PIB and AV1451
        i. PIB scans were coregistered to their MRI scans using SPM. The MRI and corresponding aparc+aseg data were moved into PET space. These steps were repeated for AV1451 scans.
4. Extracting values for aparc+aseg regions
    a. PIB and AV1451
        i. The mean values from the pib_dvr file were extracted across all aparc+aseg regions. A csv file was created with all mean values along with each region's total volume (to enable regions to be combined). These steps were repeated using tau_suvr files.
5. Creating .csv files

a. PIB
    i. Reference region – We used a gray matter only cerebellum reference region (volume weighted across hemisphere
        1. Mean.Left.Cerebellum.Cortex, Mean.Right.Cerebellum.Cortex, Volume_mm3.Left.Cerebellum.Cortex, and Volume_mm3.Right.Cerebellum.Cortex were used to create this reference region). Because the values in the amyloid PET csv files are normalized to this cerebellar gray reference region, the values in this column ("bi_Cerebellum.Cortex") are 1.
    ii. Bilateral regions - We additionally created bilateral regions taking a volume weighted average across hemispheres for all aparc+aseg regions.
    iii. Large ROIs - We additionally included 4 volume-weighted large target regions following ADNI pipelines (see "UC Berkeley – AV45 Analysis Methods" PDF that is downloadable from LONI). These large ROIs are called "ADNI.frontal", "ADNI.accpcc", "ADNI.latpar", and "ADNI.lattemp" in the amyloid csv file.
        1. Frontal
            a. 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
            b. 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
        2. ACC/PCC
            a. ctx.lh.caudalanteriorcingulate, ctx.lh.isthmuscingulate, ctx.lh.posteriorcingulate, ctx.lh.rostralanteriorcingulate
            b. ctx.rh.caudalanteriorcingulate, ctx.rh.isthmuscingulate, ctx.rh.posteriorcingulate, ctx.rh.rostralanteriorcingulate
        3. Lateral Parietal
            a. ctx.lh.inferiorparietal, ctx.lh.precuneus, ctx.lh.superiorparietal, ctx.lh.supramarginal
            b. ctx.rh.inferiorparietal, ctx.rh.precuneus, ctx.rh.superiorparietal, ctx.rh.supramarginal
        4. Lateral Temporal
            a. ctx.lh.inferiortemporal, ctx.lh.middletemporal, ctx.lh.superiortemporal
            b. ctx.rh.inferiortemporal, ctx.rh.middletemporal, ctx.rh.superiortemporal
    ii. Global composite - A global composite, called "ADNI.global.composite", was created from the average of the 4 large regions in the amyloid csv file. This ADNI global composite is similar to the FLR region used in Sanchez et al.[1] (Figure 3).

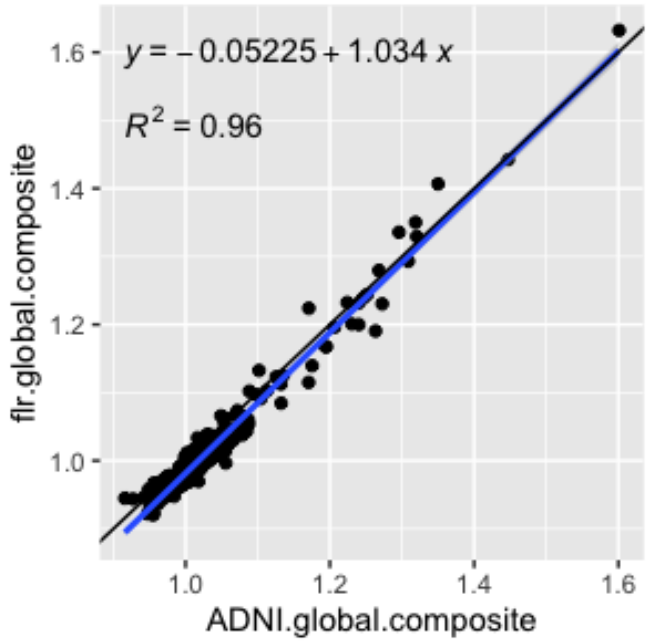


Figure 3. Comparison of PiB DVRs using the ADNI global region and the FLR global region used in Sanchez et al.[1]. The blue line is the regression line fitting the data. The black line is the identity line.

iii. Determining amyloid positivity – Although the Sanchez et al.[1] paper used a DVR cutoff of 1.35 for amyloid positivity, this value was applied to data using the FLR region with partial volume correction. Instead of applying this cutoff value, we used a data-driven approach to determine a cutoff for this specific dataset. Note that the current DVRs are not partial volume corrected, so will have systematically lower values as compared to the DVRs used by Sanchez et al.[1]. Gaussian mixture modeling (GMM) demonstrated that 2 distributions with unequal variance best fit the data (Figure 4) and that a cutoff value of 1.098 best separated the distributions (Figure 5). The selection of a 2-cluster solution is consistent with our previous work[4,5].

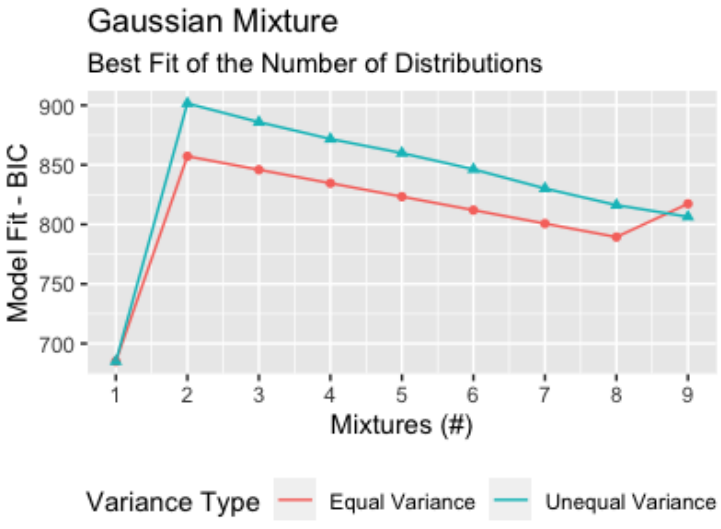


Figure 4. GMM demonstrated that 2 distributions best fit the data. We examined 18 possible solutions that varied by cluster size (N=1 to 9) and variance for each cluster (equal versus unequal).

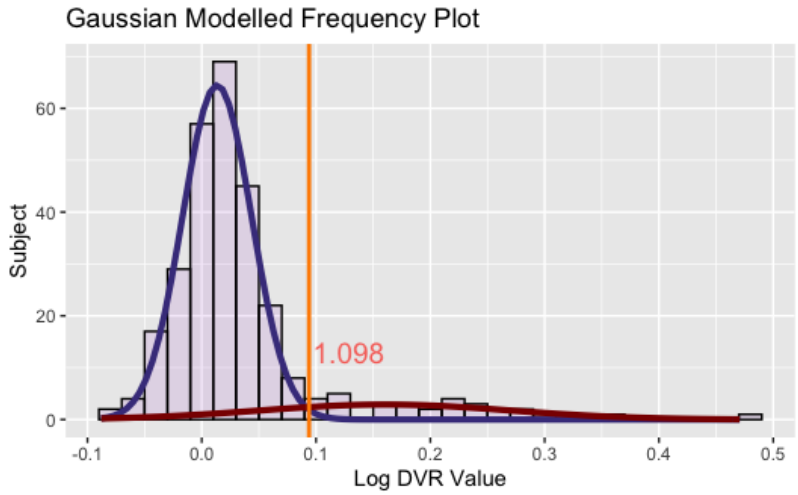


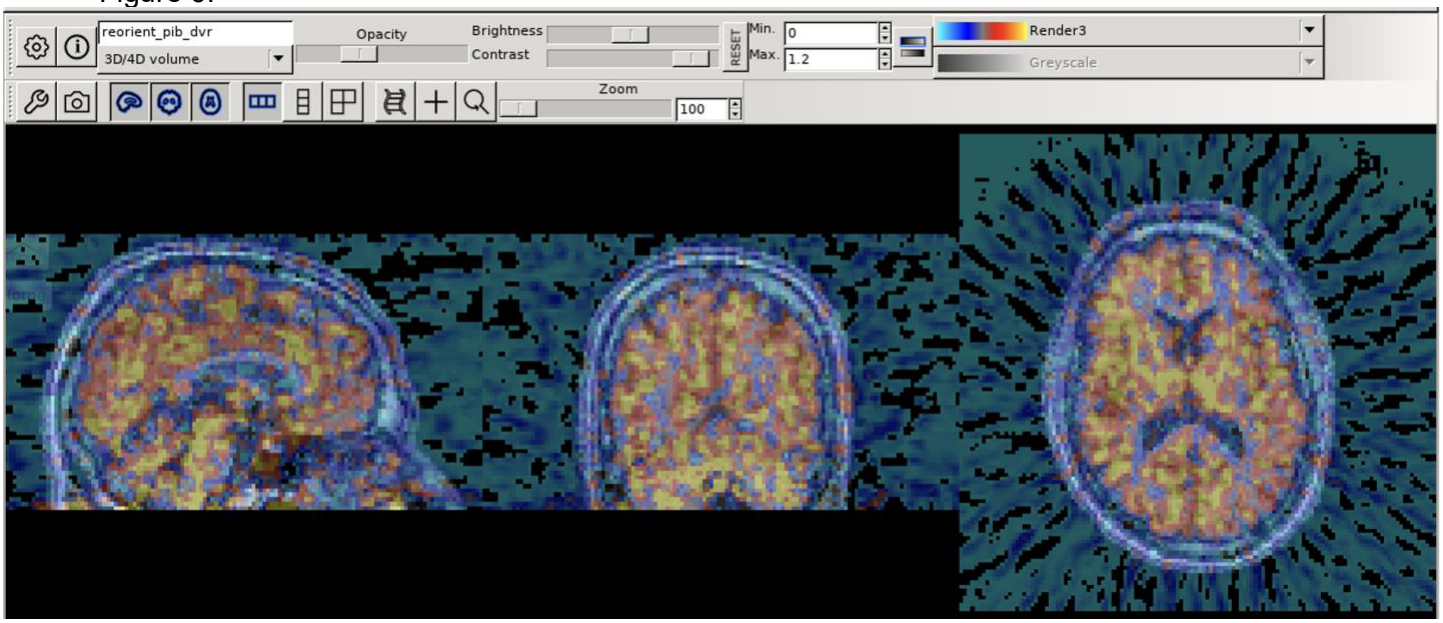
Figure 5. GMM demonstrated that a 50% probability of belonging to the A+ cluster (red) corresponds to a DVR value of 1.098. With this cutoff, 253 participants are A- and 31 participants are A+.

b. AV1451
   i. Reference region - We used a gray matter only cerebellum reference region (volume weighted across hemisphere.
      1. Mean.Left.Cerebellum.Cortex, Mean.Right.Cerebellum.Cortex, Volume_mm3.Left.Cerebellum.Cortex, and Volume_mm3.Right.Cerebellum.Cortex columns). Because the values in the tau PET csv files are normalized to this gray matter only cerebellum reference region, the values in this column ("bi_Cerebellum.Cortex") are 1.
   ii. Bilateral regions - We additionally created bilateral regions taking a volume weighted average across hemispheres for all aseg+aparc regions.

Appendix

1. 1 subject had corrupt PiB data.
2. 1 subject had noisy PiB data with part of the cerebellum cut off (see Figure 6). Because the cerebellum is required for the reference region, this subject was excluded from further analyses.

Figure 6.



3. Pending questions and discrepancies regarding PET acquisition
   a. Timing and number of frames used to create AV1451 SUVRs

b. Bolus injection amount for PiB
c. Timing of PIB frames
d. Discrepancies
    i. Raw data on server
        1. PiB – 39 frames
        2. AV1451 – 6 frames
    ii. Email from Cody with quoted response from Sanchez: “Raw data is acquired over a time window — **39 frames** from 0-60 minutes for PIB, and **6 frames** from 75-105 minutes for TAU — which gives the fourth dimension (time) in the raw images. These images are processed to give single-frame (no fourth dimension) SUVR or DVR images, which we use for analyses.”
    iii. Sanchez et al.[1] paper
        1. “PiB…DVR by Logan (40-60 min) with cerebellar cortex reference”
        2. “FTP…SUVr (80-100 min) with cerebral white matter reference”
        3. Also referenced Johnson Ann Neurol. 2016 paper, which stated:
            a. PiB – 8.5 to 15 mCi bolus injection followed immediately by a 60-minute dynamic acquisition in 69 frames (12x15 seconds, 57x60 seconds)
            b. AV1451 – 80-100 minutes after a 9.0 to 11.0 mCi bolus injection in 4 x 5-minute frames
    iv. Gonzales et al.[2] paper
        1. “PiB PET images were acquired with a 10 to 15 mCi bolus injection followed by a 60 min dynamic acquisition”
        2. “FTP PET images were obtained across 80 to 100 min using 4 x 5 min frames after a single 9 to 11 mCi bolus injection”

References

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2. Gonzales MM, Samra J, O’Donnell A, et al. Association of Midlife Depressive Symptoms with Regional Amyloid-β and Tau in the Framingham Heart Study. *J Alzheimers Dis JAD*. 2021;82(1):249-260. doi:10.3233/JAD-210232

3. Johnson KA, Schultz A, Betensky RA, et al. Tau PET imaging in aging and early Alzheimer’s disease. *Ann Neurol*. 2016;79(1):110-119. doi:10.1002/ana.24546

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5. Raghavan NS, Dumitrescu L, Mormino E, et al. Association Between Common Variants in RBFOX1, an RNA-Binding Protein, and Brain Amyloidosis in Early and Preclinical Alzheimer Disease. *JAMA Neurol*. 2020;77(10):1288-1298. doi:10.1001/jamaneurol.2020.1760