

Centiloid Level-2 Analysis of [¹⁸F]Florbetaben (FBB) and [¹⁸F]Florbetapir (FBP) PET Image Data using the ADNI Pipeline

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1. Data Analysis Summary

Centiloid (CL) Level-2 analysis as defined by Klunk et al. (2015) was performed on [¹⁸F]florbetaben (FBB) data (90-110 min) and [¹⁸F]florbetapir (FBP) data (50-60 min) for the purpose of creating direct SUVR to CL transformations for the ADNI FreeSurfer 5.3-based data processing pipeline (Landau and Jagust, 2015). Determination of these transformations required the use of test subject cohorts in which FBP or FBB images were available with complementary PiB PET image data.

The ADNI FreeSurfer 5.3 pipeline yields a global SUVR measure representing a non-weighted average of radiotracer retention in four FreeSurfer-defined regions (frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal cortices) normalized to whole cerebellum as previously described (Landau & Jagust, 2015). In order to convert FBB and FBP ADNI-pipeline SUVR values to CL units, linear regressions were performed to relate global FBB and FBP ADNI-pipeline SUVR outcomes to global PiB CL-pipeline SUVR outcomes in a calibration subject cohort. The equations from these linear regressions were used to scale FBB and FBP ADNI-pipeline SUVR values to the range of CL-pipeline PiB SUVR values. The rescaled PiB-equivalent FBB and FBP SUVR values were then converted to CL units using a previously determined transformation equation (see equation 2.2.3 in Klunk et al., 2015). A second linear regression was performed between the CL-scaled FBB and FBP values and the original unscaled FBB and FBP ADNI-pipeline SUVR values to yield a linear transformation useful for the direct conversion of FBB or FBP ADNI-pipeline SUVR values to CL units.

We determined the equations to directly convert FBB and FBP data to CL values using the ADNI pipeline to be as follows:

$$CL = (159.08 \times SUVR_{FBB}) - 151.65 \quad (\text{Eq. 1a})$$

$$CL = (196.9 \times SUVR_{FBP}) - 196.03 \quad (\text{Eq. 1b})$$

Where $SUVR_{FBB}$ and $SUVR_{FBP}$ refer to the ADNI-pipeline SUVR values using a whole cerebellum reference region.

2. Subject Cohorts

For the FBB conversion, 35 subjects (25 elderly, 10 young control) with FBB (90-110 min) and PiB (50-70 min) PET scans collected at Austin Hospital, Melbourne, Australia were used (Rowe et al., 2017). For the FBP conversion, 46 subjects (33 elderly, 13 young control) with FBP (50-60

min) and PiB (50-70 min) PET scans collected by Avid Radiopharmaceuticals (Navitsky et al., 2018) were used. All PET and MR image datasets used in these analyses were downloaded from the Global Alzheimer’s Association Interactive Network (GAAIN) website: <http://www.gaain.org>. Both sites that contributed data to GAAIN for this analysis previously applied the standard CL pipeline to derive linear conversion equations for expressing FBB and FBP outcomes in CL units. These equations have been previously published by the contributing sites for FBB (Rowe et al, 2017):

$$CL = 153.4 \times SUVR_{FBB} - 154.9$$

and also for FBP (Navitsky et al., 2018):

$$CL = 183 \times SUVR_{Avid} - 177$$

3. Methods

3.1 Validation and Verification Procedures

As described in section 2.2.2. of Klunk et al. (2015), the first step of a Level-2 analysis begins with a replication of the Level-1 analysis. As such, to validate our CL pipeline implementation, the standard Centiloid 34 YC-0 and 45 AD-100 PiB 50-70 min scans were downloaded from the

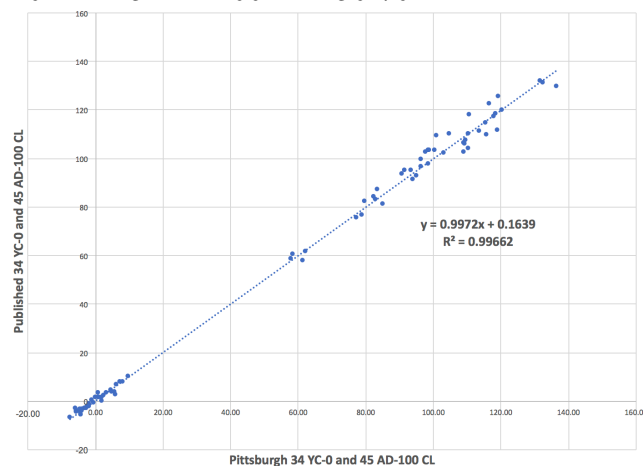


Figure 1 : Plot of CL outcomes derived from Pittsburgh’s Level-1 analysis of the standard 34 YC-0 and 45 AD-100 scans vs. published CL values. The equation and r^2 indicate that the CL pipeline was applied correctly.

GAAIN website to replicate published Level-1 CL analyses. Linear regression of our Level-1 Centiloid outcomes against published CL outcomes (Klunk, et al., 2015) yielded a fit equation with a slope and correlation coefficient near unity ($y = 0.9972x + 0.1639$, $r^2 > 0.996$; **Figure 1**).

Local implementation of the ADNI FreeSurfer 5.3 pipeline was also validated. To accomplish this, The University of California, Berkeley provided 100 FBP PET images and corresponding MR images previously analyzed using the ADNI pipeline implemented at UC Berkeley, along with summary cortical SUVR outcomes. The ADNI processing pipeline was replicated at the University of Pittsburgh and verified using the same UC Berkeley dataset. Regression of SUVR

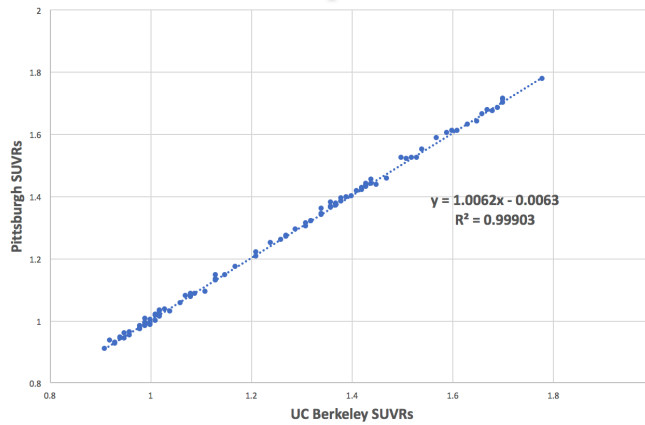


Figure 2 : Plot of Pittsburgh and UC Berkeley FBP SUVRs derived from the ADNI FreeSurfer 5.3 pipeline. The equation and r^2 indicate appropriate local implementation of the ADNI pipeline.

outcomes determined by the two sites yielded a result that approximated unity ($y = 1.0062x + 0.0063$, $r^2 > 0.999$; **Figure 2**), indicating a high degree of concordance.

3.2 Data Processing

3.2.1 ADNI Pipeline: In order to process the GAIN FBB and FBP scans using the ADNI pipeline, each subject’s MR image was converted from DICOM format to NIFTI using SPM12’s “DICOM Import” tool. MRs were then processed using FreeSurfer 5.3 to generate a native-space ADNI ROI atlas for each MR. FBB and FBP PET DICOM images were converted to NIFTI using PMOD v3.7. These PET images were co-registered to their corresponding MR images and resliced with SPM12’s “Coregister: Estimate and Reslice” tool using default parameters. PET images were then sampled for the mean tracer uptake in reference and cortical regions. Global FBB and FBP SUVR values were determined for each subject by calculating a non-weighted average uptake across the FreeSurfer-derived frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal lobes and dividing this average by the whole cerebellum uptake.

3.2.2 Centiloid Pipeline: For processing the PiB GAIN scans using the standard Centiloid processing pipeline, MR images were co-registered to SPM12’s MNI-space tissue prior map (TPM.nii) using “Coregister: Reslice” and segmented using “Segment” in SPM12. Subjects’ PiB PET images were converted from DICOM to NIFTI format using PMOD v3.7 and co-registered to their corresponding MR images using “Coregister: Estimate and Reslice” in SPM12. PiB PET images were subsequently normalized using SPM12’s “Normalise: Write” tool using subject-specific forward transformations generated by the MRI segmentation procedure. The standard Centiloid ROIs were downloaded from GAIN and used to sample the normalized PiB PET images. Global PiB SUVRs were calculated by dividing the standard Centiloid cortical target region uptake by the Centiloid whole cerebellum region uptake.

3.2.3 ADNI-Centiloid Conversion: Because the ADNI pipeline implements “non-standard” VOIs, the methods described in section 2.2.2.3.2 of Klunk et al. (2015) were implemented for subsequent processing. Using the corresponding PiB image data from the GAIN FBB and FBP subjects, SUVR outcomes were plotted against FBB and FBP SUVR outcomes and a linear regression was performed to determine slope ($^{Tracer}m_{NS}$) and y-intercept ($^{Tracer}b_{NS}$) values consistent with equation 2.2.3.2a:

$$Tracer\text{SUVR}_{IND} = Tracer\text{m}_{NS} \times (PiB\text{SUVR}_{IND**}) + Tracer\text{b}_{NS}$$

Conversion of FBB and FBP to CL units requires scaling $Tracer\text{SUVR}_{IND}$ values to “PiB calculated” SUVR values ($PiB\text{-Calc}\text{SUVR}_{IND}$) using Equation 2.2.3.2b from Klunk et al. (2015):

$$PiB\text{-Calc}\text{SUVR}_{IND} = (Tracer\text{SUVR}_{IND} - Tracer\text{b}_{NS}) / Tracer\text{m}_{NS}$$

As a final step, the $PiB\text{-Calc}\text{SUVR}_{IND}$ values are converted to CL units using Equation 2.2.3 from Klunk et al. (2015):

$$PiB\text{-Calc}\text{CL} = \frac{100(PiB\text{-Calc}\text{SUVR}_{IND} - PiB\text{SUVR}_{YC-0*})}{(PiB\text{SUVR}_{AD-100*} - PiB\text{SUVR}_{YC-0*})}$$

4. Results

4.1 Transformations

ADNI pipeline FBB and FBP SUVR outcomes were plotted and regressed against corresponding Centiloid pipeline PiB SUVRs using the GAAIN data to determine transformation equations in accordance with Equation 2.2.3.2a from Klunk et al., (2015). Linear regressions of FBB and FBP SUVR values against PiB SUVR values showed a high degree of correlation ($r^2 > 0.7$; **Figure 3**).

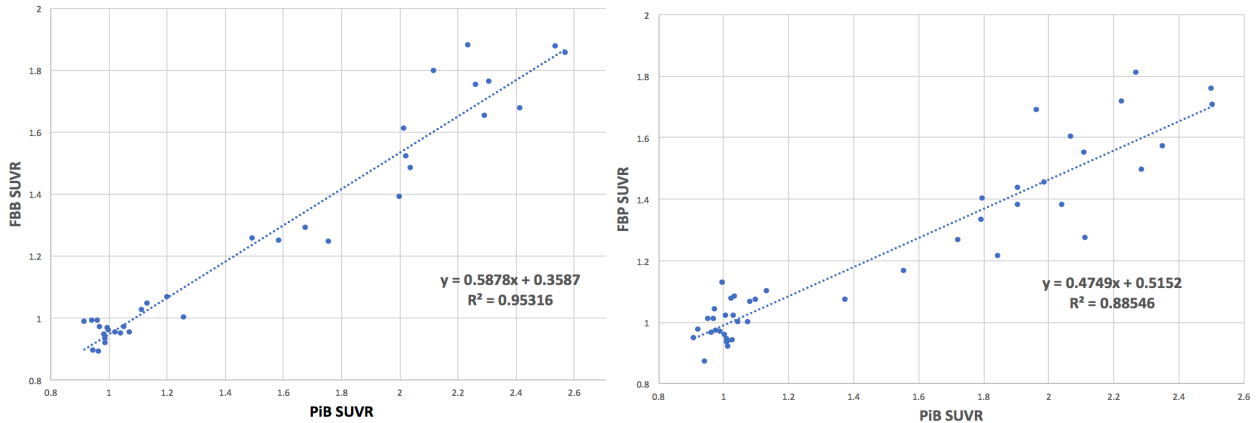


Figure 3 : Plot showing the linear regressions of SUVR values derived from ADNI FreeSurfer 5.3 pipeline and PiB SUVRs derived from CL pipeline for FBB (left) and FBP (right). A linear transformation from these regressions was used to create “Calculated” PiB SUVRs from FBB and FBP SUVRs.

The slope and intercept values derived from each of these regressions were used to determine “Calculated” PiB SUVRs using Equation 2.2.3.2b from Klunk et al. (2015) for FBB:

$$PiB\text{-Calc}\text{SUVR}_{IND} = (FBB\text{SUVR}_{IND} - 0.3587) / 0.5878$$

And also FBP:

$$^{PiB-Calc}SUVR_{IND} = ({}^{FBP}SUVR_{IND} - 0.5152) / 0.4749$$

Using Equation 2.2.3 from Klunk et al. (2015) and substituting our Level-1 YC-0 and AD-100 CL values:

$${}^{PiB-Calc}CL = \frac{100({}^{PiB-Calc}SUVR_{IND} - 1.012)}{(2.081 - 1.012)}$$

${}^{PiB-Calc}CL$ values determined from this equation were plotted against original ADNI FreeSurfer FBB and FBP SUVR outcomes (**Figure 4**) and linear regressions were performed. The resulting regressions allow for direct conversion of ${}^{18}F$ -A β tracer SUVRs to CL values using the whole cerebellum reference region.

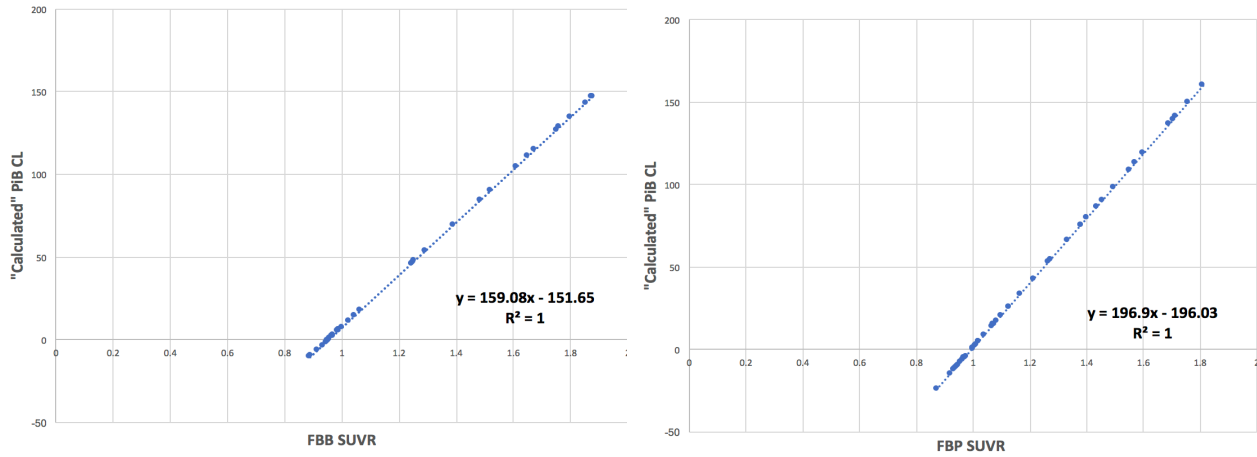


Figure 4: “Calculated” PiB CL values plotted against FBB and FBP ADNI FreeSurfer SUVRs. The equations allow for direct conversion from SUVRs to CL units for FBB (left) and FBP (right).

The resulting transformation for converting FBB ADNI FreeSurfer 5.3 to CL units is therefore:

$$CL = 159.08 \times SUVR_{FBB} - 151.65$$

and the equation to convert FBP SUVRs directly to CL units is:

$$CL = 196.9 \times SUVR_{FBP} - 196.03$$

4.2 Comparison of ADNI-pipeline CL values (FBB, FBP) to CL-pipeline CL values (PiB)

The FBB and PiB mean and variance CL values of the young adult controls were -1.32 ± 4.42 and -1.21 ± 3.57 , respectively. This yielded a variance ratio (SD_{FBB}/SD_{PiB}) of 1.24. The FBP and PiB mean and variance CL values of the young adult controls were -0.99 ± 9.39 and -1.11 ± 3.45 , respectively. This yielded a variance ratio (SD_{FBP}/SD_{PiB}) of 2.72. Results for both FBB and FBP

are outlined in greater detail in **Table 1**. The significant correlations between PiB SUVR values and both FBB ($r^2 = 0.95$) and FBP ($r^2 = 0.89$) SUVR values suggest that conversion to Centiloid units is appropriate for both tracers when using the ADNI FreeSurfer 5.3 pipeline.

[F-18]Florbetaben Cohort				[F-18]Florbetapir Cohort			
Summary Statistics				Summary Statistics			
[C-11]PiB Data				[C-11]PiB Data			
		SUVR	CL			SUVR	CL
Elderly	mean	1.72	66.0	Elderly	mean	1.62	57.2
	SD	0.57	52.9		SD	0.55	51.1
	CV (%)	33			CV (%)	34	
YC	mean	1.00	-1.2	YC	mean	1	-1.1
	SD	0.04	3.6		SD	0.04	3.5
	CV (%)	4			CV (%)	4	
[F-18]Florbetaben Data				[F-18]Florbetapir Data			
		SUVR	CL			SUVR	CL
Elderly	mean	1.37	66.1	Elderly	mean	1.29	57.3
	SD	0.34	54.7		SD	0.28	55.0
	CV (%)	25			CV (%)	22	
YC	mean	0.94	-1.3	YC	mean	0.99	-1.0
	SD	0.03	4.4		SD	0.05	9.4
	CV (%)	4			CV (%)	5	
Variance Ratio: 1.24				Variance Ratio: 2.72			

Table 1: SUVR and CL values for both FBB and FBP and their respective PiB scans, where FBB and FBP scans were processed using the ADNI FreeSurfer 5.3 pipeline and PiB scans were processed using the standard CL pipeline.

5.0 References

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