Visual classification of Amyloid accumulation subtypes on PET imaging

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Comments & feedback are welcome

BACKGROUND

Amyloid PET imaging is currently assessed as a binary result (positive/negative) in routine clinical practice. Automated approaches have suggested distinct subtypes of amyloid deposition beyond this binary classification. However, the clinical feasibility and biological significance of these subtypes remains unclear.

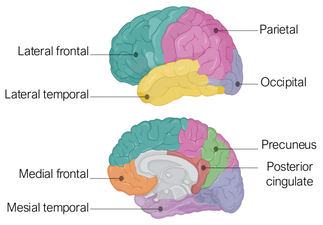
This study aims to evaluate the feasibility of visual classification of amyloid deposition subtypes on amyloid PET scans.

METHODS

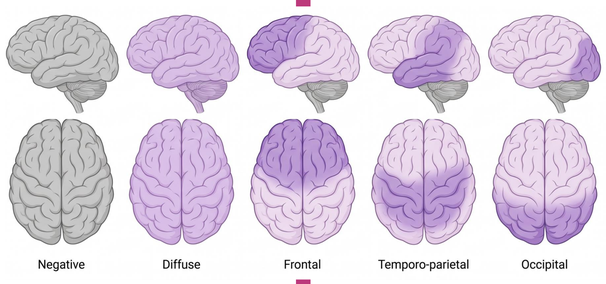
Amyloid PET scans ranging from a negative to moderate amyloid load (10 to 70 CL) were retrospectively included and visually assessed by two independent nuclear medicine physician :

- Global status (+/-)
- Uptake in 8 bilateral regions

0 No uptake
1 Moderate uptake ≃ white matter
2 High uptake (> white matter)



SUBTYPE CLASSIFICATION

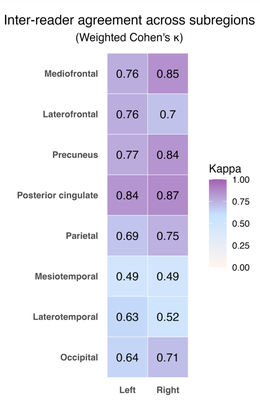


- **Inter-reader agreement** : Cohen's Kappa.
- **Clinical variables and biomarkers** : comparisons using the χ^2 test or Fischer's exact test for categorical variables, and the Kruskal-Wallis test for continuous variables, with post hoc when appropriate.
- **Cognitive decline** : Linear mixed-effects model (LMM).

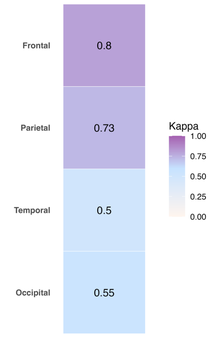
RESULTS

[^{18}F]Florbetapir (N = 45)

Inter-reader agreement across subregions (Weighted Cohen's κ)

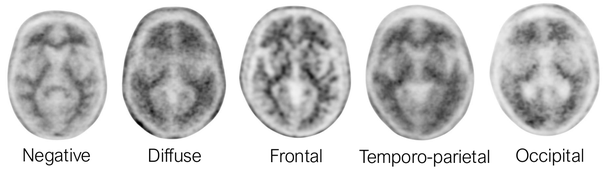


Inter-reader agreement across regions (Cohen's κ)



Inter-reader agreement on visual subtype

Cohen's K = 0.68



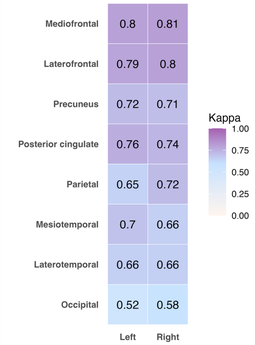
	Frontal N = 9	Temporo-parietal N = 10	Occipital N = 2	P Value
Age	69.7 (6.86)	75.0 (5.31)	71.0 (1.41)	0.174
Gender (Female / Male)	4 (44.4%) / 5 (55.6%)	5 (50%) / 5 (50%)	2 (100%) / 0 (0%)	0.572
Family history of dementia (no / yes)	4 (44.4%) / 5 (55.6%)	5 (50%) / 5 (50%)	2 (100%) / 0 (0%)	0.571
Years of education	11.1 (3.92)	13.5 (3.54)	11.5 (0.71)	0.403
MMSE	26.1 (2.57)	25.8 (3.19)	29.5 (0.71)	0.090
APOE4 carriership (ε4 carrier / ε4 non-carrier)	3 (60%) / 2 (40%)	0 (0%) / 3 (100%)	0 (0%) / 0 (0%)	0.196
Diagnosis				0.82
Cognitively unimpaired	0 (0%)	1 (10%)	0 (0%)	
Subjective cognitive decline	2 (22.2%)	1 (10%)	2 (100%)	
Mild cognitive impairment	5 (55.6%)	7 (70%)	0 (0%)	
Dementia	2 (22.2%)	1 (10%)	0 (0%)	

	Frontal N = 9	Temporo-parietal N = 10	Occipital N = 2	P Value
Centiloid	39.5 (18.9)	24.9 (10.6)	49.1 (17.1)	0.098
Global SUVR	1.05 (0.07)	1.02 (0.05)	1.15 (0.09)	0.110
Anterior cingulate SUVR	1.33 (0.12)	1.17 (0.07)	1.26 (0.12)	**0.019** [a]
Posterior cingulate SUVR	1.44 (0.07)	1.34 (0.19)	1.46 (0.17)	0.299
Lateral temporal SUVR	1.09 (0.08)	1.11 (0.06)	1.21 (0.03)	0.120
Precuneus SUVR	1.08 (0.09)	1.08 (0.09)	1.27 (0.20)	0.199
Parietal SUVR	0.99 (0.07)	0.98 (0.05)	1.15 (0.08)	0.074
Frontal SUVR	1.05 (0.08)	0.99 (0.06)	1.09 (0.09)	0.152
Occipital SUVR	1.06 (0.06)	1.11 (0.08)	1.36 (0.04)	**0.047** [b]
Striatum SUVR	1.16 (0.11)	1.12 (0.11)	1.04 (0.02)	0.438
Tau PET SUVR	1.20 (0.06)	1.25 (0.14)	-	0.286
Tau PET (Braak stage)				1.000
0	2 (50%)	3 (50%)	0 (0%)	
I-III	2 (50%)	2 (33.3%)	0 (0%)	
IV	0 (0%)	0 (0%)	0 (0%)	
V	0 (0%)	1 (16.7%)	0 (0%)	
VI	0 (0%)	0 (0%)	0 (0%)	
Boston criteria				1.000
No CAA	1 (25%)	2 (50%)	1 (100%)	
Possible CAA	1 (25%)	1 (25%)	0 (0%)	
Probable CAA	2 (50%)	1 (25%)	0 (0%)	

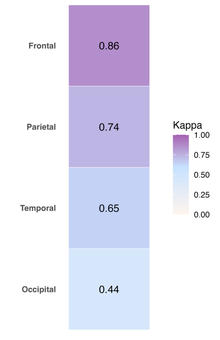
[a] Frontal ≠ Temporo-parietal ; [b] Frontal ≠ Occipital.

[^{18}F]Flutemetamol (N = 145)

Inter-reader agreement across subregions (Weighted Cohen's κ)

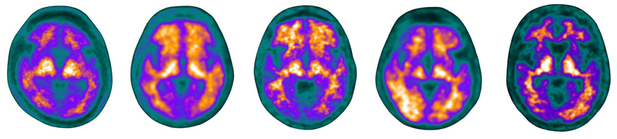


Inter-reader agreement across regions (Cohen's κ)



Inter-reader agreement on visual subtype

Cohen's K = 0.71

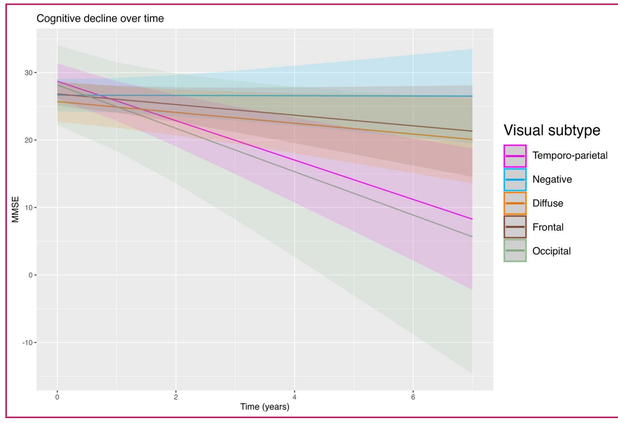


	Frontal N = 30	Temporo-parietal N = 19	Occipital N = 2	P Value
Age	75.0 (4.78)	76.3 (4.60)	80.0 (0.00)	**0.219**
Gender (Female / Male)	15 (50%) / 15 (50%)	7 (36.8%) / 12 (63.2%)	2 (100%) / 0 (0%)	0.189
Family history of dementia (no / yes)	16 (55.2%) / 13 (44.8%)	16 (84.2%) / 3 (15.8%)	1 (50%) / 1 (50%)	0.093
Years of education	14.3 (5.33)	11.7 (4.27)	12.0 (2.83)	0.161
MMSE	25.4 (4.21)	25.4 (3.15)	27.0 (0.00)	**0.799**
APOE4 carriership (ε4 carrier / ε4 non-carrier)	10 (52.6%) / 9 (47.4%)	3 (37.5%) / 5 (62.5%)	1 (100%) / 0 (0%)	0.678
Diagnosis				**0.510**
Cognitively unimpaired	0 (0%)	0 (0%)	0 (0%)	
Subjective cognitive decline	9 (30%)	3 (15.8%)	0 (0%)	
Mild cognitive impairment	16 (53.3%)	11 (57.9%)	2 (100%)	
Dementia	5 (16.7%)	5 (26.3%)	0 (0%)	

	Frontal N = 30	Temporo-parietal N = 19	Occipital N = 2	P Value
Centiloid	46.3 (13.5)	40.1 (14.7)	22.7 (3.92)	**0.042** [x]
Global SUVR	1.10 (0.09)	1.11 (0.08)	1.02 (0.06)	0.364
Anterior cingulate SUVR	1.43 (0.13)	1.23 (0.13)	1.10 (0.08)	**< 0.001** [a, b]
Posterior cingulate SUVR	1.50 (0.18)	1.53 (0.19)	1.58 (0.18)	0.804
Lateral temporal SUVR	1.10 (0.10)	1.10 (0.12)	1.05 (0.01)	0.736
Precuneus SUVR	1.17 (0.11)	1.31 (0.15)	1.32 (0.12)	**0.005** [a]
Parietal SUVR	1.03 (0.10)	1.13 (0.13)	1.06 (0.11)	**0.013** [a]
Frontal SUVR	1.13 (0.11)	1.08 (0.09)	0.93 (0.06)	**0.030** [x]
Occipital SUVR	1.01 (0.08)	1.12 (0.15)	1.14 (0.02)	**0.011** [a]
Striatum SUVR	1.24 (0.13)	1.12 (0.13)	1.03 (0.04)	**0.005** [a]
Tau PET SUVR	1.22 (0.23)	1.57 (0.47)	1.52 (-)	0.212
Tau PET (Braak stage)				0.228
0	8 (61.5%)	2 (33.3%)	0 (0%)	
I-III	3 (23.1%)	1 (16.7%)	0 (0%)	
IV	1 (7.7%)	0 (0%)	0 (0%)	
V	0 (0%)	2 (33.3%)	1 (100%)	
VI	1 (7.7%)	1 (16.7%)	0 (0%)	
CSF aβ42	653.1 (241.1)	667.0 (402.6)	867.0 (-)	0.610
CSF pTAU	72.4 (36.3)	83.0 (45.7)	64.0 (-)	0.815
CSF tTAU	511.7 (309.4)	606.8 (339.3)	420.0 (-)	0.752
Blood Glial fibrillary acidic protein (GFAP)	204.35 (60.20)	296.18 (124.22)	442.41 (-)	0.076
Boston criteria				0.377
No CAA	1 (11.1%)	0 (0%)	1 (50%)	
Possible CAA	4 (44.4%)	6 (54.5%)	1 (50%)	
Probable CAA	4 (44.4%)	5 (45.5%)	0 (0%)	

[a] Frontal ≠ Temporo-parietal ; [b] Frontal ≠ Occipital.
[x] Post-hoc pairwise comparisons adjusted using the Holm method did not reveal significant differences between individual groups.

Cognitive decline over time



LMM adjusted for age, sex, baseline tau burden, and baseline amyloid burden in the [^{18}F]Flutemetamol cohort.

Temporo-parietal subtype showed the steepest MMSE decline (−2.92 points/year). Compared with this group, decline was significantly slower in the negative (p = 0.001), diffuse (p = 0.015), and frontal (p = 0.017) subtypes, whereas the occipital subtype showed no significant difference.

Baseline tau burden was independently associated with lower MMSE scores (p < 0.001).

CONCLUSION

Visual subtype classification of amyloid PET appears **feasible and reproducible**, shows concordance with semi-quantitative measures, and may capture distinct spatial profiles beyond global amyloid burden. The association observed with differential cognitive decline further supports its potential clinical relevance.

Further studies in larger cohorts are needed to refine and standardise this approach, and to better define its potential added value in clinical practice.