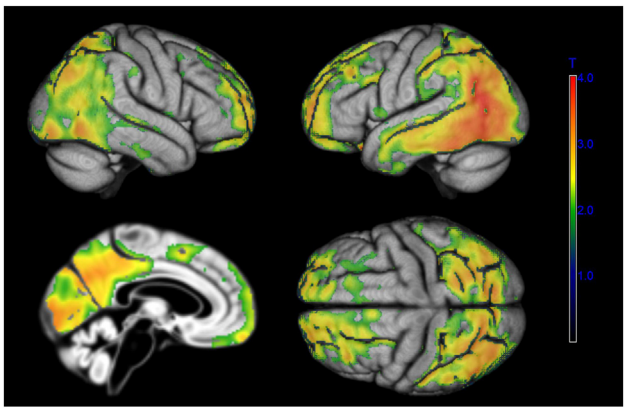

Figure 2. **Voxel-wise analysis of reduced amyloid load in non-demented older APOE2 carriers**
Significant effects of a voxel-wise two-sample t-test assessing reduced AV45-SUVR in APOE2 carriers compared to the APOE3 control group, controlled for age, gender, education, and clinical diagnosis. Statistical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

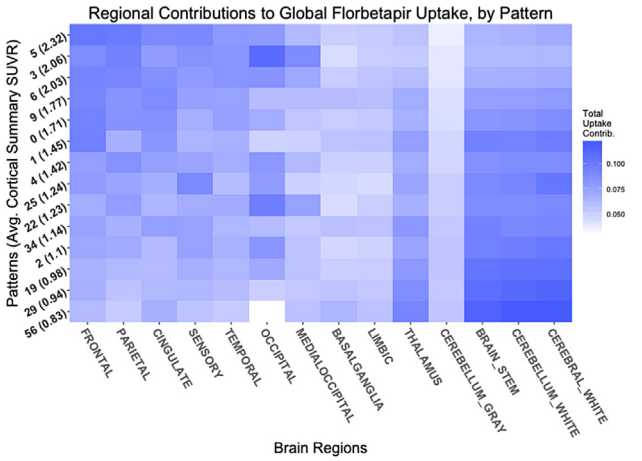

Figure 1. The columns map to brain regions, while each row represents an uptake pattern, sorted by the average cortical summary SUVR of its members. Each uptake pattern is broken down by uptake contribution per region, i.e. regional SUVR divided by summed SUVR across all brain regions, and thus the values 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

Andy Horng, William J. Jagust, Susan M. Landau, *University of California Berkeley, Berkeley, CA, USA. Contact e-mail: andyhorng@berkeley.edu*

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

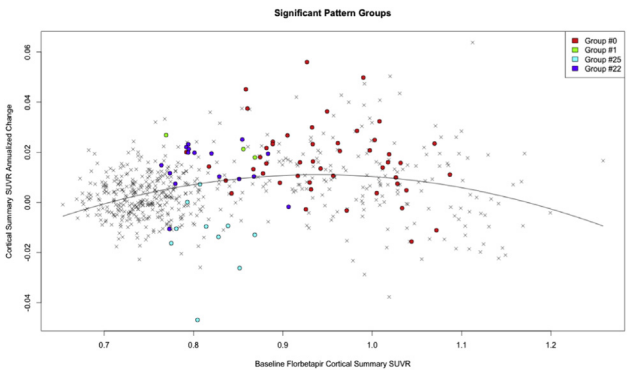

Figure 2. Each point represents the pre-existing relationship between baseline florbetapir cortical summary SUVR and subsequent annualized change in SUVR, for 368 CN and 554 MCI ADNI subjects. The black line represents predicted annual change by baseline SUVR. The colored points represent members of 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.

change, even after correcting for baseline cortical summary SUVR and other demographic variables (Fig 2). 3 uptake patterns predicted relative increases of 0.01 to 0.02 SUVR/year, while one uptake pattern predicted a relative decrease of 0.02 SUVR/year. **Conclusions:** These findings suggest that expression of specific uptake patterns provides predictive information about amyloid accumulation that is not available using global amyloid measures, and which would aid in identifying subsets of individuals at higher risk of accelerated accumulation.

IC-P-010 INCREASED SENSITIVITY OF AV45-PET FOR THE DETECTION OF EARLY STAGE AMYLOIDOSIS AFTER CORRECTION OF WHITE MATTER SPILL-IN EFFECTS

Michel J. Grothe[1], Jorge Sepulcre[2,3], Gabriel Gonzalez-Escamilla[1], Christian Sorg[4], Stefan J. Teipel[1,5], *[1]German Center for Neurodegenerative Diseases (DZNE), Rostock, Germany; [2]Harvard Medical School, Boston, MA, USA; [3]Massachusetts General Hospital, Charlestown, MA, USA; [4]University Hospital Klinikum rechts der Isar, Technical University of Munich, Munich, Germany; [5]Clinic for Psychosomatics and Psychotherapeutic Medicine, Rostock, Germany. Contact e-mail: michel.grothe@dzne.de*

Background: Amyloid-sensitive PET is an increasingly used biomarker for the detection of cerebral amyloid pathology but its sensitivity may critically depend on the way the PET scans are analyzed. Here we explored the effect of different image processing strategies on the concordance of amyloid-PET findings with cerebrospinal fluid (CSF) Aβ42 levels; an alternative biomarker of cerebral amyloidosis which typically shows only weak to modest associations with amyloid-PET findings in early phases of amyloid accumulation. **Methods:** We investigated the effects of 2- and 3-compartment models of partial volume correction (PVC-2/-3) and choice of reference region on the correlation between cortical AV45-PET uptake ratios (AV45-SUVR) and CSF-Aβ42 levels using data from 603 subjects enrolled in ADNI-2. Furthermore, in a subset of 152 cognitively normal subjects the ability to detect regional AV45-SUVR increases in groups with decreased CSF-Aβ42 levels was compared between the different processing approaches using voxel-wise analyses. **Results:** When using a whole cerebellar reference region, PVC-3, which also controls for spill-in effects of white matter (WM) signal, resulted in a significantly increased correlation of AV45-SUVRs with CSF-Aβ42 levels. This effect was most pronounced for the lower range of AV45-SUVRs (Figure-1), and was not observed for the simpler PVC-2 model that only controls for CSF dilution. Using PVC-3, cognitively normal subjects within the 3rd quintile of CSF-Aβ42 values (mean = 202 pg/ml) showed significantly increased AV45-SUVR values in fronto-temporo-parietal association areas compared to subjects within the highest CSF-Aβ42 quintile (≥ 241 pg/ml), and amyloid signal further extended across the cortex in subjects within the lowest CSF-Aβ42 quintiles (Figure-2). In uncorrected data, significant AV45-SUVR increases were only detected in subjects within the two lowest CSF-Aβ42 quintiles. Use of a WM reference region increased the correlation with CSF-Aβ42 in uncorrected PET data to a similar degree as PVC-3, and these effects were non-additive. **Conclusions:** Preprocessing techniques that account for the contamination of gray matter signal by unspecific WM binding can uncover biologically meaningful signal in AV45-PET scans that would typically be regarded as "amyloid-negative", and thus increase their sensitivity for detecting early stage amyloidosis.

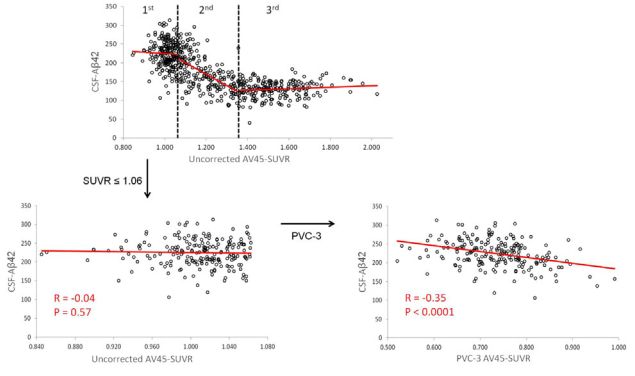

Figure 1. The effect of PVC-3 on the relation between cortical AV45-SUVRs and CSF-Aβ42 at the low range of AV45-SUVR values

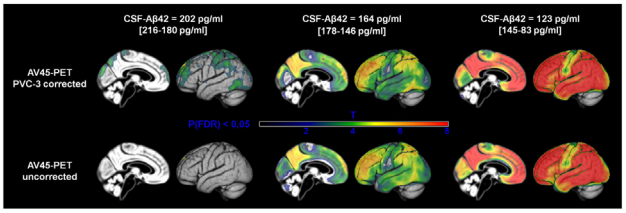

Figure 2. Regional AV45-SUVR increases in groups of cognitively normal subjects with decreased CSF-Aβ42 levels

IC-P-011 THE DIAGNOSTIC VALUE OF AMYLOID PET IN AN UNSELECTED COHORT OF MEMORY CLINIC PATIENTS

Arno de Wilde[1], Wiesje M. van der Flier[2], Femke H. Bouwman[3], Rik Ossenkoppele[4], Wiesje Pelkmans[1], Colin Groot[5], Marissa D. Zwan[6], Maqsood M. Yaqub[7], Vanessa Newman[8], Adriaan A. Lammertsma[5], Bart N. M. van Berckel[7], Philip Scheltens[6], *[1]Alzheimer Center, Department of Neurology, VU University Medical Center, Amsterdam, Netherlands; [2]Alzheimer Center, VU University Medical Center, Amsterdam, Netherlands; [3]Alzheimer Center and Department of Neurology, VU University Medical Center, Amsterdam, Netherlands; [4]VU University Amsterdam, Amsterdam, Netherlands; [5]Department of Radiology and Nuclear Medicine, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, Netherlands; [6]VU University Medical Center, Amsterdam, Netherlands; [7]Department of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, Netherlands; [8]Piramal Life Sciences, Havant, United Kingdom. Contact e-mail: arnodewilde@gmail.com*

Background: Earlier studies evaluating the diagnostic value of amyloid PET used highly selected study samples. We offered amyloid PET to all patients visiting our memory clinic and studied how amyloid PET impacted clinical diagnosis. In addition, we investigated whether appropriate use criteria (APUC) adequately identified patients that benefitted most from amyloid PET. **Methods:** From March to December 2015, we offered [^{18}F] florbetaben PET to all patients (n=443) visiting our memory clinic. Of all patients, 170/443 (38%) participated (64±7yrs; 61%M). PET scans were visually assessed as amyloid positive or negative. Before and after disclosure of PET results, one dedicated neurologist determined syndrome diagnosis and suspected etiology for each patient. Retrospectively and blinded to amyloid status, we applied APUC, which were positive when patients [A] had persistent or unexplained mild cognitive impairment (MCI), [B] satisfied core clinical criteria for possible AD with atypical clinical course or