Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Different alterations in brain functional networks according to direct and indirect topological connections in patients with schizophrenia

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ARTICLE INFO

Article history:
Received 25 August 2016
Received in revised form 13 January 2017
Accepted 13 January 2017
Available online xxxx

Keywords:
Schizophrenia
fMRI
Graph-theoretical analysis
Efficiency
Adjacency
Indirect adjacency

ABSTRACT

Schizophrenia displays connectivity deficits in the brain, but the literature has shown inconsistent findings about alterations in global efficiency of brain functional networks. We supposed that such inconsistency at the whole brain level may be due to a mixture of different portions of global efficiency at sub-brain levels. Accordingly, we considered measuring portions of global efficiency in two aspects: spatial portions by considering sub-brain networks and topological portions by considering contributions to global efficiency according to direct and indirect topological connections. We proposed adjacency and indirect adjacency as new network parameters attributable to direct and indirect topological connections, respectively, and applied them to graph-theoretical analysis of brain functional networks constructed from resting state fMRI data of 22 patients with schizophrenia and 22 healthy controls. Group differences in the network parameters were observed not for whole brain and hemispheric networks, but for regional networks. Alterations in adjacency and indirect adjacency were in opposite directions, such that adjacency increased, but indirect adjacency decreased in patients with schizophrenia. Furthermore, over connections in frontal and parietal regions, increased adjacency was associated with more severe negative symptoms, while decreased adjacency was associated with more severe positive symptoms of schizophrenia. This finding indicates that connectivity deficits associated with positive and negative symptoms of schizophrenia may involve topologically different paths in the brain. In patients with schizophrenia, although changes in global efficiency may not be clearly shown, different alterations in brain functional networks according to direct and indirect topological connections could be revealed at the regional level.

1. Introduction

In patients with schizophrenia, connectivity deficits have been shown over connections in local brain regions, including fronto-frontal (Cole et al., 2011), fronto-temporal (Friston and Frith, 1995; Horn et al., 2012; Khadka et al., 2013; Meyer-Lindenberg et al., 2005), fronto-parietal (Kim et al., 2003; Tan et al., 2006), and occipito-temporal regions (Kim et al., 2005). Also, at the whole brain level, alterations in brain functional networks have been shown in terms of network parameters such as global efficiency, which is the average of efficiency for every pair of nodes in a whole brain network. But there were inconsistencies in the findings: in the resting state, global efficiency changed (Alexander-Bloch et al., 2010; Lo et al., 2015; Lynall et al., 2010) or not (Liu et al., 2008; Zhu et al., 2016); in the context of experimental tasks, global efficiency altered (Yu et al., 2011) or not (Fornito et al., 2011).

Schizophrenia is described in terms of positive and negative symptoms as well as cognitive dysfunction. Such a wide variety of symptoms and associated brain changes in schizophrenia may not be well summarized as a single measure of global efficiency. We supposed that a mixture of different portions of global efficiency could be a possible cause for inconsistent findings at the whole brain level. Portions of global efficiency could be thought in two aspects. First, global efficiency is a summary for a whole brain network, such that portions of global efficiency at sub-brain levels may be different even for two brain functional networks with the same global efficiency. For this concern, we divided the whole brain network into sub-brain networks. We measured each sub-brain network's contribution to global efficiency to search for changes in spatial portions of global efficiency in patients with schizophrenia.

Second, global efficiency is a distance-based network parameter and it can be contributed by different portions depending on distance-based attributes of connections. For this concern, we separated portions of

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http://dx.doi.org/10.1016/j.schres.2017.01.025
0920-9964/

global efficiency according to whether topological connections were direct or indirect. Here, the classification between direct and indirect topological connections has been motivated by the distinction between monosynaptic and polysynaptic pathways in neuronal pathways, but its application is not necessarily subject to a biological basis. The meaning of direct and indirect topological connections may or may not be concerned with being anatomically or functionally direct or indirect of connections depending on the way a network is constructed. We defined new network parameters attributable to direct and indirect topological connections and measured them to examine changes in topological portions of global efficiency in patients with schizophrenia.

We thought that spatial and topological portions of global efficiency would be useful, as they could provide detailed views about alterations in brain functional networks, specifically in relation to different contributions of brain regions and topological connections to global efficiency. We hypothesized that alterations in brain functional networks may be unclear in terms of a single measure of global efficiency, as found to be inconsistent in the literature, but they could be identified in terms of spatial and topological portions of global efficiency.

2. Methods

2.1. Subjects

Twenty-two patients with schizophrenia (32.9 ± 8.3 years, 14 females) participated in this study. Controls consisted of age- and sex-matched 22 healthy subjects (30.4 ± 6.3 years, 14 females). Demographic and clinical characteristics are described in Table 1. The shared exclusion criteria for participants were meeting DSM-IV-TR criteria (American Psychiatric Association, 2000) based on the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) for any other psychiatric disorders other than schizophrenia. Also, participants who had alcohol, cigarettes or substance abuse history within the 6 months, history of receiving electroconvulsive therapy in the prior 6 months, chronic neurological disorders, severe or acute medical conditions, breast-feeding, or any contraindications to magnetic resonance imaging scanning were excluded.

This study was conducted with the understanding and full written consent of each participant according to the Declaration of Helsinki. The Institutional Review Board of Uijeongbu St. Mary's Hospital, College of Medicine, the Catholic University of Korea approved the study.

2.2. Symptom severity

Symptom severity of patients was measured using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Patients' total scores as well as subscale scores for the positive scale, negative scale, and general psychopathology scale of the PANSS are presented in Table 1.

Table 1
Demographic and clinical variables of participants in this study.

		Patients with schizophrenia (n = 22)	Healthy controls (n = 22)	p value
Age (years)		32.9 ± 8.3	30.4 ± 6.3	0.255
Sex ratio (males:females)		8:14	8:14	1.000
Medication[a]		10 paliperidone 8 aripiprazole 3 olanzapine 2 blonanserin 1 amisulpride 1 quetiapine 1 risperidone	n/a	
PANSS score	Positive scale	16.1 ± 7.4	n/a	
	Negative scale	15.8 ± 4.5		
	General psychopathology scale	35.1 ± 11.1		
	Total	67.0 ± 20.7		

[a] Multiple medications duplicately counted. PANSS, Positive and Negative Syndrome Scale.

2.3. Imaging data acquisition

Magnetic resonance images were acquired using a 1.5 T Avanto system (Siemens AG, Erlangen, Germany). For each participant, resting state fMRI data of 150 volumes were obtained using a T2*-weighted gradient echo echo-planar imaging sequence: repetition time (TR) = 2000 ms, echo time (TE) = 24 ms, number of slices = 29, slice thickness = 4 mm, matrix size = 128 × 128, and in-plane resolution = 1.80 mm × 1.80 mm. Structural MRI data were also acquired using a magnetization-prepared rapid gradient echo sequence: number of slices = 160, slice thickness = 1 mm, matrix size = 512 × 512, and in-plane resolution = 0.45 mm × 0.45 mm.

2.4. Preprocessing of fMRI data

Preprocessing of fMRI data was performed using the routines in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) and DPARSF (http://rfmri.org/DPARSF/). Preprocessing steps were followed in the order of spatial realignment for correcting for head movement, normalisation into the same coordinate frame as the template brain conforming to the Montreal Neurological Institute space, and spatial smoothing with a Gaussian kernel of 4 mm full width at half maximum. The transformation parameters for normalisation was derived from segmentation of the high-resolution structural image coregistered to the mean functional image. In addition, a linear trend mainly due to a systematic increase or decrease of signal was removed, and nuisance covariates including six head movement parameters estimated during spatial realignment, and the cerebrospinal fluid and white matter signals were regressed out. The functional images were then band-pass (0.01–0.08 Hz) filtered to reduce the effects of very low frequency and high frequency physiological noise.

2.5. Brain network construction

A brain functional network was constructed by defining nodes and estimating edges between them. Nodes were defined on 264 elements of brain organization, which were modelled as 10 mm diameter spheres around coordinates presented in (Power et al., 2011). We extracted the representative signal of each node as a principal eigenvariate in singular value decomposition of voxel-wise signals (Friston et al., 2006), as implemented in SPM8. Edges were estimated from Pearson's correlation-based functional connectivity between the representative signals of the 264 nodes.

We modelled a brain functional network as unweighted and undirected. Functional connectivity between all pairs of 264 nodes composed a 264 × 264 matrix of correlation coefficients. A specific selection of a threshold would yield a sparse matrix consisting of 1's (presence of edges) and 0's (absence of edges) corresponding to correlation coefficients above and below the threshold respectively. Since choosing a specific threshold value is arbitrary, we used a set of different threshold values, which corresponded to a range of sparsity or cost of the brain functional network.

2.6. Efficiency, adjacency, and indirect adjacency

We employed efficiency to assess functional integration in brain functional networks. It was introduced to measure how efficiently information is exchanged over a network (Latora and Marchiori, 2001). Shortest path length, d_{ij}, is the minimum number of edges between two nodes i and j, and the efficiency, e_{ij}, between them is defined as the inverse of shortest path length: $e_{ij} = 1 / d_{ij}$, such that $0 \le e_{ij} \le 1$ (Rubinov and Sporns, 2010).

Please cite this article as: Park, C., et al., Different alterations in brain functional networks according to direct and indirect topological connections in patients with schiz..., Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.01.025