Standardizing Quantification of Amyloid PET using the Centiloid Scale

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INTRODUCTION

Amyloid PET has played an important role in the detection of brain amyloid ß (Aß) plaque density, an indicator of Alzheimer's disease (AD). Its importance has led to the development of numerous tools and tracers that enable qualitative and quantitative evaluation of tracer uptake. One such quantitative measure is a Standard Uptake Value ratio (SUVr), which has proven to be a useful measure in adjunct to visual reads [1]. However, there are several sources of variability in amyloid PET quantification, including: method of analysis, tracer type, target and reference regions, and choice of units [2]. This variability in quantification makes it challenging to identify a universal SUVr cutoff and compare results across sites.

The Centiloid scale created by Klunk et al. [2] aims to overcome these challenges by standardizing the quantitation for various amyloid PET tracers and analysis methods. The proposed Centiloid scale is a 0 to 100 scale, where the 0-anchor represents young, cognitively normal amyloid-negative patients, and the 100-anchor represents a typical patient with Alzheimer's disease. The proposed scale aims to be a standard quantitative approach which addresses the variability in quantification and presents the possibility for a standard definition of a positive amyloid PET scan.

MIMneuro® offers quantitative analysis of PET-based amyloid scans with three commercially available tracers: Amyvid™ (18F-Florbetapir), Vizamyl™ (18F-Flutemetamol), and Neuraceq™ (18F-Florbetaben). This white paper goes through the process of calibrating MIM's quantitative outputs to the Centiloid scale. Calibration was accomplished for all three tracers by using SUVr values from cortical target regions defined in the Centiloid Project [2] and Florbeatapir Clark atlas regions defined in Fleisher et al. [3]. MIMneuro's Centiloid workflow generates SUVr values from these regions and uses tracer-specific equations to convert those values into the standard Centiloid scale. Validation was performed by comparing Centiloid results for independent data sets to expert visual reads given a Centiloid cutoff.

GENERATING THE CENTILOID EQUATIONS

MIMneuro supports three amyloid PET tracers which have been previously calibrated to the Centiloid scale in the referenced publications [2, 4-6]. To generate Centiloid equations for MIMneuro, we followed the methods described in the following section. Klunk et al. [2] defines cortical target regions of interest (CTX regions) which are provided from GAAIN [7] to calculate SUVr. However, MIMneuro uses Florbetapir Clark atlas regions provided by Avid Radiopharmaceuticals (AVID regions). MIMneuro follows the amyloid processing method described in Navitsy et al. [4] to calculate the global cortical SUVr value as an average of six VOIs (medial orbital frontal, lateral temporal, parietal, anterior cingulate, posterior cingulate, and precuneus) in reference to the whole cerebellum. Global SUVr values from the CTX and AVID regions were compared to ensure that there was an adequate correlation between MIMneuro's Centiloid analysis and previously published methods.

Methods

Calibration to the Centiloid scale requires processing of young control (YC-0) and Alzhemier's disease (AD-100) patients for a desired tracer and the corresponding PIB PET data (PIB_{Tracer}). Amyvid [4], Vizamyl [5], and Neuraceq [6] scans each consist of a PIB data set and tracer data set containing 46, 74, and 35 subjects, respectively. All images, published SUVr reference data, and documentation used to replicate the standardized Centiloid process can be found on the GAAIN website (http://www.gaain.org/centiloid-project) [7].

The acceptance criteria for correlation is $R^2 > 0.7$ for linear regression of the MIMneuro tracer SUVr values ($^{Tracer}SUVr_{IND}$) plotted against the published PIB_{Tracer} SUVr values ($^{PIB}SUVr_{IND}$). The linear regression yields a slope ($^{Tracer}m_{std}$) and intercept ($^{Tracer}b_{std}$) resulting in the following equation:

$$^{Tracer}SUVr_{IND} = {}^{Tracer}m_{std} * {}^{PIB}SUVr_{IND} + {}^{Tracer}b_{std} \qquad \text{Eq. 1 [2]}$$

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Equation 1 can be rearranged to solve for $^{PIB}SUVr_{IND}$ allowing for the conversion of $^{Tracer}SUVr_{IND}$ values into calculated PIB SUVr values, $^{PIB\text{-}Calc}SUVr_{IND}$:

$$^{PIB\text{-}Calc}SUVr_{IND} = \frac{^{Tracer}SUVr_{IND} - {}^{Tracer}b_{std}}{^{Tracer}m_{std}} \quad \text{Eq. 1a [2]}$$

$^{PIB\text{-}Calc}SUVr_{IND}$ can then be inserted in the Centilod equation:

$$^{Tracer}CL_{STD} = \frac{^{PIB-Calc}SUVr_{IND} - {}^{PIB}SUVr_{YC-0}}{^{PIB}SUVr_{AD-100} - {}^{PIB}SUVr_{YC-0}} * 100 \quad \text{Eq. 2 [2]}$$

Using the mean SUVr values calculated with a cerebellar reference region for AD patients ($^{PIB}SUVr_{AD\text{-}100}$) and young controls ($^{PIB}SUVr_{YC\text{-}0}$) from Klunk et al. [2], we arrive at the final Centiloid equation, where $^{PIB\text{-}Calc}SUVr_{IND}$ is dependent on the tracer-specific SUVr:

$$^{Tracer}CL_{STD} = \frac{^{PIB-Calc}SUVr_{IND} - 1.009}{1.067} * 100 \quad \text{Eq. 3 [2]}$$

The calibration process was repeated for CTX and AVID regions to generate Equation 3 for each tracer: Amyvid, Vizamyl, and Neuraceq.

Results

For all three tracers, there was high agreement between the CTX regions and the AVID regions. The Centiloid equations generated for MIMneuro can be found in Table 1 along with the equations which convert MIMneuro tracer SUVr values to calculated PIB SUVr values. All R^2 values in Table 1 meet the repeatability requirements ($R^2 > 0.7$) outlined in Klunk et al. [2].

Figure 1 shows the performance of the MIMneuro Centiloid analysis by plotting MIM® Centiloid values against the published Centiloid values for each tracer [4-6]. The correlation plots showed strong agreement between MIMneuro and published Centiloid values, and the Bland-Altman plots showed no trending errors across all tracers. The intermediary calibration plots for each tracer are included in Figures 3-5 in the Appendix. These are correlation plots for (1) Published PIB SUVr vs. MIM PIB SUVr, (2) Published tracer SUVr vs. MIM tracer SUVr, (3) Published PIB SUVr vs. MIM tracer SUVr, and (4) Published tracer Centiloid vs. MIM tracer Centiloid (also shown in Figure 1). Plots (1), (2), and (3) contain the results for the CTX and AVID regions.

Tracer	PIB Calculated Value ($^{PIB\text{-}Calc}SUVr_{ind}$)	R^2	Centiloid Value ($^{Tracer}CL_{std}$)	R^2
Amyvid	$\frac{^{Tracer}SUVr_{IND} - 0.4786}{0.5221}$	0.9036	$179.51 * {}^{Tracer}SUVr_{IND} - 180.48$	0.9669
Vizamyl	$\frac{^{Tracer}SUVr_{IND} - 0.1639}{0.7784}$	0.9203	$120.402 * {}^{Tracer}SUVr_{IND} - 114.298$	0.9587
Neuraceq	$\frac{^{Tracer}SUVr_{IND} - 0.3751}{0.5817}$	0.9510	$161.115 * {}^{Tracer}SUVr_{IND} - 155.00$	0.9818

TABLE 1. MIMneuro Centiloid calibration equations. This table includes equations and R^2 values for (1) converting MIMneuro tracer SUVr values to calculated PIB SUVr values and (2) converting MIMneuro tracer SUVr values to Centiloid. These equations were created using AVID target regions.

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MIM Centiloid Equation Generation and Comparison to Standard Centiloid Values

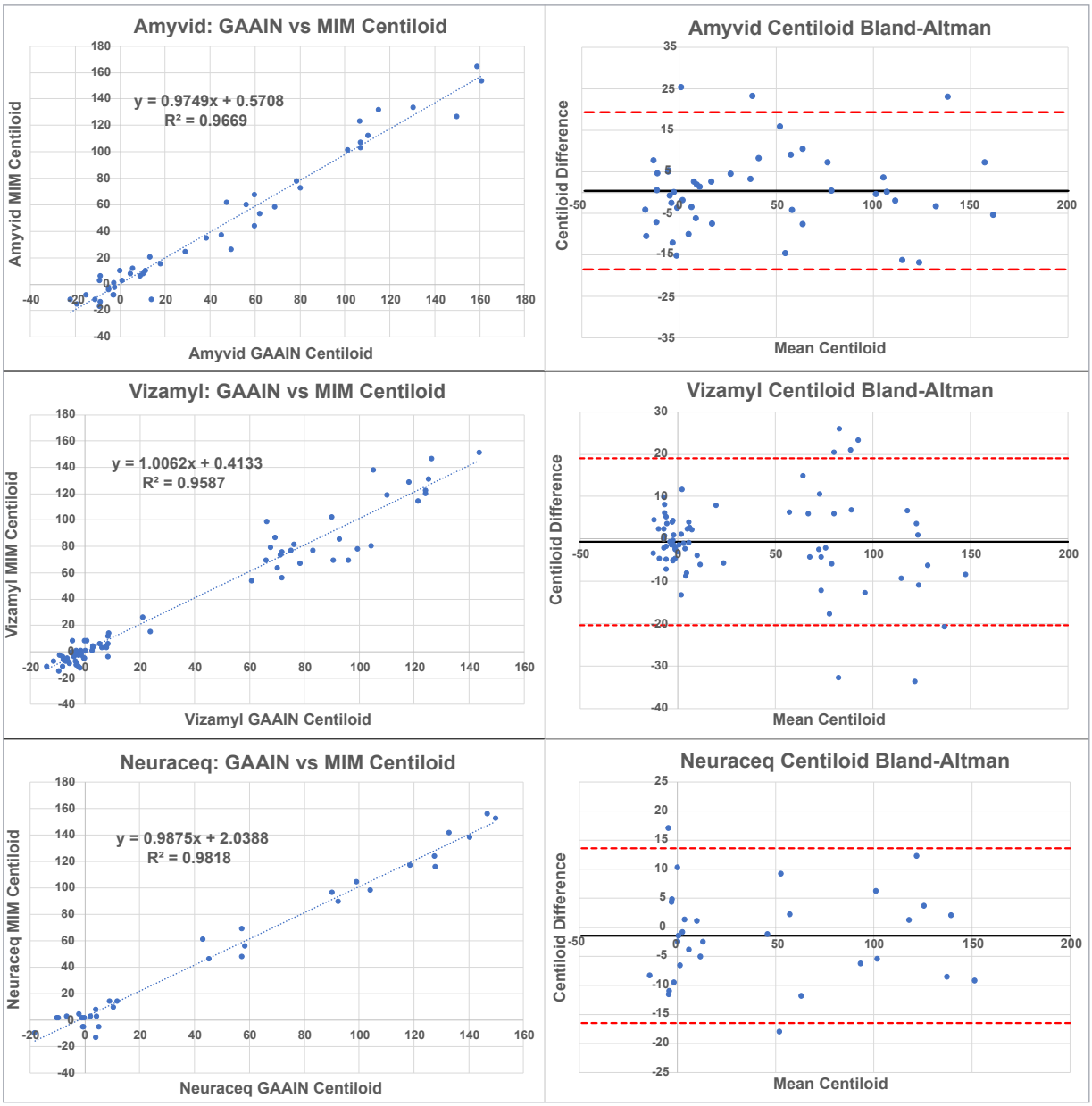

FIGURE 1. Performance evaluation of MIMneuro's Centiloid analysis. The above correlation and Bland-Altman plots compare MIMneuro Centiloid values and published Centiloid values for each tracer. Results are shown for AVID regions only.

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VALIDATION OF CENTILOID EQUATIONS WITH INDEPENDENT DATA SETS

Data Collection

PET scans selected for analysis included 100 Amyvid, 72 Vizamyl, and 109 Neuraceq exams. Amyvid exams were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) [8] in 2012. We randomly selected 100 scans from the ADNI2 study including exams from the following populations: elderly healthy controls, early mild cognitive impairment, late mild cognitive impairment, and mild AD. Neuraceq exams were obtained from a multi-center phase two clinical trial [9] that included probable AD patients and elderly healthy controls.The selected Amyvid and Neuraceq scans were classified as visually positive or negative by three readers with the majority classification taken. Vizamyl exams were obtained from the Australian Imaging Biomarkers and Lifestyle Flagship study of ageing (AIBL) (www.aibl.csiro.au) [10] which includes mild AD patients and elderly normal controls. 54 of the elderly healthy controls from AIBL, that are also part of the MIMneuro normal database, were used for the Vizamyl amyloid negative cohort. The exams in the normal database have a global SUVr < 1.12 and a visually negative reading by a single expert physician.

Methods

To validate the derived Centiloid equations, independent Amyvid, Vizamyl, and Neuraceq data sets were processed using MIMneuro's Centiloid analysis workflow. Centiloid values were calculated using AVID target regions. A Centiloid cutoff of 24 as defined by La Joie R et al. [12] was used to classify exams as amyloid negative or positive, and those classifications were compared to expert visual reads. Each exam was automatically registered to the corresponding tracer-specific template using an affine registration followed by a deformable registration [1]. Adjustments were made to the affine registration only when necessary. To examine inter- and intra-user variability of Centiloid results when adjustments to the registration were required, each misregistered exam was processed three times by one individual, and one time by three different individuals.

Results

Given a Centiloid cutoff of 24, the overall accuracy of amyloid negative and positive classification compared to visual reads for Amyvid, Vizamyl, and Neuraceq was 92%, 97%, and 94% respectively. Table 2 below shows the percentage of correctly classified total, negative, and positive subjects. The plots in Figure 2 show the Centiloid value and expert read for each exam in relation to the Centiloid cutoff.

Tracer	Accuracy	% of Correctly Classified Negative Subjects	% of Correctly Classified Positive Subjects
Amyvid	*92%*	*49/54 (91%)*	*43/46 (93%)*
Vizamyl	*97%*	*54/54 (100%)*	*16/18 (89%)*
Neuraceq	*94%*	*47/52 (90%)*	*55/57 (96%)*

TABLE 2. The accuracy, percent of correctly classified negative subjects, and percent of correctly classified positive subjects based on a Centiloid cutoff of 24.

* AIBL study methodology has been reported previously in Ellis et al. 2009 [11].

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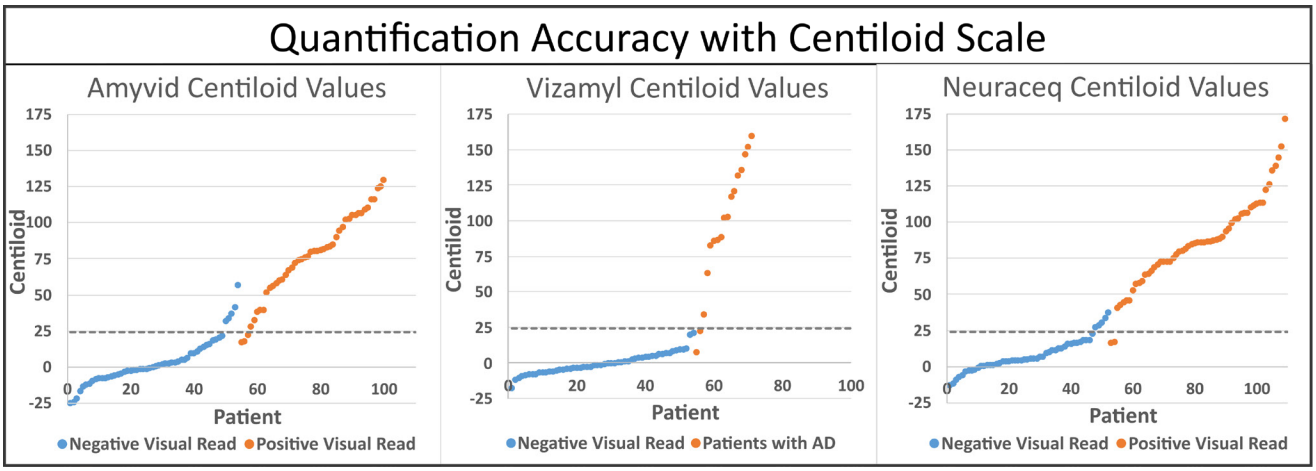

FIGURE 2. The Centiloid values for each exam plotted from lowest to highest with the 24 Centiloid cutoff denoted. Colors indicate whether the subject was defined as negative or positive by experts.

A small percentage of exams were misaligned after automatic registration and required manual adjustments to the affine registration: 2% of Amyvid, 3% of Vizamyl, and 3% of Neuraceq exams. Variability in Centiloid results was greater in exams which required major registration correction (major scaling and some rotation) compared to minor registration corrections (some scaling with no rotation). Intra-user variability was less than inter-user variability, and no Centiloid results crossed the Centiloid cutoff of 24 for any single exam in variability testing. Overall, small sample sizes make it difficult to draw conclusions from variability testing.

CONCLUSIONS

Centiloid neuro analysis with MIMneuro was successfully validated for each tracer using independent data sets with expert visual reads. The proposed universal Centiloid cutoff yielded high accuracy, >92%, across all tracers showing promise in standardized classification with the Centiloid scale.

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*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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APPENDIX

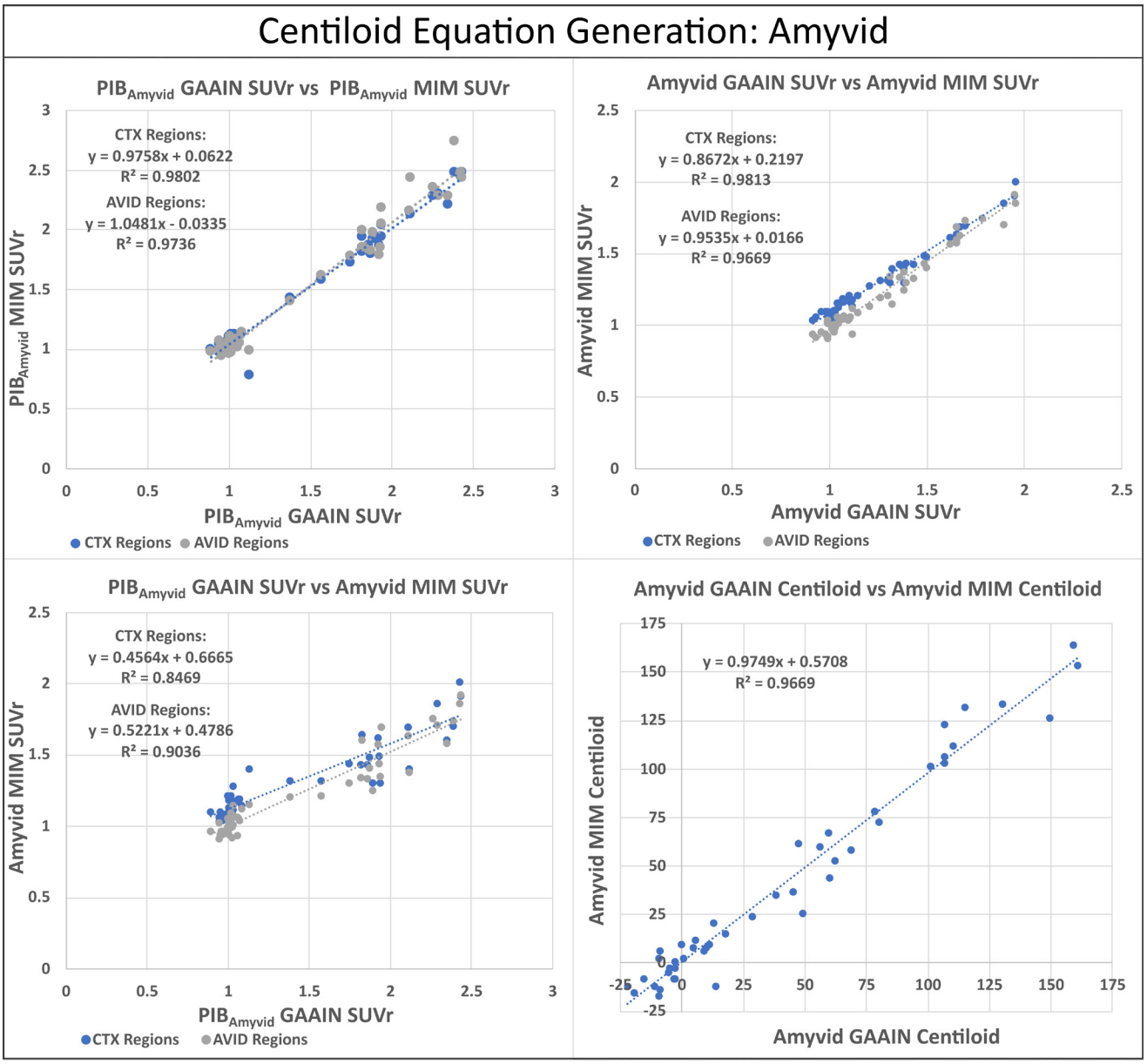

FIGURE 3. Amyvid Centiloid Calibration. SUVr results shown for CTX and AVID regions. Centiloid results are shown for AVID regions only.

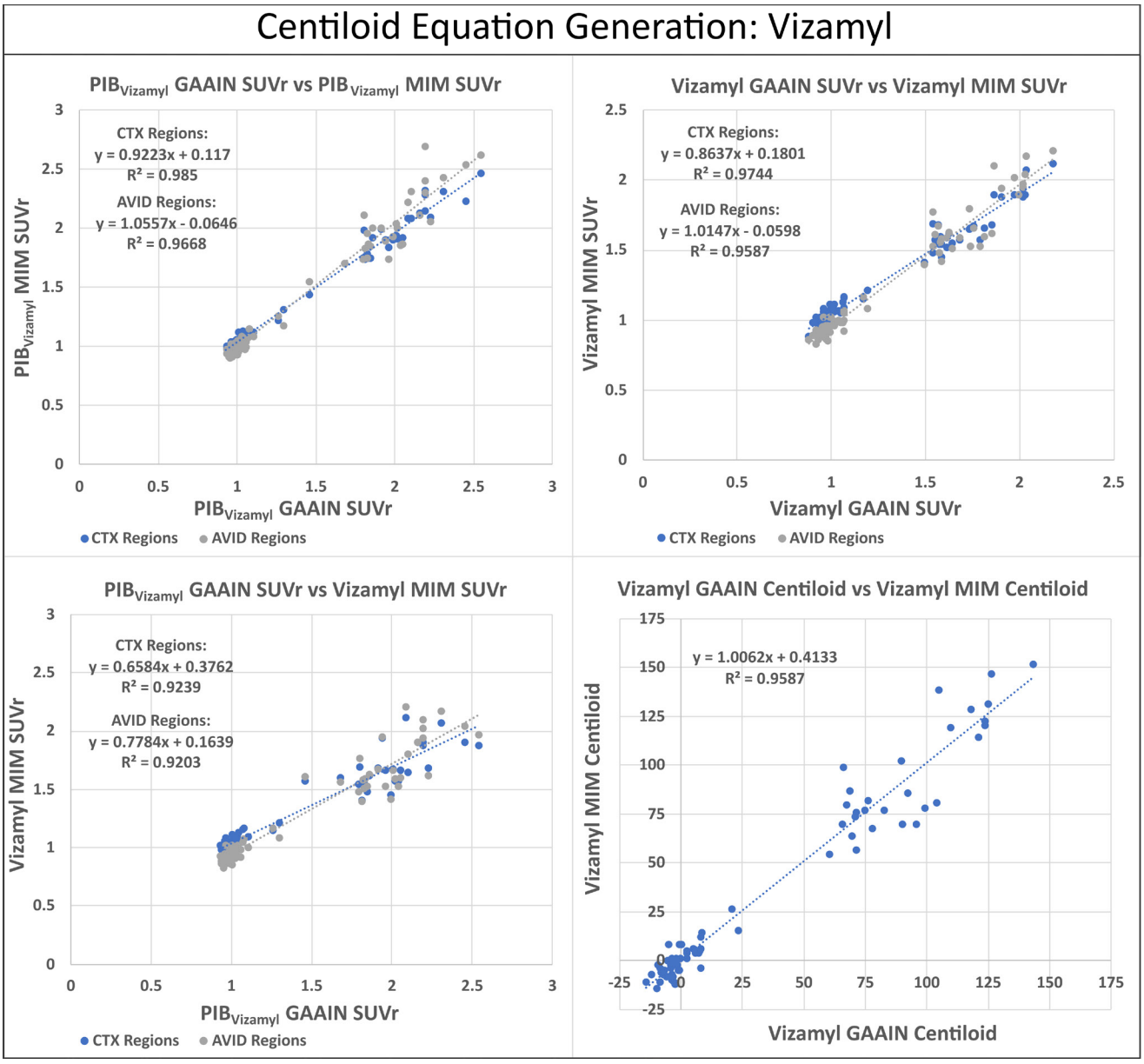

FIGURE 4. Vizamyl Centiloid Calibration. SUVr results shown for CTX and AVID regions. Centiloid results are shown for AVID regions only.

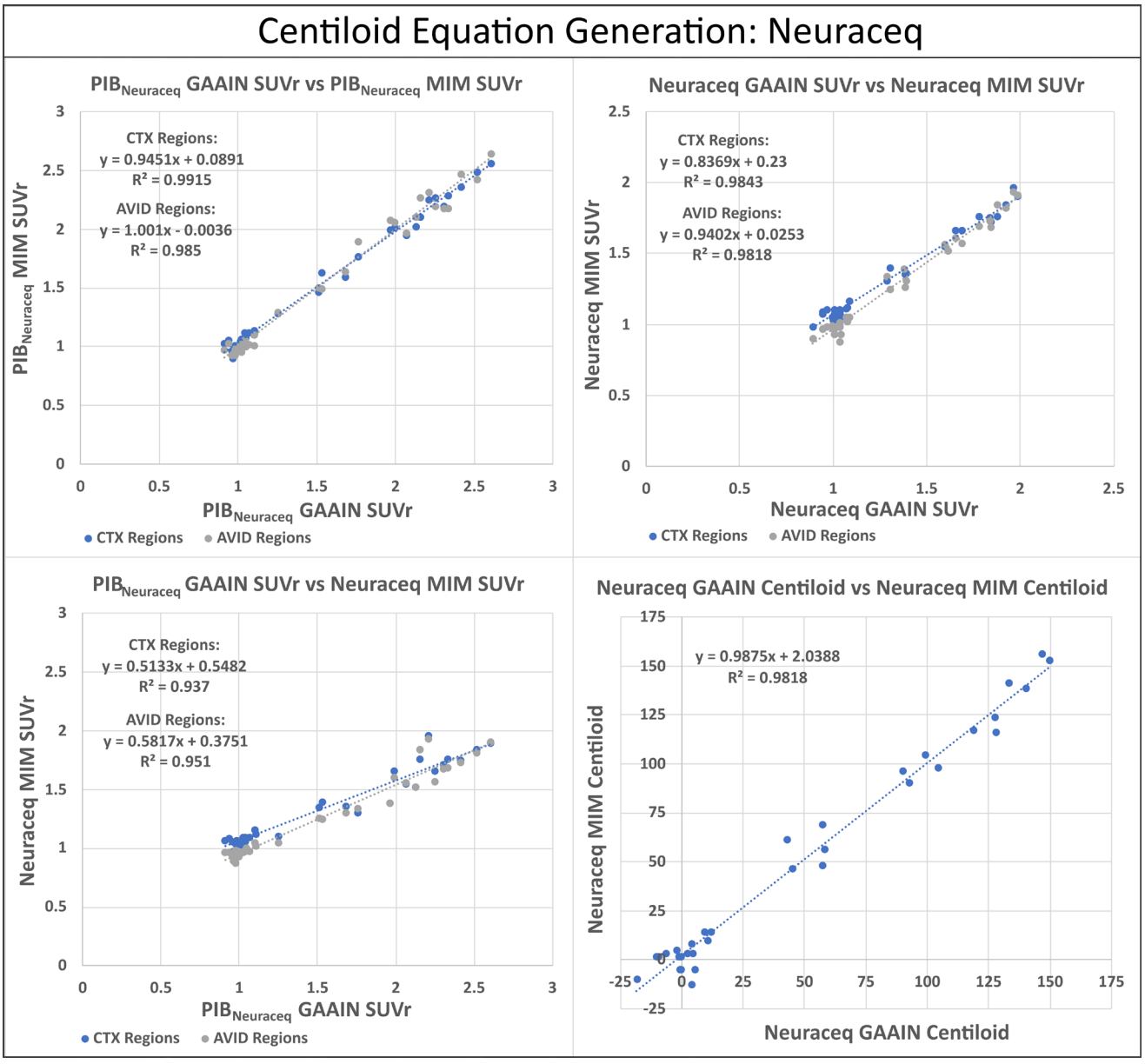

FIGURE 5. Neuraceq Centiloid Calibration. SUVr results shown for CTX and AVID regions. Centiloid results are shown for AVID regions only.