Regional amyloid accumulation predicts memory decline in initially cognitively unimpaired individuals

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Background

Current secondary prevention trials are aimed at either removing established plaque deposition or halting its accumulation, and upcoming trials may focus on subjects with only moderate Aβ burden or even move towards primary prevention strategies. This shift towards early intervention warrants the need for detecting subtle changes of both Aβ burden as well as cognitive functioning. Therefore, understanding trajectories of Aβ accumulation and its relationship with cognitive decline in initially asymptomatic individuals may be relevant to improve clinical trial design.

Aim

Assess whether longitudinal and regional dynamic [^{11}C]PiB positron emission tomography (PET) improved the prediction of cognitive change in a initially cognitively unimpaired (CU) population

Material and Methods

Data: Data was obtained from the OASIS-3 dataset, which is a longitudinal neuroimaging, clinical, cognitive, and biomarker dataset for normal aging and Alzheimer's Disease (www.oasis-brains.org). This study included 133 participants who had 1) two or more [^{11}C]PiB scans at least 1 year apart, 2) at least two neuropsychological assessments, and 3) a Clinical Dementia Rating score of 0 at baseline.

Cognitive assessments: Global cognition (Minimal Mental State Examination [MMSE]) and different aspects of memory, including immediate and delayed episodic memory (Logical Memory IA and IIA, respectively), working memory (Digit Span Backward), and semantic memory (animal and vegetable Categorical Fluency) were investigated. Subjects underwent 2-13 assessments of global cognition over a period of 7.9±2.5 years, and 2-5 neuropsychological assessments over a period of 4.0±1.9 years.

PET imaging: Global amyloid burden (DVR) was determined based on a mean cortical composite consisting of FreeSurfer-defined frontal, parietal, temporal, and precuneal cortices. In addition, regional amyloid burden was assessed for 4 clusters of cortical regions, representing different stages in the amyloid accumulation process. All subjects underwent 2-5 PET scans over a period of 4.4±1.9 years.

Statistical analyses: Linear mixed models with subject-specific random intercept and slope were fitted. Predictors were global and regional DVR measures at baseline and yearly rate of change. Covariates were age at baseline, sex, years of education, and time between baseline [^{11}C]PiB and baseline neuropsychological assessments. Model preference was based on AIC and BIC.

Regional amyloid accumulation rates improve risk-profiling and supports selection of preclinical subjects at high risk of cognitive decline

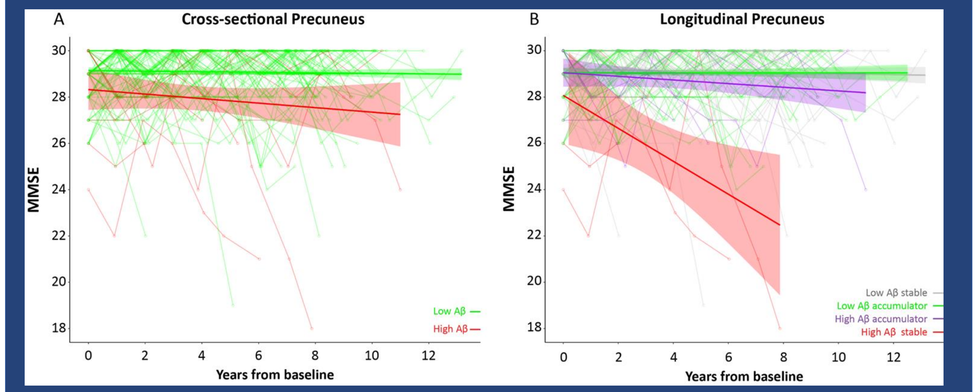

Figure 2. Relationship between Aβ pathology and decline in global cognition
Illustration of the association between continuous amyloid burden (baseline and longitudinal [^{11}C]PiB PET DVR) and global cognitive functioning (MMSE) over time. For illustrative purposes, these continuous measures were reduced to categorical groups, with baseline amyloid burden divided into 3 groups based on k-mean clustering (low [green], grey-zone [not shown], high [red]) and accumulator was defined as percentage change above 0.85% based on ([^{11}C]PiB test-retest data. **A)** Changes in MMSE score over time are provided for the subjects with a low Aβ burden (green) and high Aβ burden (red) at baseline. While the differences in cognitive trajectories between the two groups is apparent, **B)** the largest change in MMSE score is observed in those subjects with both high amyloid burden and low accumulation (red), illustrating the value of both cross-sectional and longitudinal amyloid measures to identify subjects a high risk for decline.

Longitudinal amyloid PET measurements are relevant for individuals on both sides of the spectrum, i.e. with early and established amyloid pathology

Results

Mean age was 72.2±5.8 years at the time of the first neuropsychological assessment, on average 15.7±2.5 years of education were completed, the majority of subjects were female (59.4%), and 32.3% of subjects were APOE-ε4 carriers.
Based on global amyloid burden, 30.1% of subjects were Aβ+ (i.e. DVR>1.12) at the time of the first PET-scan. Mean baseline global amyloid burden was 1.14 DVR (SD=0.21, range=0.92-1.87) and mean change in DVR (i.e. slope or ΔAβ) was 0.01 (SD=0.01, range=-0.01-0.05). A non-linear relationship was observed between baseline amyloid burden and slope, with the peak of accumulation around 1.31 global DVR (**Figure 1**).

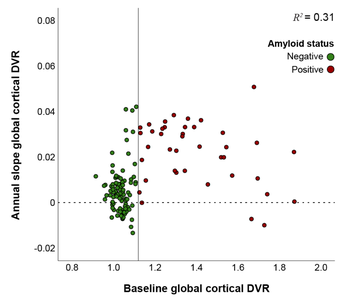

Figure 1. Quadratic relationship between baseline DVR and annualized rates of change.
Color-coded for negative (dark green) and positive (dark red) baseline amyloid-β (Aβ) burden. The solid line represents the positivity threshold at 1.12 DVR derived from GMM and taking the mean plus two standard deviations from the normal population.

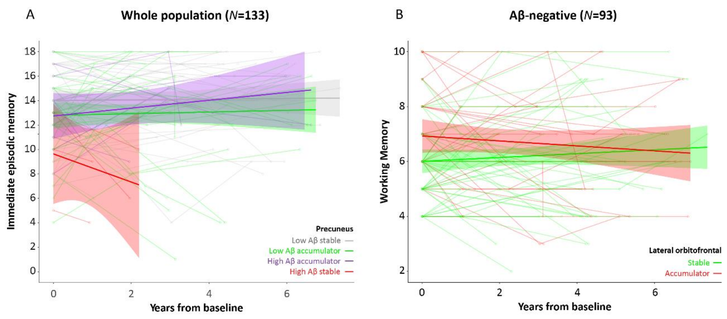

Figure 2. Relationship between Aβ pathology and decline in specific memory tasks
Illustration of the association between continuous amyloid burden (baseline and longitudinal [^{11}C]PiB PET DVR) and **A**) immediate episode memory (Logical Memory IA) performance for the whole population and **B**) working memory performance (DIGIB) in the at baseline Aβ- group. For illustrative purposes, the continuous measure slope was reduced to categorical groups, with accumulator defined as percentage change above 0.85% based on [^{11}C]PiB test-retest data.

Conclusion

Quantifying longitudinal and regional changes in Aβ can improve the prediction of cognitive functioning in initially CU individuals. .

Acknowledgement(s): This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115952. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. www.imi.europa.eu
Data were provided by OASIS3: Principal Investigators: D. Marcus, R, Buckner, J. Csernansky, J. Morris; P50 AG05681, P01 AG03991, P01 AG026276, R01 AG021910, P20 MH071616, U24 RR021382

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