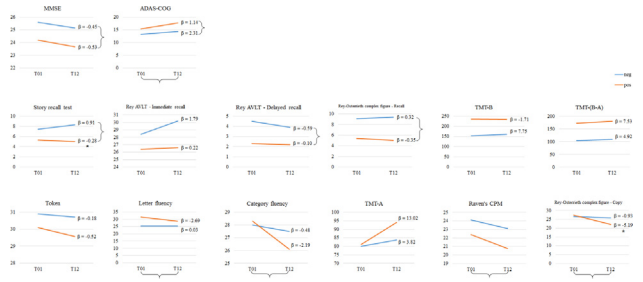

Figure. Cognitive decline in MCI patients over a 12-month follow-up. Horizontal parentheses indicate significant effect of the factor 'time', vertical parenthese indicate significant effect of the factor 'FBP-PET result' and '*' indicates significant interaction of these factors.

Patients with positive scan had overall worse performance on tests of global functioning (MMSE, p=0.005, η_p^2=0.11; ADAS-COG, p=0.007, η_p^2=0.10) and on tests involving memory (Story recall, p=0.002, η_p^2=0.13; Rey AVLT – Delayed recall, p=0.005, η_p^2=0.11; Rey-Osterrieth complex figure – Recall, p = 0.001, η_p^2=0.15). A significant worsening over 12 months was observed in ADAS-COG (p=0.003, η_p^2=0.12), Rey-Osterrieth complex figure – Copy (p<0.001, η_p^2=0.19), Raven's CPM (p=0.039, η_p^2=0.06), Letter (p=0.044, η_p^2=0.06) and Category fluency (p=0.021, η_p^2=0.08). Finally, positive patients showed a significantly greater cognitive decline over the time in the Story recall test (p=0.026, η_p^2=0.07) and the Rey-Osterrieth complex figure – Copy (p=0.018, η_p^2=0.08) (Figure). **Conclusions:** The cognitive performance of MCI patients positive to amyloid-PET is overall worse than in negative ones, but significantly greater deterioration over 12 months emerged in only a minority of tests. Longer time or more specific episodic memory tests may be useful for more sensitive monitoring of performance. Differences with previous studies may be due to different selection of tests or to our shorter follow-up. These data contribute information to define the proper time window for repeated testing for neuropsychology used as a biomarker for AD.

IC-P-008 MULTIMODAL IMAGING OF APOE2 EFFECTS IN THE AGED BRAIN: SPECIFICITY FOR REDUCED AMYLOID PATHOLOGY

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Background: The epsilon-2 allele of the APOE gene (APOE2) has been shown to reduce the risk for late-onset (sporadic) Alzheimer's disease (AD) dementia. Little is known about APOE2-related brain changes that may underlie this protective effect. **Methods:** We used multimodal neuroimaging data to comprehensively examine potential protective brain effects of the APOE2 genotype compared to the risk-neutral homozygous APOE3 genotype in a large sample of non-demented older individuals (cognitively normal subjects and those with mild cognitive impairment). Imaging data was obtained from a total of 572 APOE genotyped individuals enrolled in the ADNI study and included assessments of regional amyloid load using AV45-PET, glucose metabolism using FDG-PET, and gray matter volume using structural MRI. Group differences in imaging

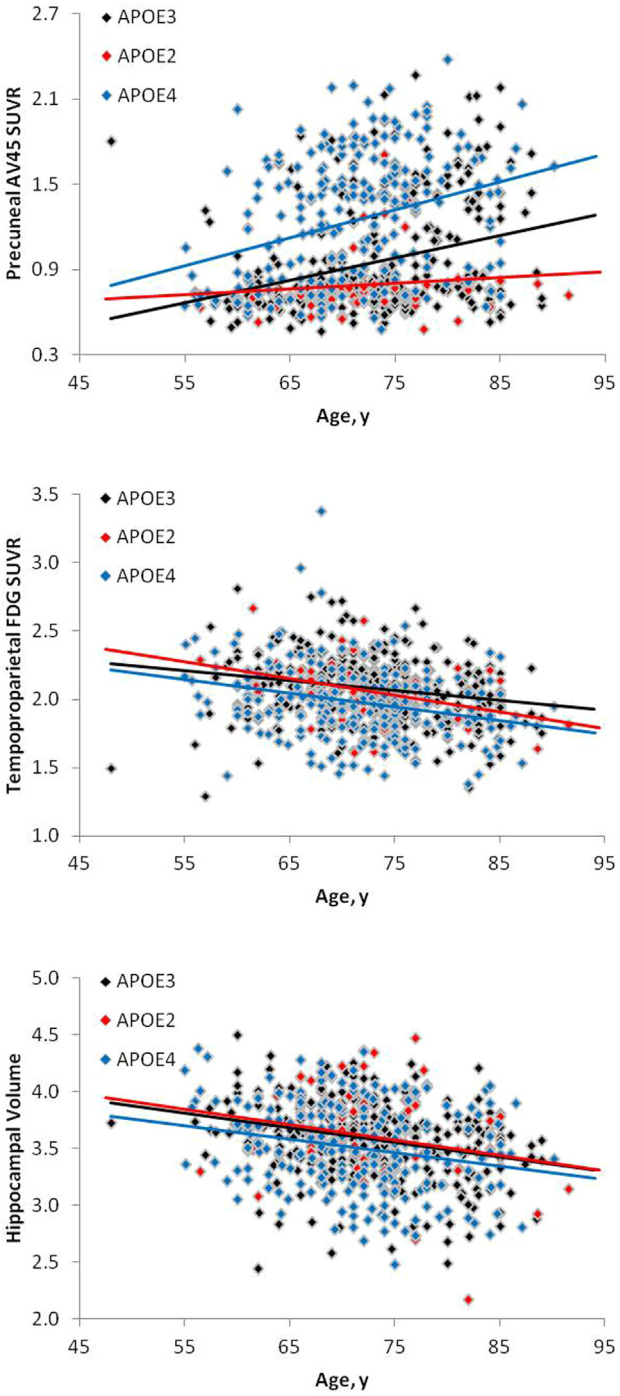

Figure 1. **Effects of age and APOE genotype on multimodal imaging markers**. Precuneal AV45-SUVR (top), temporoparietal FDG-SUVR (middle), and hippocampal volume (bottom) are plotted against age for APOE3 (black) and APOE2 (red) genotypic groups. APOE4 carriers (blue) are included for comparison. Separate linear regression lines are fitted for each group.

markers were assessed using region-of-interest (ROI) and voxel-based analyses, controlled for age, sex, education, and clinical diagnosis. Additional linear regression models examined genotype-specific effects of age on the distinct imaging markers. In secondary analyses, cerebrospinal fluid (CSF) markers of amyloid and tau

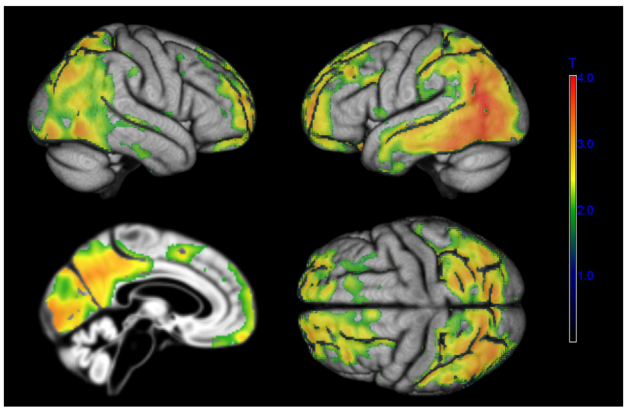

Figure 2. **Voxel-wise analysis of reduced amyloid load in non-demented older APOE2 carriers**
Significant effects of a voxel-wise two-sample t-test assessing reduced AV45-SUVR in APOE2 carriers compared to the APOE3 control group, controlled for age, gender, education, and clinical diagnosis. Statistical map was thresholded at p(FDR) < 0.05. Analogous analyses for FDG-SUVR or gray matter volume did not reveal any significant effects

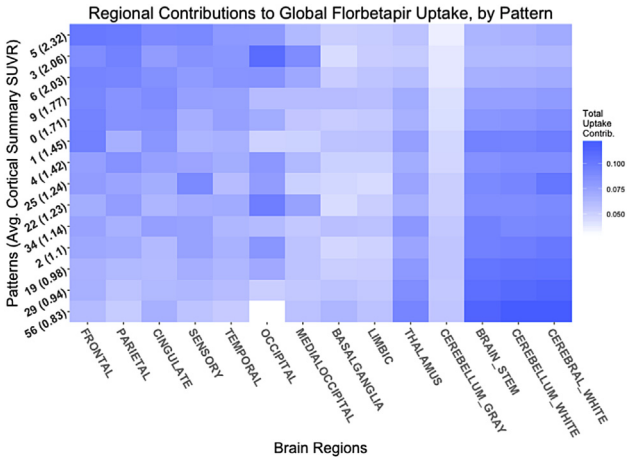

Figure 1. The columns map to brain regions, while each row represents an uptake pattern, sorted by the average cortical summary SUVR of its members. Each uptake pattern is broken down by uptake contribution per region, i.e. regional SUVR divided by summed SUVR across all brain regions, and thus the values in each row sum to 1. Uptake contributions range from 0.03 to 0.12, presented on a white (low) to blue (high) spectrum.

pathology were examined to assess the reproducibility of the main imaging findings using fluid biomarkers. **Results:** In region-of-interest based analyses, APOE2 carriers had less precuneal amyloid pathology ($p = 0.009$) and did not show the typical age-related increase in amyloid load ($\beta = 0.10$, $p = 0.49$; Figure 1). By contrast, parietal metabolism and hippocampal volume did not differ between APOE2 and APOE3 genotypes, and both groups showed comparable negative effects of age on these markers. The amyloid-specificity of APOE2-related brain changes was corroborated in spatially unbiased voxel-wise analyses (Figure 2), as well as by a significant APOE2 effect on CSF markers of amyloid ($p = 0.02$), but not tau, pathology. **Conclusions:** The reduced dementia risk associated with the APOE2 allele may be mediated by a relatively specific reduction of amyloid accumulation. Whether amyloid-lowering therapeutic interventions may yield similar decreases in dementia risk remains to be established in controlled clinical trials.

IC-P-009 EFFECTS OF BASELINE REGIONAL AMYLOID DEPOSITION PATTERNS ON SUBSEQUENT ACCUMULATION

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Background: Cortical summary measures of amyloid depend on the choice of regions to include in calculations and ignore potentially meaningful information in disproportionate amyloid deposition between specific regions. We define a set of "uptake patterns" that are independent of assumptions of reference region, regions of interest, or positivity threshold, and examine the utility of these patterns in predicting subsequent amyloid accumulation. **Methods:** Each uptake pattern was derived from the partial volume-corrected florbetapir means of 46 bilateral Freesurfer-defined brain regions. We fit an Infinite Gaussian Mixture Model (IGMM) to uptake patterns calculated from 1067 baseline florbetapir PET scans in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, belonging to 368 Cognitively Normal (CN), 304 Early Cognitive Impairment (EMCI), 250 Late Cognitive Impairment (LMCI), and 144 Alzheimer's Disease (AD) subjects. The IGMM clustered scans into 16 uptake patterns, each representing a distinct regional profile. We tested the efficacy of uptake patterns as predictors of longitudinal amyloid accumulation in normal and MCI subjects by fitting linear regression models to annualized amyloid change, as measured by cortical summary SUVR using a composite reference region (whole cerebellum, brainstem/pons, and subcortical WM). **Results:** We examined cortical summary SUVRs for the 14 baseline florbetapir patterns with at least 2 members. Applying a previously-validated positivity threshold revealed that 5 patterns were expressed predominantly by florbetapir- subjects, 3 patterns by a combination of florbetapir- and florbetapir+ subjects, and 6 by florbetapir+ subjects. Low-SUVR patterns exhibit dominant uptake in cerebral and cerebellar WM, while high-SUVR patterns are dominated by the frontal, parietal, and cingulate cortices (Fig 1). Linear regression analyses revealed that increased probability of membership in several uptake patterns was associated with subsequent amyloid

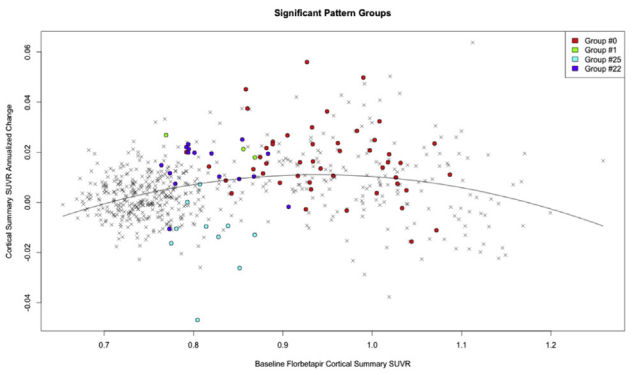

Figure 2. Each point represents the pre-existing relationship between baseline florbetapir cortical summary SUVR and subsequent annualized change in SUVR, for 368 CN and 554 MCI ADNI subjects. The black line represents predicted annual change by baseline SUVR. The colored points represent members of the pattern groups which exhibit significant effects on annualized change, despite correcting for non-pattern factors including baseline SUVR, age, sex, education, and Apoe4 status.