Amyloid PET centiloid: impact of calibration and processing steps

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Background

Centiloids (CL) were introduced to consistently quantify amyloid load across tracers and analysis pipelines. CL linearly scale activity ratios so that in two reference groups (young healthy subjects (HC), converted AD subjects) an average load of 0 and 100 CL, respectively, is measured. Such linear scalings are unique for each combination of tracer, analysis algorithm, and reference region [1].

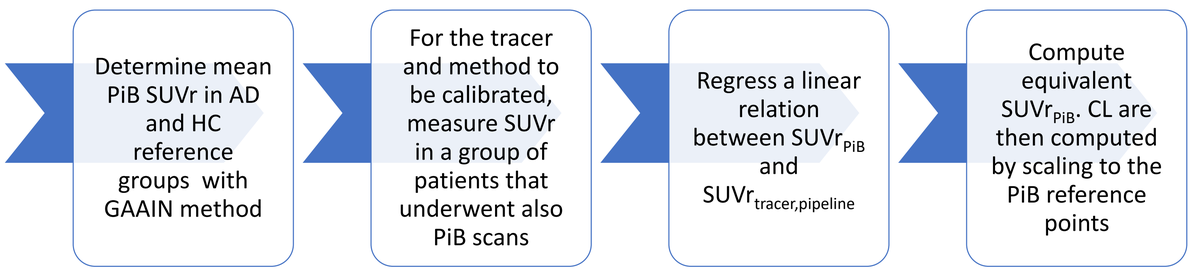

Figure 1: Centiloid calibration process

Objective

As part of centiloid calibration in the AMYPAD project, the impact of applying different processing steps on centiloid analysis results were compared. Here, we **summarize key options considered and present the impact on centiloid analysis in two AMYPAD cohorts**.

Methods

As a first step, CL equations were computed using the GAAIN Flutemetamol datasets.

Two linear regression strategies were compared:

1. calibrated pipeline Flutemetamol vs GAAIN PiB values, then apply GAAIN provided anchor points
2. both PiB SUVr and anchor points estimated with the calibrated pipeline.

Three approaches were compared to obtain a segmentation of the global cortical average (GCA) target region:

I. registering a GCA template [1] from MNI space using NiftyReg for registration
II. like I) but using SPM for registration
III. using a subject-specific segmentation from a multi-atlas segmentation approach (LEAP) to define the GCA.

Four reference regions obtained from LEAP were compared:

a) whole cerebellum
b) cerebellar grey matter
c) Pons
d) white matter

The effect of the different options was evaluated on datasets independent from the calibration dataset from two cohorts in non-demented participants of at least 50 years of age: 83 datasets from the EPAD cohort and 163 datasets from the PreclinAD Twin60++ cohort. Data in the PreclinAD study was acquired on a single PET/MR scanner and data in the EPAD cohort was acquired from a range of PET/CT scanners with a separate MRI scan. Approaches were considered to be comparable if the mean CL difference were below 2 CL (within the error), and r2>0.9.

Results

On both validation datasets the **different linear regression options (1. / 2.) impacted average CL values by less than 1.5 CL**. This is less than the statistical error on the anchor points used for CL definition.

Registering the GCA region **using NiftyReg (I.) or SPM (II.) resulted in no notable differences** (r2>0.94, TWINS: no difference, EPAD: -2.6±0.6, whole cerebellum reference). Comparing GCA vs subject specific segmentation (III.) also shows that CL scaling is robust (r2=0.96, TWINS: no bias, EPAD: -1.5±0.5, whole cerebellum reference)

Comparing alternative reference regions to the whole cerebellum has a significant impact:

	Mean difference in centiloid value when compared to **whole cerebellum** reference region	
Reference region	**EPAD**	**TWINS**
Gray cerebellum	-5.5	-5.3
Pons	+17.1	+22.1
White matter	+7.9	+10.3

Table 1: Impact of reference region

Conclusion

The CL approach appears to be **robust to different technical implementations, including definition of the target region and spatial registration algorithm**. **Different reference regions, however, are not comparable over multiple cohorts**. Su et al previously reported that comparing different reference regions in a cohort independent from the calibration dataset can result in bias [2]. Longitudinal studies (e.g. Chen et al) also showed that using different reference regions can impact data comparison [3]. Additional work is required to understand the impact of the technique used to segment reference regions.

References

[1] Klunk, William E., et al. "The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET." *Alzheimer's & dementia* 11.1 (2015): 1-15.

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[3] Chen, Kewei, et al. "Improved power for characterizing longitudinal amyloid-β PET changes and evaluating amyloid-modifying treatments with a cerebral white matter reference region." *Journal of Nuclear Medicine* 56.4 (2015): 560-566.