Evaluating robustness of the Centiloid scale against variations in amyloid PET image resolution

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BACKGROUND

- The Centiloid method enables direct quantitative comparison among different amyloid PET tracers
- Centiloid method standardize amyloid PET quantification by scaling the standard uptake value ratio (SUVr) for each amyloid tracer between 0 and 100
- Centiloid method does not account for differences in image reconstruction parameters and effective image resolution
- Differences in image resolution and selection of reference regions can affect the quantification of PET images.

AIM

- Evaluating the stability of Centiloid as a function of effective image resolution
- Assessing the impact of reference region selection on the stability of Centiloid quantification with/without smoothing

METHODS

Imaging Data: A total of 318 participants from the ADC and EMIF-AD Twin 60++ cohorts are included in this study (**Table1**). A T1-weighted MRI and a [^{18}F]flutemetamol PET scan were available for each subject. PET scans were reconstructed with the LOR-Ramla algorithm (Local reconstruction). Additionally, ADC and EMIF-AD Twin 60++ images were smoothed by an isotropic Gaussian filter of **8.4 and 8** mm respectively, to get an effective resolution of 8mm. ***PET Quantification:*** All images were quantified with a validated Centiloid pipeline**[1]** using the GAAIN cortical composite and five different reference regions (whole cerebellum, cerebellum gray, pons, whole cerebellum+brainstem, and eroded white-matter). **Data Analysis:** To assess the impact of reconstruction settings on CL values, we calculated the mean absolute difference between CL values of the original reconstructions vs. the smoothed images (**ΔCL**). Differences above 5CL were considered relevant. Finally, Bland-Altman plots were used to assess whether any proportional bias was present between these outcome measures.

Cohort	ADC (total: 135)	EMIF-AD Twin 60++ (total: 184)
Age	62.35±5.63	70.31±27.14
Sex	52% Women	57% Women
MMSE	23.46±3.27	28.97±1.14
Clinical Diagnosis	AD (58.5%),Impaired (7.4%), non-AD (32.6%),SCD (1.4%)	Cognitively Unimpaired
Local Reconstruction	LOR-Ramla, 2 Iterations, 4 subsets	LOR-Ramla, 2 Iterations, 4 subset2

*Table1. Demography of Amsterdam Dementia Cohort (ADC), and TWINS, **SCD: Subjective cognitive decline AD: Alzheimer dementia; MMSE: Mini-mental State Examination; LOR-Ramla: Line of response row-action maximum likelihood algorithm*

RESULTS

- **Figure1** displays visual inspection of image quality between local reconstruction settings (A, C) and post-smoothed images (B, D) for Twin 60++ and ADC, respectively
- **Figure2** shows the inverse linear relationship between CL of local reconstruction and ΔCL for all reference regions except for pons
- Centiloid was highly affected by image resolution when using the pons as reference region, introducing constant bias of 11.6±1.45 (ADC) and 6.27±0.58 (Twin 60++) for all ranges of amyloid burden **(Figure2(c))**
- Centiloid values were not significantly affected by differences in effective image resolution using whole cerebellum (3.48±2.35 and 1.71+0.56), whole cerebellum+brainstem (1.97±1.28 and 2.68±0.7), and subcortical with matter (3.88±2.4 and 3.28±1.03) as reference region for ADC and Twin 60++, respectively **(Table2)**
- Bland-Altman plots showed ΔCL higher than 5 using whole cerebellum as reference region for the PET images representing a higher level of amyloid accumulation **(Figure2(a))**
- Using cerebellum gray, ΔCL was below 5CL for subjects with low to the moderate amyloid burden, and differences above 5CL were observed for images with CL above 80 **(Figure2(d))**

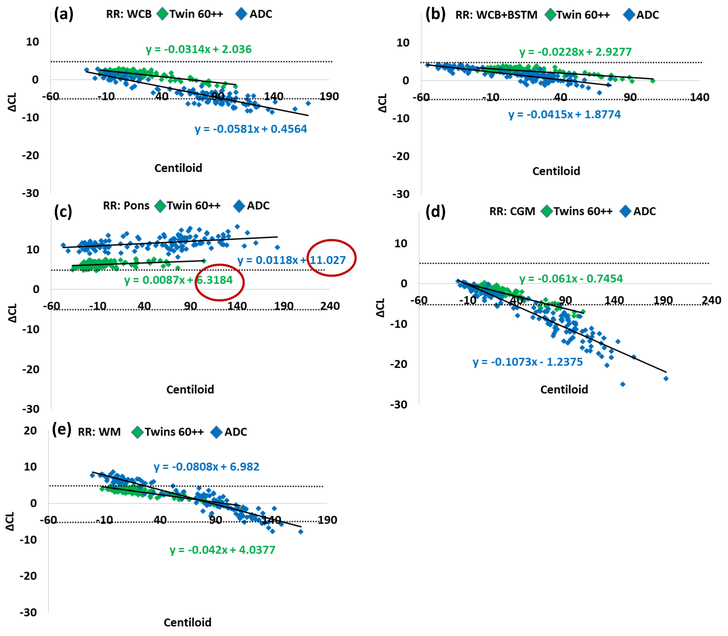

*Fig2. Bland-Altman plots comparing the differences in Centiloid values using GAAIN composite for 2 different image resolutions with respect to 5 different reference regions for ADC (blue) and TWINS (green). The black dot line corresponds to acceptable CL fluctuation (ΔCL=±5). The X-axis corresponds to the Centiloid values corresponding to the original reconstruction protocol (LOR-Ramla) and the y-axis corresponds to Centiloid differences after smoothing with local reconstruction. **WCB: Whole cerebellum; WCB+BSTM: Whole cerebellum+brainstem; CGM: Cerebellum gray matter; WM: White-matter*

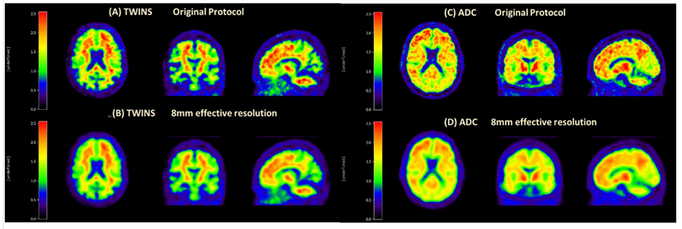

Figure1. Visual comparison of PET images reconstructed with in house protocol (A, C) and after applying a post-smoothing filter leading to 8mm effective resolution (B, D) for EMIF-AD TWIN 60++ and ADC

Reference Region	ADC ΔCL (Mean ± SD)	EMIF-AD Twin 60++ ΔCL (Mean ± SD)
Whole cerebellum	3.48±2.35	1.71+0.56
Whole cerebellum+ Brainstem	1.97±1.28	2.68±0.7
Cerebellum grey matter	**7.79±5.58**	1.91±1.61
Pons	**11.6±1.45**	**6.27±0.58**
White matter	3.88±2.4	3.28±1.03

Table2. Absolute Centiloid scaling changes with respect to reconstruction protocol and reference region for ADC and EMIF-AD TWIN 60++ cohorts using GAAIN cortical composites. Average Centiloid difference (ΔCL) above 5 highlighted with red

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CONCLUSIONS

- ✓ Reference region selection is essential for centiloid quantification, especially in multi-central studies
- ✓ The whole cerebellum and whole cerebellum+brainstem, recommended for centiloid quantification, can provide stable centiloid values irrespective of effective image resolution
- ✓ Higher effective resolution (smoother image) resulted in spilling out of activity from the pons to adjacent regions, increasing global SUVr and corresponding Centiloid value while using pons as reference regions
- ✓ In the images with a higher level of smoothness, spilling out activity from cerebellum white matter to cerebellum grey matter resulted in a decrease in global SUVr and Centiloid value while using cerebellum grey matter as reference region

References

[1] Klunk, et al. *Alzheimer's & Dement.* (2015)

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