SATURDAY, JULY 23, 2016
ALZHEIMER'S IMAGING CONSORTIUM (AIC)
IC-03
BRAIN NETWORKS AND CONNECTOMICS

IC-03-01 REGIONAL GRAY MATTER VOLUME AND DEFAULT MODE NETWORK CONNECTIVITY ARE ASSOCIATED WITH AGE RELATIVE TO PARENTAL SYMPTOM ONSET IN SPORADIC ALZHEIMER'S DISEASE

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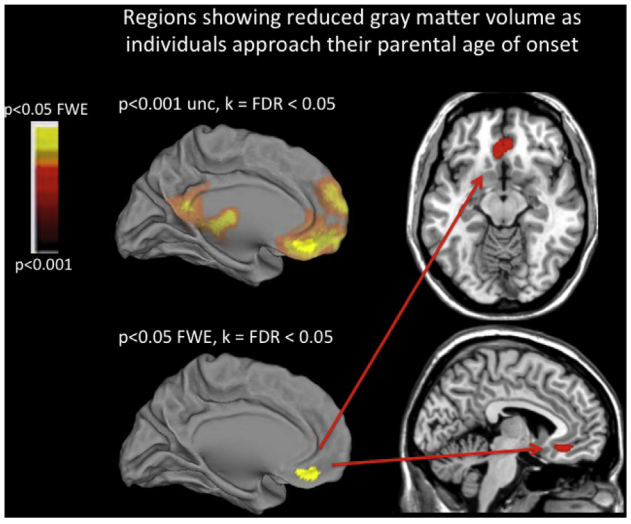
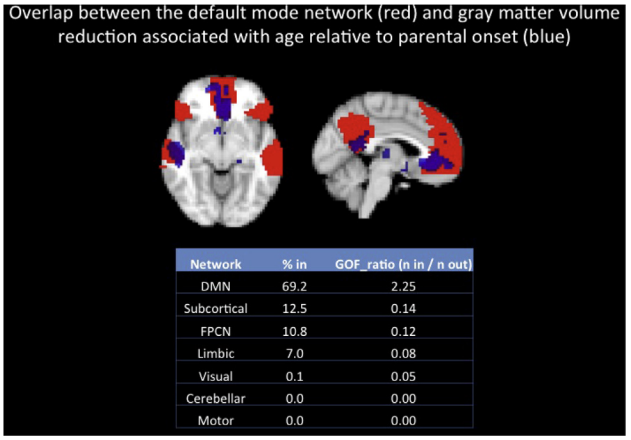
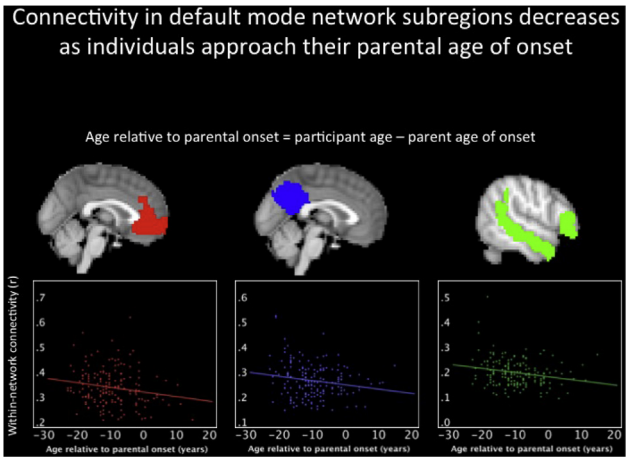
Background: In autosomal-dominant familial Alzheimer's disease, individual age of symptom onset correlates with parental onset age. Various AD biomarkers precede dementia onset and show increasing abnormality as mutation carriers approach their parent's onset age. We investigated whether this same principle applies in individuals with a family history of sporadic AD. We explored the association between age relative to parental symptom onset (aPSO) and AD biomarkers in PREVENT-AD, a cohort of cognitively intact persons aged 60+ with a parental history of AD. **Methods:** In 219 individuals, we assessed structural magnetic resonance (MR) images for regional gray matter (GM) volume, as well as functional brain connectivity (resting state fMRI) within the default mode network (DMN). Structural volumes were preprocessed and analyzed with SPM12, using the DARTEL method to define a population-specific template. Voxel-based morphometry (VBM) analysis was performed assessing the relation of aPSO with GM volume, adjusting for age, gender, ApoE4 status and total intracranial volume. Functional connectivity data were preprocessed and analyzed using NIAK. The association between aPSO and functional connectivity was explored within DMN regions defined on an independent dataset, again controlling for age, gender, and ApoE4 status, as well as motion. **Results:** VBM analysis revealed a region in the medial prefrontal cortex (mPFC) that displayed reduced GM volume as individuals approached their parental age of onset ($p < 0.05$ FWE corrected). Relaxing the statistical threshold revealed an atrophy pattern that extended into the posterior cingulate, the left middle temporal lobe, and large portions of the mPFC, as well as in the thalamus (Figure 1). The affected regions overlapped substantially with the DMN (Figure 2). We next carried out functional connectivity analysis within DMN subregions. As individuals approached their parental age of onset, within-region connectivity decreased in the anterior DMN and the lateral DMN (FDR < 0.05), with a similar trend for the posterior DMN (FDR $p < 0.1$; Figure 3). **Conclusions:** In individuals with a parental history of sporadic AD, brain structure and functional connectivity in the DMN appear to covary with aPSO. Longitudinal analyses and replication in separate samples are necessary to determine the predictive potential of tPAO in sporadic AD.







IC-03-02 GREY MATTER CONNECTIVITY IS ASSOCIATED WITH CLINICAL PROGRESSION IN NON-DEMENTED, AMYLOID POSITIVE PATIENTS

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Background: Accumulation of amyloid in the brain is among the first changes leading to Alzheimer's disease (AD), yet its prognostic value is limited. Grey matter connectivity is disrupted in AD, and these disruptions are associated with worse cognitive functioning. We studied whether grey matter connectivity has prognostic value, by comparing amyloid positive patients with subjective cognitive decline (SCD) and mild cognitive impairment (MCI) and analyzing its association with clinical progression. **Methods:** CODA (COnnectivity in DementiA) includes 222 non-demented patients (62 (28%) SCD; 160 (78%) MCI;109 (49%) female; 68 ± 8 years; 28 ± 2.4 MMSE) with abnormal amyloid CSF (<640 pg/ml), T1-weighted structural MRI and ≥1 year annual follow up data available selected from the Amsterdam Dementia Cohort. The main outcome parameter was clinical progression (CDR change ≥ 0.5). Single-subject networks were based on grey matter segmentations. We calculated the degree, connectivity density, path length, clustering, and small world parameters. All measures were Z transformed and inverted. ANCOVAs were used for cross-sectional comparisons of disease outcome and baseline diagnosis. Separate Cox proportional hazard models were fitted for each connectivity predictor for time to dementia onset and corrected for age, gender, whole brain volume and scanner. **Results:** After 2.2 (IQR 1.3–3.1) years 122 (55%) people showed clinical progression (N=23 SCD; N=99 MCI). Normalized clustering and small world property showed main effects of diagnosis and clinical progression, which is suggestive of a linear trend (Figure 1). Cox analyses indicated that lower values of 5 grey matter network parameters were related to clinical progression: degree (HR = 1.48; 95%CI = 1.09–2.02), connectivity density (HR = 1.49; 95%CI = 1.09-1.81), clustering (HR = 2.92; 95%CI = 1.27–6.69; Figure 2), normalized clustering (HR = 1.47; 95%CI = 1.13–1.91), and small world value (HR = 1.45; 95%CI = 1.13–1.87). No interaction effects of baseline diagnosis and network properties on time to dementia onset were found (all p_{ia} >.05). **Conclusions:** In non-dementia phases of AD, grey matter networks disruptions suggestive of a change towards a more random network organization were associated with time to clinical progression. Our findings suggest that connectivity based markers have prognostic value in amyloid positive individuals.

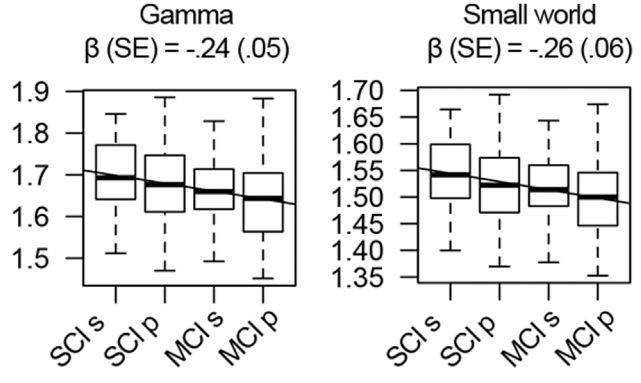

Figure 1. Linear trend analysis of normalized clustering coefficient (gamma) and the small world parameter. Both these network parameters had highest values in patients with subjective cognitive decline who remained stable over time, and the lowest in MCI patients who progressed to dementia.

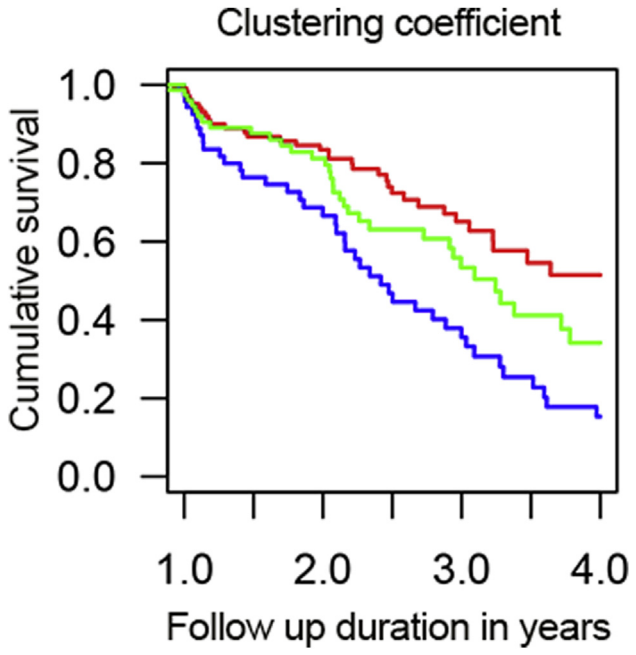

Figure 2. Survival curves for the time to dementia onset in subjects with subjective cognitive impairment or mild cognitive impairment due to Alzheimer's disease with separate lines for clustering coefficient tertiles: blue represents subjects with the most lowest values, green represents intermediate values and red line represents subjects with the highest values.

IC-03-03 COGNITIVE COMPLAINTS IN OLDER ADULTS AT RISK FOR ALZHEIMER'S DISEASE ARE ASSOCIATED WITH ALTERED RESTING STATE NETWORKS

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Background: Pathophysiological changes that may have a disruptive influence on brain networks accompany or anticipate early clinical symptoms in prodromal Alzheimer's disease (AD). Resting state fMRI (rsfMRI) combined with brain connectomics permits assessment of changes in whole-brain functional connectivity (FC) including downstream effects on neuronal processes. FC patterns