Applied Informatics

RESEARCH

Open Access

Structural covariance model reveals dynamic reconfiguration of triple networks in autism spectrum disorder

Zhiliang Long, Xujun Duan, Heng Chen, Youxue Zhang and Huafu Chen[*]

*Correspondence:
chenhf@uestc.edu.cn
Key Laboratory
for Neuroinformation
of Ministry of Education,
Center for Information
in BioMedicine, School of Life
Science and Technology,
University of Electronic
Science and Technology
of China, Chengdu 610054,
China

Abstract

The data open sharing provides us opportunity to investigate mechanisms underlying autism spectrum disorder (ASD) by employing advanced techniques. In the current study, we employed structural covariance (SC) model to investigate the development of triple networks in ASD. Three hundred and seven ASD and 337 typical controls were collected and further classified into four distinct age cohorts. Night brain seeds belonging to default modal network, salience network, and central executive network were obtained. SC between those seeds, as well as its topological properties, was calculated for each group within each age cohort. Statistical analysis revealed that ASD had dynamic reconfigurations of SC of the triple networks, especially the right fronto-insular cortex. The results might indicate that ASD had specific mechanism within distinct age cohort. Additionally, the big data sharing, together with the SC modal, was able to facilitate understanding of the mechanism underlying ASD.

Keywords: Big data, Structural covariance, Triple networks, Autism spectrum disorder

Background

In the last decades, much progress has been made to the data open sharing, especially in the neuroimaging studies of brain function and disease (Russell et al. 2014). On the one hand, the increasing big data sharing has profound impact on research in cognitive neuroscience and psychiatry, resulting in advances in the diagnosis and treatment of psychiatric and neurological disease. On the other hand, the big data sharing is able to facilitate development of advanced analysis methods, which in turn help find the new biomarkers in brain diseases. The structural covariance (SC) model is such a method that has its potential value in understanding of various psychiatric conditions (Aaron et al. 2013).

The SC is a phenomenon that inter-individual differences in the structure of a brain region often covary with the inter-individual structural difference of other brain areas. It has been recognized that the genetics, behavior, and plasticity together contributed to covariance between brain areas (Krista et al. 2009; William et al. 2001). The SC is usually characterized by the linear dependence between two large samples of human datasets using the product-moment correlation coefficient, the Pearson's r. The method has been widely employed to investigate the development of brain structures across lifespan (Brandon et al. 2010), and also the neurodegenerative disorders, such as the Alzheimer's

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disease (Yong et al. 2008) and Schizophrenia (Serge et al. 2005). Question surrounding the SC in autism spectrum disorder (ASD) still remains.

The ASD is a neurodevelopment disorder characterized by deficits in communication and social interaction, along with repetitive patterns of behavior and interests. Neuroimaging studies have demonstrated that dysfunction of triple networks [including central executive network (CEN), salience network (SN), and default modal network (DMN)] were associated with ASD (Vinod et al. 2011). To the best of our knowledge, there were no studies investigating the SC of those networks, especially their dynamic configuration across ages in ASD. The lack of investigation of the SC in ASD is probably due to the limited number of participants recruited in previous studies. Therefore, in the current study, we collected big datasets from the Autism Brain Imaging Data Exchange (ABIDE). Then we employed the SC modal to investigate the SC and topological properties of the triple networks and their development across ages in ASD.

Methods

Participants and data preprocessing

The datasets supporting the conclusions of this article are available from the ABIDE (http://fcon_1000.projects.nitrc.org/indi/abide/) database. The datasets involved 307 ASD and 337 typical controls (TC). Participants were further classified into four groups based on different age cohorts. They are group 1 (59 ASD, 63 TC, age, 6–11 years), group 2 (109 ASD, 114 TC, age, 11–15 years), group 3 (46 ASD, 52 TC, age, 15–18 years), and group 4 (93 ASD, 107 TC, age, >18 years). Written informed consent was obtained from all participants. Experimental protocols were approved by the local Institutional Review Boards.

All participants were scanned using a 3 Tesla SIEMENS scanner following diagnostic assessment. Subjects were asked to relax and look at a white cross-hair against a black background. The anatomical image was then acquired for each participant.

Data preprocessing was conducted using SPM8 software. First, all T1-weighted anatomical images were manually reoriented to place the anterior commissure at the origin of the three-dimensional Montreal Neurological Institute (MNI) space. The images were then segmented into gray matter, white matter, and cerebrospinal fluid (John et al. 2005). A diffeomorphic non-linear registration algorithm was used to spatially normalize the segmented images (John et al. 2007). This procedure generated a template for a group of individuals. The resulting images were spatially normalized into the MNI space using affine spatial normalization, and resampled into $1.5 \times 1.5 \times 1.5$ mm³. Finally, the resulting gray matter images were smoothed with a 6 mm full-width half-maximum (FWHM) isotropic Gaussian kernel.

Structural connectivity estimation

Nine coordinates in MNI space were obtained from a previous study (Lucina et al. 2011). The brain areas corresponding to those coordinates were left and right fronto-insular cortex (lFIC/rFIC), anterior cingulate cortex (ACC), left and right dorsolateral prefrontal cortex (lDLPFC/rDLPFC), left and right posterior parietal cortex (lPPC/rPPC), ventromedial prefrontal cortex (VMPFC), and posterior cingulate cortex (PCC). The lFIC/rFIC and ACC belong to SN. The lDLPFC/rDLPFC and lPPC/rPPC belong to CEN. The

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VMPFC and PCC belong to DMN. Night spherical regions of interests (ROIs) were generated with radius of 8 mm based on those coordinates. Those ROIs were multiplied with a gray matter mask to exclude voxels outsides the gray matter. The gray matter density value was averaged across voxels within each ROI for each participant. The SC analysis was then conducted as follows:

The Pearson correlation analysis was performed between pairs of ROIs to characterize the SC in ASD and HC. The permutation test was employed to determine the statistical significance level. Briefly, we first calculated the between-group difference of the correlation value. We then randomly assigned each participant to one of the two groups with the same size as the origin groups of ASD and HC. This randomization procedure was repeated for 10,000 permutations, which generated a null permutation distribution. For each permutation, the new between-group difference was calculated. We then assigned a p value to the between-group difference by computing the proportion of differences exceeding the null distribution values. The multiple comparisons were corrected using an exploratory threshold of 1/N (here, N is number of edges, which is 9*8/2). Notably, the effect of sites and full IQ were regressed out before the Pearson correlation analysis. The whole procedure mentioned above was repeatedly conducted on each of the four groups.

Topological properties calculation

Within each age cohort, we computed the topological properties of SC networks including clustering coefficient, shortest path length, local efficiency and global efficiency, for ASD group and HC group, and compared those properties between the two groups.

The connectivity sparsity was firstly employed to threshold SC network. Connectivity sparsity was computed as number of existing edges divided by maximum possible number of edge in a network. Here, a connectivity sparsity of 40 % was used to ensure that all SC networks were full connected. We then computed those topological properties for each SC network.

The clustering coefficient of a node i is calculated as:

$$C_i^{\mathrm{w}} = \frac{1}{k_i(k_i - 1)} \sum_{j,h \in N} (w_{ij} w_{ih} w_{jh})^{1/3},$$

where w_{ij} is the weight between node i and node j; k_i is the degree of node i; N is the number of nodes. The clustering coefficient of a network is computed as:

$$C^{\mathrm{w}} = \frac{1}{N} \sum_{i \in N} C_i^{\mathrm{w}}$$

This measure indicates the extent of local interconnectivity or cliquishness in network. The characteristic shortest path length of a network is defined as:

$$L^{\mathrm{w}} = \frac{N(N-1)}{\sum_{i=1}^{N} \sum_{j \neq i}^{N} 1/L_{ij}},$$

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where L_{ij} is the path between node i and node j with shortest length. This measure quantifies the ability for information propagation in parallel.

The global efficiency of a network is computed as:

$$E_{\text{global}} = \frac{1}{N(N-1)} \sum_{i \neq j \in N} \frac{1}{L_{ij}}$$

which is a measure of parallel information transformation.

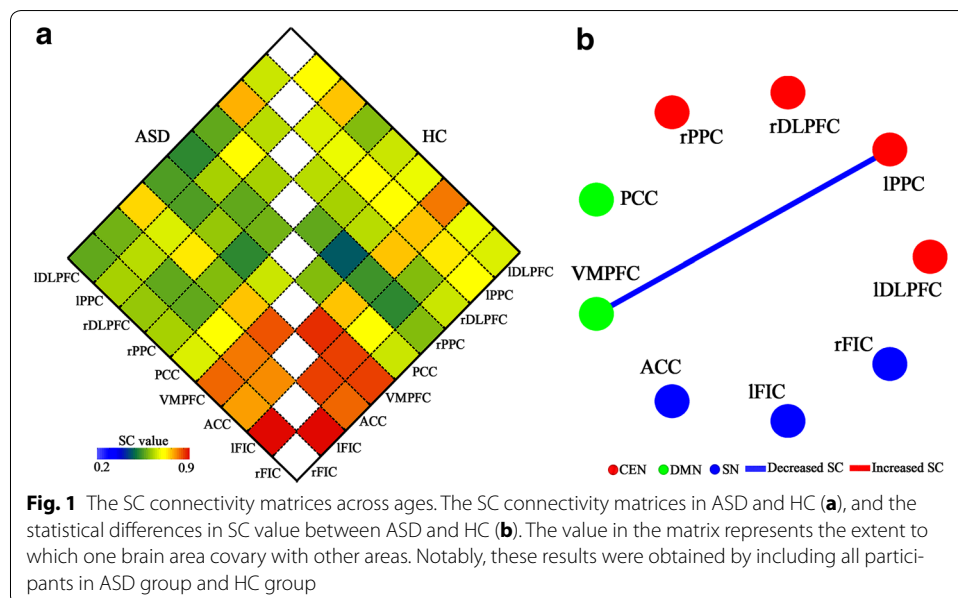While the local efficiency of a network is defined as:

$$E_{\text{local}} = \frac{1}{N} \sum_{i \in G} E_{\text{global}}(G_i),$$

where $E_{\text{global}}(G_i)$ is the global efficiency of the neighborhood sub-graph G_i of the node i. The local efficiency can be understood as a measure of fault tolerance of the network, indicating how well each sub-graph exchanges information when the index node is eliminated.

The statistical test was conducted using permutation test, as we did in the "Participants and data preprocessing" section. The statistical level of $p < 0.05$ was considered as significant.
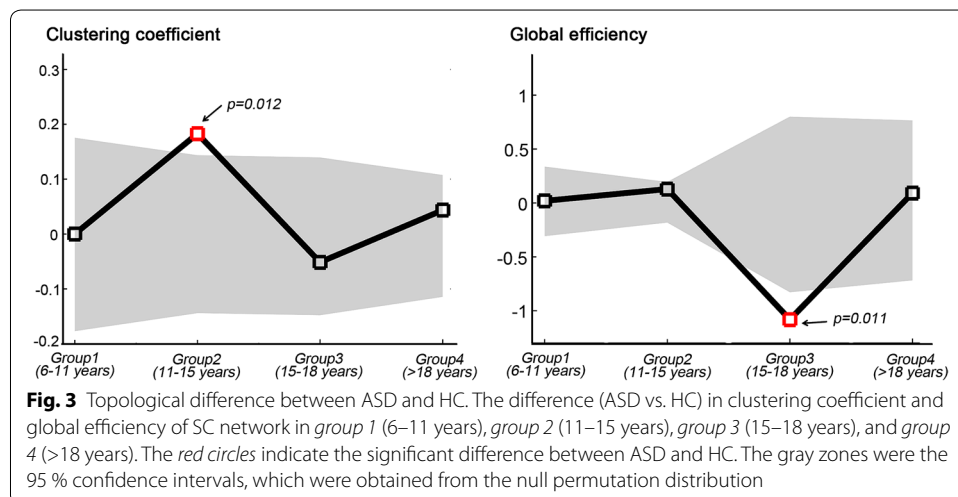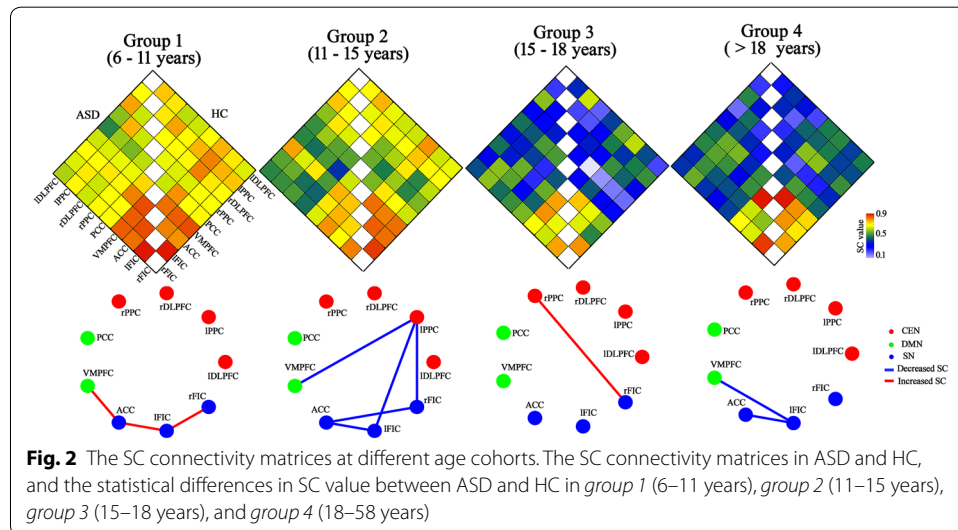
Results

The gray matte density value of each ROI strongly covaries with the values of rest ROIs in both ASD group and HC group (Fig. 1a). The SC value within SN was much higher, compared to those within DMN and CEN, and also those between the three networks (Fig. 1a). Further, ASD had significant reduced SC value between lPPC and VMPFC (Fig. 1b).

Fig. 1 The SC connectivity matrices across ages. The SC connectivity matrices in ASD and HC (**a**), and the statistical differences in SC value between ASD and HC (**b**). The value in the matrix represents the extent to which one brain area covary with other areas. Notably, these results were obtained by including all participants in ASD group and HC group

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We then observed different SC pattern between distinct age cohorts. In group 1, ASD had increased SC between ACC and lFIC, between ACC and VMPFC, and between rFIC and lFIC. In group 2, ASD had reduced SC between lPPC and rFIC, lFIC and VMPFC, between ACC and rFIC, lFIC. In group 3, increased SC was found in ASD between rPPC and rFIC. While in group 4, decreased SC was observed in ASD between ACC and lFIC, between VMPFC and lFIC (Fig. 2).

We further found that patients with ASD had significantly higher clustering coefficient at early adolescent, and lower global efficiency at late adolescent, compared to HC (Fig. 3). There was no difference in characteristic shortest path length and local efficiency between ASD and TC within each cohort.

Fig. 2 The SC connectivity matrices at different age cohorts. The SC connectivity matrices in ASD and HC, and the statistical differences in SC value between ASD and HC in *group 1* (6–11 years), *group 2* (11–15 years), *group 3* (15–18 years), and *group 4* (18–58 years)

Fig. 3 Topological difference between ASD and HC. The difference (ASD vs. HC) in clustering coefficient and global efficiency of SC network in *group 1* (6–11 years), *group 2* (11–15 years), *group 3* (15–18 years), and *group 4* (>18 years). The *red circles* indicate the significant difference between ASD and HC. The gray zones were the 95 % confidence intervals, which were obtained from the null permutation distribution

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Discussion

In the current study, we observed dynamic SC reorganization of triple networks, especially the rFIC, by employing the SC model. It has been demonstrated that the rFIC, a critical component of SN, mediates interaction between CEN and DMN (Vinod et al. 2010; William et al. 2007). A developmental study had shown that the maturation of rFIC connectivity plays a critical role in the brain network maturation to support complex cognitive processes (Lucina et al. 2011). Those results probably suggested abnormal development of cognitive processes in ASD.

More specifically, we firstly found decreased SC between lPPC and VMPFC, which might suggest impaired executive function in ASD (Timothy et al. 2006). Interestingly, we then observed dramatically distinct SC patterns, especially the connectivity of rFIC in ASD across age cohorts. The findings here provided structural substrates for functional deficits of rFIC observed in ASD (Jyri-Johan et al. 2010), and might suggest specific mechanism underlying ASD in different age cohort. Additionally, a lower global efficiency in ASD was observed at specific age cohort, indicating that the altered information communication pattern within the triple networks was affected by ages. Overall, we were the first to report the dynamic SC reconfiguration of the triple networks in ASD using SC modal, and highlighted the importance of age effect in autistic research.

Conclusions

This study investigated the dynamic changes of SC and its topological properties as function of age cohorts in patents with ASD by employing a large dataset. The results suggested the crucial role of triple network abnormalities in pathology of ASD at specific age ranges, and highlighted effect of age on autistic development.

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