Analysis of resting state sub-networks from high-dimensional ICA: disconnections in Alzheimer's disease

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Target audience: Researchers and clinicians interested in resting state fMRI and its application in aging and dementia.

Purpose: Independent Component Analysis (ICA) is a powerful data-driven method used for functional connectivity analysis of the resting state fMRI (rfMRI) data. It decomposes fMRI data into distinct networks, the resting state networks (RSNs), that are correlated in their spontaneous fluctuations but also maximally independent in the spatial domain[1]. In this work ICA was used to explore rfMRI data with a traditional low-dimensional approach and with an innovative high-dimensional one, gaining further insight into functional connectivity and related changes in Alzheimer's disease (AD). The low-dimensional analysis was used to verify the consistency of our study with previous literature[2, 3], while the high-dimensional analysis was used to split the traditional RSNs in sub-networks for a detailed analysis of their functional connectivity and its alterations in AD. The study mainly focused on the Defaut Mode Network (DMN), the most damaged RSN in AD, and on the Sensory Motor Network (SMN), in order to investigate if the AD damage extends to other areas not involved in memory processes.

Methods: The study was conducted on 15 healthy subjects (HS) (70.80±4.21 yrs, M/F:7/8) and 15 AD patients in a mild or moderate stage (74.07±5.16 yrs, M/F:6/9). For each subject, rfMRI and BOLD EPI images were acquired using a 1.5 T MRI scanner. After standard preprocessing with FSL, rfMRI data were temporally concatenated across subjects and group-ICA was performed. It returned the temporal response of all the independent components (ICs) and the corresponding spatial maps. Two model orders were used for group-ICA: the "low-dimensional" one (30 components) and the "high-dimensional" one (70 components). Dual regression approach was then used to recover subject-specific spatial maps and time series from group components used as templates[4]. We focused on three ICs detected by low-dimensional ICA: Posterior Cingulate Cortex (PCC) and Medial Frontal Cortex (MFC), both parts of the DMN, and SMN. For the low-dimensional study, we performed temporal analysis (between-group comparison of correlation values among ICs time series) and spatial maps analyses (voxel-wise two-sample t-test between HS and AD). For the high-dimensional analysis, a classification algorithm was used for automatic recognition of the high-dimensional components relative to the selected RSNs. The algorithm was based on spatial and temporal comparisons between RSN templates (low-dimensional ICs) and high-dimensional components. For each subject, correlations among the selected high-dimensional ICs time series were derived (temporal analysis). Similarly to low dimensional analysis, we evaluated differences in correlations among ICs time series between HS and AD patients (two-sample t-test), aiming to study in more detail the functional connectivity alterations among the selected sub-networks.

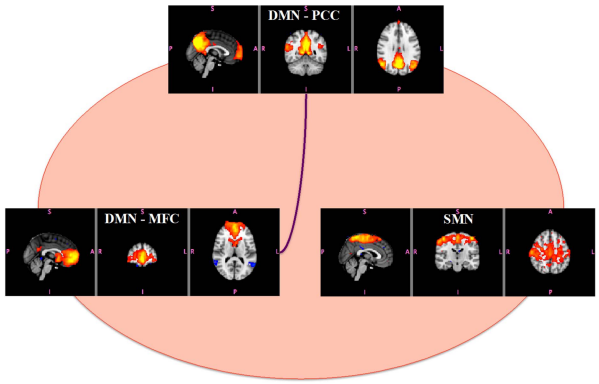

Fig. 1: Graphical representation of low dimensional time series analysis. The purple line indicates a significant ($p<0.05$) anterior-posterior disconnection.

Results: As regards low-dimensional results, only the correlation between PCC and MFC time series was found to be lower for AD than for HS with a significance level of $p \leq 0.05$ (Fig. 1), while the spatial analysis highlighted significantly lower activations in AD compared to HS in all the three considered RSNs, especially the PCC. The classification algorithm found 3 PCC sub-networks (PCC_1, PCC_{20}, PCC_{35}), 2 MFC sub-networks (MFC_{17}, MFC_{22}) and 4 SMN sub-networks (SMN_2, SMN_{10}, SMN_{25}, SMN_{33}). As regards high dimensional results, a significantly reduced ($p<0.05$) functional connectivity in AD was found in both short distance (PCC_{35}-SMN_2, MFC_{17}-MFC_{22}; Fig.3, red lines) and long-distance connections (PCC_1-MFC_{22}, PCC_{20}-SMN_{25}, MFC_{17}-MFC_{22}, SMN_2-SMN_{25}; Fig.3, purple lines).

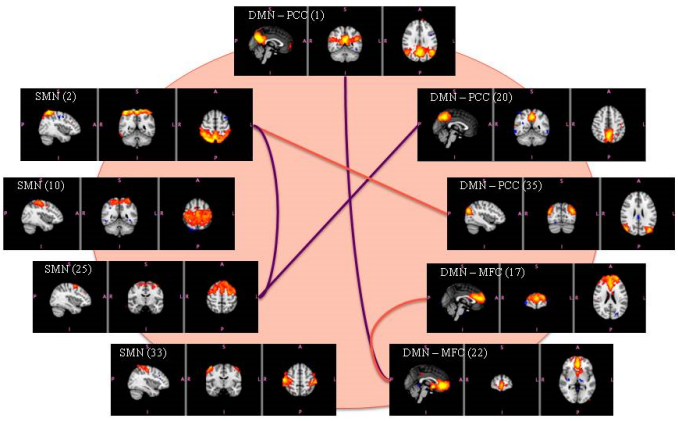

Fig. 1: Graphical representation of high dimensional time series analysis. All the lines indicate significant decrease of functional connectivity ($p<0.05$); purple lines highlight anterior-posterior disconnections.

Discussion: From the low-dimensional temporal analysis, it emerged that AD patients showed a significantly decreased average correlation ($p<0.05$) between PCC and MFC, which is in line with previous literature[2, 3]. The innovative high-dimensional study allowed to better localize the disconnection between the PCC and the MFC and to highlight alterations in other long-distance connections, which were not identifiable with the low-dimensional analysis. This anterior-posterior disconnection phenomenon is in line with previous studies[5], which suggest that AD affects long-range connectivity between frontal and parieto-occipital regions. Also from the high-dimensional analysis we observed that the connectivity damage is not confined into the DMN sub-networks, but it extends to other areas not involved in memory processes[6].

Conclusion: This study yielded further evidence to the hypothesis that networks with a possible hub role can be usefully parceled by high-dimensional ICA into sub-networks. The decomposition in sub-networks better localized the functional connectivity alterations in AD with respect to the more standard low-dimensional analysis. This could represent a useful insight for future research on AD and other neurodegenerative diseases, for the study of functional connectivity alterations at different stages of the pathology as surrogate biomarkers.

References:

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