

# A comparison of techniques for quantifying amyloid burden on a combined PET/MR scanner

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## BACKGROUND

Amyloid-specific PET tracers provide quantitative measurements of amyloid load in vivo. These measurements may help identify asymptomatic individuals at an early stage of Alzheimer's disease. Quantitative measures of amyloid deposition are often dichotomised into positive and negative groups through cutpoints. When these are based on post-mortem pathology, they are highly specific, but may not be sensitive to the initial signs of amyloid deposition[1]. These methods are also highly dependent on numerous analytical choices[2], such as the region of interest (ROI), reference ROI, partial volume correction, and statistical criteria for choosing the cutpoint[3].

PET-MR scanners are now commercially available; while they provide simultaneous, co-aligned acquisition of these modalities and may also reduce patient burden and radioactive dose, these scanners present methodological challenges for important reconstruction steps like attenuation correction. We examined these aspects on quantifying amyloid burden using a PET-MR scanner using a large UK sample of individuals born in the same week in 1946.

## METHODS

**Subjects** The first 250 participants enrolled in Insight 46, a neuroimaging sub-study of 500 individuals from the MRC National Survey of Health and Development (NSHD)[4].

**Image acquisition and processing** All data were acquired on a Siemens Biograph PET-MR scanner

Volumetric T1-weighted data acquired at 1.1 mm isotropic resolution was parcellated into anatomical ROIs [5].

18F-florbetapir Amyloid PET images were reconstructed from list mode data acquired 50-60 minutes post-injection. Two methods of attenuation correction were used: an ultrashort echo time (UTE) MR sequence and a pseudo CT (pCT) method[6].

PET and MRI data were co-registered to provide anatomical ROIs in PET space. For multiple ROIs, standard uptake value ratios (SUVR) were computed using four reference regions: whole cerebellum (WCB), cerebellar grey matter (CGM), pons, and subcortical white matter (SCWM).

Data were processed both with no partial volume correction and with the Iterative Yang technique [7] on PET data resampled into T1 space, using an isotropic kernel of 6.8mm and ten iterations.

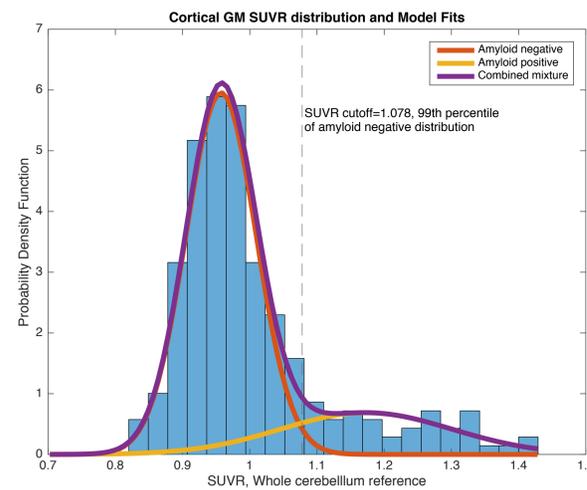
Cut point definition: Data were fitted with a Gaussian mixture model, using one to three clusters, choosing the best fit according to Bayes Information Criteria. The cutpoint was defined as the 99<sup>th</sup> percentile of the amyloid negative distribution (Figure 1).

## REFERENCES

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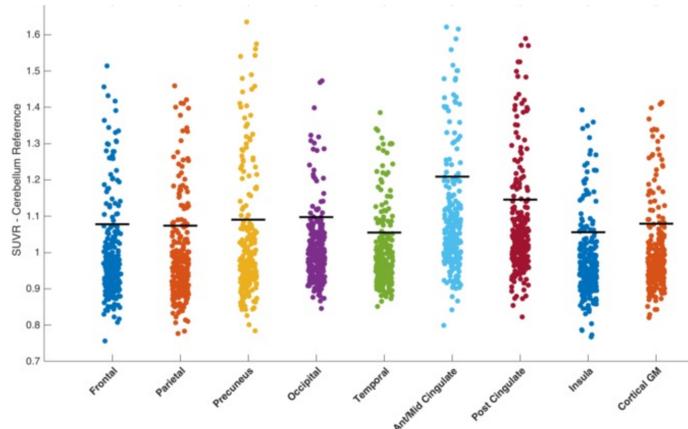
## RESULTS

240 participants with suitable T1 and amyloid PET data were included. For cortical ROIs, the mixture model typically produced two clusters, confirming the expected bimodal distribution of amyloid deposition. Across the different reference regions, amyloid positive individuals were consistently 15-18% without PVC correction and 19-23% with PVC correction (Table). The precuneus and posterior cingulate ROIs, regions often implicated early in AD, had slightly more amyloid-positive participants, while occipital lobe ROIs had a lower prevalence (Figure 2,3). Subcortical ROIs provided inconsistent evidence of bimodal distributions. Across the various pipelines, agreement with regard to amyloid positivity was high, with a Fleiss Kappa score over all 144 different SUVR measures being 0.714. The results from all the different pipelines have been combined and standardized against the amyloid negative distribution for comparison in Figure 3.



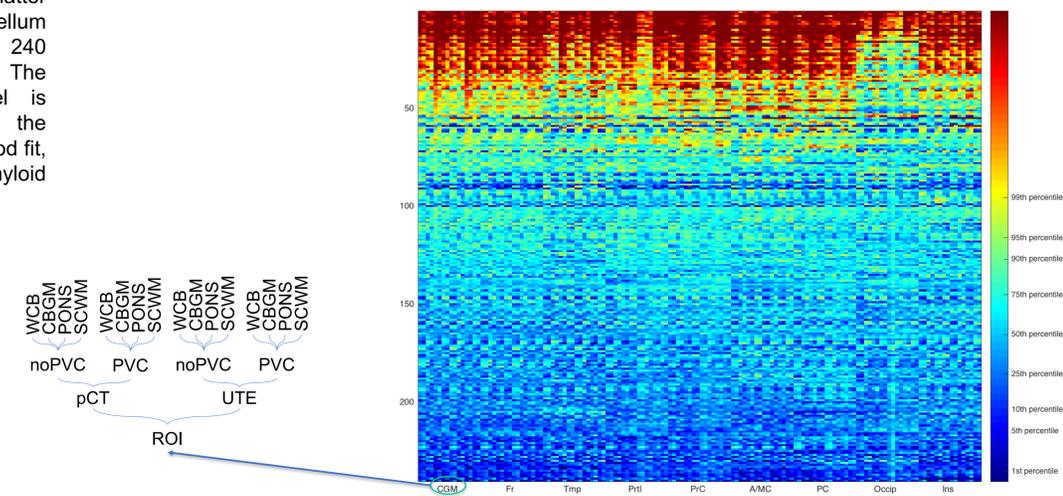
**Figure 1** Histogram of SUVR values (cortical grey matter ROI, whole cerebellum reference ROI) from the 240 included participants. The Gaussian mixture model is overlaid on top of the histogram, showing the good fit, particularly of the amyloid negative distribution.

**Figure 2** Regional variability of SUVR cutpoints, using the whole cerebellum as a reference, pseudoCT attenuation correction and no volume correction



**Table** The effects of reference region, partial volume correction, and attenuation correction on the SUVR (cortical GM ROI) cutpoints.

Reference ROI	Method	Amyloid Negative Mean (SD)	Amyloid Positive Mean (SD)	Cut point	% Amyloid Positive
Whole Cerebellum	pCT, no PVC	0.959 (0.053)	1.218 (0.100)	1.080	17.5%
	UTE, no PVC	0.996 (0.054)	1.255 (0.106)	1.120	18.5%
	pCT, with PVC	0.759 (0.059)	1.129 (0.183)	0.899	23.3%
	UTE, with PVC	0.784 (0.063)	1.153 (0.190)	0.917	24.5%
Cerebellar Grey Matter	pCT, no PVC	1.103 (0.077)	1.424 (0.113)	1.275	15.4%
	UTE, no PVC	1.156 (0.077)	1.485 (0.113)	1.326	14.7%
	pCT, with PVC	1.019 (0.109)	1.581 (0.267)	1.253	20.4%
	UTE, with PVC	1.053 (0.106)	1.574 (0.269)	1.260	24.1%
Pons	pCT, no PVC	0.575 (0.040)	0.754 (0.066)	0.664	15.8%
	UTE, no PVC	0.557 (0.037)	0.729 (0.058)	0.641	17.6%
	pCT, with PVC	0.462 (0.049)	0.729 (0.118)	0.574	18.8%
	UTE, with PVC	0.450 (0.045)	0.709 (0.131)	0.552	20.7%
Subcortical White Matter	pCT, no PVC	0.541 (0.036)	0.688 (0.053)	0.621	17.5%
	UTE, no PVC	0.535 (0.035)	0.677 (0.049)	0.611	16.8%
	pCT, with PVC	0.444 (0.055)	0.705 (0.105)	0.565	17.8%
	UTE, with PVC	0.438 (0.050)	0.694 (0.120)	0.548	19.4%



**Figure 3** Comparison across all SUVR measures. All measures are standardized to create z-scores which are based on the amyloid negative distribution from the Gaussian mixture model, with the 99<sup>th</sup> percentile (Z=2.33) corresponding to the cutpoint. Each row represents the SUVR measures for a single individual. Each column represents a different SUVR measure, grouped first by ROI, then attenuation correction method, partial volume correction and reference ROI. Key: CGM=cortical GM, Fr=Frontal Lobe, Temp=Temporal Lobe, Ptrl=Parietal Lobe, PrC=precuneus, A/MC=Anterior and Middle Cingulate, PC=Posterior Cingulate, Occip=Occipital, Ins=Insula, WCB=Whole Cerebellum, CGM=Cerebellar GM, SCWM=subcortical WM

## CONCLUSIONS

There is good agreement between SUVR measures on a PET-MR scanner across different choices of region, reference regions, and attenuation correction methods. Rates of amyloid positivity for this age group are consistent with recent meta-analyses[8]. Participants in this substudy will also soon begin to have longitudinal follow up with PET-MR, which will further help assess these pipelines.