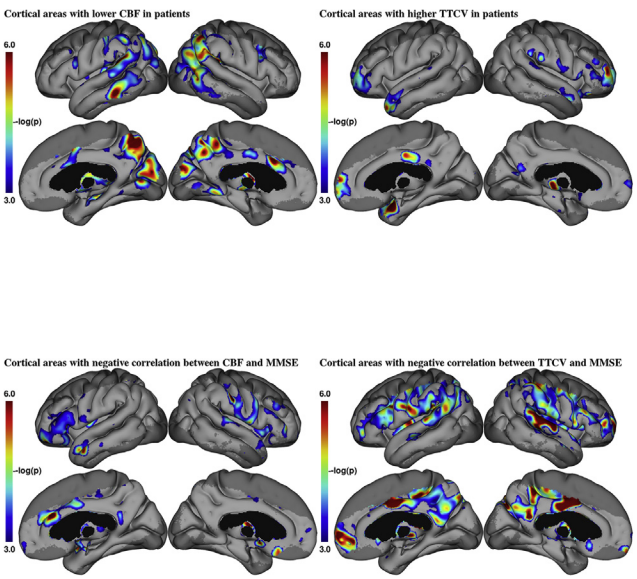
Background: Vascular risk factors are suspected to play a role in the etiology of Alzheimer's disease. Recently, a model that relates capillary dysfunction to the development of AD was proposed [1]. The model predicts that capillary dysfunction in form of increased capillary transit time heterogeneity (CTH) leads to inefficient oxygen extraction and eventually to tissue hypoxia. In this study we investigated regional cerebral blood flow (CBF) and CTH in cortical gray matter of AD patients and controls using dynamic susceptibility contrast (DSC) magnetic resonance imaging (MRI) and surface based statistics. **Methods:** Sixteen patients with clinically suspected possible or probable AD (MMSE:24.8±2.7, age:70.4±6.3) and 19 cognitively normal (MMSE≥28) agematched (age:67.5±7.2) and healthy controls were scanned using DSC and T1-weighted (T1w) MRI. From the DSC-MRI we measured CBF, mean transit time (MTT), and CTH using a parametric model assuming a gamma distribution of the capillary transit times [2]. Capillary dysfunction was evaluated as the flownormalized CTH, the transit time coefficient of variation: TTCV=CTH/MTT. Cortical perfusion estimates were mapped onto a surface fitted to the middle layer of the subject's individual cortex using the T1w images [3] and mapped to a standard surface in MNI space [4]. Surface based linear regression was performed to examine patient/control differences and the association between MMSE and perfusion. Age and gender were used as covariates in the analyses. **Results:** Cortical CBF was significantly reduced bilaterally in the precuneus and parietal and temporal lobes in patients (Fig.1). Capillary dysfunction as measured by TTCV was significantly higher bilaterally in the frontal lobe, the temporal pole, and posterior cingulate gyrus in patients (Fig.1). In parts of the frontal and temporal lobes and the right cingulate gyrus we found a negative association between CBF and MMSE in patients (Fig.2). Finally, we found widespread negative correlations between TTVC and MMSE in all major lobes except the occipital lobe (Fig.2). **Conclusions:** Our findings are consistent with the capillary dysfunction hypothesis of AD of increased capillary transit time heterogeneity in patients. We found a negative association between CBF and MMSE. We speculate that, in these areas, CBF is increased to compensate for the rising CTH and thus the imminent capillary dysfunction.



IC-04-02 THE RELATIVE IMPORTANCE OF IMAGING MARKERS FOR THE PREDICTION OF ALZHEIMER'S DISEASE DEMENTIA IN MILD COGNITIVE IMPAIRMENT: THE CURSE OF DIMENSIONALITY

Stefan J. Teipel[1], Michel J. Grothe[2], [1]*DZNE, German Center for Neurodegenerative Diseases, Rostock, Germany, Rostock, Germany;* [2]*German Center for Neurodegenerative Diseases (DZNE), Rostock, Germany. Contact e-mail: stefan.teipel@med.uni-rostock.de*

Background: Selecting a set of relevant markers to predict conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD) has become a challenging task given the wealth of regional pathologic information that can be extracted from multimodal imaging data. **Methods:** We used regularized regression approaches with an elastic net penalty for best subset selection of multiregional information from AV45-PET, FDG-PET and volumetric MRI data to predict conversion from MCI to AD. The study sample consisted of 127 MCI subjects from ADNI-2 who had a clinical follow-up between 6 and 31 months. Additional analyses assessed the effect of partial volume correction on predictive performance of AV45- and FDG-PET data. **Results:** Predictor variables were highly collinear within and across imaging modalities (see Figure 1). Penalized Cox regression yielded more parsimonious and neurobiologically plausible prediction models compared to unpenalized Cox regression. Within single modalities, time to conversion was best predicted by increased AV45-PET signal in posterior medial and lateral cortical regions, decreased FDG-PET signal in medial temporal and temporobasal regions, and reduced gray matter volume in medial, basal, and lateral temporal regions. Logistic regression models reached up to 72% cross-validated accuracy for prediction of conversion status, which was comparable to cross-validated accuracy of non-linear support vector machine classification. Regularized regression outperformed

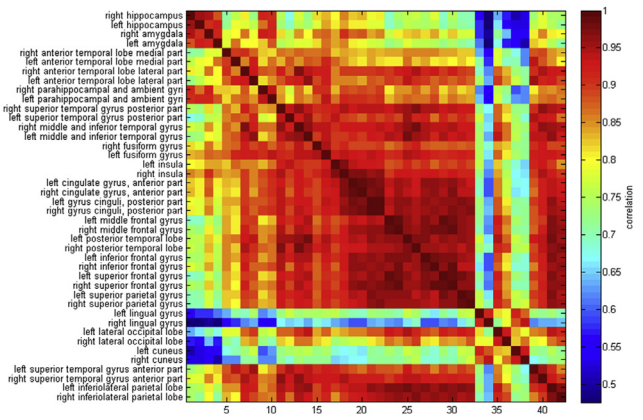


Figure 1. Cross-correlation matrix across AV45-PET regions

unpenalized stepwise regression when number of parameters approached or exceeded the number of training cases. Partial volume correction had a negative effect on the predictive performance of AV45-PET, but slightly improved the predictive value of FDG-PET data. **Conclusions:** Penalized regression yielded more parsimonious models than unpenalized stepwise regression for the integration of multiregional and multimodal imaging information. The advantage of penalized regression was particularly strong with a high number of collinear predictors.

IC-04-03 GREY MATTER NETWORK DISRUPTIONS ARE RELATED TO AMYLOID-BETA IN COGNITIVELY HEALTHY ELDERLY

Betty M. Tijms[1], Alle Meije Wink[1,2], Mara ten Kate[1], Pieter Jelle Visser[3,4], Mirian Ecay[5], Andrea Izagirre[5], Ainara Estanga[5], Montserrat Clerigue[5], Maite Garcia-Sebastian[5], Jorge Villanua[5], Pablo Martinez-Lage[5], Wiesje M. van der Flier[1,2], Philip Scheltens[1,2], Ernesto Sanz-Arigita[5], Frederik Barkhof[1,2], *[1]VU University Medical Center, Amsterdam, Netherlands; [2]Neuroscience Campus Amsterdam, Amsterdam, Netherlands; [3]Alzheimer Center, VU University Medical Center, Amsterdam, Netherlands; [4]Alzheimer Center Limburg, School for Mental Health and Neuroscience, Maastricht University, Maastricht, Netherlands; [5]CITA Alzheimer Foundation, San Sebastian, Spain. Contact e-mail: b.tijms@vumc.nl*

Background: Grey matter networks are disrupted in Alzheimer's disease. It is unclear when these disruptions start during the development of Alzheimer's disease. Amyloid deposition is among the earliest changes. A recent study demonstrated that abeta 42 affects grey matter networks. But since this network was derived at a group level these results could not be associated with risk of individual patients. Here we studied the effects of abeta 42 on single- subject grey matter networks in cognitively healthy elderly. **Methods:** Study participants were 193 cognitively healthy middle aged adults enrolled in the Gipuzkoa Alzheimer Project (GAP), a longitudinal study on pre-clinical AD recruiting subjects from the general population. Inclusion criteria were a MMSE $>$ 25 and a clinical dementia rating $=$ 0. CSF was obtained by lumbar puncture following international consensus recommendations. Levels of abeta 42 were determined with ELISA kits (InnotestTM β Amyloid1 42, Fujirebio Innogenetics). T1 weighted structural MRI scans were obtained at 3T. Native space grey matter segmentations (obtained with SPM8) were used to extract single subject grey matter networks. Normalized clustering coefficient γ and normalized path length λ were computed. Non parametric testing (based on 10.000 random permutations) was used to determine the significance of relationships between abeta42 deposition (dependent variable) and network property values (independent variable), including gender, whole brain volume and age as covariates. Multiple hypotheses testing was corrected for with false discovery rate (FDR). **Results:** All subjects had an age range between 39 and 79 years old (mean age $=$ 57 years), and 58% were female. Lower abeta42 CSF levels, indicative of a higher plaque load in the brain, were associated with lower connectivity density (β = 0.20; SE .07); p $<$ .05), lower clustering values (β = .18; SE =.08; p $<$ .05) and higher path length values (β = .21, SE =.08, p $<$ .01). Figure 1 shows the anatomical areas where lower clustering coefficient was related to decreased abeta42 CSF levels, and 6 areas in which higher path length values were associated with decreased abeta42 CSF levels. **Conclusions:** These results suggest that grey matter networks might have use as an early marker for AD pathology.

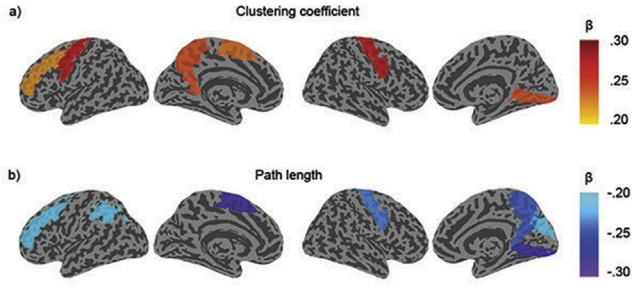


Figure 1. Surface plot of the standardised β values of the relationship between abeta42 with clustering and path length that were significant ($p_{FDR} < .05$). a) Lower clustering values were associated with low Aβ42 values in the bilateral precentral gyri, left precuneus, supplementary motor area, middle frontal gyrus and right lingual gyrus. b) Higher path length values in the left supplementary motor area, inferior parietal gyrus, middle temporal gyrus, right precuneus, lingual gyrus, precentral gyrus and cuneus were associated with low abeta42 CSF values.

IC-04-04 OPTIMIZING PIB-PET CHANGE-OVER-TIME MEASUREMENT BY ANALYSIS OF LONGITUDINAL RELIABILITY, PLAUSIBILITY, AND SEPARABILITY

Christopher G. Schwarz, Matthew L. Senjem, Jeffrey L. Gunter, Nirubol Tosakulwong, Scott A. Przybelski, Stephen D. Weigand, Anthony J. Spychalla, Prashanthi Vemuri, Ronald C. Petersen, Val J. Lowe, Clifford R. Jack, Jr., *Mayo Clinic, Rochester, MN, USA. Contact e-mail: schwarz.christopher@mayo.edu*

Background: Automatic measurement of Standardized Uptake Value Ratio (SUVR) from PiB-PET images is complicated by many methodological and implementational choices, such as reference region, gray matter (GM) target segmentation, and use of partial volume correction (PVC). These variations directly influence measurement reproducibility and confound cross-site comparability. Such choices have been hotly debated in the literature, but few studies have examined reliability, plausibility, or separability of change-over-time values, despite their potential importance for amyloid-modifying clinical trials. **Methods:** We studied 68 participants in the Mayo Clinic Study of Aging and Alzheimer's Disease Research Center studies with 3 serial PiB-PET scans each. Pseudo-steady-state (late uptake) PiB scans were registered to corresponding 3T T1-w MP-RAGE MRI, and an in-house standard template/atlas was warped to each MRI using ANTs software. Cortical GM was segmented using SPM12b and Longitudinal Freesurfer 5.3. PiB scans were (optionally) PVC'ed using a two-compartment (Meltzer) model. We calculated SUVR values for each PiB scan using 180 total variations, each with a different combination of reference, target, and PVC. **Results** were analyzed using a linear mixed-effects model. We compared methods on three independent criteria: longitudinal reliability (R^2 of serial