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Altered brain network topology in left-behind children: A resting-state functional magnetic resonance imaging study

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ABSTRACT

Whether a lack of direct parental care affects brain function in children is an important question, particularly in developing countries where hundreds of millions of children are left behind when their parents migrate for economic or political reasons. In this study, we investigated changes in the topological architectures of brain functional networks in left-behind children (LBC). Resting-state functional magnetic resonance imaging data were obtained from 26 LBC and 21 children living within their nuclear family (non-LBC). LBC showed a significant increase in the normalized characteristic path length (λ), suggesting a decrease in efficiency in information access, and altered nodal centralities in the fronto-limbic regions and motor and sensory systems. Moreover, a decreased nodal degree and the nodal betweenness of the right rectus gyrus were positively correlated with annual family income. The present study provides the first empirical evidence that suggests that a lack of direct parental care could affect brain functional development in children, particularly involving emotional networks.

1. Introduction

Parental care can affect not only child behavior but also the maturation of the brain systems that support psychological and emotional development in human beings (Callaghan & Tottenham, 2016; Rifkin-Graboi et al., 2015). Numerous animal experiments have provided evidence that maternal deprivation can lead to the deterioration of emotional and cognitive processes during adulthood (Akillioglu, Yilmaz, Boga, Binokay, & Kocaturk-Sel, 2015; Marco et al., 2015; Xiong, Yang, Cao, Mao, & Xu, 2015). However, it remains unclear whether and how the lack of direct parental care can affect brain function in children.

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This issue is potentially of considerable public health significance. Millions of parents in developing countries migrate to other countries for economic or political reasons, leaving their children behind (Liu et al., 2015; Lu, 2015; Siriwardhana et al., 2015). In China, for example, there are more than 60 million left-behind children (LBC) (China Women's Federation, 2013), and among these LBC, there is a significantly higher prevalence of negligence (Zhao et al., 2014), higher level of suicidal ideation (Gao et al., 2010) and greater risk of developing depression and anxiety (Cheng & Sun, 2015; Wang et al., 2015) than there is among children living within their nuclear family (non-LBC). However, the effect of a lack of parental care on brain function in LBC largely remains unknown.

In the past few years, neuroimaging technologies have been increasingly used to study the neurobiological mechanism underlying the effects of adverse psychosocial experiences on brain development (Bick et al., 2015). Neglected children and adolescents have demonstrated impaired functioning in the dorsal executive regions (Mueller et al., 2010) and hyperactivation in the amygdala and hippocampus in response to seeing fearful and angry faces (Maheu et al., 2010). Early institutional care has been shown to be associated with long-lasting effects on neuroanatomic development, such as reduced total grey and white matter volumes (Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012) and diminished white matter connectivity in the uncinate fasciculus region (Eluvathingal et al., 2006) in institutionalized children in comparison with non-institutionalized controls. Furthermore, removal from conditions of negligence in early life and entry into a high-quality family environment has been reported to normalize the trajectory of white matter growth (Bick et al., 2015). In addition, children who experienced early maternal deprivation have exhibited acceleration in the maturation of amygdala–prefrontal connectivity, which is considered an ontogenetic adaptation in humans in response to early adversity (Gee et al., 2013). These results support the notion that separation from the primary caregiver may have an adverse effect on children (Mueller et al., 2010) and influence brain development. However, the conditions faced by institutionalized children are at times more dire and extreme than the conditions faced by LBC in the care of relatives.

The human brain is a complex network, and recent advances in graph-based theoretical approaches have allowed the noninvasive characterization of its topological properties; this has proven to be an effective and informative way to explore brain function and human behavior (Bullmore & Bassett, 2011; Bullmore & Sporns, 2009). In this approach, the brain is modeled as a network composed of a number of nodes connected by edges. For instance, a normal brain is functionally organized in a small-world fashion (characterized by high local specialization and high global integration between brain regions), a prominent feature shared by various social, economic, and biological networks (Bullmore & Bassett, 2011). That is, the nodes of the network have greater local interconnectivity or cliquishness than a random network, but the minimum path length between any pair of nodes is smaller than a regular network or lattice (He, Chen, & Evans, 2007; Watts & Strogatz, 1998). Furthermore, such an organization pattern is disrupted in neuropsychiatric disorders, such as major depressive disorder (Zhang et al., 2011) and schizophrenia (Liu et al., 2008). Although different brain diseases show different changes, the topology of the functional network of an abnormal brain can be regarded as less optimal when it deviates more from the small-world network topology, suggesting both a possible role in pathophysiology and a potential biomarker. However, the topological centralities of the functional connectomes in LBC have not yet been investigated.

In general, we hypothesized that both global and local topological features would differ significantly between LBC and non-LBC. To test our hypothesis, we collected resting-state functional magnetic resonance imaging (r-fMRI) data from 26 LBC and 21 non-LBC and analyzed their intrinsic brain connectivity networks using graph theoretical approaches. Between-group differences and relationships with clinical variables were also investigated.

2. Materials and methods

2.1. Participants

A total of 47 subjects were recruited, including 26 LBC and 21 age and sex-matched non-LBC. All subjects were classmates or schoolmates from the same local primary schools with similar educational environments in a town of southeastern China. All LBC subjects were living with their grandparents as their parents had immigrated abroad for work. They communicated with their parents occasionally over the phone or via internet audiovisual software. In contrast, non-LBC lived with their nuclear family throughout their childhood. Subjects' intelligence quotient (IQ) was measured using the Chinese Wechsler Intelligence Scale for Children (C-WISC), administered by an experienced child psychologist. All subjects were screened by an experienced child psychiatrist using the Chinese modified version of SCID-I (Non-patient Edition) (Wang, Yang, Jiang, & Michael, 2009) to exclude any Axis I psychiatric diagnoses, and all of their first-degree relatives were free of psychiatric illness. Exclusion criteria for all subjects included the presence of (a) head trauma; (b) a history of organic brain disorders, neurological disorders, or cardiovascular diseases; (c) any physical illness, as assessed by personal history and laboratory analysis; (d) MRI contraindications; and (e) recent medication that might affect brain function. The demographic and clinical characteristics of these subjects are summarized in Table 1.

MR images of all subjects were first reviewed by a neuroradiologist to ensure that there were no structural abnormalities or data quality flaws. This study was approved by the Research Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. The guardians of the children were provided with a detailed information

Table 1
Demographics and clinical characteristics of the subjects[a].

Variables	LBC (n = 26)	non-LBC (n = 21)	P value
Age(years)[b]	10 ± 1.96 (range: 7–12)	10.57 ± 1.78 (range: 8–14)	0.3[c]
Gender(male/female)	14-Dec	16-May	0.11[d]
Delivery mode(eutocia/caesarean)[b]	Feb-24	May-16	0.12[d]
Height(cm)	141.73 ± 12.11	145.00 ± 11.45	0.35[c]
Weight(kg)	36.91 ± 1065	39.07 ± 12.80	0.54[c]
Years of guardian's education[b]	3.80 ± 2.22	8.60 ± 2.94	**0.00**[c]
Annual family income(10000RMB)[b]	15.73 ± 10.27	15.14 ± 8.88	0.83[c]
Full scale IQ	92.81 ± 13.21	97.52 ± 15.84	0.28[c]
Verbal IQ	90.16 ± 12.47	96.33 ± 17.77	0.21[c]
Performance IQ	96.31 ± 13.39	99.57 ± 13.50	0.41[c]
Separation time (years)[b]	7.08 ± 2.37 (range: 2–11)	–	–
Age at parental departure (months)[b]	22.62 ± 29.78 (range: 1–84)	–	–

Abbreviations: IQ, intelligence quotient; LBC, left-behind children; non-LBC, children living within the nuclear family.

[a] Data are presented as the mean ± SD (range of minimum–maximum).

[b] Age, delivery mode, years of guardian's education, annual family income, separation time and the age at parental departure were reported by participants' parents/guardians at the time of magnetic resonance scanning.

[c] P value obtained by two-tailed two-sample *t*-test.

[d] P value obtained by two-tailed Pearson chi-square test.

sheet about the study, and their written informed consent was obtained. The methods were carried out in accordance with the approved guidelines.

2.2. R-fMRI data acquisition and preprocessing

The r-fMRI dataset was acquired using a 3-T magnetic resonance system (Signa HDxt EXCITE, General Electric, Milwaukee) with an eight-channel phased array head coil. All participants were instructed to keep their eyes closed and to think of nothing in particular during the acquisition. The sequence parameters were as follows: repetition time/echo time (TR/TE) 2400/40 ms; flip angle 90°; 34 axial slices per volume; 4 mm slice thickness (no slice gap); matrix 64 × 64; field of view (FOV) 220 × 220 mm^2; voxel size 3.4375 × 3.4375 × 4 mm^3. A total of 128 vols were collected for each subject.

Image preprocessing was carried out using GRETNA (http://www.nitrc.org/projects/gretna/). Data preprocessing included the removal of the first 5 vols, slice timing correction, head movement correction, spatial normalization (T1 segmentation), smoothing (FWHM Gaussian kernel of 4 mm), removal of linear trend, temporal bandpass filtering (0.01–0.08 Hz) and nuisance signal regression (24-parameter head motion profiles, global signal, CSF signal and WM signal).

The first 5 time points were discarded to avoid the instability of the initial MRI signal. First, the images were corrected for intra-volume acquisition time differences between slices using the Sinc interpolation and were corrected for inter-volume geometric displacement because of head movement using a six-parameter (rigid-body) spatial transformation. After these corrections, the images were spatially normalized to the standard space of the Montreal Neurological Institute using an optimum 12-parameter affine transformation and nonlinear deformations, and they were resampled to 3-mm cubic voxels. The resulting data were further temporally bandpass filtered (0.01–0.08 Hz) to reduce the effects of low-frequency drift and high-frequency physiological noises. Finally, the global signal, the white matter signal, the cerebrospinal fluid signal, and the motion parameters (three translational and three rotational parameters) were regressed out.

2.3. Functional connectivity matrix and graph construction

The network was constructed using GRETNA (http://www.nitrc.org/projects/gretna/) (Suo et al., 2015; Zhang et al., 2011). A network is composed of nodes and edges between nodes. Herein, nodes represent brain regions, and edges represent the statistical interdependence in blood oxygen level-dependent signals between different regions. First, the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) was used to divide the whole brain into 90 cortical and subcortical regions of interest, and each was considered a network node. Next, to define the network edges, we calculated the partial correlation coefficients between the regional mean time series of all possible pairs of brain regions. The partial correlation coefficient between any two regions represents their conditional dependences by excluding the effects of the other 88 regions defined in the AAL atlas (Suo et al., 2015; Zhang et al., 2011). Before the correlation analysis, the representative mean time series of each region was acquired by averaging the time series of all voxels within that region, followed by a correction of head motion effects by regressing out the head motion profiles estimated in the image realignment from the mean time course. The residuals of the regression analyses were used to compute the partial correlation in this study, resulting in a 90 × 90 partial correlation matrix for each subject (Fig. S1). Finally, individual partial correlation matrices were converted into binarized matrices (i.e., adjacency matrices) $A_{ij} = [a_{ij}]$ according to a predefined threshold (see below for the threshold selection), where entry a_{ij} was 1 if the absolute value of the partial correlation between regions 'i' and 'j' was larger than the threshold and 0 otherwise.

The networks of individual subjects differed in the number of edges (Wen et al., 2011). To address this difference, we applied a range of sparsity thresholds, 'S', to the correlation matrices to provide each graph with the same number of edges. For each subject, 'S' was defined as the fraction of the total number of edges remaining in a network. This approach normalized all resultant networks to have the same number of nodes and edges by applying a subject-specific correlation coefficient threshold and minimized the effects of possible discrepancies in the overall correlation strength between groups, thereby enabling us to explore the between-group differences in relative network organization (He et al., 2009). Instead of selecting a single threshold, we thresholded each correlation matrix repeatedly over a wide range of sparsity levels according to the following criteria: 1) The average degree (the degree of a node is the number of connections linked to the node) of all nodes in each thresholded network was larger than log(N) with N = 90 here, denoting the number of nodes; and 2) the small-worldness scalar, σ, of the thresholded networks was larger than 1 for all participants (He, Chen, & Evans, 2008; Watts & Strogatz, 1998). This procedure generated a threshold range of $0.10 < S < 0.40$ with an interval of 0.01. For the brain networks at each sparsity level, we calculated both global and node network metrics.

2.4. Small-world properties and network efficiency

For brain networks at each sparsity threshold, we calculated both global and regional network measures. The global measures included 1) small-world parameters (Watts & Strogatz, 1998) involving a clustering coefficient (C_p), a characteristic path length (L_p), a normalized clustering coefficient (gamma, γ), a normalized characteristic path length (lambda, λ), and small-worldness (sigma, σ); and 2) network efficiency (Latora & Marchiori, 2001) involving local efficiency (E_{loc}) and global efficiency (E_{glob}). We calculated L_p as the harmonic mean distance between all possible pairs of regions to address the disconnected graphs dilemma (Newman, 2003). The regional measures included three nodal centralities: the nodal degree (κ), nodal efficiency (e), and nodal betweenness (b).

2.5. Statistical analysis

We calculated the area under the curve (AUC) for each network metric. The AUC for a general metric γ was calculated over the sparsity range from S_1 to S_n with an interval of D_S, here $S_1 = 0.10$, $S_n = 0.40$, and $D_S = 0.01$. The AUC provided a summarized scalar for the topological characterization of brain networks, that is, independent of a single threshold selection and sensitive to topological alterations in brain disorders (Suo et al., 2015; Zhang et al., 2011). The integrated AUC metric has been used in previous brain network studies and is sensitive in detecting topological alterations of brain disorders (He et al., 2009).

Group comparisons of topological metrics (global metrics and nodal centralities) were carried out by nonparametric permutation tests (Suo et al., 2015; Zhang et al., 2011) using Matlab (www.mathworks.com) while controlling for age and gender. Briefly, we first calculated the between-group difference in the mean value of each network metric. To test the null hypothesis, we randomly reallocated all of the values for each network metric into two groups and recomputed the mean differences between them. This randomization procedure was repeated 10,000 times, and the 95th percentile points of each distribution were used as the critical values for a two-tailed test of the null hypothesis with a type I error of 0.05. Of note, before the permutation tests, multiple linear regression analyses were applied to remove the confounding effects of age and gender for each network metric (independent variable: the AUC of each network metric; dependent variables: age and gender). To address the problem of multiple comparisons, we adopted a Benjamini Hochberg false discovery rate (FDR) correction method at a significance level of 0.05 (Benjamini, Drai, Elmer, Kafkafi, & Golani, 2001).

Once significant between-group differences were observed in any network metric, we further assessed the relationships between these metrics and guardians' years of education, annual family income, subjects' full-scale IQ scores, verbal IQ scores, and performance IQ scores, the separation time, and subjects' age at parental departure in the LBC group, performed by multiple linear regression analyses with age and gender as covariates.

The statistical analysis of the demographic and clinical data was performed with SPSS software (http://www.spss.com), version 19.0 (Chicago, IL).

3. Results

3.1. Demographic and clinical comparisons

There were no significant differences in age, gender, delivery mode, height, weight, annual family income or IQ between LBC and non-LBC ($P > 0.05$; Table 1). Guardians' education level was significantly lower in the LBC group than in the non-LBC group ($P < 0.001$; Table 1).

3.2. Global topological organization of the functional connectome

The topological properties of brain networks depend on the choices of thresholds. In this study, we determined a data-specific small-world regime at a sparsity range of $0.10 < S < 0.40$ (Fig. 1). In the defined threshold range, both the LBC group and the non-LBC group showed a small-world topology in the brain functional connectome (Fig. 1). The LBC group, compared with the non-LBC group, showed a significantly increased normalized characteristic path length (λ) ($P = 0.04750$), with no

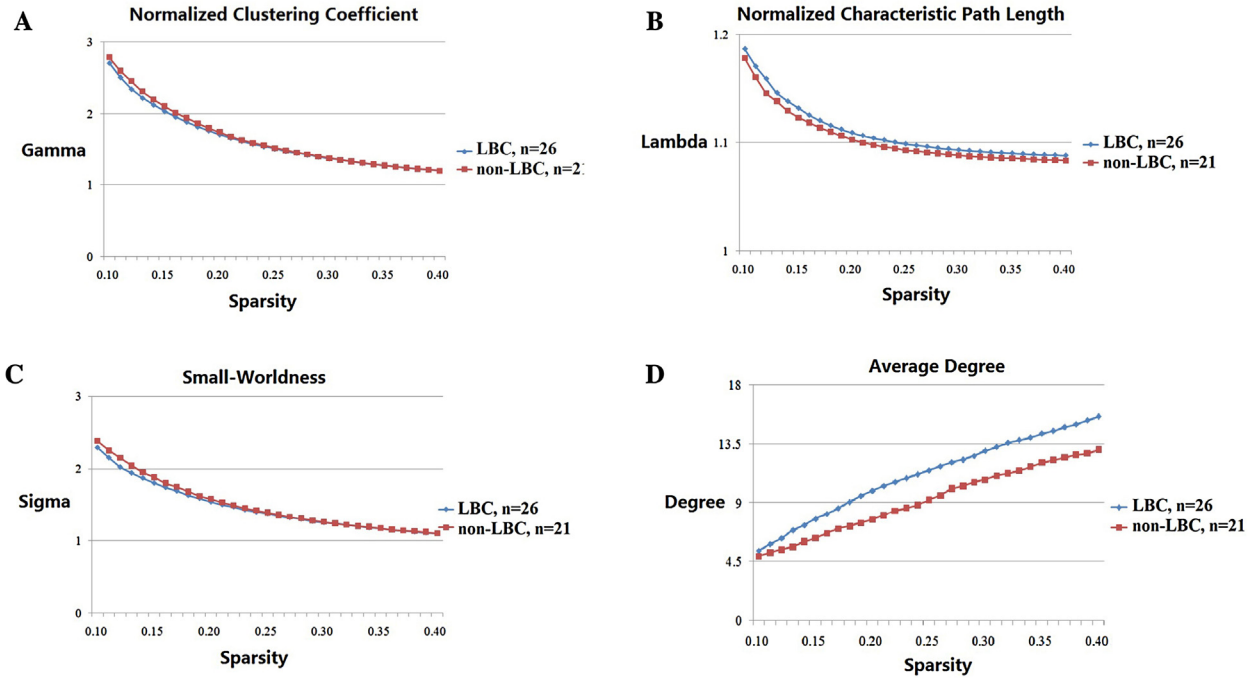

Fig. 1. The key small-world parameters of the functional connectome as a function of the sparsity threshold. Both the LBC group and the non-LBC group showed (A) a normalized clustering coefficient greater than 1 and (B) a normalized characteristic path length approximately equal to 1, indicating that both groups exhibited a small-world topology. In this study, the small-world regime was defined as $0.10 < S < 0.4$, where (C) the individual σ values were larger than 1 and (D) the average degree of all nodes of each thresholded network was larger than 4.5. Abbreviations: LBC, left-behind children; non-LBC, children living within the nuclear family.

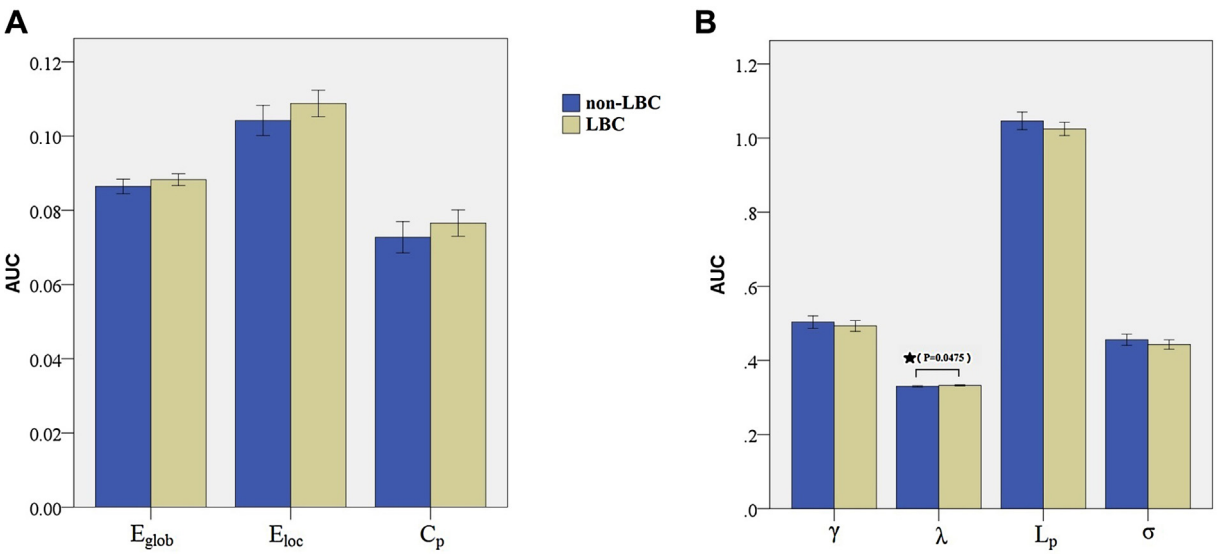

Fig. 2. The differences in topological properties of the brain functional connectome between the LBC and non-LBC groups. The black stars (★) indicate a statistically significant difference in λ between the two groups ($P < 0.05$, uncorrected). Error bars denote standard deviations. Abbreviations: AUC, area under the curve; C_p, clustering coefficient; E_{glob}, global efficiency; E_{loc}, local efficiency; LBC, left-behind children; L_p, characteristic path length; non-LBC, children living within the nuclear family; γ, normalized clustering coefficient; λ, normalized characteristic path length; σ, small-worldness.

significant differences in clustering coefficient C_p ($P = 0.1561$), characteristic path length L_p ($P = 0.1264$) or the normalized clustering coefficient (γ) ($P = 0.3367$). With regard to network efficiency, the two groups showed no significant difference in local efficiency E_{loc} ($P = 0.0874$) or global efficiency E_{glob} ($P = 0.1326$) (Fig. 2).

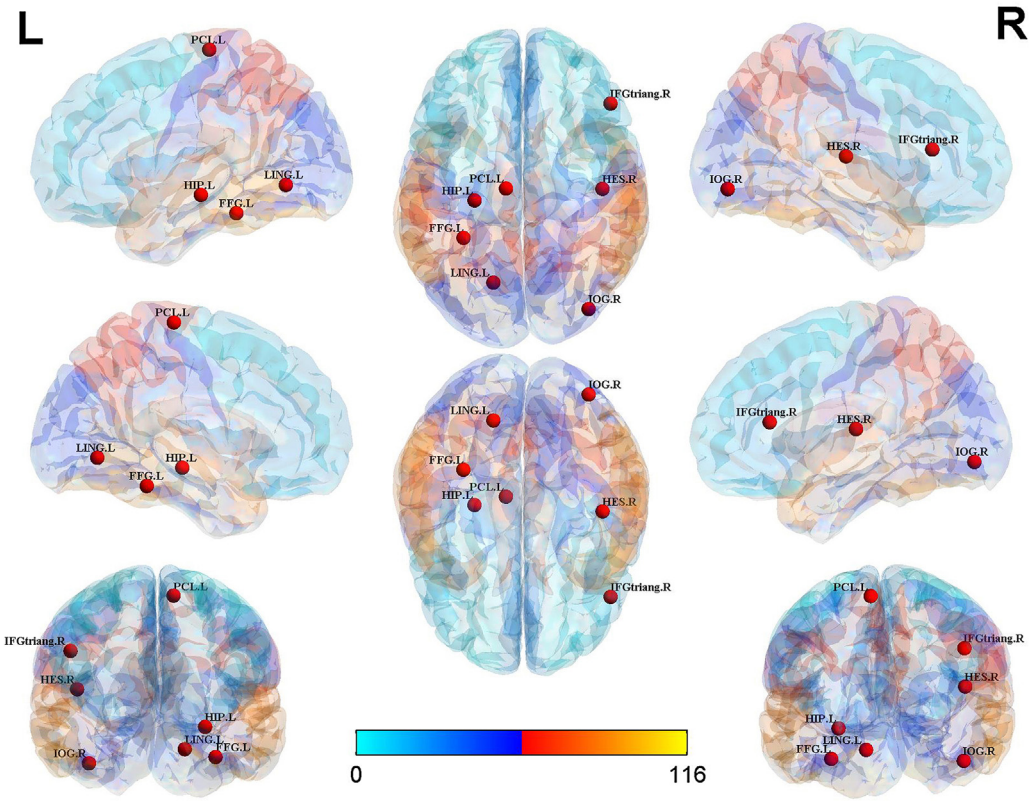

Fig. 3. LBC showed significantly increased nodal centralities in comparison with non-LBC controls. Abbreviations: FFG.L, left fusiform; HES.R, right Heschl; HIP.L, left hippocampus; IFGtriang.R, right inferior frontal gyrus triangular part; IOG.R, right inferior occipital; L, left; LBC, left-behind children; Ling.L, left lingual; non-LBC, children living within the nuclear family; PCL.L, left paracentral lobule; R, right.

Table 2
Regions showing altered nodal centralities in the LBC group when compared with the non-LBC group[a].

	P value		
Brain Areas	Nodal Degree	Nodal Efficiency	Nodal Betweeness
LBC > HC			
Right inferior frontal gyrus, triangular part	0.098	0.161	**0.019**
Left paracentral lobule	0.551	0.336	**0.03**
Left hippocampus	0.095	**0.031**	0.051
Left fusiform	**0.038**	**0.044**	0.326
Right Heschl	0.326	0.174	**0.041**
Left lingual	0.098	**0.049**	0.202
Right inferior occipital	0.179	**0.05**	0.43
LBC < HC			
Right superior frontal gyrus, orbital part	**0.003**	**0.007**	0.448
Right olfactory	**0.041**	**0.05**	0.064
Right rectus	**0.002**	**0.01**	**0.048**

Abbreviations: LBC, left-behind children; non-LBC, children living within the nuclear family.
[a] Regions were considered abnormal in the LBC if they exhibited significant between-group differences ($P < 0.05$, uncorrected) in at least one of the three nodal centralities (shown in bold font).

3.3. *Regional topological organization of the functional connectome*

We identified the brain regions showing significant between-group differences in at least one nodal centrality ($P < 0.05$, uncorrected). Compared with non-LBC, LBC showed increased nodal centralities in the right inferior frontal gyrus triangular part (IFGtriang.R), left paracentral lobule (PCL.L), left hippocampus (HIP.L), left fusiform (FFG.L), right Heschl (HES.R), left lingual (ling.L) and right inferior occipital (IOG.R) (Fig. 3, Table 2). Decreased nodal centralities were found in the right superior frontal gyrus orbital part (ORBsup.R), right olfactory (OLF.R) and right rectus (REC.R) (Fig. 4, Table 2).

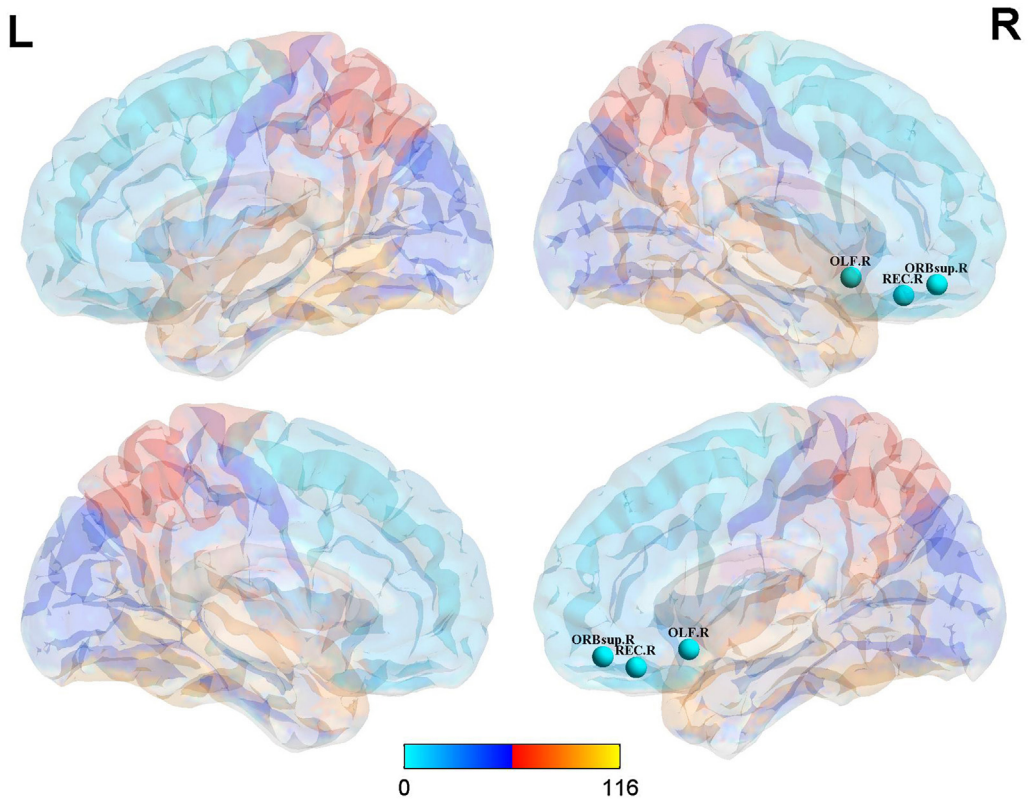

Fig. 4. LBC showed significantly decreased nodal centralities in comparison with non-LBC controls. Abbreviations: L, left; LBC, left-behind children; non-LBC, children living within the nuclear family; OLF.R, right olfactory; ORBsup.R, right superior frontal gyrus orbital part; R, right; REC.R, right rectus.

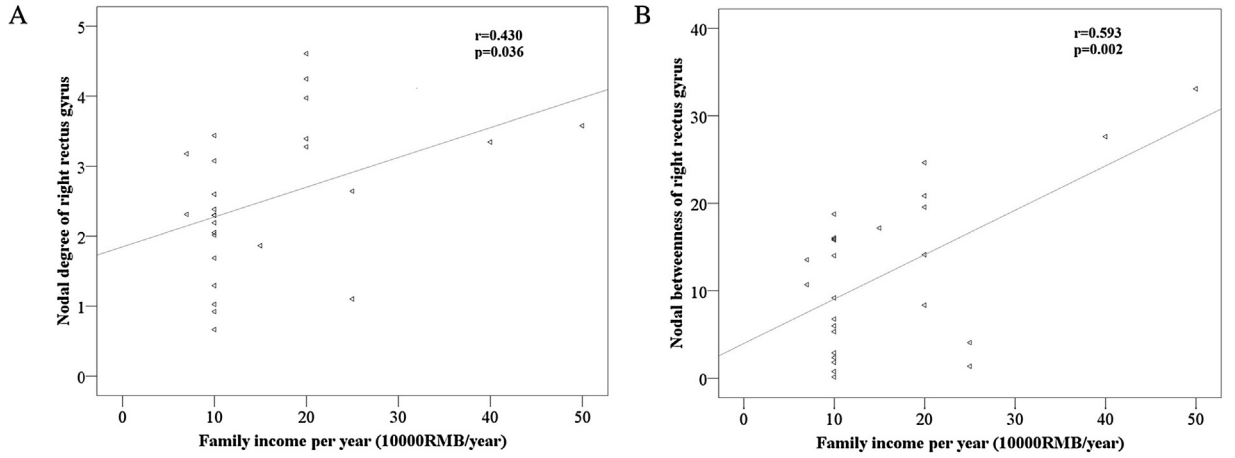

Fig. 5. Scatter plots of the nodal degree (A) and the nodal betweenness (B) of the right rectus gyrus compared to the annual family income in the LBC group. Abbreviations: LBC, left-behind children.

3.4. Relationships between network metrics and clinical variables

Guardians' years of education, subjects' full-scale IQ scores, verbal IQ scores, and performance IQ scores, the separation time and subjects' age at parental departure in the LBC group showed no correlations with the global or nodal metrics with between-group differences. The nodal degree ($P = 0.036$; Fig. 5A) and the nodal betweenness ($P = 0.002$; Fig. 5B) of the right rectus gyrus were positively correlated with annual family income but not with the other nodal centralities or global metrics.

4. Discussion

To the best of our knowledge, this is the first empirical study to use graph theoretical analysis to investigate the brain functional connectome topology in LBC. We found that brain functional networks exhibited an economical small-world topology in both groups. At the global level, however, LBC had a significantly increased normalized characteristic path length (λ), suggesting a decrease in efficiency in information access. At the nodal level, LBC showed altered nodal centralities in the fronto-limbic regions and motor and sensory systems, including increased nodal centralities in the right inferior frontal gyrus triangular part, left paracentral lobule, left hippocampus, left fusiform, right Heschl, left lingual and right inferior occipital gyrus and decreased nodal centralities in the right superior frontal gyrus orbital part, right olfactory and right rectus gyrus. Moreover, the decreased nodal degree and the nodal betweenness of the right rectus gyrus were positively correlated with annual family income. In short, our study provides the first empirical evidence for the altered topological organization in functional networks in LBC.

These brain differences may be explained by the different direct parental care in the two groups. It has been found that a long duration of separation from parents is associated with an increased risk of mental health problems in LBC (Cheng & Sun, 2015). Previous studies from our lab and peers (Reuveni et al., 2016; Suo et al., 2015) have also revealed, with sample sizes similar to this study's, that intense training or major stress events can induce acute changes in the human brain network. Separation from parents can be considered an emotional stressor to LBC. Abnormal structural rich-club organization was evident in clinical subjects at high risk for psychosis (Schmidt et al., 2016), suggesting that abnormal structural brain network organization may reflect an endophenotypic marker of psychosis. Therefore, brain network technology may be more sensitive in detecting neural developmental changes than physiological and behavioral measurements, and our findings may be related to LBC's psychological deficits in later stages (Cheng & Sun, 2015; Fan, Su, Gill, & Birmaher, 2010; He et al., 2012; Mou, Griffiths, Fong, & Dawes, 2013).

Although LBC showed an overall small-world topology, a significantly increased normalized characteristic path length (λ) was found in LBC in comparison to non-LBC. In the brain network, the characteristic path length (L_p) is the shortest path length required to transfer from one brain area to another averaged over all pairs of areas, whereas λ is the normalized measure of L_p. The path length of a brain area reflects how closely it is connected globally to other areas of the brain network, and the shorter path lengths reflect higher levels of efficient access to information (Rubinov & Sporns, 2010). Thus, the longer path length indicates a lower efficiency in information access in LBC than in non-LBC. This is not surprising; direct parental care can directly improve the maturation of brain systems (Rao et al., 2010; Rifkin-Graboi et al., 2015). In particular, it can improve the psychological and emotional development of human beings by influencing the hypothalamic-pituitary-adrenal axis stress reactivity and regulation in response to emotional challenges (Blair, Granger, Willoughby, & Kivlighan, 2006). Our findings are also supported by previous animal experiments, which have found maternal deprivation leads to the deterioration of emotional and cognitive processes during adulthood (Akillioglu et al., 2015; Marco et al., 2015; Xiong et al., 2015). Furthermore, given that the small-world topology is an optimal balance between local specialization and global integration (because networks have evolved over time to cope with the high complexity of dynamic behavior) (Bullmore & Sporns, 2009), our findings of an increased normalized characteristic path length (λ) in LBC networks also indicate a shift away from an optimal small-world network organization towards an imbalanced functional architecture with a more random configuration in brain networks.

We also observed altered nodal centralities, particularly within the fronto-limbic regions and motor and sensory systems. We calculated three parameters of the nodal centrality, i.e., nodal degree (κ), measuring the connectivity of a node with the rest of the nodes in a network; nodal efficiency (e), estimating the information-propagation ability of a node with the rest of the nodes in the network; and nodal betweenness (b), capturing the influence of a node on the information flow between all other nodes in the network. Notably, these nodal centralities correlate with each other (e.g., a node with a high degree tends to have high nodal betweenness and efficiency), all of which reflect the roles of nodes in information transport and integration across the network (Sporns, Honey, & Kotter, 2007), and the altered nodal centralities indicate the changed regional function. For example, increased nodal centralities, especially within the fronto-limbic regions, have been found to reflect the strengthened functional communication among these regions in people with emotional deficits such as major depressive disorder (Luo et al., 2015), bipolar disorder (Leow et al., 2013) and seasonal affective disorder (Borchardt et al., 2015). Such increased nodal centralities might be compensatory changes for other brain regions showing deficient activities (Liu et al., 2014), which requires further exploration in future LBC research. Although these LBC showed no obvious emotional changes, the elevated nodal centralities within the fronto-limbic regions were consistent with the notion that parental care can influence neuroanatomical trajectories that are important for future cognitive and emotional functioning (Rifkin-Graboi et al., 2015). The exact mechanism of the increased nodal centralities, especially within the emotional circuit, is unclear; however, our findings provide evidence to support the altered function within the fronto-limbic circuit in LBC.

In addition to the increased nodal centralities, our study showed lower nodal centralities in the right orbital frontal gyrus (Li et al., 2014); this decrease may indicate reduced regional activity, which is consistent with a previous study on Romanian orphans (Chugani et al., 2001). Using positron emission tomography (PET), the study found decreased glucose metabolism in the orbital frontal gyrus in Romanian orphanages, which may represent the mechanism underlying part of the persistent behavioral disturbances (Chugani et al., 2001). The orbital frontal gyrus projects to many diverse areas, including the amygdala (Eden et al., 2015), and is thought to be involved in negative affect regulation (Liu et al., 2013). Reduced functioning of the orbital frontal cortex has been reported to be related to emotion processing and regulation in a number

of psychiatric disorders, including depression (Robertson et al., 2007), anxiety (Mohlman et al., 2009), and autism spectrum disorders (Green et al., 2013). Thus the mild reduced nodal centralities of the orbital frontal gyrus in LBC indicate a reduced down regulation of the orbital frontal gyrus on the emotional circuit (Lui et al., 2013).

Furthermore, the decreased nodal degree and the nodal betweenness of the right rectus gyrus were positively correlated with the annual family income in the LBC group. This is also supported by previous structural research on individuals exposed to early-life poverty, who exhibited a lower orbital frontal cortex volume (Holz et al., 2015). Adults who had a lower socio-economic status (SES) in childhood showed reduced connectivity during the processing of reward stimuli between the anterior cingulate cortex and the orbital frontal cortex (Gianaros et al., 2011). Studies have also found that children with low a SES are at greater risk for depression or anxiety than those with a high SES (Cheng & Sun, 2015; Liu, Li, & Ge, 2009). Thus, LBC with lower family income may have more severe deficits in the neural regulation of emotional behavior.

It should be noted that guardians' education level was significantly higher in the non-LBC group than in the non-LBC group; all non-LBC were living with their nuclear family, whereas LBC lived with their grandparents. In China, the rapid economic development and social reforms that have taken place in recent decades—e.g., 9 years of free education—have had a great influence on people's life. The grandparents of many LBC have experienced starvation and a low SES, so they may pay more attention to providing them adequate food and clothing rather than essential emotional needs, such as care. Additionally, guardians with a lower level of education tend to beat or scold their children for the betterment of their future (Gabrielli, Jackson, & Brown, 2015). Furthermore, with better education, parents are better at guiding child behavior and mental growth, and they represent a better model for children to imitate than their grandparents. The negative effect of being left behind on child mental health may be related to the interruption of attachment with their parents and elevated emotional neglect (Cheng & Sun, 2015).

There are a few issues that must be addressed when explaining the results. First, the nodal centrality results did not survive the FDR correction with $p = 0.05$ to address the multiple-comparison problem, perhaps due to the relatively small sample size. Therefore, this study should be considered exploratory. Second, we used the AAL atlas to parcellate the entire brain into 90 regions; however, differences in template parcellations might have caused certain variations in graph-based theoretical parameters, which must be explicitly compared in future work (Suo et al., 2015). Third, physiological noise, including respiratory and cardiac fluctuations, might have compromised our results, though we used nuisance signal regression (24-parameter head motion profiles, global signal, CSF signal and WM signal) to minimize these physiological noises. Fourth, all subjects were screened by an experienced child psychiatrist using the Chinese version of SCID-I (Non-patient Edition) (Wang et al., 2009) to exclude any Axis I psychiatric diagnoses; they did not meet the criteria for the diagnosis of depression and anxiety disorder. That's why we were not able to evaluate the severity of anxiety and depression symptoms with assessment scales, which indeed is one of our limitations. Future studies will benefit from the use of assessment scales to quantify LBC's anxiety and depression symptoms and their relationship to brain structure and functional changes.

Taken together, the present study provides the first empirical evidence that a lack of direct parental care could affect brain-function development in children, particularly involving the emotional networks. The functional connectome of LBC showed an increased normalized characteristic path length, suggesting a decrease in efficiency in information access and altered nodal centralities in the fronto-limbic regions and motor and sensory systems. Thus, our findings help elucidate the potential role of parental care in the development of the brain in children. More longitudinal studies with larger sample sizes that measure LBC's and control subjects' psychological states at different time points or explore the long-term effects of different parental situations are needed. From a public health perspective, this study highlights the importance of parental care for children and indicates that more emotional care and support may be needed for LBC in developing countries.

Competing financial interests

The authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.chiabu.2016.10.013.