Stress testing the Centiloid Precision and variability of PET quantification of amyloid pathology

Mahnaz Shekari, David Vállez García, Lyduine E. Collij, Daniele Altomare, Fiona Heeman, Hugh Pemberton, Núria Roé Vellvé, Santiago Bullich, Christopher Buckley, Andrew Stephens, Gill Farrar, Giovanni Frisoni, William E. Klunk, Frederik Barkhof, Juan Domingo Gispert, ADNI and the AMYPAD consortium

Abstract:

Introduction: Assessing the potential sources of bias and variability of the Centiloid (CL) scale is fundamental for its appropriate clinical application.

Methods: We included 533 participants from AMYloid imaging to Prevent Alzheimer's Disease (AMYPAD DPMS) and Alzheimer's Disease Neuroimaging Initiative (ADNI) cohorts. Thirty-two CL pipelines were created using different combinations of reference region (RR), RR and target types, and quantification spaces. Generalized estimating equations stratified by amyloid positivity were used to assess the impact of the quantification pipeline, radiotracer, age, brain atrophy, and harmonization status on CL.

Results: RR selection and RR type impact CL the most, particularly in amyloid-negative individuals. The standard CL pipeline with the whole cerebellum as RR is robust against brain atrophy and differences in image resolution, with 95% confidence intervals below ± 3.95 CL for amyloid beta positivity cutoffs (CL < 24).

Discussion: The standard CL pipeline is recommended for most scenarios. Confidence intervals should be considered when operationalizing CL cutoffs in clinical and research settings.

Highlights:

- We developed a framework for evaluating Centiloid (CL) variability to different factors.
- Reference region selection and delineation had the highest impact on CL values.
- Whole cerebellum (WCB) and whole cerebellum plus brainstem (WCB+BSTM) as reference regions yielded consistent results across tracers.
- The standard CL pipeline is robust against atrophy and image resolution variation.
- Estimated within- and between-pipeline variability (95% confidence interval) in absolute CL units.