found in AD patients [3, 4]. These deficits could be related to amyloid pathology, inflammation or WM disorganization as suggested by histopathology. For further information please refer to www.alzheimer-europe.org. **References**. [1] Stahl R, et al. 2007. Radiology; 243(2):483-92. [2] Liu Y, et al. 2011. Neurobiol Aging. 32(9):1558-71. [3] Teipel SJ, et al. 2002. Arch Neurol; 59(2): 243-248. [4] Moon WJ, et al. 2008. AJNR Am J Neuroradiol; 29(7): 1308-1313.

O4-03-02 BRAIN NETWORK ALTERATIONS IN ALZHEIMER'S DISEASE MEASURED BY EIGENVECTOR CENTRALITY IN FMRI ARE RELATED TO COGNITION AND CEREBROSPINAL FLUID BIOMARKERS

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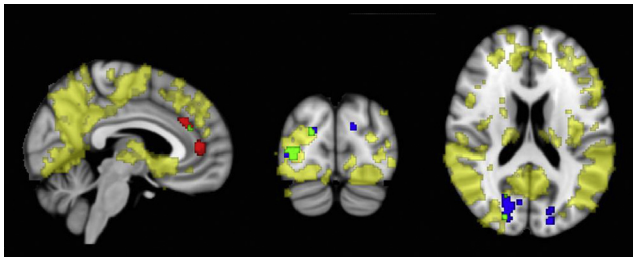
Background: Recent imaging studies have demonstrated functional brain network changes in patients with Alzheimer's disease (AD). Eigenvector centrality (EC) is a graph analytical measure that identifies prominent regions in the brain network hierarchy and detects localized differences between patient populations. **Methods:** In this study we included 39 AD patients and 43 healthy controls from the memory clinic based Amsterdam Dementia Cohort. Voxel-wise fast eigenvector centrality mapping (ECM) was used to analyze individual whole-brain 1.5 Tesla resting-state functional MRI scans. Between-group differences were assessed by a permutation-based method (5000 permutations) with family-wise error (FWE) correction for multiple comparisons. Associations of EC with biomarkers for AD pathology in cerebrospinal fluid (CSF) and Mini Mental State Examination (MMSE) scores were examined using Spearman correlation analyses. **Results:** Compared to controls (age 69±7, 47% female, MMSE 29±1), AD patients (age 67±8, 41% female, MMSE 22±3) showed lower EC values bilaterally in the occipital cortex in four clusters (cluster sizes: 112, 87, 71 and 6 voxels; FWE-corrected $p<0.05$). Regions of higher EC were identified in the anterior cingulate and paracingulate gyrus in AD patients compared to controls in two clusters (cluster sizes: 166 and 135 voxels, FWE-corrected $p<0.05$). Across groups, frontal and occipital EC changes were associated with pathological concentrations of CSF biomarkers (amyloid: rho=-0.43 frontally and rho=0.44 occipitally, $p<0.01$; total tau: rho=0.42 frontally and rho=-0.33 occipitally, $p<0.05$) and with cognition (rho=-0.57 frontally and rho=0.68 occipitally, $p<0.001$). In controls, lower EC values in the occipital regions were related to lower MMSE scores (rho=0.38, $p<0.05$) (See Figure.). **Conclusions:** Our main finding is that ECM, a hypothesis-free and computationally efficient analysis method of functional MRI data, identifies changes in brain network organization in AD patients that are related to cognition and underlying AD pathology. The relation between AD-like EC changes and cognitive performance suggests that resting-state functional MRI measured EC is a potential marker of disease severity for AD.



O4-03-03 DISRUPTED FUNCTIONAL CONNECTIVITY IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE DEMONSTRATES NETWORK SPECIFICITY AND PRECEDES BRAIN VOLUME LOSS: FINDINGS FROM THE DOMINANTLY INHERITED ALZHEIMER NETWORK

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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 (See Figure 1A.). However, we observed greater measurement variability in fcMRI relative to other measures, reducing the discriminative ability of fcMRI (See 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.

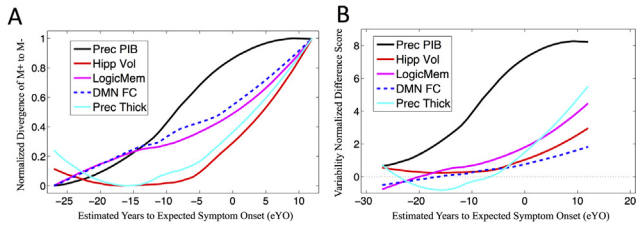

Figure 1. **A**. *Temporal phasing of biomarkers*. The Y- axis depicts the divergence of the M+ group from the M- group as estimated by the difference between the Loess fits for each group. Each difference function was rescaled to a range of 0 to 1 to highlight differences in the trajectories of change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

O4-03-04 DELINEATING THE RELATIONSHIP BETWEEN COGNITIVE MEASURES AND FUNCTIONAL CONNECTIVITY IN ALZHEIMER'S DISEASE

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Background: Resting state functional connectivity MRI (fcMRI) of the Default Mode Network (DMN) has been shown to be impaired in Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI). In addition, cognitive measures such as the CDR and CERAD scores are sensitive to changes in cognition, distinguishing healthy controls from both MCI and AD. The aim of this study was to investigate whether a relationship existed between fcMRI measures of brain networks and either CERAD or CDR scores. **Methods:** fcMRI was collected in 19 health controls (HC), 21 MCI and 21 early-onset AD subjects. Data were analyzed using regression between CERAD total score and relevant subscores or CDR scores and resting state functional connectivity. These relationships were also explored by two multivariate statistical Methods: Barycentric Discriminant Analysis (BADA) and Multiblock Analysis. **Results:** Functional connectivity, primarily in the Default Mode Network (DMN) was inversely correlated with CERAD total score, verbal fluency and Boston naming task across all subjects. Further, decreased frontal connectivity was correlated with decreased constructional praxis scores. BADA of connectivity in core regions of the DMN differentiated between the 3 cohorts independent of cognitive performance with a precision of 75% (random effects analysis). Multiblock analysis differentiated the three cohorts using a combination of DMN connectivity and CERAD and CDR scores. This analysis showed that the cognitive data and functional connectivity were negatively correlated, but CERAD and CDR were positively correlated, as expected. **Conclusions:** Cohort differences between HC, MCI and early AD were expressed as decrements in DMN connectivity that related to CERAD total scores, as well as verbal fluency and naming tasks. Furthermore, decreasing performance on CERAD constructional praxis was correlated with decreased frontopolar connectivity.

O4-03-05 WIDESPREAD DISRUPTION OF FUNCTIONAL BRAIN ORGANIZATION IN EARLY-ONSET ALZHEIMER'S DISEASE PATIENTS

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Background: Early-onset Alzheimer's disease (AD) patients often present a different clinical profile than late-onset AD patients. Although the origin of this heterogeneous cognitive profile is unknown, changes in the organization of brain connectivity might be related to it. The aim of this study was to examine functional connectivity within resting state networks in early-onset and late-onset AD patients. **Methods:** Functional connectivity was examined by analyzing resting-state fMRI scans of 20 early-onset AD patients and 28 late-onset AD patients. Standard space masks were used as input to create subject-specific voxelwise network regression maps. Group differences were examined using a non-parametric permutation test, with gender and voxel-wise gray matter probability maps as covariates. In addition, a voxel-based morphometry analysis was performed to examine spatial overlap of atrophy and functional connectivity changes. Cognition was assessed in five cognitive domains and correlated with functional connectivity across all patients. **Results:** We found widespread reductions in functional connectivity in early-onset AD patients as compared to late-onset AD patients in the auditory-, sensory-motor system, default mode network, and bilateral dorsal visual system (See Figure.), and less pronounced differences in spatial atrophy patterns. A small part of the precuneus showed both atrophy and functional connectivity decreases in early-onset AD patients. Lower functional connectivity of the default mode network (r=0.43, p=0.02) and right dorsal visual stream (r=0.36, p=0.049) was associated with poorer performance on visuoconstructive tasks. Lower functional connectivity of the sensory-motor system (r=0.37, p=0.02) and right dorsal visual stream (r=0.34, p=0.03) was associated with poorer performance on cognitive tasks involving attention. **Conclusions:** Functional brain organization appears to be more widely affected in early-onset AD than in late-onset AD patients, possibly explaining differences in clinical manifestation.

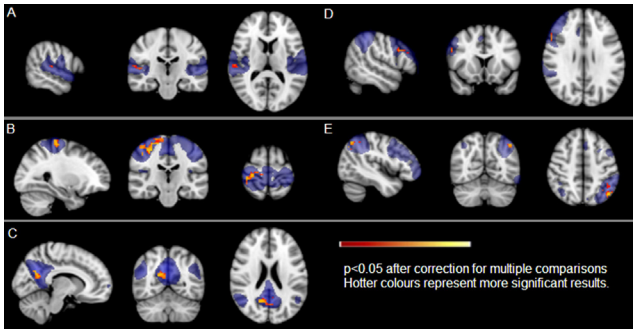

Figure 1. Decreased functional connectivity (in red) was found in early-onset AD patients when compared to late-onset AD patients within the Auditory System (A), the Sensory-Motor System (B), the DMN (C) and the right (D) and left (E) dorsal visual stream. Standard maps of the Resting State Networks (RSNs) are shown in transparent blue. Results are displayed in radiological orientation on standard MNI space (MNI152 2mm).

O4-03-06 ABNORMALITIES OF FRONTO-STRIATO-THALAMIC TRACT STRUCTURE AND EFFECTIVE CONNECTIVITY IN FAMILIAL ALZHEIMER'S DISEASE

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Background: Diffusion-weighted magnetic resonance imaging (MRI) and resting-state fMRI enable study of brain network structure and function. Connectivity abnormalities within networks supporting cognitive functions known to be impaired in AD could provide new biomarkers. These markers are particularly interesting in early-stage AD, which familial AD (FAD)