Available online at www.sciencedirect.com

ScienceDirect

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

Original Research Article

Altered modular organization in schizophrenia patients and analysis using supervised association rule mining

R. GeethaRamani, K. Sivaselvi *

College of Engineering, Anna University, Guindy, Chennai, India

ARTICLE INFO

Article history:
Received 22 July 2015
Received in revised form
18 February 2016
Accepted 18 February 2016
Available online 16 March 2016

Keywords:
Schizophrenia
Graph theory
Data mining
Resting state fMRI
Functional connectome
Modularity

ABSTRACT

Complex neuro-degenerative disorders affect the intrinsic topological architecture of brain connectivity. There are very few studies concentrating on the occurrence of modular changes in the structural and functional connectome of people diagnosed with Schizophrenia. In this study, group averaged analysis on modular organization of 15 healthy and 12 Schizophrenic subjects were performed to understand the topological alterations occurring in brain networks of diseased against normal. The major contributing regions for changes in optimal brain architecture were also identified. It also involves the investigation of individual subject's functional connectivity and the attempts were made to extract the modular specific roles of brain regions through supervised association rule mining. On comparison with group average measurements, it was found to produce similar results and it was understood that inter and intra-module connections evidently varied in Schizophrenia because of alterations in extremely organized modular architecture. This is believed to provide new insights in understanding the complex neuro-degenerative disorder through analysis on modular organization of functional brain networks. Highly influential regions were also determined. These regions were found to be potential biomarkers for Schizophrenia diagnosis.

1. Introduction

Schizophrenia is a heterogeneous disorder that exhibits multiple symptoms which are classified into positive (Hallucinations, bizarre delusions) [1,2], negative (social engagement, speech disturbances, motivational problems), cognitive (memory, attention, executive functioning problem) and affective depression (mostly associated with bipolar disorders). These symptoms occur due to abnormalities in the components of brain [3–5] leading to functional malformation in aspects relating to attention, memory, language processing, emotional processing and social cognition [6–8].

* Corresponding author at: College of Engineering, Anna University, Guindy, Chennai 600025, India.
E-mail addresses: rgeetha@yahoo.com (R. GeethaRamani), sivaselvik@yahoo.co.in (K. Sivaselvi).

http://dx.doi.org/10.1016/j.bbe.2016.02.002

One percent of world population is affected by this neuro-disorder [9,10] and it leads to loss of economy due to unemployment, health care, etc. [11]. Early detection of disease will be helpful for better treatment [12]. The causes for Schizophrenia are not well defined and it is hypothesized due to some genetic or environmental factors [13–15]. The behaviour and experiences of subjects alone reveal Schizophrenia patients to the society.

The application of complex network analysis in brain disorders have been revealed in previous research works. Complex network analysis has received increased level of attention in recent days due to the easy representation and examination of any structure in an efficient manner. Network analysis has its application in diverse fields viz. social group, marketing, metabolic networks, etc. It has extended its application to analyse typical human brain structure. The complicated brain structure is represented in the form of graph where nodes are regions or voxels and edges are white fibre density or temporal correlations. This network model is termed as human brain connectome. These connectome can be extensively studied using graph theoretical approaches to understand composite brain structure in healthy or diseased as well as age related changes.

Connectome has become a buzzing word among neuroscientists since minimal alterations can also be detected through network analysis. Brain network can be derived from neuroimages through pre-processing techniques namely slice timing, realignment, de-trending, filtering, smoothing, etc. Structural connectome can be obtained from DTI (Diffusion Tensor Imaging), DWI (Diffusion Weighted Imaging), etc., and functional connectome from EEG (Electroencephalography), fMRI (functional Magnetic Resonance Imaging), etc. The topological alterations in human brain are caused due to various diseases namely Alzheimer's disease, Schizophrenia, etc. This research aims to investigate modular organization of functional brain network of complex neuro-disorders namely Schizophrenia and unearth the aberrations in brain regions.

Schizophrenia can be diagnosed with various neuroimaging techniques namely structural MRI, DTI, task based fMRI and resting state fMRI. Both structural [16] and functional connectivity [17,18] were analysed in Schizophrenia at different stages (chronic and early onset) [19–21]. Schizophrenia has been studied by many researchers in the perspective of discrimination of patients from healthy subjects. Various structural images have been used to analyse the alterations in Schizophrenia affected brain by previous studies. Apart from structural connectivity studies, functional connectome analysis can be performed with the aid of either resting state fMRI (RS-fMRI) or task based fMRI. Due to its benefits over task based fmri, RS-fMRI is employed in this investigation. It does not involve any complex processes and is acquired in a relaxed state [22] and it overcomes few disadvantages like cognitive changes or performance incapability which is very common in task based fMRI acquisition [23]. BOLD (Blood Oxygen Level Dependent) signals obtained in RS-fMRI may unravel knowledge patterns by involving multiple patients and analysing multiple cortical systems [24].

Functionally organized brain can be studied elaborately using RS-fMRI. Generally univariate tests and random effect analysis forms the resting state networks based on functional connectivity [18,25]. Due to its benefits, Resting State Networks (RSN) constructed from RS-fMRI [26] finds its application in classifying mentally diseased patients affected by Alzheimer's disease [27–30], bipolar disorder, depression [25], ADHD (Attention Deficit Hyperactivity Disorder) [31], etc., from normal. Some earlier studies have shown hyper-connectivity within Default Mode Network (DMN) [14,32] whereas few others have found hypo-connectivity within DMN [33,34]. The above case can be observed in other resting state networks also [32,34].

Researchers have applied various data mining techniques to discriminate normal from Schizophrenia patients and few of them are presented in Text S1. Graph theoretical approaches were used to understand the functional segregation and integration of whole brain in the network model. Global and local measurements are supportive for comprehending brain connectivity. Modularity is one of the graph theoretical measures that can depict fundamental organization of brain and can combine regions into functional modules [35,36]. This measure can maintain local specialization and global integration [35]. It can develop module without affecting other module's functionality [37]. It can be used to study the changes in connectivity aroused due to infancy, aging [38] or neuropsychiatric diseases [39,40]. To understand the modular transformation in structural and functional connectivity of human brain due to neuro-disorders, extensive studies are being made in the literature. Multimodal images of Schizophrenia had been analysed in the perspective of functional segregation in earlier studies. The detail on the investigation of Schizophrenia based on the structural MRI can be obtained from Text S2. The research works involving functional MRI of Schizophrenia is presented below.

Liu et al. [41] worked with resting state functional magnetic resonance imaging obtained from 62 participants out of which 31 were affected by Schizophrenia and others were healthy. They investigated the functional brain connectivity using graph theory approaches to study topological properties of brain and have reported changes in prefrontal, parietal and temporal lobes. They have also found major variations in small world properties of the network. Wang et al. [42] worked on functional correlation of 33 normal and 23 Schizophrenia patients and determined hubs through degree centrality. They found hubs were increased in frontal and occipital regions whereas reduced in temporal and limbic areas.

Yu et al. [43] reported weaker connectivity and worst clustering coefficient in functional networks of Schizophrenia. The changes in regional role were also evident. Van den Heuvel et al. [44] analysed white matter correlations of 45 normal and 48 Schizophrenic people. They determined connectivity declination between the frontal and parietal association areas based on the calculation of degree centrality and rich-club coefficient.

Topological and modular organization studies were carried out for various neuro-disorders to understand the changes related to the specific disorders. He et al. [45] examined modular organization of spontaneous neuronal activity at spatial and temporal scales to identify highly influential region and path in the brain network. Lyoo et al. [46] studied structural abnormalities in cortical areas of patients diagnosed with Type 1 Diabetes Mellitus. They found loss of hubs in prefrontal regions and disturbances in regions contributing for the functions like