Brain anatomical networks in early human brain development

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A B S T R A C T

Recent neuroimaging studies have demonstrated that human brain networks have economic small-world topology and modular organization, enabling efficient information transfer among brain regions. However, it remains largely unknown how the small-world topology and modular organization of human brain networks emerge and develop. Using longitudinal MRI data of 28 healthy pediatric subjects, collected at their ages of 1 month, 1 year, and 2 years, we analyzed development patterns of brain anatomical networks derived from morphological correlations of brain regional volumes. The results show that the brain network of 1-month-olds has the characteristically economic small-world topology and nonrandom modular organization. The network’s cost efficiency increases with the brain development to 1 year and 2 years, so does the modularity, providing supportive evidence for the hypothesis that the small-world topology and the modular organization of brain networks are established during early brain development to support rapid synchronization and information transfer with minimal rewiring cost, as well as to balance between local processing and global integration of information.

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Introduction

Since the Caenorhabditis elegans’ nervous system was first described as a small-world brain network (Watts and Strogatz, 1998), there has been a keen interest in the small-worldness of human brain networks in the neuroimaging research community since neuroimaging techniques facilitate in-vivo studies of the human brain anatomy and function (Bassett and Bullmore, 2006; Bullmore and Sporns, 2009). Using graph theoretic analysis approaches, the human brain has been described and analyzed as a graph (network) with brain regions as graph nodes and regional connections as graph edges, derived from correlations of morphological or functional measures, or white matter fiber tracts (Bassett and Bullmore, 2006; Bullmore and Sporns, 2009; Sporns et al., 2005). Functional human brain networks have been studied using electroencephalography (EEG), magnetoencephalography (MEG), and functional MRI (fMRI). Regional functional connectivity is typically estimated using cross-correlations, partial correlations, or mutual information in time series of regional signal at one or several specific frequency (Achard and Bullmore, 2007; Achard et al., 2006; Bartolomei et al., 2006; Breakspear et al., 2006; Ferré et al., 2007; Salvador et al., 2005a, b; Stam, 2004). The anatomical network of the human brain has been studied using diffusion MRI techniques which offer a relatively direct estimation of brain anatomical regional connection (Gong et al., 2009; Hagmann et al., 2007; Iturria-Medina et al., 2007; Iturria-Medina et al., 2008; Lewis et al., 2009). Comparable human anatomical networks can also be inferred from structural MRI data with brain regional connectivity estimated as correlations in cortical thickness or volume (Bassett et al., 2008; He et al., 2007). Despite the difference in experimental methodologies, the studies of human brain networks reveal a convergent fact that the human brain networks, anatomical and functional, have the small-world topology that can be equivalently characterized by efficiency measures of networks (Latora and Marchiori, 2001, 2003).

Recent neuroimaging studies of the human brain have also demonstrated that, parallel to the small-worldness, human brain networks have a modular organization (Chen et al., 2008; Fair et al., 2009; Meunier et al., 2009), which partitions a network into a set of modules, each module comprising nodes densely connected within the module and loosely connected to other modules (Girvan and Newman, 2002). Interestingly, it has been demonstrated that the modularity of functional brain networks changes little over the age ranging from 8 to 25 years (Fair et al., 2009), while the functional brain network of old individuals displayed a relatively lower modularity than the brain network of young adults (Meunier et al., 2009). It is unclear whether structural networks display age related changes.

Despite the rapidly increasing evidence of the small-worldness and the modular organization of human brain networks, it remains largely unknown when these properties of human brain network emerge and how they change in the course of brain development. It has been hypothesized that the small-world architecture and the modular organization of brain networks has been a result of the brain...
development and competitively selected to support rapid synchronize
and efficient information transfer with minimal rewiring cost, as
well as to balance between local processing and global integration
of information (Bassett and Bullmore, 2006; Bullmore and Sporns,
2009; Tononi et al., 1994). The hypothesis is supported by studies that
demonstrated the efficiency of brain functional networks of normal
people (Achard and Bullmore, 2007), impaired efficiency of networks
in diseased brains (Liu et al., 2008), as well as decreased efficiency and
modularity of brain networks of old individuals (Achard and
Bullmore, 2007; Meunier et al., 2009). It has been suggested in
(Bullmore and Sporns, 2009) to explore and test this hypothesis more
directly using evolutionary algorithms in computation models of
brain network selection (Sporns and Kötter, 2004).

In this study, we investigated efficiency and modularity of the
human brain anatomical networks in the early childhood, focusing on
the following questions: 1) Do the brain networks have economic
small-world topology in early development? 2) Do the brain networks
have modular organization in early development? And 3) how does
the efficiency and modularity of the brain networks change in the
course of early development?

Materials and methods

Subjects and MRI data acquisition

The study subjects were part of a large study of brain development
in normal children (Gilmore et al., 2007). Informed consent was
obtained from the parents and the experimental protocols were
approved by the institutional review board. None of the subjects was
sedated for MR imaging. Before the subjects were imaged, they were
fed, swaddled, and fitted with ear protection. All subjects slept
during the imaging examination. A 3D MP-RAGE sequence was used to obtain
T1 and T2 scans. The imaging parameters were as follows: repetition
time (TR) = 1820 ms; echo time (TE) = 4.38 ms; inversion
t1 and t2 scans. The imaging parameters were as follows: repetition
time (TR) = 1820 ms; echo time (TE) = 4.38 ms; inversion
time = 1100 ms; 144 slices; and voxel size = 1 × 1 × 1 mm3. We
identified 28 normal subjects (10 males/18 females), having longitudi-
dinal structural MRI brain images at the gestational ages of 41.2 ± 1.7
(standard), 49.4 ± 2.8, and 145.9 ± 5.9 weeks, corresponding to postnatal
ages of 6.1 ± 2.8, 59.3 ± 3.0, and 110.7 ± 6.8 weeks, respectively. For
comparison purpose, structural MRI brain images of 27 healthy adult
subjects (13 males/14 females, 24 ± 3 years) were obtained.

Post-processing

The images of each subject were first skull stripped, brain tissue
segmented (Shi et al., 2010), and spatially normalized to a standard
template atlas with 90 anatomically labeled cortical and subcortical
regions (Tzourio-Mazoyer et al., 2002) using an image registration
algorithm (Shen and Davatzikos, 2002). From the resulting deformation
fields, voxel-wise tissue density maps were computed to represent the
local brain volume changes relative to the selected template (Shen and
Davatzikos, 2003). Based on the tissue density maps, gray matter
volume measures of 90 cortical and subcortical regions were computed for
all subjects at different time points (see also Table S1 and ref.
(Tzourio-Mazoyer et al., 2002) for details of these regions). For each age
group, we used linear regression to model effects of total brain volume,
gender, and age on gray matter volume measures for each region
separately. The effects of total brain volume size, gender, and age were
removed by using the residuals of the regression as corrected gray
matter volume estimates.

Anatomical brain network construction

The cortical and subcortical regions were used as nodes to construct
brain networks of the early development brain using graph theoretic
approaches (Bassett et al., 2008; Bullmore and Sporns, 2009), with
connections between nodes defined as correlations in regional gray
matter volume measures (Bassett et al., 2008; He et al., 2007). The
connection between each possible pair of nodes was estimated as
Pearson correlation coefficient between their corrected regional gray
matter volume measures of 28 subjects for each age group separately.
These pair-wise correlation measures were assembled to form a
symmetric connection matrix M with zero diagonal elements, the M_{ij},
\{i \neq j\} element of which is the correlation coefficient between nodes i and
j. Positive entries in the connection matrix indicate connected nodes.
Similarly, a correlation matrix was obtained for the adults. The
connection matrices of these 4 age groups are shown in Fig. S1.

An unweighted brain network can be derived from each connection
matrix and represented by a binary adjacent matrix by applying a
threshold to the correlation matrix. The elements of the binary adjacent
matrix are zero if their corresponding correlation coefficients are less than
a given threshold, otherwise are unity. The nonzero elements of the binary
adjacent matrix indicate that a node (row index) is connected to another
node (column index) via an edge. For unweighted networks, the number of
edges in a network is related to how expensive it is to build a network
(Latora and Marchiori, 2001, 2003). The cost of a network can be
quantified by the ratio of number of edges in a network to the maximum
possible number of edges (Latora and Marchiori, 2001, 2003). Shown in
the left column of Fig. S1 are adjacent matrices corresponding to a network
cost of 0.16 that is the minimum network cost at which brain regions
become fully connected in the brain networks of all age groups (Fig. 2).

Network analysis

We investigated properties of the early development brain networks
and compared with those of the adult brain network, focusing on their
efficiency and modularity. We first studied global properties of the
networks obtained by thresholding the connection matrices over a
range of thresholds. To facilitate comparison among brain networks of
different age groups at same network costs, we used the network cost to
control the threshold to be used for deriving an unweighted brain
network (Achard and Bullmore, 2007; Bullmore and Sporns, 2009;
Meunier et al., 2009). Thus, a metric of network property can be
evaluated as a function of network cost. With this functional
representation of network property measures, we investigated the
brain networks of different age groups with respect to their global
efficiency, local efficiency, cost efficiency, and modularity. For examin-
ing the small-worldness and nonrandom modular organization of the
brain anatomical networks, comparable regular lattices and random
graphs with the same degree distributions to brain networks (1000 at
each cost) were generated over the same range of network costs
(Maslov and Sneppen, 2002; Stam and Reijneveld, 2007). The mean
metrics of random graph were computed for comparison. In the case of a
small-world network, the global efficiency is greater than a comparable
lattice but less than a random graph, and the local efficiency is greater
than a random graph but less than a lattice (Latora and Marchiori, 2001).
Similarly, a network with nonrandom modular organization shall have
modularity larger than that of a random network.

The modular organization of a network was detected using a fast
algorithm by partitioning the network into subsets to achieve the
maximum network modularity (Clauset et al., 2004). The modularity
metric quantifies how different intra-modular links in a network are
from a random network with the same modular organization (Newman
and Girvan, 2004).

A bootstrap resampling strategy was used to assess how the network
efficiency and modularity vary with the change of data (Efron and
Tibshirani, 1993). In particular, 1000 bootstrap sampling of the study
subjects with replacement were performed. For a study with n subjects,
each bootstrap sampling consists of n pseudo-random values drawn from
a uniform distribution of subject IDs. For each bootstrap sample of the
pediatric subjects, 3 brain networks corresponding to the brain scans of
different ages were constructed and their network efficiency and
modularity were obtained as described above. The network efficacy and modularity of adult networks were obtained in the same way.

To investigate the difference between brains at two different ages with respect to a brain network metric, a permutation test was used to assess the statistical significance. A permutation samples was obtained by randomly assigning the corrected regional gray matter volume measures of two age groups to one or another while keeping the same sample sizes as the original groups. Particularly, for comparisons within the pediatric age groups, the longitudinal nature of the data was taken into account so that the regional volume measures of the same subject at two different time points were always assigned to different age groups. Based on the randomly resampled regional measures, regional correlation matrix was then computed for each age group. For each permutation, the network metric measures at different network costs were then computed and their differences between younger and older groups were calculated. Finally, the one-sided p-value of the difference was calculated as the proportion of 1000 sampled permutations where the difference was greater than or equal to the observed difference.

We also investigated the characteristics of individual nodes in brain networks of different age groups, including their nodal global and local efficiency, intra-modular degree, participation coefficient, as well as betweenness centrality.

Network metrics used in this study for characterizing brain networks

Given an unweighted network (graph) $G$ with $N$ nodes, its metrics for global and local efficiency can be computed as (Latora and Marchiori, 2001, 2003)

$$ E_{glob} = \frac{1}{N} \sum_{i=1}^{N} E_{glob}(i), \quad E_{glob}(i) = \frac{1}{N-1} \sum_{j \neq i \in G} d_{ij}, $$

$$ E_{loc} = \frac{1}{N} \sum_{i=1}^{N} E_{loc}(i), \quad E_{loc}(i) = \frac{1}{N_{i} \left( N_{i} - 1 \right)} \sum_{j \in G \setminus i} d_{ij}, $$

where $d_{ij}$ is the distance between nodes $i$ and $j$, $G_{i}$ is a subgraph comprising nodes directly connected to node $i$, and $N_{i}$ is the number of nodes of $G_{i}$. $E_{glob}(i)$ and $E_{loc}(i)$ are nodal efficiency metrics. Specifically, $E_{glob}$ measures the efficiency of parallel information transfer in the network, whereas $E_{loc}$ measures the local efficiency of information transfer in the immediate neighborhood of each node.

A module of $G$ is a subset of nodes which are more densely connected to each other in the same module than to nodes outside the module. For a configuration of modular organization $m$ with $n_{m}$ modules, its modularity $Q(m)$ is defined as (Newman and Girvan, 2004)

$$ Q(m) = \sum_{i=1}^{L} \left( \frac{l_{i}}{L} - \frac{d_{ii}}{2L} \right)^{2}, $$

where $L$ is the total number of edges of $G$, $l_{i}$ is the total number of edges in module $s$, and $d_{ii}$ is the sum of the degrees of the nodes in module $s$. The modularity of a graph is defined as the largest value of modularity measures associated with all possible configurations of modules, which can be found by optimization algorithms (Newman and Girvan, 2004). We adopted a fast modularity finding algorithm (Clauset et al., 2004), which has been demonstrated capable of achieving a fast solution with comparable quality to other modularity optimization algorithms, including simulated annealing (Guimera and Amaral, 2005; Meunier et al., 2009).

Once an optimal configuration of modules is found, topological roles of nodes in terms of their intra-modular and inter-modular connectivity patterns can be quantified by normalized intra-modular degree and participation coefficient. The normalized intra-modular degree $z(i)$ measures how dense a node $i$ connects to other nodes in the same module, and the participation coefficient $p(i)$ measures how a node $i$ connects to nodes in other modules. They are defined as, respectively (Guimera and Amaral, 2005),

$$ z(i) = \frac{n_{i} - \bar{n}}{\bar{n}}, $$

$$ p(i) = 1 - \frac{\sum_{s \neq n} K_{s}}{K(i)}, $$

where $n_{i}$ is the number of edges connecting the $i^{th}$ node to other nodes in its module $n^{th}$, referred to as intra-modular node degree; $\bar{n}$ and $\bar{n}$ are the mean and standard variance of intra-modular node degrees of all nodes in the $n^{th}$ module, $K_{s}$ is the number of edges of the $i^{th}$ node to module $s$, and $K(i)$ is the number of edges that connect node $i$ to all other nodes. Nodes with $z(i)$ greater than (mean + standard deviation) of all nodes’ normalized intra-modular degree are classified as modular hubs, otherwise classified as non-hubs. Nodes with $p(i)$ greater than 0.3 are classified as connectors, otherwise classified as non-connectors (Guimera and Amaral, 2005).

Betweenness centrality: the betweenness centrality of a node $i$ is defined as

$$ B(i) = \sum_{j \neq i, k \neq i} \frac{o_{jk}(i)}{o_{jk}}, $$

where $o_{jk}$ is the number of shortest paths from node $j$ to $k$, and $o_{jk}(i)$ is the number of the shortest paths that traverse node $i$.

Results

Using graph theory analysis approaches (Bullmore and Sporns, 2009), we studied brain anatomical networks during early development brain at ages of 1 month, 1 year, and 2 years. The brain anatomical networks were derived from longitudinal structural MRI data of 28 healthy pediatric subjects, and compared with those derived from MRI scans of 27 adults.

The brain networks in early development have the economic small-world topology

Brain networks were studied and compared with comparable random networks and lattices over a range of network costs in terms of their global efficiency, local efficiency, and cost efficiency (Achard and Bullmore, 2007; Latora and Marchiori, 2001, 2003). The cost of a network is measured by the number of edges or connections in the network, while the efficiency measures of networks are functions of the minimum path length between network nodes, reflecting communication efficiency of networks. As shown in panels A, B, C and D of Fig. 1, the curves of global efficiency and local efficiency of anatomical networks of the early development brain locate in-between of curves of random networks and lattices, indicating that both the early childhood and the adult brain networks have characteristically economic small-world topology (Latora and Marchiori, 2001, 2003; Watts and Strogatz, 1998). The curves of global efficiency display a pattern of consistent and statistically significant increasing with the brain development from 1 month to 2 years, and to adulthood, over a wide range of network costs. The pattern of increasing efficiency of the developing brain is expected since functional development needs support from structural substrate of improved efficiency (Sporns et al., 2004). However, the curves of local efficiency of brain networks display a complicated pattern, and the networks of 2-year-olds have higher efficiency at some network costs than networks of younger children’s and adult brains. As shown in panels E and F of Fig. 1, the early childhood and adult brain networks all exhibit behavior of cost efficiency, i.e., positive difference between global efficiency and network cost (Achard and Bullmore, 2007).
Similar to the measures of global efficiency, the cost efficiency increases with the brain development.

The brain networks in early development have nonrandom modular organization

The early development brain networks were analyzed with respect to network modularity (Clauset et al., 2004; Newman and Girvan, 2004) over a range of network costs and compared with random networks and adult brain networks. As shown in panels A and B of Fig. 2, the brain networks have higher modularity than the comparable random networks, indicating that both in early development and the adult brain, networks have nonrandom modular organization (Newman and Girvan, 2004). The modularity of the brain networks of two-year-olds is higher than the modularity of the brain networks in younger and adult brains, a similar trend to the local efficiency.

In panels C and D of Fig. 2, sizes of the largest connected components corresponding to different network costs are shown for the brain

![Fig. 1. Global efficiency (A, B), local efficiency (C, D), and cost efficiency (E, F), as functions of network cost (x-axis) for brain networks. Global and local efficiency of random graphs and regular lattices are also shown in the plots of global efficiency and local efficiency for testing the small-worldness of brain networks. The plots in panels A, C, and E show the results derived directly from the imaging data, while the plots in panels B, D, and F show the distribution (mean ± standard deviation) of network parameters derived from bootstrap sampling. In these plots, significant difference (p < 0.05) is indicated for comparisons: 1 yr > 1 mon, 2 yr > 1 yr, and adult > 2 yr, respectively.](image-url)
networks of 4 age groups. With the relatively lower network costs, the size of the largest connected component of the early development brain networks is positively correlated with the stage of the brain development. For the brain networks of adults and 2-year-olds, the brain regions became fully connected at the network cost of 0.1, while the same parameters are 0.13 and 0.16 for the brain network of 1-year-olds and 1-month-olds, respectively, indicating that it requires a larger network cost for younger brain to make the brain network fully connected.

The developmental change pattern of brain networks in early development is complex.

We investigated modular organization of brain networks in early development with a network cost of 0.16 that is the minimum network cost to make all brain regions fully connected for all age groups (see Fig. 2). The modular organization of the brain networks was anatomically visualized using brain surface rendering and topologically visualized using a spring-embedding algorithm (Kamada and Kawai, 1989), as shown in panels of Fig. 3 (see Table S1 for modular assignment and abbreviation for each region).

The brain network of 1-month-olds comprises 5 modules. Module 1 consists of 4 regions, including right middle frontal gyrus, right rolandic operculum, left anterior cingulate gyrus, and left inferior parietal lobule. Module 2 consists of 21 regions, most of them from subcortex region, including bilateral hippocampus, bilateral parahippocampal, and bilateral thalamus. Module 3 includes 34 regions, distributed mainly in parietal and occipital lobes, as well as subcortical area, such as bilateral caudate. Module 4 consists of 26 regions, most of them from orbitofrontal cortex, inferior frontal gyrus, and temporal lobe. Module 5 had 5 regions, namely, bilateral posterior cingulate gyrus, bilateral calcarine cortex, and left superior occipital gyrus. The modular organization of brain network of 1-month-olds is shown in panel A of Fig. 3.

The brain network of 1-year-olds has 4 modules, two of them (module 2 and module 4) having 37 regions and other two (module 1 and module 3) having 12 and 4 regions, respectively. In particular, module 2 consists of 37 regions, including most regions of 1-month-old network's modules of 2 and 4, distributed mainly in frontal and temporal lobes. Module 4 also consists of 37 regions, most of them being in 1-month-old network's module 3. Module 5 of 1-year-old network also integrated the 1-month-old network's module 5. Module 1 of 1-year-old network has 12 regions, including temporal pole area, regions of superior frontal gyrus, and subcortex regions, like right putamen and left parahippocampal gyrus. Module 3 of 1-year-old network only has 4 regions, including bilateral caudate, left middle frontal gyrus and left supramarginal gyrus. The modular organization of brain network of 1-year-olds is shown in panel B of Fig. 3.

The brain network of 2-year-olds also comprises 4 modules. However, its organization is dramatically different from those of younger brain networks. In particular, module 1 consists of 38 regions,
Fig. 3. Surface rendering and spring-embedding visualization of brain networks of 1-month-olds (A), 1-year-olds (B), 2-year-olds (C), and adults (D). For the surface rendering visualization, each network node (brain region) is projected onto the brain surface of its corresponding hemisphere by minimizing its distance to the brain surface. The brain surfaces were generated with the Freesurfer image analysis suite, which is documented and freely available for download online (surfer.nmr.mgh.harvard.edu). Nodes are color-coded by modules and larger nodes are connector hubs or provincial hubs. Lateral, medial, and top views of both hemispheres are shown. The spring-embedding visualization of networks is implemented with Kamada-Kawai layout algorithm using Pajek software package (pajek.imfm.si/doku.php). The nodes and intra-modular connections are colored-coded by modules, while inter-modular connections are color-coded with light-gray. The abbreviation of region labels can be found in Table S1.
most of them from subcortex, and some from temporal and frontal lobes. Module 2 has 10 regions, including bilateral insular, bilateral olfactory, bilateral medial and superior orbitofrontal cortex, left orbitofrontal cortex (middle), and left rectus gyrus. Module 3 has 9 regions, including bilateral supplementary motor area, bilateral posterior cingulate gyrus, bilateral calcarine cortex, bilateral paracentral lobule, and left superior occipital gyrus. Module 4 has 33 regions, distributed mainly in temporal, occipital, and parietal lobes.

The modular organization of brain network of 2-year-olds is shown in panel C of Fig. 3.

The brain network of adults has only 3 modules and their sizes are relatively close to each other. It is a result of reorganization of 2-year-old network. In particular, module 1 has 42 regions, including majority of the 2-year-old network's module 1 and module 4. The module 2 of the adult network consists of 11 regions, mainly distributed in temporal lobe and frontal lobe. Module 3 consists of 37 regions, including regions mainly from modules 1 and 4 of the 2-year-old network. The modular organization of adult brain network is shown in panel D of Fig. 3.

The visualization results of the modular organization of the early development brain networks, as shown in Fig. 3, indicate that the temporal developmental change pattern of the brain networks through early childhood is complex with respect to their modular organization. Over ages from 1 month to 2 years, as the brain develops, the modular assignment for brain regions changes dramatically, reflecting dynamic anatomical segregation and integration of brain regions. The spring-embedding based visualization of brain networks also reflects the complex developing pattern. Anatomical spatial location based visualization of these brain networks and their modular organizations are shown in Fig. S2, for easy inspection of their development pattern.

We also investigated each node's topological role based on its intra- and inter-modular connections (Guimera and Amaral, 2005; Meunier et al., 2009). Intra-modular connectivity was quantified by the normalized intra-modular degree that measures the number of links of a node to other nodes in the same module. A higher value of the intra-modular degree of a node indicates that it has a larger number of intra-modular connections compared with other nodes in the same module. The intra-modular degree can be used to determine if a node is a hub. Inter-modular connectivity was measured by the participation coefficient that measures how a node connects to different modules. A node with a higher participation coefficient extensively connects to different modules, referred to as a connector. Using these two measures, a node can be assigned a topological role from the following 4 categories: connector hub (H), non-connector (provincial) hub (P), connector non-hub (C), and non-connector and non-hub (N) (Guimera and Amaral, 2005).

The measures of participation coefficient and intra-modular degree of all the nodes and their topological roles in the early development and the adult brain networks are shown in Fig. 4 (A) and (B). These results demonstrate interesting patterns of brain networks in early development with respect to participation coefficient and intra-modular degree. Over the early brain development stages of 1 month, 1 year, and 2 years, over 1/3 nodes consistently served as brain network connectors and over 2/3 of them served as connectors in the adult network as well, indicating that the early brain development did not dramatically change the connection patterns of brain regions with dense connections to different modules, even for the brain development from 1 month to 1 year during which the brain development is extremely dynamic (Knickmeyer et al., 2008). However, the change of the nodes' role as network hubs is relatively large. Each node's global topological role was also measured using the normalized betweenness centrality, which quantifies the number of the shortest paths between all other node pairs in the network passing through a given node (Bullmore and Sporns, 2009). Nodes with high betweenness centrality are global hubs, crucial to efficient communication (Freeman, 1977).

In Fig. 4 (C), the nodes with high betweenness centrality are modular connectors, but not necessarily modular hubs, indicating that the global topological roles are not equivalent to modular topological properties. The relatively large changes in measures of nodal topology roles over age reflect the dynamic development pattern of the early development brain networks.

**Discussion**

This study demonstrates that brain networks in early development have economic small-world topology and nonrandom modular organization which have been discovered in the adult brain networks (Achard and Bullmore, 2007; Bullmore and Sporns, 2009; Chen et al., 2008; He et al., 2007; Meunier et al., 2009). Also, brain networks in early development display a pattern of increasing efficiency and modularity with the brain development, albeit complex is their developmental change pattern. These findings, along with results of adult brain networks (Achard and Bullmore, 2007; Bullmore and Sporns, 2009; Chen et al., 2008; He et al., 2007; Meunier et al., 2009), support the hypothesis that the characteristics of brain networks have been competitively selected to solve the economic problem of optimizing the brain information processing (Bassett and Bullmore, 2006; Bullmore and Sporns, 2009).

The first two years of life are the most dynamic of human postnatal brain development. Total brain volume increases 130% from birth to age 2, 80–90% of adult volumes, while cortical gray matter volume increases by 185% (Knickmeyer et al., 2008). White matter is also maturing rapidly in this time period, with the overall pattern of adult myelination present by age 2 year (Sampaio and Truwit, 2001); diffusion tensor properties of white matter also demonstrate a similar rapid maturation during this period (Gao et al., 2009a; Gilmore et al., 2007a). Resting state fMRI studies in this age group also indicate significant development of functional networks, including visual, sensorimotor and "default" networks (Gao et al., 2009b; Lin et al., 2008). This study reveals the development pattern of anatomical brain networks in this important period of early brain development.

This is the first longitudinal study of brain networks with respect to their efficiency and modular organization in early brain development, providing a picture of the emergence and developmental change of brain networks at its early development stages, complementing the existing studies of brain development and brain network research (Fair et al., 2008, 2009; Fransson et al., 2007; Gao et al., 2009b; Huang et al., 2006; Kelly et al., 2009; Knickmeyer et al., 2008; Lin et al., 2008; Matsuzawa et al., 2001; Sowell et al., 1999). The development pattern of brain networks has been investigated with a focus on functional default mode network or connection among specific brain regions (Fair et al., 2008; Fransson et al., 2007; Gao et al., 2009b; Kelly et al., 2009; Lin et al., 2008). In particular, recent studies of default mode network's emergence and developmental change have documented the trajectory of default mode network from infancy, adolescence, to adulthood, primitive default mode network emerging in the brain of neonates and gradually maturing with the brain development (Fair et al., 2008; Gao et al., 2009b). However, the efficiency and modular organization of the development brain networks has not been explored so far. The emergence and developmental change pattern of the early development brain revealed in this study sheds light on the development pattern of brain network's efficiency and modular organization. The dynamic developmental change pattern of modular organization of the early development brain networks is consistent with the observations in default mode networks which reorganize their topological architecture and composition of brain regions over the brain development from infancy, adolescence, to adulthood (Fair et al., 2008; Gao et al., 2009b). However, the pattern of brain development might be different from changes rendered by aging or diseases (Meunier et al., 2009; Paterson et al., 1999), which merits further investigation.
The early development brain networks were derived from longitudinal structural MRI brain images scanned at ages of 1 month, 1 year, and 2 years. The brain network consists of 90 nodes which are cortical and subcortical regions defined by automated anatomical labeling (AAL) (Tzourio-Mazoyer et al., 2002). The connectivity between any possible pair of nodes is defined as correlation between their regional volume measures that were computed through nonrigidly warping the AAL atlas onto each individual brain image. Therefore, the image registration between the AAL atlas and individual images plays an important role in the construction of the brain networks and its performance is directly related to the robustness of the brain networks. We adopted an image registration algorithm which has potential to achieve good registration accuracy (Shen and Davatzikos, 2002). Prior to the image registration, the brain images were segmented into white matter, gray matter, and cerebrospinal fluid using a subject-specific atlas based image segmentation, specially designed for achieving accurate segmentation of neonate images (Shen and Davatzikos, 2002; Shi et al., 2010). In particular, segmentation results of two-year-old images were used to guide the segmentation of one-year-old and one-month-old images of the same subject. These two techniques were utilized together to achieve accurate computation of regional volume measures, thus facilitating the robust construction of the early development brain networks. One limitation of this study is that the sample size is relatively small. However, the longitudinal design may increase its statistical power since the temporal individual variance is much smaller than that in cross-sectional studies (Giedd et al., 1999; Ment et al., 2009). Another caveat in interpretation of the results of this study is that anatomical brain regions defined in the AAL atlas might not match very well with function and anatomy of the early development brains. However, the effect of utilization of this adult brain template in this study shall be similar to that in adult brain network analysis, taking into consideration the following fact that the adult brain templates have been successfully used to label brain images of two-year-old (Gossiaux et al., 2008). For the general issue in terms of definition of network nodes in graph theory analysis of brain networks (Sporns et al., 2005), a better solution is needed.


In conclusion, we present a study of the early development brain network and reveal a complex temporal developmental change pattern of increased efficiency and modularity with the brain development. The developmental pattern of the brain network displays a picture of the human brain network’s emergence and developmental change, which merits further investigation with respect to its difference from aging and diseased brain networks.

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Appendix A. Supplementary data


References


