Comparing parametric methods for longitudinal measurement of β-amyloid pathology with PET in elderly individuals

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Background

Amyloid-β (Aβ) PET is commonly used for studying the earliest phases of Alzheimer's disease (AD) in cognitively unimpaired (CU) individuals.

In this group, the expected changes in Aβ pathology are small, which emphasizes the importance of selecting the most accurate method for measuring these changes.

Methods

Dataset

- AMYPAD PNHS dataset (release June 2023, 10.5281/zenodo.8017084)
- Participants underwent at least 2 [^{18}F]flutemetamol (FMM) or [^{18}F]florbetaben (FBB) dual-time window PET acquisitions and had a T1 weighted MRI scan

Pre-processing and modelling

1. Early and late parts of each dual-time window PET scan were registered to the MRI and combined.
2. Between-frame motion was corrected for (if applicable)
3. SUVRs were calculated, and parametric modelling was performed using SRTM2, RPM, RLogan, MRTM0, and MRTM[1-5] using PPET software to generate parametric BP_{ND} or DVR images for a global cortical target region (GAAIN)[6], all with cerebellar cortex as reference tissue.

Statistical analyses

1. Linear Mixed Effect models (LME's) were used for establishing individual yearly rates of change in Aβ, which were normalized to baseline Aβ burden to obtain Aβ annual % change (APC)
2. APC estimates from various methods (i.e., SUVR, SRTM2, RPM, Rlogan, MRTM0 and MRTM) were correlated using Pearsons's correlation (*r*).
3. The optimal LME was selected per method (using AICc) to assess the effect of known risk-factors (age, sex, *APOE*e4-carriership, education (categorical), CDR)[7] on yearly rates of change in Aβ.
4. Baseline (BL) Centiloid (CL) grouping (neg, pos, gz) was added to the optimal LME (selected per tracer) to check for between-group differences in Aβ accumulation.

$p<0.05$ was considered significant.

Objective

To define the optimal method for analysis of longitudinal Aβ PET using [^{18}F]flutemetamol and [^{18}F]florbetaben in an elderly cohort of mostly cognitively unimpaired individuals.

Demographics	[^{18}F]flutemetamol *N*=200	[^{18}F]florbetaben *N*=40
Age (M±SD)	68.4 ± 9.8	67.5 ± 12.5
Females	55.0 %	47.5 %
Visual Aβ-PET positive	13.0 %	32.5 %
CDR=0 CDR=0.5 NA	97.5 % 2.0 % 0.5 %	77.5 % 17.5 % 5.0 %
*APOE*e4 carriers *APOE*e4 non-carriers NA	35.5 % 64.5 % 0.5 %	40.0 % 42.5 % 17.5 %
Centres	Edinburgh, BBRC, Vumc, Geneva	VUmc

Results

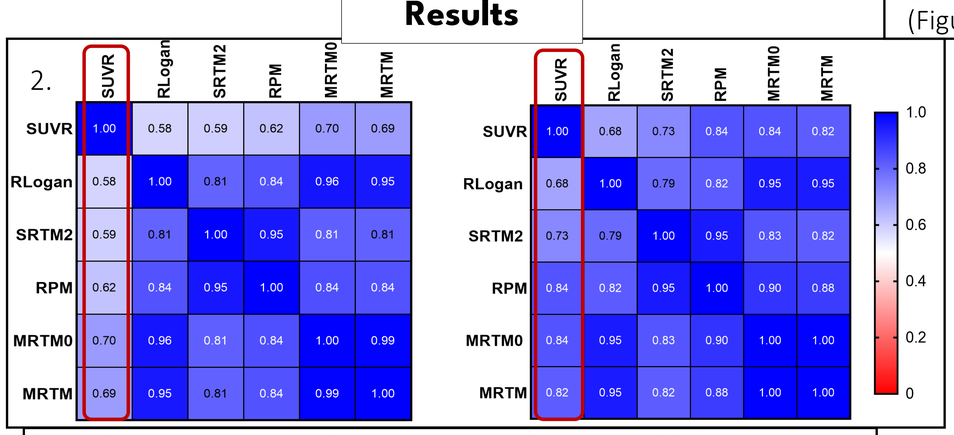

Figure 1. Pearsons' correlations of APC between methods, left FMM and right FBB.

3. For FMM, optimal LME's per method included interactions between **time** and/or **age**, ***APOE*e4-carriership**, **education**. For FBB, optimal LME's included interactions between **time** and/or **age, CDR.**

- FMM: Participants with post-secondary education had significantly lower yearly Aβ accumulation (estimates: ≥0.11), (SUVR, MRTM0, MRTM).
- *APOE*e4-carriers had significantly higher yearly Aβ accumulation of varying magnitude (estimates: 0.006-0.017) (SRTM2,SUVR).
- FMM & FBB, the effect of age on yearly Aβ accumulation, was significant but negligible in magnitude (max 0.002). SRTM2, RPM, MRTM0, MRTM, RLogan (FMM only).

Conclusion

Based upon the current dataset and analyses, SUVR and SRTM2 appear most suitable for detecting changes in Aβ accumulation as they showed an expected increase in Aβ accumulation in the CL positive and *APOE*e4-carrier group[8,9]. However, given the poor correlations between SUVR APC and all other methods, SUVR results should be interpreted with care. For FBB, there was no clear method preference, possibly due to the smaller sample size.

Results

For FMM, most methods included **time*age** and **time****APOE*e4**, while for FBB, most methods included only **time*age**, resulting in the following optimal LME's per tracer:

time + bl_age + *APOE*e4+ CDR + **time*age + time****APOE*e4 +** (1 | id)
time + bl_age+ *APOE*e4+ CDR + **time*age** + (1 | id)

4. For FMM, the CL pos group showed significantly higher yearly Aβ accumulation than the CL neg (estimates: 0.015, 0.024) and CL gz group (estimates: 0.012, 0.020) for SRTM2 and SUVR, respectively (Figure 1). No between-group differences were observed for FBB.

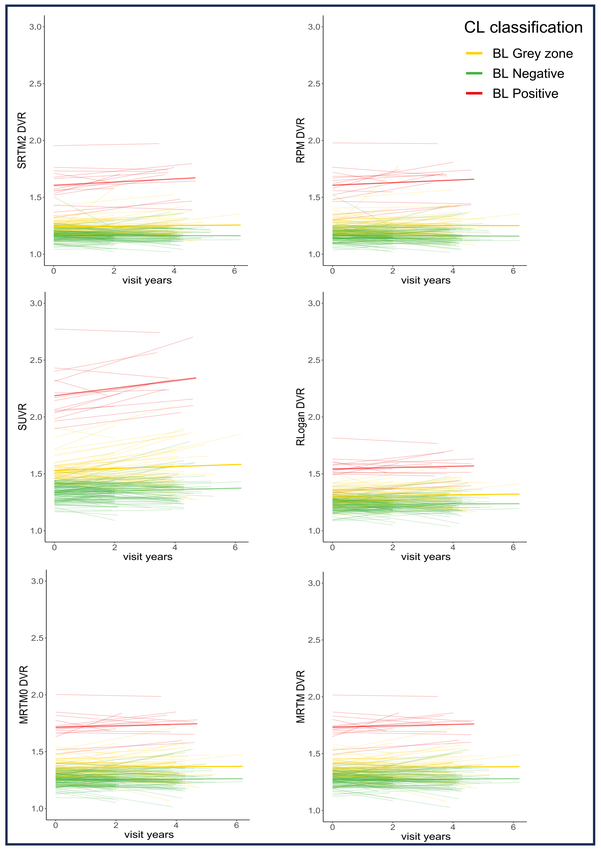

Figure 2. FMM: Aβ accumulation colour-coded by baseline CL group, across methods.

1.Lammertsma and Hume, 1996 Dec;4(3 Pt 1):153; 2.Gunn et al., 1997 Nov;6(4):279-87; 3.Logan et al., 1996 Sep;16(5):834-40; 4.Wu and Carson, 2002 Dec;22(12):1440-52; 5.Ichise et al., 2003 Sep;23(9):1096-112, 6. Klunk et al. 2015 Jan;11(1):1-15.e1-4; 7.Jansen, 2015:1924–1938; 8.Lopes Alves, 2021 Apr 19;13(1):82; 9. Mishra, 2018 Jun 1;141(6):1828-1839.

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