Local signal complexity and dynamic functional connectivity associated with Alzheimer's severity

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Introduction: Alzheimer's disease (AD) has been characterized as a disconnection-syndrome (Villain, 2010). Depending on the disease severity, atrophy in grey matter and disruptions in white matter (WM) are observed. These structural changes are accompanied by functional decline on a symptomatic level, and in intrinsic functional connectivity (FC) of brain networks. In AD, FC alterations are found in several resting-state networks (RSN) such as default mode network (DMN), salience network (SAL) or executive control networks (ECNs). These RSNs can be characterized by their properties of region to region static FC across the duration of an MRI BOLD scan, the variability of the dynamic modulations of this FC (dynFC). In addition to the relation between signal fluctuations between brain areas, the regularity/complexity of BOLD signal fluctuations can be assessed by means of multi-scale entropy (MSE; Smith, 2014) and has been shown to be related to cognitive function in elderly controls (Yang, 2013). Hence, we investigated alterations of dynFC between and MSE of signals within brain regions of these RSNs in early AD patients as compared to elderly controls (EC). Furthermore, we were interested in the relationship of these network characteristics and the MMSE score.
Methods: Data from 14 EC (age=67.9, SD=3.7; MMSE=28.6, SD=0.8) and 16 patients with AD (age=67.3, SD=9.7; MMSE=25.2, SD=3.6; Mann-Whitney $U_{EC\text{-}AD}$=19.5, p<0.001) were analyzed. BOLD fMRI acquisition was done on a Siemens 3T scanner (400 volumes, 26 slices, 3x3x4mm, TR/TE 1600ms/35ms). Preprocessing included motion realignment, regression of 12 motion parameters and WM and CSF signal fluctuations, normalization to MNI space and smoothing (8mm FWHM Gaussian kernel). DMN, ECNs and SAL nodes were defined from template-RSNs (Shirer, 2012; Fig. 1). Using a sliding window approach (length 20TRs), the dynamic changes in interregional FC was computed. MSE was calculated with the average sample-entropy across 30 coarse-sampled temporal scales (pattern length m=2, matching threshold r=0.3). We first tested for differences in MSE and dynFC between networks and groups using ANOVA. Second, a potential global association between network connectivity and network complexity was investigated with a correlation of overall dynFC and overall MSE. Finally, we correlated dynFC with MMSE scores to identify aberrant connections related to AD severity.
Results: The ANOVA for MSE yielded a group effect, but no network effect (F(network)=0.38 p=n.s. F(group)=4.00 p<0.05). The DMN showed a reduced MSE in AD compared to EC (t=2.23, p<0.05). No differences in dynFC were found on the network level. For the combined groups a correlation between MSE and dynFC (Fig. 1) was observed for SAL and both ECNs (r_{LECN}=-0.58 p<0.001, r_{RECN}=-0.42 p<0.05, r_{SAL}=-0.46 p=0.01). In other words, the more variable the connections, the less predictable the network. The correlation between MMSE and MSE/dynFC was negative in the DMN and SAL between MMSE and global dynFC (r_{DMN}=-0.40 p<0.05, r_{SAL}=-0.46 p<0.05). No correlation was found for the ECNs and MMSE. A detailed region-to-region analysis (Fig. 2) revealed that the dynFC specifically in LECN was positively correlated with MMSE in EC whereas in AD this was lacking. In contrast, the AD group showed overall negative relations between MMSE and dynFC within the other networks (except LECN).
Discussion: We did not find any dynFC differences between the groups in any RSN. This unexpected outcome might be explained by the mild AD severity and small sample size; however, future studies need to investigate this speculation. Nevertheless, there is a negative relation between the signal complexity within network nodes and variability in connectivity, which indicates a reduced potential to establish stable connections with remote areas. This is in line with the finding that in AD most networks displayed an inverse relation between MMSE and dynFC suggesting that communication between network nodes is impaired.

References:

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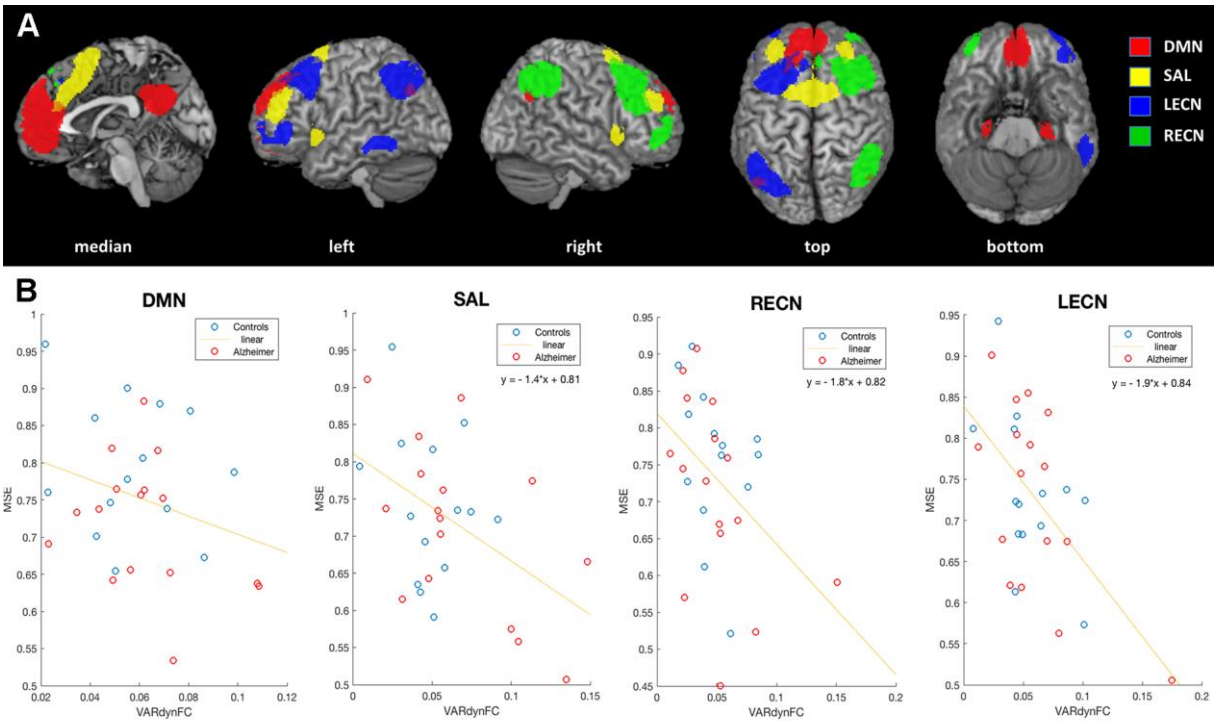

Fig. 1: (A) Display of networks and the areas that contribute to each of them. DMN: Default Mode Network; SAL: Salience Network; LECN: Left Executive Network; RECN: Right Executive Network. (B) Correlation between network level Multi-Scale Entropy (MSE) and variability of dynamic functional connectivity (VARdynFC).

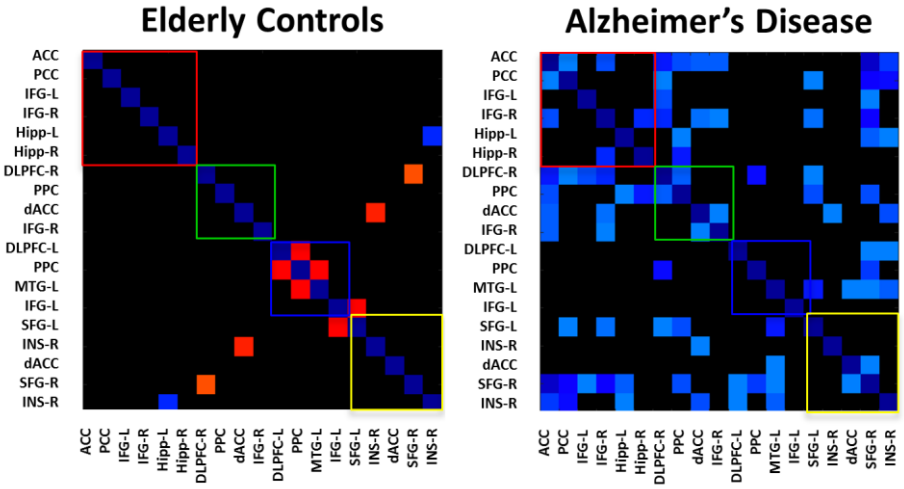

Fig. 2: Correlation between region-to-region variability of dynFC and MMSE scores.