CHARACTERIZATION OF THE DEFAULT MODE FUNCTIONAL CONNECTIVITY IN NORMAL AGING AND ALZHEIMER’S DISEASE: AN APPROACH COMBINING ENTROPY-BASED AND GRAPH THEORETICAL MEASUREMENTS

PJ Toussaint, S Maizé, D Coyne, A Messé, V Perlbarg, MO Habert, H Benali

Laboratoire d’Imagerie Fonctionnelle and LINeM, INSERM, UPMC, UMR-S 678 Paris, France

ABSTRACT

We have investigated functional connectivity of the default mode network (DMN) in normal aging and Alzheimer’s disease (AD) using resting state fMRI at 3T. Images from young and elderly controls, and patients with AD were processed using spatial independent component analysis to identify the DMN. Functional connectivity was quantified using integration and indices derived from graph theory. Four DMN sub-systems were identified: Frontal (medial frontal, superior frontal), Parietal (precuneus-posterior cingulate, lateral parietal), Temporal (medial temporal cortices), and Hippocampal (left and right). There was a decrease in antero-posterior interactions (lower global efficiency), but increased interactions within the Frontal and Parietal sub-systems (higher local clustering) in elderly compared to young controls. The decreased antero-posterior integration was more pronounced in AD patients compared to elderly controls, particularly in the precuneus-posterior cingulate region. The approach allows for a complete characterization of connectivity changes and could be applied to other resting state networks and pathologies.

Index Terms — Resting state fMRI, functional connectivity, functional networks, hierarchical integration, graph theoretical analysis

1. INTRODUCTION

Alzheimer’s disease (AD) is the most common form of dementia. This progressive disorder afflicts millions of elderly individuals worldwide, with symptoms that evolve from an initial mild memory loss to a decline of all cognitive functions. The disease is characterized by early structural changes in medial temporal structures, and early functional changes in the PCC. Diagnosis of AD is classically based on clinical and cognitive assessments, and research in the past decades has been aimed at increasing diagnostic accuracy and enabling earlier detection. Recently, there is an accruing interest in developing magnetic resonance imaging (MRI) based measures to evaluate disease stage and to predict likely progression of future cognitive decline. Volumetric measures of atrophy in cortical and hippocampal areas [1], ventricular measures [2], as well as tensor-based morphometry [3], have been proposed as biomarkers of disease progression to complement clinical and standard cognitive assessments. Resting state functional connectivity magnetic resonance imaging (fcMRI) studies constitute an increasing proportion of the search for biomarkers of disease. This approach detects temporal correlations of blood oxygen level-dependent (BOLD) signal fluctuations within spatially distinct groups of cortical and subcortical regions during task-free conditions [4, 5]. The default mode network (DMN) is one such group of brain regions that has been identified through resting state studies [6]. However, few studies have investigated the strength of functional interactions within the DMN. In this work, we have used a measure originating from information theory called integration to quantify functional connectivity [7, 8]. This approach allows to characterize the global integrative state of a functional network and describes covariation between regions. The method can be adapted for quantification of functional interactions between systems with multiple regions. We have measured functional connectivity within the DMN in cognitively normal young and aged individuals, as well as in patients with AD during a no-task condition. Our goal was to characterize the resting state functional connectivity changes in normal aging and Alzheimer’s disease using a method combining entropy-based and graph theory measures applied to fcMRI data. Using spatial independent component analysis (sICA), we identified regions of the DMN where changes in functional connectivity at rest due to neurodegeneration differ significantly between cognitively intact elderly controls and young subjects in a first step, and between elderly controls and patients with AD in the second, in order to differentiate the effects due to disease progression from those arising from normal aging. Indices from graph theory were then used to better characterize the DMN and its components.

2. METHODS

2.1. Subjects

Two control groups of 19 young (mean age±SD = 20 ± 1; M/F = 12/7) and 19 elderly (mean age±SD = 61 ± 1; M/F = 15/4 ) subjects, and a group of 20 patients with Alzheimer’s
disease (mean age±SD = 62 ± 9, interval 55-84 years old; M/F = 9/11) participated in the study. Subjects were assessed according to a clinical protocol which involved medical history recording, physical, neurological and neuropsychological examinations, as well as blood tests.

2.2. Data acquisition

All MRI acquisitions were performed at the CENIR (Pitié-Salpêtrière Hospital, Paris) with a 3T Siemens TRIO. During the resting state study, subjects were lying supine with their eyes closed. For each acquisition of gradient echo images, 45 contiguous transaxial slices were obtained using an echoplanar imaging (EPI) sequence with repetition time TR = 3 s, echo time TE = 40 ms, flip angle = 90°, bandwidth = 1.56 Hz per pixel, matrix size = 64 × 64, field-of-view FOV = 192×192 mm², and voxel size 1 × 1 × 1 mm³. A total of 119 EPI volumes were collected for each subject. High resolution T1-weighted 3D structural images were also acquired to serve as anatomical reference, using a magnetization prepared rapid gradient echo (MP-RAGE) sequence with TR = 14 ms, TE = 7.61 ms, matrix size = 256 × 256, and FOV = 256×256 mm², yielding in-plane resolution of 1×1 mm/pixel and slice thickness = 1 mm (contiguous slices).

2.3. Image preprocessing

All data preprocessing steps were performed using SPM8 software [9] and Matlab 7 (The MathWorks Inc., Natick, MA, USA). Slice time corrections were applied, followed by spatial realignment to a reference volume for each run and reslicing using 4th degree B-spline interpolation. Volumes were then co-registered with the Montreal Neurological Institute (MNI) EPI template image using an affine transform implemented in SPM8. Finally, the images were smoothed with an isotropic Gaussian filter of 5 mm full-width at half-maximum.

2.4. Selection of regions of interest

In order to quantify functional connectivity in the DMN, an exploratory data-driven method based on spatial independent component analysis (sICA) and hierarchical classification was applied to extract group representative large-scale functional networks [10]. Spatial ICA was applied on two groups for comparison: first on a group consisting in young and aged control subjects, and then on a group including the aged controls and Alzheimer’s disease patients. Hierarchical classification was used to identify the DMN amidst the obtained networks for each group as the pattern that showed co-activation of the regions described in Greicius et al. [6, 11], and the regions of interest were localised anatomically on the corresponding spatial maps. Based on correlation measures, we defined the default mode network as comprising four sub-systems of comparable size (same average number of edges) to avoid bias during group comparisons for global connectivity [12]. Each sub-system comprised highly correlated regions within the DMN: Frontal (F; medial frontal and superior frontal cortices), Parietal (P; precuneus - posterior cingulate, left and right lateral parietal areas), Temporal (T; left and right medial temporal cortices), and Hippocampal (H; left and right hippocampi). Regions of interest (ROIs) were defined using an iterative region growing algorithm around the corresponding voxel with maximum t-score.

2.5. Integration measures

Hierarchical integration is derived from mutual information (entropy) and informs on the global integration within a network [7, 8]. For a given network defined by a set of regional time courses $Y$, global integration $I(Y)$ is defined as $I(Y) = \sum_{i=1}^{N} H(y_i) - H(Y)$, with $N$ being the number of regions in the network, $y_i$ the associated regional time series, and $H(Y)$ the entropy of the system. In case of data with Gaussian distribution (a good approximation for signal averaged over tens of voxels), with mean $\mu$ and covariance matrix $\Sigma$, $I(Y) = \frac{1}{2} \ln \left( \frac{1}{\det(\Sigma)} \right)$, with $\Sigma_{ii}$ the diagonal elements, and $\det$ the matrix determinant. If $Y$ is composed of $K$ sub-systems $S_k$ ($k \in [1, \ldots, K]$) of the $N$ regions, such that $Y = \{Y_{S_1}, \ldots, Y_{S_K}\}$, integration can be decomposed into a sum of terms representing integration between sub-systems ($I_{inter}$), and within each sub-system ($I_{intra}$): $I(Y) = \sum I_{intra} + \sum I_{inter}$, where $I_{intra} = \sum_k I(Y_{S_k})$ and $I_{inter} = I(Y_{S_1}, \ldots, Y_{S_K}) = \sum_k H(Y_{S_k}) - H(Y_{S_1}, \ldots, Y_{S_K})$. In terms of covariance, integration between sub-systems is written: $I_{inter} = \frac{1}{2} \ln \left( \frac{\prod_{i=1}^{K} \Sigma_{S_i}}{\Sigma} \right)$, where $\Sigma_{S_i} S_k$ represent the portion of $\Sigma$ corresponding to $S_k$. Integration within a sub-system becomes: $I_{intra} = \frac{1}{2} \ln \left( \frac{\prod_{k=1}^{K} \Sigma_{S_k}}{\Sigma_{S_k S_k}} \right)$.

The covariance matrix can also be expressed as a function of the correlation matrix $R$ of signals of $Y$ as: $\Sigma = \sqrt{\text{diag}(\Sigma)} R \sqrt{\text{diag}(\Sigma)}$, where diag is the diagonal, and $R$ is the matrix of correlation coefficients ($r_{ij}$) calculated between the mean regional time courses. Total integration thus becomes: $I = \frac{1}{2} \ln | R |$ which shows that integration derives from functional connectivity. The total integration of the default mode network was calculated as $I_{DMN} = \sum I_{intra} + \sum I_{inter}$. Posterior probabilities were used to calculate the evidence, a measure of integration significance, as: $e(A | Y) = 10 \log_{10} \left( \frac{p(A | Y)}{p(A)} \right)$ (in decibels, dB), where $p(A | Y)$ is the posterior probability of an assertion $A$ related to any pair of integration measure (total, inter- or intra-system), given the regional time courses $Y$.

2.6. Graph analysis

Graphs are sets of vertices (or nodes) and corresponding sets of edges that can be used to represent networks [12]. An
edge connecting two vertices can be interpreted as the presence of interaction or connection between them. Information about the connectivity structure of the graph is contained in the adjacency matrix $A$, whose elements $A_{ij} = 1$ when an edge exists between vertices $i$ and $j$, and $A_{ij} = 0$ otherwise. The previously calculated correlation matrix was thresholded (from 0.1 to 0.9, with steps of 0.05) and used to approximate the adjacency matrix. For each threshold value, three indices were calculated to obtain representative graphs of each index as a function of correlation threshold, in order to characterize functional connectivity within the network: the degree, which is the number of edges (connections) arriving at or leaving a given node (region); the mean path length, which is the shortest distance between two nodes; and the mean clustering coefficient, which is defined as the ratio of the number of existing links to the number of possible links between neighbours of a given node. Metrics were calculated for the weighted original graph (with weight $w_{ij} = 1 - r_{ij}$) as well as 1000 completely random graphs.

3. RESULTS

Independent component analysis resulted in a DMN co-activation pattern for each group. The 10 regions of interest selected for the study are shown on an MRI template for young vs elderly controls (Fig. 1), and for elderly controls vs AD patients (Fig. 1). Thresholded correlation matrices for all groups are shown in Fig. 2. Compared to young controls, elderly controls showed decreased fronto-parietal (antero-posterior) integration within the network and its constituents. Graph theoretical measures complemented the approach and helped to better characterize the functional architecture of this network. The findings of decreased PCC resting state functional connectivity with frontal, temporal, and parietal cortices in cognitively normal aged individuals without amyloid beta deposits (as corroborated by positron emission tomography with $^{11}$C-PIB, a marker of amyloid deposition) compared to young controls confirms that the aging process itself is associated with disrupted functional connectivity in the DMN, even in the absence of pathology.

4. DISCUSSION

The current results describing decreased DMN functional connectivity in Alzheimer’s disease are in line with previous reports of DMN dysfunction in AD [11, 13, 14]. Characterising functional integration in the brain involves the identification of interacting regions, as well as quantification of the functional interactions between them [15]. Several previous resting state studies focused on the first step [4, 6, 16]. Our work attempted to provide insight on the functional connectivity of the DMN by studying the strength of functional interactions between its constituting regions. The DMN was first identified using a method based on sICA. Splitting the DMN into four sub-networks using correlation and hierarchical integration measures allowed to quantify functional connectivity within the network and its constituents. Graph theoretical measures complemented the approach and helped to better characterize the functional architecture of this network. The findings of decreased PCC resting state functional connectivity with frontal, temporal, and parietal cortices in cognitively normal aged individuals without amyloid beta deposits (as corroborated by positron emission tomography with $^{11}$C-PIB, a marker of amyloid deposition) compared to young controls confirms that the aging process itself is associated with disrupted functional connectivity in the DMN, even in the absence of pathology.

Fig. 1. Mask of 10 regions obtained by spatial ICA on young (YC) and elderly (EC) controls (top), and elderly controls with AD patients (bottom) superposed on an MRI template, showing the four sub-systems Frontal (F), Hippocampal (H), Temporal (T), and Parietal (P) (see section 2.4 for details).

5. REFERENCES

Fig. 2. Thresholded correlation matrices (threshold = 0.197; p < 0.05) for young controls (YC), elderly controls (EC), and patients with Alzheimer’s disease (AD).

Fig. 3. Mean graph measures as a function of threshold for young vs elderly controls (top row) and elderly controls vs patients with AD (bottom row).


