Physica A 478 (2017) 113–119

Contents lists available at ScienceDirect

Physica A

journal homepage: www.elsevier.com/locate/physa

Network analysis in detection of early-stage mild cognitive impairment

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HIGHLIGHTS

- For EMCI patients, abnormal brain functional connectivities have already appeared.
- The brain areas affected by EMCI mainly distribute in frontal and temporal lobes.
- A trend of brain lateralization appears in the left hemisphere of EMCI patients.
- The E_{DD} index of brain functional networks, may be helpful for detecting EMCI.

ARTICLE INFO

Article history:
Received 24 July 2016
Received in revised form 21 November 2016
Available online 6 March 2017

Keywords:
Network analysis
Mild cognitive impairment
Resting-state functional magnetic resonance imaging
Entropy of the degree distribution

ABSTRACT

The detection and intervention for early-stage mild cognitive impairment (EMCI) is of vital importance However, the pathology of EMCI remains largely unknown, making it be challenge to the clinical diagnosis. In this paper, the resting-state functional magnetic resonance imaging (rs-fMRI) data derived from EMCI patients and normal controls are analyzed using the complex network theory. We construct the functional connectivity (FC) networks and employ the local false discovery rate approach to successfully detect the abnormal functional connectivities appeared in the EMCI patients. Our results demonstrate the abnormal functional connectivities have appeared in the EMCI patients, and the affected brain regions are mainly distributed in the frontal and temporal lobes In addition, to quantitatively characterize the statistical properties of FCs in the complex network, we herein employ the entropy of the degree distribution (E_{DD}) index and some other well-established measures, i.e., clustering coefficient (C_C) and the efficiency of graph (E_G). Eventually, we found that the E_{DD} index, better than the widely used C_C and E_G measures, may serve as an assistant and potential marker for the detection of EMCI.

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http://dx.doi.org/10.1016/j.physa.2017.02.044
0378-4371/

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia [1], which causes the patients suffer from progressively worsening memory, reasoning, and other aspects of cognition [2]. Disappointing outcomes from clinical trials and treatment for AD have prompted much focus on its early detection and intervention [3].

Mild cognitive impairment (MCI), characterized by memory impairment, is widely recognized as a highly risky stage of conversion to AD [4]. Recently, because of its vital importance, increasing researchers are tending to clarify the pathology and characteristic of the earliest and mildest symptomatic phase of MCI, called early-stage mild cognitive impairment (EMCI). Genetic risk factors on the transitional normal to EMCI phase are evaluated [5] and the role of a certain genotype in EMCI subjects is assessed [6]. Neuropsychological methods are used to investigate differences in cognitive function between EMCI patients and normal controls (NC) [7,8]. Based on the concerned imaging data, Ye et al. [9] made a comparison of cortical thickness in EMCI patients versus NC by using structural magnetic resonance imaging (MRI) With the help of diffusion tensor images, Lim et al. [10] divided the EMCI and NC into different subgroups according to the cerebrospinal fluid (CSF) biomarkers and investigated the differences of white matter connectivity among them. Moreover, Jing et al. [11] used resting-state functional MRI (rs-fMRI) to determine whether there are any abnormalities in different frequency bands between NC and EMCI patients via the analysis of amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF).

However, the pathology of EMCI remains largely unknown, making it be challenge to the clinical diagnosis [12,13]. More work on exploring, tracking, and identifying markers of EMCI-related transitions needs to be conducted. In practice, the Mini-Mental State Examination (MMSE) has been widely used for the dementia detection, but it is reported to have limited effectiveness for detecting cognitive impairment [14]. In order to investigate the underlying characteristics of brain functional networks in EMCI and explore the auxiliary diagnosis methods, we herein adopt the theory of complex network [15], which has been extensively applied for diverse complex system, including markets, ecosystems, computer circuits and gene–gene interactiomes [16]. Especially, modern network approaches are also explored in brain studies to reveal the fundamental principles of brain architecture and function [17]. The complex network theory can provide a relatively simple and increasingly popular way of modeling the human brain connectome [18] and has been demonstrated to be a powerful tool for revealing the inherent information in fMRI data derived from AD patients [19–21]. Nonetheless, its application to the detection of EMCI patients is still limited.

Therefore, in this paper, we aims to investigate the inherent changes of functional brain networks in EMCI by employing the rs-fMRI data derived from age- and gender-matched NC and EMCI patients. After parcellating the fMRI volumes according to the atlas, multiple-regional time series are extracted and the binary network is constructed by using the Pearson's correlation analysis between each pair of the time series. Afterwards, some of the classical topological indexes of the network are assessed. Our results validate the hypothesis that the entropy of the degree distribution of the network may serve as an assistant and potential marker for detecting EMCI.

2. Materials & methods

2.1. Participants

In this study, we studied the rs-fMRI data, consisting of 25 EMCI and 18 age- and gender-matched normal controls (NC). These data were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database [22], and the same data preparation process has been published in Ref. [23]. The including criterions in this paper are: (i) the subjects were scanned under the same preset parameters; (ii) the subject's MMSE score was given in the ADNI database; (iii) the ages for the subjects were restricted within 80 years. The detailed information was summarized in Table 1. Note that there is no significant difference in the baseline MMSE scores between the EMCI group and NC group.

2.2. Image acquisition and transformation into time series

MRI images were acquired on a 3.0 T MRI scanner (Philips) with TR/TE as 3000/30 ms and flip angle (FA) of 80°. Each rs-fMRI series had 140 volumes, and each volume consisted of 48 slices with the dimension of 64×64 and the voxel size of $3.31 \times 3.31 \times 3.31$ mm^3. The 3D T1-weighted sagittal structural images with a resolution of $1 \times 1 \times 1.2$ mm^3 were acquired using a magnetization prepared rapid gradient echo (TR = 6.8 ms; TE = 3.16 ms; FA = 9°). After discarding the first ten volumes, standard rs-fMRI preprocessing was conducted with the SPM8-based DPARSFA toolbox [24], including (i) slice timing; (ii) motion correction; (iii) normalization; (iv) spatial smoothing; (v) nuisance regression including white matter, CSF signals and six head-motions; (vi) de-trending linear drift and temporal filter (0.01–0.08 Hz). None of the subjects had head movements exceeding 1.5 mm or 1.5°. Finally, the volumes were parcellated into 90 cerebral regions of interest (ROIs) by automated anatomical labeling (AAL) atlas [25] and the regional mean time series of each ROI were extracted. The illustration of the ROIs and their regional mean time series are shown in Fig. 1.