Amsterdam, Amsterdam, Netherlands; [2]Alzheimer Center and Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, Netherlands; [3]Alzheimer Center, VU University Medical Center, Amsterdam, Netherlands; [4]VU University Medical Center, Amsterdam, Netherlands; [5]Neurocampus Amsterdam, VU University Medical Center, Amsterdam, Netherlands; [6]Department of Radiology and Nuclear Medicine, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, Netherlands; [7]University College London, London, United Kingdom. Contact e-mail: b.tijms@vumc.nl

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.

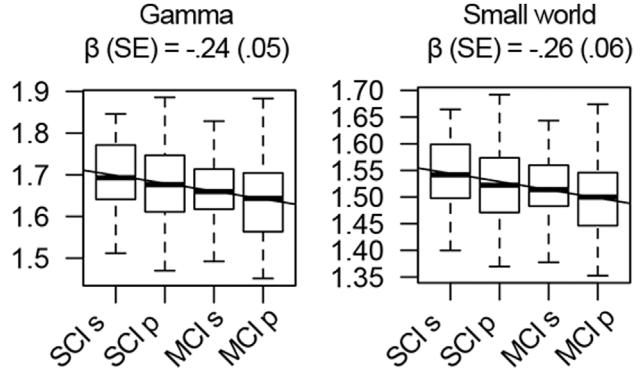


Figure 1. Linear trend analysis of normalized clustering coefficient (gamma) and the small world parameter. Both these network parameters had highest values in patients with subjective cognitive decline who remained stable over time, and the lowest in MCI patients who progressed to dementia.

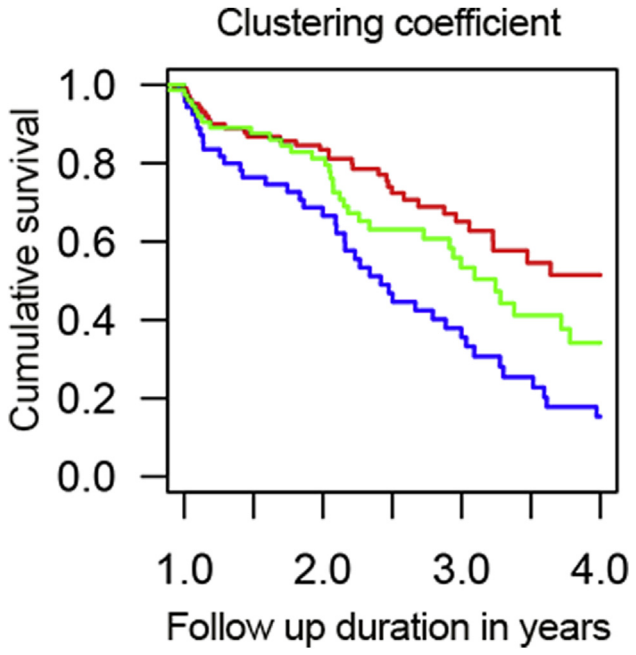
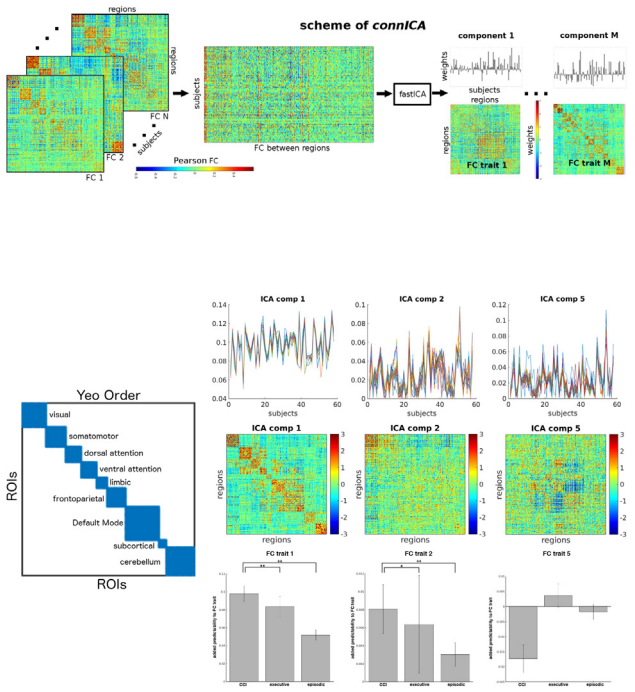


Figure 2. Survival curves for the time to dementia onset in subjects with subjective cognitive impairment or mild cognitive impairment due to Alzheimer's disease with separate lines for clustering coefficient tertiles: blue represents subjects with the most lowest values, green represents intermediate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

Joey A. Contreras[1,2,3], Joaquín Goñi[2,3,4], Shannon L. Risacher[1,5], John D. West[1,5], Mario Dzemidzic[1], Brenna C. McDonald[1,5], Martin R. Farlow[1,5], Olaf Sporns[2,3], Andy J. Saykin[1,5,6], *[1]Indiana University School of Medicine, Indianapolis, IN, USA; [2]Indiana University Network Science Institute, Indianapolis, IN, USA; [3]Indiana University Alzheimer Disease Center, Indianapolis, IN, USA; [4]School of Industrial Engineering and Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN, USA; [5]Indiana Alzheimer Disease Center, Indianapolis, IN, USA; [6]Indiana University Network Science, Indianapolis, IN, USA. Contact e-mail: joeacont@iupui.edu*

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



can be grouped into resting-state networks (RSNs) allowing analysis of higher-order changes within and between networks. Here we investigate the relationship of self-perceived cognitive changes to rsfMRI FC changes in a sample from the Indiana Memory and Aging Study. **Methods:** Participants included 58 older adults classified as cognitively normal (CN, 13), subjective cognitive decline (SCD, 16), early amnestic MCI (EMCI, 5), late MCI (LMCI, 16), and mild AD dementia (AD, 8) who underwent baseline rsfMRI processed with an in-house pipeline after Power et al, [1] to extract FC matrices based on a functional parcellation including 278 regions. An independent component analysis (ICA) connectivity data-driven approach (*connICA*) was used to extract FC independent patterns (FC traits). FastICA decomposition (15 independent components) was performed over a matrix of all subjects FC connectivity profiles (Figure 1). Each component signal was then used as a response in a multilinear regression model with cognitive variables (Cognitive Complaint Index (CCI) [2] scores, episodic memory and executive function domain scores) serving as the predictors and nuisance variables (age, gender, and education) included as covariates. **Results:** Two *connICA* components were strongly associated with CCI scores (FC-traits 1, 2). FC trait 1 involves a decrease in FC within each RSN whereas FC trait 2 involves an increased FC within specific somatomotor regions, and increased inter-RSN FC between somatomotor and dorsal attention networks and a general FC decrease between somatomotor and other RSNs. In both cases CCI is shown to be the best predictor of FC traits 1 and 2. FC trait 5 could not be attributed to a specific variable but is worth noting due to its robust finding (Figure 2). **Conclusions:** Self-reported cognitive complaints are strongly associated with a pattern of specific rsFC network changes as the disease progresses. Further examination of psychometric performance and FC patterns is required.

[1] Power et al (2014) Neuroimage; [2] Saykin et al. (2006) Neurology.

IC-03-04 NETWORK-BASED TAU DEPOSITION PATTERNS ARE RELATED TO FUNCTIONAL NETWORK FAILURE LARGELY VIA BETA-AMYLOID ACROSS THE ALZHEIMER'S SPECTRUM

David T. Jones, Val J. Lowe, Heather J. Wiste, Matthew L. Senjem, Jonathan Graff Radford, Bradley F. Boeve, David S. Knopman, Ronald C. Petersen, Clifford R. Jack, Jr, *Mayo Clinic, Rochester, MN, USA.*
Contact e-mail: jones.david@mayo.edu

Background: The cascading network failure model of Alzheimer's disease (AD) pathophysiology hypothesizes that synaptic activity related to shifts in large-scale functional network organization is causally related to observed beta-amyloid accumulation via alteration in amyloid precursor protein processing. Once the large-scale network reorganization interacts with vulnerable brain systems, a tau-related neurodegenerative process initiates within that system. To test these predications we investigated the relationship between Tau-PET, task-free fMRI, and beta amyloid-PET in a cross-sectional sample spanning the Alzheimer's disease spectrum. **Methods:** Tau-PET (AV-1451), beta amyloid-PET (PiB), and TF-fMRI were obtained in a cohort of subjects across the AD spectrum ($n = 218$). All subjects who were clinically impaired (MCI = 12, dementia = 29) had PiB SUVR > 1.5. Tau-PET scans were intensity normalized to the cerebellar gray matter, spatially normalized to standard space, and smoothed. An independent component analysis was performed, with biologically relevant components being identified via a strong amyloid effect (Bonferroni corrected $p < 0.01$). A goodness-of-fit (GOF) analysis of these components with a functional connectivity atlas was then performed. Tau-PET memory system component scores were included in a mediation analyses with PiB-PET and a marker of functional network failure we term the network failure quotient (NFQ). **Results:** Five biologically relevant tau-PET components were identified. These components had high GOF scores with visual, executive, and memory-related networks likely reflecting phenotypic heterogeneity in the AD cohort given the visual and executive components were associated with age-of-

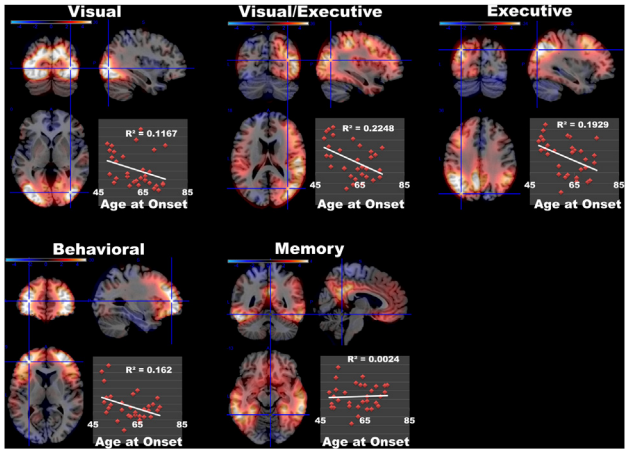


Figure. The spatial extent of the five biologically relevant Tau-PET independent components are overlaid on orthogonal slices of a template brain (color bar encodes z-score from -5 to 5). The cognitive associations of the functional connectivity atlas components associated with each Tau-PET pattern are listed above. Inset, the component scores are plotted vs. age-of-onset for the dementia cases. Note that the memory Tau-PET component is elevated across age-of-onset.