Staging cortical amyloid deposition using PET imaging

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Background

- Amyloid beta (Aβ) accumulation is observed decades prior to cognitive impairment in Alzheimer's dementia
- 20-40% of cognitively normal (CN) subjects between the ages of 60 and 90 years have abnormal Aβ.
- These subjects are considered to have Alzheimer's pathological changes, which provides a unique opportunity for secondary prevention.
- Consequently, developing an amyloid staging model using regional standard uptake value ratio (SUVr) measures of amyloid burden has been of great focus in recent work.

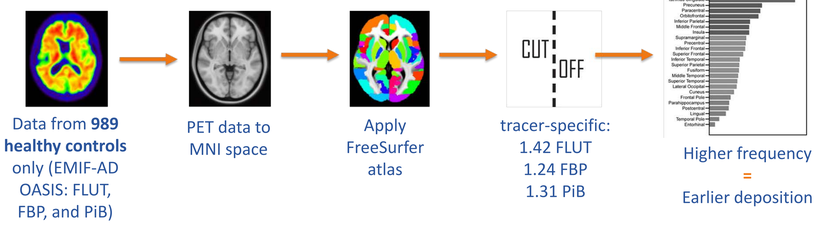
Aim

The purpose of this study was to develop and evaluate an *in vivo* model for staging cortical amyloid deposition using PET imaging data across cohorts and radiotracers.

Methods

3025 subjects (1520 CN, 274 SCD, 705 MCI, 422 AD dementia, 104 non-AD dementia) were included from **6 cohorts** (ADNI, OASIS-3, EMIF-AD, ABIDE, ALFA, and ADC).

Constructing the cortical amyloid staging model (Figure 1)



Data from **989 healthy controls** only (EMIF-AD OASIS: FLUT, FBP, and PiB)

PET data to MNI space

Apply FreeSurfer atlas

tracer-specific: 1.42 FLUT 1.24 FBP 1.31 PiB

Higher frequency = Earlier deposition

Statistical analysis

- **Cross-sectional:** Chi-squared tests and linear regression analyses to assess the distribution of stages vs. several clinical measures **(Figure 2).**
- **Longitudinal:** Kaplan-Meier survival analyses plied to investigate the effect of baseline amyloid stage and global SUVr positivity on reaching an MMSE score ≤ 27. A linear mixed model to investigate the effect of baseline stage on MMSE changes, corrected for age, sex, and time between follow-up visits **(Figure 3**).

Results

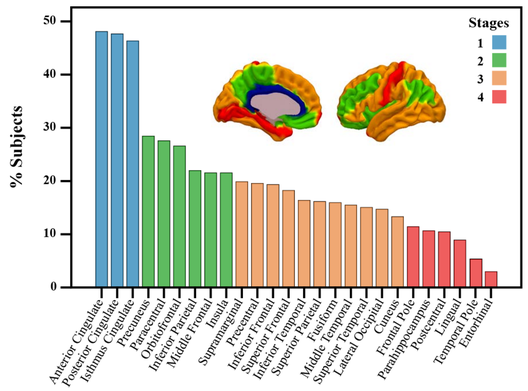


Figure 1. The 4-stage cortical amyloid staging model.
Frequency plot and anatomical image displaying the brain regions involved in each stage. Amyloid positivity was most frequently observed in the cingulate, followed by orbitofrontal, precuneal, and insular cortices, followed by then associative and temporal regions, and finally medial temporal regions.

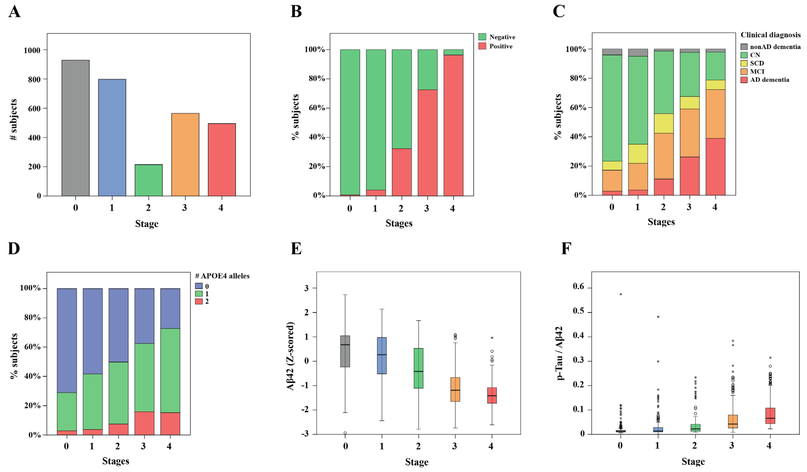


Figure 2. Results cross-sectional analyses.
A) 929 subjects were classified as normal, 799 subjects as stage 1, 215 subjects as stage 2, 566 subjects stage 3, and 495 subjects as stage 4.
B) Based on a binary cortical threshold, 1.8%, 5.6%, 33.0%, 72.4%, and 96.0% of subjects had globally abnormal SUVr across stage 0-4, respectively.
C) There was a significant association between cortical amyloid stage and syndromic diagnosis ($\chi2$=809.83, p<0.001).
D) Baseline amyloid stage was related to genetic risk (N=2790, $\chi2$=343.29, p<0.001).

Results (continued)

Figure 2 (continued).
E&F) Cortical amyloid stage was related to CSF Aβ42 levels (N=1494, β=-0.48, R=0.64, p<0.001) and to CSF p-Tau/Aβ42 ratio ratio (N=1384, β=0.02, R=0.47, p<0.001) (Aβ42 measures z-scored on a cohort basis).
Higher baseline stages were associated with lower baseline MMSE scores (N=2875, β=-0.79, R=0.39, p<0.001).

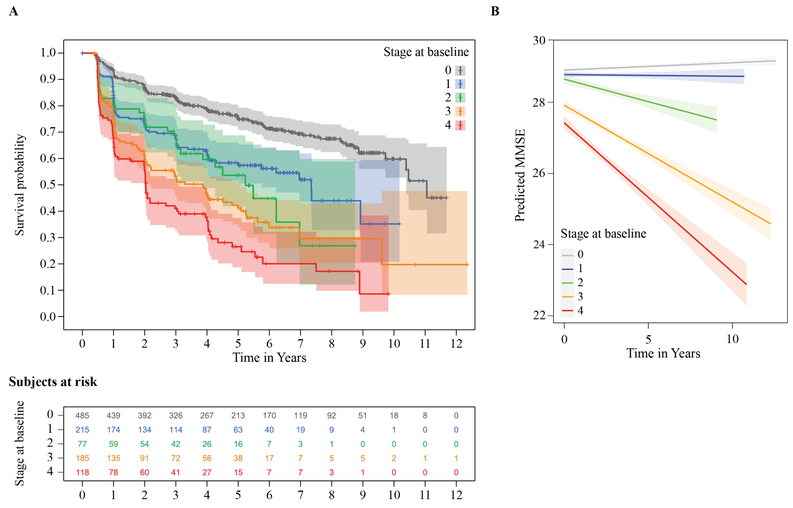


Figure 3. Results longitudinal analyses
A) Subjects at higher baseline stage progressed faster towards the event (MMSE ≤ 27), as the average time (in years) to reach the event was 9.5, 6.0, 4.5, 4.3, and 3.0 for subjects whose baseline stage was 0, 1, 2, 3, and 4 respectively (N=1267, β1=-0.67, β2=-0.85, β3=-1.15, β4=-1.51, p<0.01). This event was reached on average in 7.6 and 4.3 years for subjects with a globally normal SUVr value (N=841) and abnormal (N=239) global SUVr, respectively (βa=-0.96, p<0.001).
B) A linear mixed model (N=1346) showed that stage at baseline predicts change in MMSE (F=98.49, p<0.001).

Conclusion

An unified cortical amyloid staging model depicts amyloid pathology prior to whole-brain SUVr positivity. Amyloid PET stage based on this model relates to clinical measures and predicts future cognitive decline.

Academic partners

SMEs

Industrial partners

Patient organisation

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