IC-P-081 DIFFERENTIAL ANATOMICAL CORRELATES OF OBJECTIVE AND SUBJECTIVE MEMORY IN OLDER INDIVIDUALS ACROSS A SPECTRUM OF MEMORY IMPAIRMENT

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Background: The diagnosis of amnestic mild cognitive impairment requires evidence of both subjective and objective memory impairment. Recently, subjective memory concerns have been associated with neuroimaging biomarkers of AD pathology, even among clinically normal individuals. Thus, we sought to explore the neuroanatomic correlates of subjective and objective memory impairment within clinically normal individuals and patients with mild cognitive impairment. **Methods:** The study included 64 participants; 17 clinically normal older adults (CN; CDR=0, mean age=75±6.02), 47 individuals with mild cognitive impairment (MCI; CDR 0.5, mean age=75.11±7.97). Subjective memory function was assessed using the "general frequency of forgetting" subscale of the Memory Functioning Questionnaire (MFQ). Objective memory was measured using the Rey Auditory Verbal Learning Test 30 minute delayed recall. All subjects underwent MRI with high-resolution MPRAGE. FreeSurfer Software was used to extract neuroanatomic measurements of hippocampal volume and precuneus thickness. Diagnosis was controlled for in models relating brain measures to memory measures. **Results:** A significant relationship between objective and subjective memory was found when CN and MCI individuals were combined (r=0.40, p=0.001). Using a linear regression we found that decreased hippocampal volume was significantly related to decreased memory performance (R Hippocampus: r=0.70, p=0.047, L Hippocampus: r=0.71, p=0.018), and was similar after controlling for subjective memory (R Hippocampus: r=0.71, p=0.072, L Hippocampus: r=0.72, p=0.030). In contrast, no significant relationship was found between subjective score and hippocampal volume. Decreased thickness in the left precuneus was significantly related to worse subjective memory score (L Precuneus: r=0.57, p=0.005), and remained significant when controlling for objective memory performance (L Precuneus: r=0.58, p=0.005). In contrast, no significant relationship was found between the objective score and precuneus thickness. **Conclusions:** Neuroanatomic substrates can be dissociated for subjective and objective memory deficits such as decreased precuneus thickness relates to worse subjective complaints, while decreased hippocampal volume relates to memory impairment. This pattern suggests a differential impact of distinct brain regions on memory processes in aging and Alzheimer's disease development.

IC-P-082 DISRUPTED FUNCTIONAL CONNECTIVITY IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE DEMONSTRATES NETWORK SPECIFICITY AND PRECEDES BRAIN VOLUME LOSS: FINDINGS FROM DIAN

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Background: We previously demonstrated decreased functional connectivity (fcMRI) in the default mode network (DMN) in autosomal dominant Alzheimer's disease (ADAD). Here we compare changes in DMN-fcMRI with other resting state networks (RSNs) to examine the network specificity of connectivity changes in ADAD and the timing of fcMRI changes relative to other biomarkers using estimated years from familial symptom onset (eYO). **Methods:** Cross-sectional structural and resting state MRI, Pittsburgh Compound B (PiB) PET, and neuropsychological data from 75 mutation carriers (M+, CDR0: 48; CDR0.5: 14; CDR1+: 13) and 49 mutation non-carriers (M-) was related to eYO using locally weighted scatterplot smoothing (loess) to generate temporal patterns of change in ADAD for each measure. Template based rotation, an extension of group independent component analysis in which fcMRI data are mapped onto a priori network templates, was used to create network maps for RSNs. **Results:** We found a significant interaction between eYO and mutation status on fcMRI in the DMN ($p<0.01$) and Dorsal Attention Network (DAN;$p<0.01$), but not in Motor or Control networks (p=ns). Biomarkers significantly related to eYO in M+ included PiB PET (r 2 =0.5), hippocampal volume (r 2 =0.331), precuneus thickness (r 2 =0.40), DMN fcMRI (r 2 =0.372), and logical memory (r 2 =0.42). Group-level DMN fcMRI in M+ appeared to diverge from M- early in the course of ADAD, following PiB PET, similar to logical memory change, and preceding changes in hippocampal volume and precuneus thickness (Figure 1A). However, we observed greater measurement variability in fcMRI relative to other measures, reducing the discriminative ability of fcMRI (Figure 1B). **Conclusions:** Two networks heavily implicated in cognition, the DMN and DAN, showed significant fcMRI changes in ADAD. Though longitudinal analyses will be needed to verify the temporal patterns observed here, the present data suggest alterations in DMN-fcMRI occur early in ADAD and precede changes in brain volume. These results support using DMN-fcMRI as a secondary endpoint in AD clinical trials, but the large variability in fcMRI measurements represents an important concern in the further development of fcMRI as a biomarker.

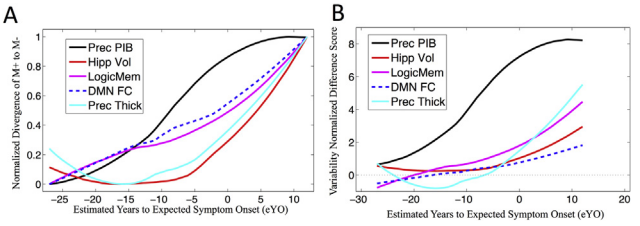

Figure 1. **A**. Temporal phasing of biomarkers. The Y-axis depicts the divergence of the M+ group from the M- group as estimated by the difference between the Loess fits for each group. Each difference function was rescaled to a range of 0 to 1 to highlight differences in the trajectories of change over time. **B**. Discriminative ability of each biomarker with respect to eYO.

The Y- axis depicts the difference between M- and M+ Loess fits to the data after normalizing each measure by the mean and standard deviation of the M- group. This metric shows the divergence between M- and M+ in units of standard deviations of the M- group.

IC-P-083 DO MICROBLEEDS PREDICT STROKE IN ALZHEIMER'S DISEASE (MISTRAL)? STUDY DESIGN AND FIRST RESULTS

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Background: The MISTRAL study investigates the prognostic value of microbleeds in Alzheimer's disease (AD), especially regarding the occurrence of intracerebral haemorrhage (ICH). Here, we describe the study design and report the first results. **Methods:** From the memory clinic based Alzheimer Dementia Cohort, we retrospectively included 111 AD patients with microbleeds on GRE or T2* MRI and 222 AD patients without, matched (1:2) for age, sex and scanner. Baseline visit was between 2002-2009 to ensure at least three years of follow-up. Main outcome measures are the occurrence of ICH and death and will be obtained via GPs and medical records. As a first step, we obtained information on mortality from the Dutch municipal population register. In the analyses, microbleed location (any lobar versus strictly non-lobar) and antithrombotic treatment were taken into account. **Results:** In the entire group of 333 patients (mean age 71 + 8, 42% female), 144 (43%) died after an average interval of 4 + 2 years. Mortality rate was higher among patients with microbleeds compared to patients without (54% vs. 38%, p<0.01). Cox proportional hazard analyses showed that the presence of at least one microbleed was related with increased risk of mortality (HR (95%CI): 1.77 (1.27;2.47)). This association was largely attributable to patients with microbleeds in lobar locations (HR (95% CI): 1.89 (1.34; 2.68)), especially when they were using antithrombotic treatment (HR (95%CI): 2.26 (1.40; 3.64)). The risk of mortality was not significant in patients with strictly non-lobar microbleeds (HR (95%CI): 1.25 (0.60; 2.58)). Results regarding microbleeds and their location did not change after additional adjustment for age, sex and dementia severity, but the additional risk associated with use of antithrombotic drugs disappeared after adjustment for these covariates. **Conclusions:** Presence of microbleeds, especially in lobar locations, is independently associated with an increased risk of mortality in AD patients. The next step in the MISTRAL study is to obtain information regarding cause of death and incidence of ICH.

IC-P-084 MORE WHITE MATTER HYPERINTENSITIES AND SMALLER BRAIN VOLUMES ARE RELATED TO LOWER CEREBRAL BLOOD FLOW AS MEASURED WITH 3T ARTERIAL SPIN LABELING MRI

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Background: Cerebral blood flow (CBF) is lower in patients with Alzheimer's disease (AD) compared to healthy controls. This lower CBF may indirectly reflect neurodegeneration, but might also be a direct consequence of co-morbid cerebral small vessel disease. We aimed to investigate the independent associations of normalized brain volume (NBV) and white matter hyperintensities (WMH) with CBF on MRI. **Methods:** From the memory clinic based Alzheimer Dementia Cohort, we included 132 patients with AD (age 66 + 7; 52%female), 78 with mild cognitive impairment (MCI) (age 65 + 7; 32%female) and 123 with subjective memory complaints (SMC) (age 60 + 9; 41%female). CBF was measured with pseudo-continuous arterial spin labeling at 3T for whole brain (WB) and in grey matter (GM) after partial volume correction (PVC). NBVs were calculated using SIENAX, which is part of FMRIB software library (FSL). WMH volumes were quantified from segmentation using in-house developed software, normalized for brain volume and log-transformed. We used linear regression analysis adjusted for age and sex to investigate independent associations for NBV (100ml) and WMH (ml) with CBF (ml/100gr/min). **Results:** Across diagnostic groups, smaller NBV was associated with lower CBF in WB (β 0.17; p<0.01) and PVC-GM (β 0.16; p<0.01). Moreover, larger WMH volume was associated with lower CBF in WB (β -0.16; p<0.01) and PVC-GM (β -0.18; p<0.01). Stratified analyses according to diagnostic group showed that in subjects with SMC, WMH volume was negatively associated with CBF for WB (β -0.18; p<0.05) and PVC-GM (β -0.19; p<0.05), whereas NBV was not associated with CBF. Neither NBV nor WMH was associated with CBF in MCI patients. In AD patients, we found negative associations between WMH volume and CBF in WB (β -0.24; p<0.05) and in PVC-GM (β -0.23; p<0.05) and in particular strong, positive, associations of NBV with CBF (WB: β 0.31; p<0.01 and PVC-GM: β 0.29; p<0.01). **Conclusions:** More WMH and smaller brain volumes are associated with lower CBF. In subjects with SMC, variability in CBF is mainly explained by WMH. In AD, lower CBF is not only explained by the severity of cerebral small vessel disease, but appears more strongly determined by neurodegeneration.

IC-P-085 EARLY PATHOLOGICAL CHANGES DUE TO ALZHEIMER'S DISEASE ARE DETECTED BY GRAPH THEORETICAL MEASURES OF FUNCTIONAL CONNECTIVITY

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Background: Alzheimer's disease (AD) is the most common cause of dementia and has a long prodromal phase. During this period, amyloid and tau pathology accumulate and exerts their pathological effects. Resting state functional connectivity MRI (rs-fcMRI) has demonstrated that brain networks degrade during symptomatic disease. However, the global character of changes in brain networks remains incompletely understood. Further, it is unclear to what extent these degradations exist prior to symptom onset. In this study, we investigated graph theory metrics of functional integration (clustering coefficient), functional segregation (path length), and functional distinctness (modularity) in participants as a function of clinical disease severity. Further, we assessed if these graph metrics were affected in cognitively normal participants with cerebrospinal fluid evidence of disease. **Methods:** Participants were evaluated using the clinical dementia rating CDR scale (205 were CDR0, 90 were CDR0.5, and 31 were CDR1). We further subdivided CDR0 individuals based on CSF analysis (132 subjects had no evidence of amyloid or tau pathology and 59 had evidence of either amyloid pathology or both amyloid and tau pathology). Each participant underwent rs-fcMRI scans that were preprocessed using standard techniques. Graph theoretical metrics were analyzed relative to cognitive or pathological status. **Results:** Both clustering coefficient and modularity, but not path length, were reduced in AD. Cognitively normal participants who harbored early AD biomarker pathology also showed reduced clustering coefficient and modularity, suggesting that these individuals demonstrated brain changes similar to symptomatic AD, but to a lesser degree. **Conclusions:** Our data also demonstrate that AD causes widespread neural dysfunction and that this dysfunction is present before symptom onset. Specifically, we show that the brain becomes less integrated during the course of AD. The loss of modularity may reflect the loss of distinct resting-state structure previously observed in AD. Finally, these changes appear to be present in presymptomatic AD, though to a lesser degree.