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Graph theoretical modeling of baby brain networks

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ABSTRACT

The human brain undergoes explosive growth during the prenatal period and the first few postnatal years, establishing an early infrastructure for the later development of behaviors and cognitions. Revealing the developmental rules during the early phase is essential for understanding the emergence of brain functions and the origin of developmental disorders. Graph-theoretical network modeling in combination with multiple neuroimaging probes provides an important research framework to explore the early development of the topological wiring and organizational paradigms of the brain. Here, we reviewed studies that employed neuroimaging and graph-theoretical modeling to investigate brain network development from approximately 20 gestational weeks to 2 years of age. Specifically, the structural and functional brain networks have evolved to highly efficient topological architectures in the early stage; where the structural network remains ahead and paves the way for the development of the functional network. The brain network develops in a heterogeneous order, from primary to higher-order systems and from a tendency of network segregation to network integration in the prenatal and postnatal periods. The early brain network topologies show abilities in predicting certain cognitive and behavior performance in later life, and their impairments are likely to continue into childhood and even adulthood. These macroscopic topological changes may be associated with possible microstructural maturations, such as axonal growth and myelinations. Collectively, this review provides a detailed delineation of the early changes in the baby brains in a graph-theoretical modeling framework, which opens up a new avenue for understanding the developmental principles of the connectome.

Introduction

During the prenatal period and the first few postnatal years, the human brain undergoes a dramatic amount of development, with prolific structural and functional changes. Before birth, the rapid proliferation and migration of neurons (Bystron et al., 2008; Stiles and Jernigan, 2010), together with exuberant axon growth and synaptogenesis (Webb et al., 2001), generate remarkable numbers of neural circuits in the brain. Immediately after parturition, the brain enters a consolidation phase characterized by prolonged myelination and competitive pruning (Huttenlocher, 1984; Miller et al., 2012; Yakovlev and Lecours, 1967) in response to its new, complex environment. These elaborate evolutions supports the emergence of the structures and functions of the brain that are essential to high-level cognitive performance in later life.

Explorations of the developing brain have entered a new era, spurred on by the advent of advanced non-invasive neuroimaging techniques that can map anatomical pathways and functional synchronizations throughout the entire brain *in vivo*. Using multi-modality neuroimaging data, researchers can further map the so-called "human connectome" to determine how neural interactions are reorganized in brain regions within a network frame during development (Cao et al., 2017b; Kelly et al., 2012; Sporns, 2011) (Fig. 1). Connection growth during this period follows typical sequences, including a limbic to association cortex order in structural pathways and a primary to higher-level emergence sequence in functional networks (Cao et al., 2017b; Cao et al., 2016; Collin and van den Heuvel, 2013; Haartsen et al., 2016). Significantly, the resulting massive network connections form elegant topologies, such as small-worldness and modular organization, which can be probed using the graph theoretical modeling method (Bullmore and Sporns, 2009; Craddock et al., 2013; He and Evans, 2010; Kaiser, 2011; Liao et al.,

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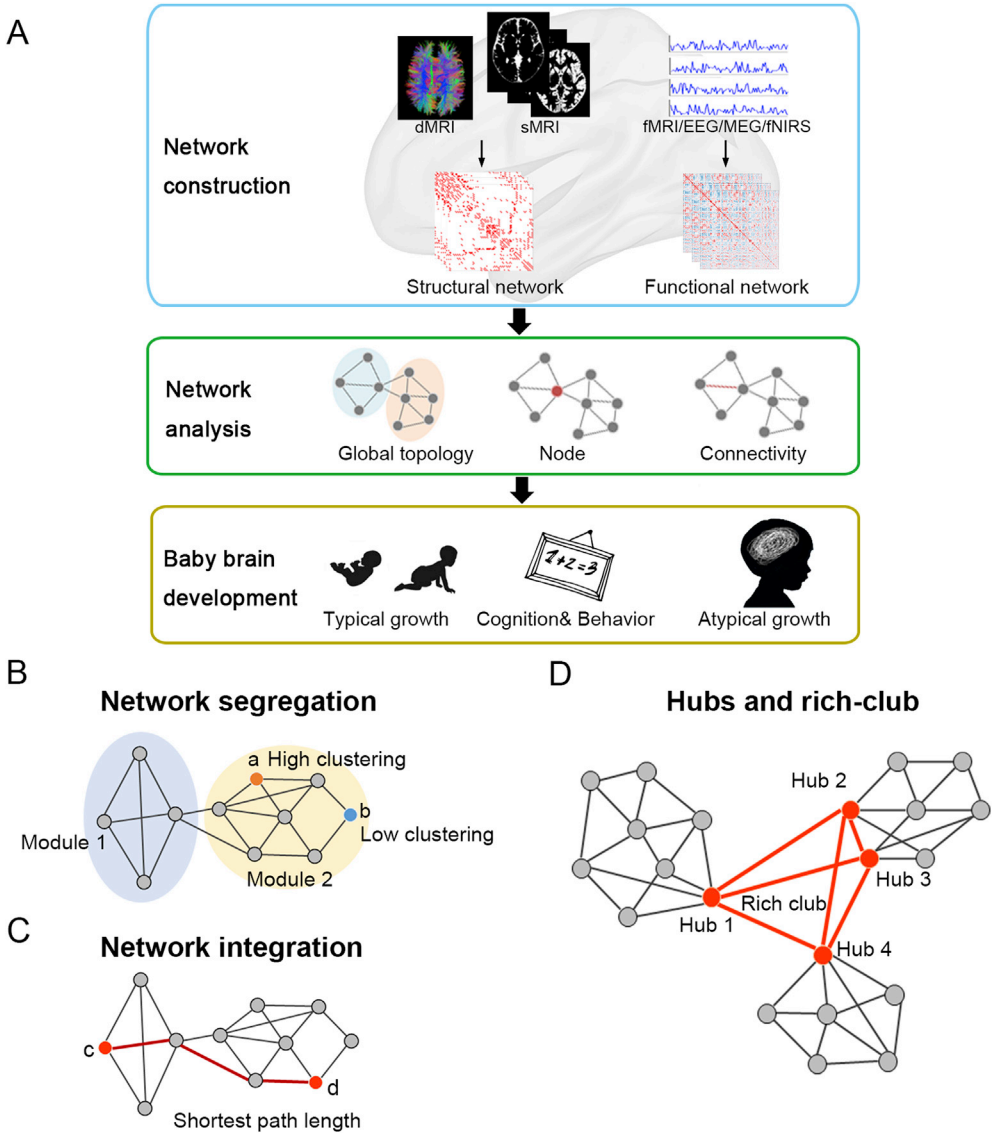

Fig. 1. Brain network construction and summary of the primary measures in graph theoretical analyses. (A) The graph-theory research framework for brain network construction and analyses. (B) Measurements of the network segregation. The clustering coefficient quantifies the tendency of local aggregation of a network. For example, the neighboring nodes of node *a* are fully connected, representing high local clustering of node *a*, whereas node *b* has low local clustering. The module represents a collection of nodes with denser links between them, but sparse links with others out of the community. (C) Metrics concerning the network integration. The shortest path length identifies the shortest pathway between two nodes, which quantifies the global efficiency for information integration. Here, red lines indicate the shortest path between nodes *c* and *d*. (D) The existence of hubs and rich club architecture. The hubs (dots in red) represent a small set of high-degree nodes. Highly connected hub nodes (lines in red) suggest the existence of rich club organization within the overall network structure. Source: reproduced from (Cao et al., 2017b).

2017; Meunier et al., 2010; van den Heuvel and Sporns, 2013; Xia and He, 2017). Accumulating studies have focused on the emergence and development of brain topology during the early stages of life, which have revealed a highly efficient and fast changing network organization that supports the initial information communication and later topological reorganization (Tables 1 and 2). These investigations present unique opportunities to explore how neural circuits emerge separately but then grow to form an integrated connectome possessing nontrivial topological patterns that support increasingly refined regional interactions and cognitive functions. It is also essential to identify the developmental milestones that occur during network maturation and define the typical/atypical growth trajectories of specific topological attributes to enable the early detection and early intervention for developmental disorders.

In this article, we reviewed the recent connectome studies that have used multiple neuroimaging modalities, including structural MRI (sMRI), diffusion MRI (dMRI), functional MRI (fMRI), electroencephalography (EEG), magnetoencephalography (MEG), and functional near-infrared spectroscopy (fNIRS), and graph theoretical modeling approaches, to reveal the developmental principles of baby brain networks from approximately 20 gestational weeks to 2 years of age. This article is organized as follows. First, we provide a brief introduction to the network-modeling framework, the construction processes of the brain network and the graph theoretical measurements. Then, we expound on studies that examined the healthy evolving baby connectome, with the aim of deriving fundamental principles of brain maturation during these early stages of life. Due to the differences in brain development between the prenatal and postnatal periods, we organized the content into two parts, each targeting a different stage (Tables 1 and 2). Furthermore, we addressed the power of infant network attributes to predict later cognitive functions and examined developmental miswiring during the early phase and the lifelong impact of these events (Table 3). Finally, we discuss the methodological challenges and future directions of the baby connectome field.

The graph theoretical modeling framework of the brain network

Under the frame of graph theory, a network is composed of certain numbers of nodes that are connected by weighted or un-weighted edges. In general, a graph can be classified as a directed or undirected type, according to the existence or absence of directional information associated with the edges. An undirected network frame is most frequently used in human brain network studies because of the lack of *in vivo* approaches that are capable of capturing the directions of connections.

Table 1
Overview of prenatal brain network development studies using graph theory modeling.

	Study	Modality	Scan state	Subject n: age	Network type	Node definition: N	Connectivity matrix	Main findings
Structural networks	Tymofiyeva et al., 2013	dMRI	Unknown (some anesthesia or sedated)	8 sub: 31.14–39.71 PMW 8 sub: 1–14 d; 10 sub: 181–211 d; 7 adults: 24–31 y	Binary	Custom atlas: 100	Deterministic tractography	Before birth: SW ↑; Modularity ↑; CP ↓; Gamma ↑;
	Brown et al., 2014	dMRI	Unknown	47 sub (longitudinal): 28.19 ± 2.12 PMW	Weighted (FN; mean FA; normalized FN)	Infant-AAL atlas: 90	Deterministic tractography	SW↑; CP↑; Gamma↑; LP↓;
	Ball et al., 2014	dMRI	Sedation	28 sub (longitudinal): 25.2–33.0 PMW 46 sub: 38.0–44.1 PMW	Binary	Custom atlas: ~500	Probabilistic tractography	Rich club exist; feeder ↑; CP ↑; LP ↓;
	van den Heuvel et al., 2015	dMRI fMRI	Sedation	27 sub (7 longitudinal): 30.0–42.3 PMW 42 adults: 29 ± 8.0 y	Binary; Weighted (FA; Pearson's correlation)	JHU atlas: 56	Deterministic tractography; Pearson's correlation	SW ↑; Modularity ↑; CP ↑; LP ↓;
	Batalle et al., 2017	dMRI	Natural sleep	65 sub: 25.3–45.6 PMW	Binary; Weighted (FS; FA; NDI; 1-ODI)	Infant-AAL atlas: 91	Anatomically Constrained Tractography	SW ↑ (rFS); Eglob ↑ (rFS,1-ODI); Eloc ↑ (Binary), ↓ (rFS); Gamma ↑ (rFS);
	Zhao et al., 2017	dMRI	Natural sleep	77 sub: 31.9–41.7 PMW	Weighted (FN × FA)	JHU atlas: 58	Deterministic tractography	Eglob ↑; Eloc ↑;
	Song et al., 2017	dMRI	Unknown	24 sub (*in vivo*): 34.3–41.6 PMW 10 sub (ex vivo): 19.1–20.9 PMW	Weighted (scaled FA)	Custom atlas: 80	Deterministic tractography	SW exist; Eglob ↑; Eloc ↑;
Functional networks	Fransson et al., 2011	fMRI	Natural sleep	18 sub: 39 + 0.2 GA (wk) 18 adults: 22–41 y	Binary	Voxel wise: 4966	Pearson's correlation	SW exist;
	Thomason et al., 2014	fMRI	Unknown	17 sub (in utero): 27.6 ± 2.88 GA (wk); 16 sub (in utero): 34.4 ± 2.31 GA (wk);	Weighted (coefficients after Fisher's z)	Custom atlas: 149	Pearson's correlation	Modularity ↓; Inter-module connection ↑;
	Cao et al., 2017a	fMRI	Natural sleep	40 sub: 31.3–41.7 PMW	Weighted (coefficients after Fisher's z)	Voxel wise: 7101	Pearson's correlation	FCS ↑; CP ↑; LP ↑; Lambda ↑; PC ↓; Connector number ↓; Hub number ↑; Rich club size ↑;
	Toth et al., 2017	EEG	Natural sleep	139 sub: 38.84 ± 1.10 GA (wk);	Weighted (phase lag index)	Sensors	Minimum spanning tree connectivity	Leaf fraction ↓; Diameter ↑; Tree hierarchy ↓;

sub: subjects; PMW: postmenstrual week; GA, gestational age; d: day; wk: week; m: month; y: year; FA: fractional anisotropy; FN: fiber number; FS: fraction of streamlines; NDI: neurite density index; ODI: orientation dispersion index; SW: small world; CP: clustering coefficient; LP: shortest path length; Gamma: normalized clustering coefficient; Lambda: normalized shortest path length; Eglob: global efficiency; Eloc: local efficiency; PC: participation coefficients; Infant-AAL template: infant brain based AAL atlases (Shi et al., 2011); JHU atlas: Johns Hopkins University neonate atlas (Oishi et al., 2011).

Additionally, brain networks can be mapped at different spatial scales ranging from the micro level (e.g., neuron populations) to the macro level (e.g., brain regions). A micro-scale network, such as the neuronal network model, is usually constructed through cultured cells *in vitro* or primitive animals, such as *C. elegans*. The macro-scale network, as a model that can record the inter-regional connections in the whole brain *in vivo* through neuroimaging data, is widely adopted in human brain development studies. In this model, network nodes are usually defined by brain partitions that are previously assigned, and the edges are determined by the structural or functional interactions between the separate brain regions. In the following part, we provide brief descriptions of brain network construction and analysis procedures that are relevant to the following reviewed baby brain network studies.

Network node definition

Due to the lack of natural node units in brain network studies, the acquisition of brain nodes relies on the modality of neuroimaging. In EEG, MEG and fNIRS studies, nodes are indisputably determined using their derived cortical locations of electrodes, sensors or detectors (da Silva, 2004). In MRI studies, a parcellation scheme or atlas is needed to divide the brain into different regions of interests (ROIs) (Bullmore and Sporns, 2009; He and Evans, 2010), which are defined based on anatomical (Tzourio-Mazoyer et al., 2002) or functional (Power et al., 2011) information or on a random algorithm (Zalesky et al., 2010). Different parcellations capture different patterns of structural/functional pathways, and the number of nodes also significantly influences the absolute value of topological attributes (Wang et al., 2009; Zalesky et al., 2010; Zhao et al., 2015). These methodological variations emphasize the importance of performing validation analyses using different parcellation schemes in research. Of note, infants dedicated atlases were also proposed in some studies (Oishi et al., 2011; Shi et al., 2011, 2017; Wright et al., 2015) and are important for network node definitions of baby brains.

Table 2
Overview of postnatal brain network development studies using graph theory modeling.

	Study	Modality	Scan state	Subject n: age	Network type	Node definition: N	Connectivity matrix	Main findings
Structural networks	Yap et al., 2011	dMRI	Natural sleep	39 sub (longitudinal): 2w, 1y, 2y	Binary	AAL atlas: 78	Deterministic tractography	SW exist; Modularity exist; Eloc ↑;
	Ratnarajah et al., 2013	dMRI	Natural sleep	124 sub: 36.6–42.7 GA (wk)	Weighted (normalized FN)	JHU atlas: 64	Deterministic tractography	SW exist; Eloc: left hemisphere > right hemisphere
	Tymofiyeva et al., 2013	dMRI	Unknown (some anesthesia or sedated)	8 sub: 31.14–39.71 PMW 8 sub: 1–14 d; 10 sub: 181–211 d; 7 adults: 24–31 y	Binary	Custom atlas: 100	Deterministic tractography	After birth: Modularity ↓; Gamma ↓; LP ↓; SW ↓;
	Huang et al., 2015	dMRI	Natural sleep	25 sub: 39.5 ± 2.3 GA (wk); 13 sub: 2.3 ± 0.5 y; 25 sub: 11.8 ± 1.8 y 18 adults: 28.5 ± 5.1 y	Weighted (connectivity probability)	AAL atlas: 80	Probabilistic tractography	SW ↓; Eglob ↑; Eloc ↑; Modularity ↓; Gamma ↓; Number of Conncectors ↑; Number of modules ↑; Robustness ↑;
	Fan et al., 2011	sMRI	Unknown (no sedation)	28 sub (longitudinal): 6.1 ± 2.8 wk, 59.3 ± 3.0 wk, 100.7 ± 6.8 wk; 27 adults: 24 ± 3 y	Binary	Infant-AAL atlas: 90	Pearson's correlation of gray matter volume	SW exist; Eglob ↑; Eloc ↑; Modularity ↑;
	Nie et al., 2014	sMRI	Unknown	73 sub (longitudinal): 1 m, 1 y, 2 y	Binary	Infant-AAL atlas: 78	Pearson's correlation of cortical thickness/ curvedness/fiber-density	Eglob ↓, Eloc ↑ (curvedness); Eloc ↓ (cortical thickness, fiber-density);
Functional networks	Gao et al., 2011	fMRI	Natural sleep	51sub: 23 ± 12 d; 50 sub: 13 ± 1 m; 46 sub: 24 ± 1 m	Binary	AAL atlas: 90	Pearson's correlation	SW ↑; Eglob ↑ (3 wk^{-1} y); Eloc ↑ (3 wk^{-1} y);
	Berchicci et al., 2015	MEG	Natural sleep; Rest; Prehension	7 sub: 2.75–6 m; 7 sub: 6.5–11.75 m; 6 sub: 24–34 m; 6 sub: 36–60 m; 6 adults: 20–39 y	Weighted (Synchronization likelihood)	MEG sensors	Synchronization likelihood between signals	CP↑; LP ↓; Eloc ↑; Eglob↑;
	De Asis-Cruz et al., 2015	fMRI	Natural sleep	60 sub: 12.5 ± 6 d	Binary	Infant-AAL atlas: 90	Pearson's correlation	SW exist;

sub: subjects; PMW: postmenstrual week; GA, gestational age; d:day; wk: week; m: month; y: year; FN: fiber number; SW: small world; CP: clustering coefficient; LP: shortest path length; Gamma: normalized clustering coefficient; Lambda: normalized shortest path length; Eglob: global efficiency; Eloc: local efficiency; PC: participation coefficients; Infant-AAL template: infant brain based AAL atlases (Shi et al., 2011); JHU atlas: Johns Hopkins University neonate atlas (Oishi et al., 2011).

Network edge definition

Brain regions are structurally connected through a large number of fiber bundles that provide biological pathways for information transfer. Typically, these fiber tracts can be reconstructed through dMRI-based tractography and then used to define edges of the structural connectivity network (Behrens et al., 2003; Mori et al., 1999; Parker et al., 2003). The number of reconstructed streamlines or averaged informative diffusion indexes of the connection can be used as the edge weight. Another type of structural network called the structural covariance network, measures the inter-regional correlations of brain morphological volumes or other anatomical indices, such as cortical-thickness, across subjects (Alexander-Bloch et al., 2013; Evans, 2013; He et al., 2007; Lerch et al., 2006). The functional network assesses the inter-regional associations of the neurons activities and usually defines edges using the temporal statistic coherence (i.e., Pearson's correlation or synchronization likelihood) of low-frequency blood oxygenation level-dependent (BOLD) signals in functional MRI (Biswal et al., 1995; Friston, 1994), electrophysiological recordings in EEG and MEG (Bassett and Bullmore, 2006; Micheloyannis et al., 2006; Stam, 2004) or diffusely reflected light signals in fNIRS (Mohammadi-Nejad et al., 2018).

Network thresholding

Before obtaining the brain network, a thresholding step is usually performed to define the edges to be used in the subsequent graph theoretical analysis. A commonly used thresholding approach is to set an absolute cut-off value to select edges with greater weights in an individual network (Bullmore and Bassett, 2011). The exclusion of weak edges may reduce the effects of weak covariance or spurious connections that could be introduced by imaging noise, head motions, or cumulative tractography errors. Another option is to use "proportional thresholding", through which a fixed number of the strongest connections are retained in each subject (Bullmore and Bassett, 2011). This method equals the network density across individuals to minimize its influence on network topological properties. However, studies have shown that the use of a thresholding step may ignore potentially valuable or real connections (Bassett and Bullmore, 2017; Goulas et al., 2015; Markov et al., 2013; Santarnecchi et al., 2014). These limitations indicate the importance of using a range of thresholds in brain network analysis to avoid an

Table 3
Overview of atypical brain network development studies using graph theory modeling.

	Study	Modality	Scan state	Subject n: age	Network type	Node definition: N	Connectivity matrix	Main findings
Structural networks	Batalle et al., 2012	dMRI	Natural sleep	32 controls: 1 y 24 IUGR: 1 y	Binary; Weighted (mean FA; FN)	Infant-AAL atlas: 93	Deterministic tractography	IUGR: Eloc ↓; Eglob ↓
	Shi et al., 2012	sMRI dMRI	Unknown (no sedation)	25 controls: 42.8 ± 2.2 GA (wk) 21 high risk (schizophrenia): 43.1 ± 3.6 GA (wk)	Binary; Weighted (FN)	Infant-AAL atlas: 90	Pearson's correlation (gray matter volume), Deterministic tractography (fiber connection)	High risk neonate (schizophrenia): Eglob ↓; Connection distance ↑; Hub number ↓
	Lewis et al., 2014	dMRI	Natural sleep	113 high risk (ASD): 2 y	Weighted (Strength = FN/surface area)	AAL atlas: 90	Probabilistic tractography	High risk infant (ASD): Eglob ↓; Eloc ↓;
	Jakab et al., 2015	dMRI	Unknown	20 CCA (in utero): 23.1 ± 1.2 GA (wk) 31.0 ± 3.3 GA (wk) 40 controls (in utero): 23.9 ± 1.1 GA (wk) 29.6 ± 2.5 GA (wk)	Weighted (FN/ regional volume, FA)	Custom atlas: 90	Deterministic tractography	CCA: Network centrality ↓; Nodal strength ↑; Clustering coefficient ↓;
Functional networks	Scheinost et al., 2016	fMRI	Natural sleep	Birth age: 12 sub: 27 ± 2.2 PMW 25 sub: 40 ± 1 PMW Scan age: 12 sub: 42.6 ± 1.0 PMW 25 sub: 42.3 ± 1.3 PMW	Binary; Weighted (coefficients after Fisher's z)	Custom atlas: 95	Pearson's correlation	Very preterm: Core connections ↓; CP ↓; Assortativity ↓; Modularity↓;
	Batalle et al., 2016	fMRI	Natural sleep	13 controls: 44.0 (1.9) PMW 20 IUGR: 43.0 (2.2) PMW	Binary; Weighted (coefficients after Fisher's z, only positive)	Infant-AAL atlas: 90	Pearson's correlation	IUGR: Eloc ↓; Eglob ↓

sub: subjects; PMW: postmenstrual week; GA, gestational age; wk: week; m: month; y: year; FA: fractional anisotropy; FN: fiber number; SW: small world; CP: clustering coefficient; LP: shortest path length; Gamma: normalized clustering coefficient; Lambda: normalized shortest path length; Eglob: global efficiency; Eloc: local efficiency; PC: participation coefficients; IUGR: intrauterine growth restriction; ASD: autism spectrum disorders; CCA: corpus callosum agenesis; Infant-AAL template: infant brain based AAL atlases (Shi et al., 2011).

arbitrary threshold. Another candidate strategy is to use the raw weighted network without thresholding. This option is easily adopted on network models such as the deterministic tractography-based white matter network, which is not fully connected. For the fully connected networks that are usually defined by inter-regional correlations or connection probabilities, novel weighted network metrics that account for all possible connections between nodes are valuable (Bolanos et al., 2013; Sporns and Betzel, 2016). Once the edges included in a brain network model are defined, the topological properties of the network can be quantitatively characterized. Here, we briefly introduce the topological metrics that are widely used in brain network studies; detailed definitions of these metrics can be found in Rubinov and Sporns (2010).

Network properties

The topology of a brain network can be characterized in terms of its global and nodal aspects. The global attributes measure the architecture of the whole network graph, whereas the nodal attributes measure topological features of a single node. Note that the same graph theoretical metrics may have different mathematical definitions between a binary and a weighted network model, separately. A valuable framework is to classify the topological metrics according to their relationship with network segregation and integration processes (Rubinov and Sporns, 2010; Sporns, 2013), which have been widely used in connectome studies of normal development (Cao et al., 2016, 2017b), neuropsychiatric disorders (Lord et al., 2017) and cognition processes (Cohen and D'Esposito, 2016).

Segregated network properties. The segregation of a network represents the ability of local information processing that is responsible for specialized functions. Specifically, the clustering coefficient and modularity are two related attributes that provide a quantitative measurement of the segregation capacity of brain networks. The clustering coefficient of a node refers to the tendency to which the neighboring nodes of a node are interconnected, reflecting the density of local clusters. The clustering coefficient of a network refers to the average nodal clustering coefficients across all nodes in the network. Another measurement, local efficiency, is similar to the clustering coefficient but can reflect the fault tolerance capacity of the network (Latora and Marchiori, 2001). Modularity measures the existence of the modular structure of a network, in which the nodes are tightly connected to one another within the same community and sparsely connected to nodes in other communities (Newman, 2004). The densely linked communities support the information specialization at local clusters. From the perspective of information processing, a network possessing a high clustering coefficient or modularity compared with random network indicates a high capacity for local information transfer and a high degree of network segregation. Notably, the module structure is also related to the network integration (see the below). Connections linking different modules may work as highways for the information integration among distinct local communities. These edges can be summarized as inter-module connections to represent network integration abilities. In contrast, connections linking within specific modules are usually considered intra-module connections and represent the network segregation capacity.

Integrated network measures. In contrast to segregation, network integration refers to the ability of parallel communication with distributed nodes, which can be quantitatively measured by the characteristic path length or global efficiency. The characteristic path length of a network is calculated by averaging the shortest path lengths between each pair of nodes in the network. Specifically, a path represents a route of edges that connect one node with others, wherein its length is defined as the sum of

the number or weights of the edges, and the shortest route between two nodes refers to the shortest path length. The global efficiency of a network is the inverse of the average values of the shortest path length between any two nodes (for more details, see (Rubinov and Sporns, 2010)). A network that possesses high global efficiency and the low shortest path length has high global information transfer efficiency and a high degree of network integration.

Balance of segregation and integration. Two extremes of segregation and integration are regular network and random network, respectively. A regular network has a high clustering coefficient and long characteristic path length, while a random network has a low clustering coefficient and short characteristic path length. An optimized topology should balance between a regular and random network, which is called a small-world network. A small-world network possesses a shorter characteristic path length than a regular network and a higher clustering coefficient than a random network to guarantee high capacity for local and global information transfer networks (Latora and Marchiori, 2001; Watts and Strogatz, 1998). This architecture has been observed in various types of networks, such as biological, social, and traffic networks (Watts and Strogatz, 1998). To quantify the small-world architecture, the normalized clustering coefficient and normalized characteristic path length are adopted. A random network is used as a null model to obtain these normalized attributes (Maslov and Sneppen, 2002; Zalesky et al., 2012). The ratio between the normalized characteristic path length and clustering coefficient is defined as small-worldness, which should be much larger than one in a small-world network (Achard and Bullmore, 2007; Humphries and Gurney, 2008).

Regional layouts. The most direct nodal metric is the number of edges linking to a node, which is called the nodal degree. High degree nodes serve as hubs in information transmission. The degree distribution of a network indicates the proportion of nodes that have a certain degree, which can indicate the resilience of a network. For example, a scale-free network whose degree distribution follows a power law is sensitive to the target attack and demonstrates robustness to random attacks because of the existence of huge hubs (Achard and Bullmore, 2007). Hubs can also be identified by other nodal metrics, such as nodal efficiency (Achard and Bullmore, 2007) or nodal betweenness centrality (Freeman, 1977). Importantly, the highly connected hubs may form rich-club organization, which is essential to the global information integration (van den Heuvel and Sporns, 2011). The rich-club organization indicates that the hub nodes tend to be more densely interconnected with one another than by random chance (van den Heuvel and Sporns, 2011). Based on the hub members, the network edges can be further classified into three types: rich-club connections, which link between rich-club nodes, feeder connections, which link between peripheral and core nodes, and local connections, which link between non-rich-club nodes (van den Heuvel and Sporns, 2011). A similar classification of connections is to use edge betweenness centrality (Freeman, 1977; Girvan and Newman, 2002; Xia et al., 2016) to classify network edges into core edges and non-core edges. Based on the given module partition, brain hubs may be classified into connector hubs or provincial hubs, according to the nodal participation coefficient, a measurement quantifying the proportion of their edges that link within certain module or across modules (Guimera et al., 2005; He et al., 2009; Power et al., 2013). Connector hubs that possess high participation coefficients spread their edges into different modules, whereas provincial hubs with a low participation coefficient concentrate connections into the same module.

Prenatal brain network development

Structural networks

Because of the difficulty in imaging fetus brains, most connectome studies have used preterm infants (Ball et al., 2014; Batalle et al., 2017; Brown et al., 2014; Tymofiyeva et al., 2013; van den Heuvel et al., 2015) or postmortem fetal brain specimens (Song et al., 2017) as a substitution model to research normal development during the mid to final trimester of gestation. These studies have found that broadly adult-like topological structures are already established in the prenatal structural network (Fig. 2). The earliest appearance of small-world architecture has been found in postmortem fetuses at 20 postmenstrual weeks (PMW) (Song et al., 2017), and this architecture has been consistently observed in other studies of the preterm network (Batalle et al., 2017; Brown et al., 2014; Tymofiyeva et al., 2013; van den Heuvel et al., 2015). Significant modular structure and rich-club organization already exist at approximately 30 PMW in preterm networks (Ball et al., 2014; van den Heuvel et al., 2015). These findings demonstrate that the structural brain network during the prenatal period is already highly efficient at local and global information transfers and possesses the specialized local communities for segregation and the high-cost backbones for integration. With development, similar developmental changes have been observed in different preterm studies, regardless of their methodological differences (Fig. 2). An increased clustering coefficient, reduced characteristic shortest path length (Ball et al., 2014; Brown et al., 2014; van den Heuvel et al., 2015), increased modularity (Tymofiyeva et al., 2013; van den Heuvel et al., 2015), and increased local and global efficiency (Batalle et al., 2017) have been found in term neonates compared to preterm neonates. As a result, the structural networks become more efficiently connected with development in terms of both network integration and segregation. Interestingly, the shaping of the network seems to lean toward segregation enforcement in prenatal stage, which is proven by the increased normalized clustering coefficient (Batalle et al., 2017; Brown et al., 2014; Tymofiyeva et al., 2013) and stable normalized shortest path length (Brown et al., 2014; Tymofiyeva et al., 2013). This developmental bias is also confirmed by the finding that the small-worldness increased with development during the prenatal period, an observation that is consistent in cross-sectional and longitudinal study designs (Batalle et al., 2017; Brown et al., 2014; Tymofiyeva et al., 2013; van den Heuvel et al., 2015).

In terms of the regional layout of the brain, the degree distribution of the network nodes has been found to follow an exponentially truncated power law during the prenatal period (Ball et al., 2014; Brown et al., 2014; van den Heuvel et al., 2015), which guarantees the existence of highly efficient hubs but not huge hubs. Various studies have found that structural hubs (Fig. 3A) in the preterm brain largely overlap with those observed in the adult brain (van den Heuvel and Sporns, 2013), in which they are primarily located in the superior and medial frontal, superior parietal, sensorimotor and posterior-medial cortices (Ball et al., 2014; Pandit et al., 2014; van den Heuvel et al., 2015; Zhao et al., 2017). The development of connections and brain regions is heterogeneous in the network. Short-range connections develop fast, with links between the primary sensorimotor cortex, occipital cortex and frontal cortex within the hemisphere (Ball et al., 2014; Zhao et al., 2017). Hub regions expand into the inferior frontal cortex and insula regions at term age (Ball et al., 2014) and develop fast on their nodal connectivity efficiency and nodal betweenness centrality (van den Heuvel et al., 2015; Zhao et al., 2017). Additionally, dramatic development was also discovered in rich-club organization, including the principal proliferation of the feeder edges (Ball et al., 2014) and a gradual escalation, in which the connection strength increases in the local, feeder, and rich-club edges in the last stage before the birth stage (Zhao et al., 2017). Furthermore, Ball and colleagues have demonstrated that the addition of feeder connections during prenatal development strengthened network integration and segregation capacities (Ball et al., 2014). Core edges with high edge betweenness also show the rapid growth during this period (Batalle et al., 2017). These changes highlight the centrality of the early-existed hub structures to make hubs more dominant among brain regions. Notably, the provincial hubs in charge of communication within specific modules develop more rapidly than the connector hubs, indicating a bias for network segregation during hub development (Zhao et al., 2017).

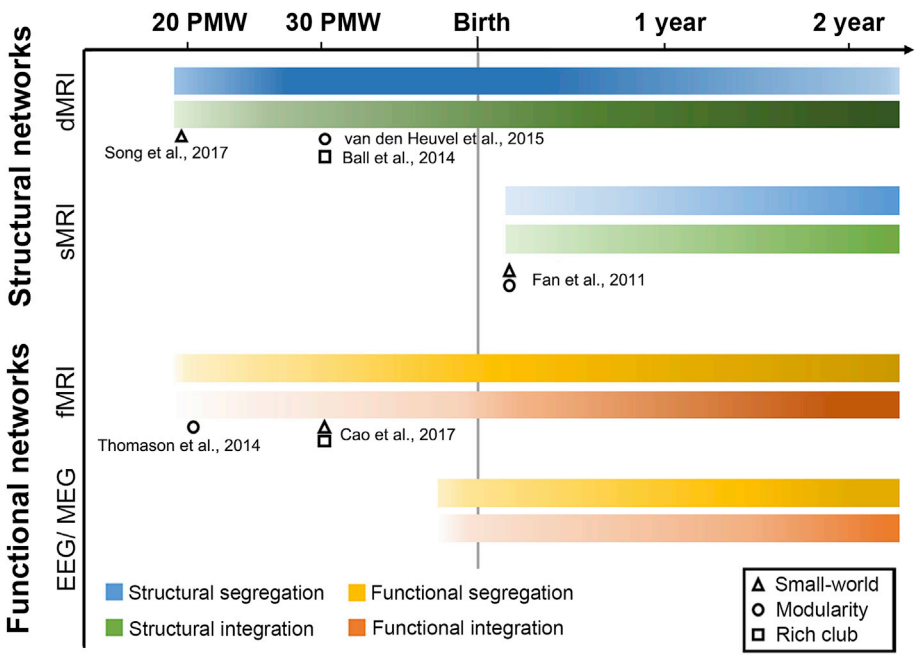

Fig. 2. A Gantt chart of the developmental processes and corresponding segregation and integration of the brain network from the mid-trimester until age two. The intensity of the color bars illustrates the intensity of the network segregation and integration. The triangle, circle, and square indicate the existence of small world, modularity, and rich club, respectively. Notably, the timing of the existence marked here is from the studies reported to date, not the exact timing of formation because the human prenatal brain network studies before 20 PMW are scarce at present. Schematic overview based on findings at present (Ball et al., 2014; Batalle et al., 2017; Berchicci et al., 2015; Brown et al., 2014; Cao et al., 2017a; Fan et al., 2011; Fransson et al., 2011; Gao et al., 2011; Huang et al., 2015; Nie et al., 2014; Song et al., 2017; Thomason et al., 2014; Toth et al., 2017; Tymofiyeva et al., 2013; van den Heuvel et al., 2015; Yap et al., 2011).

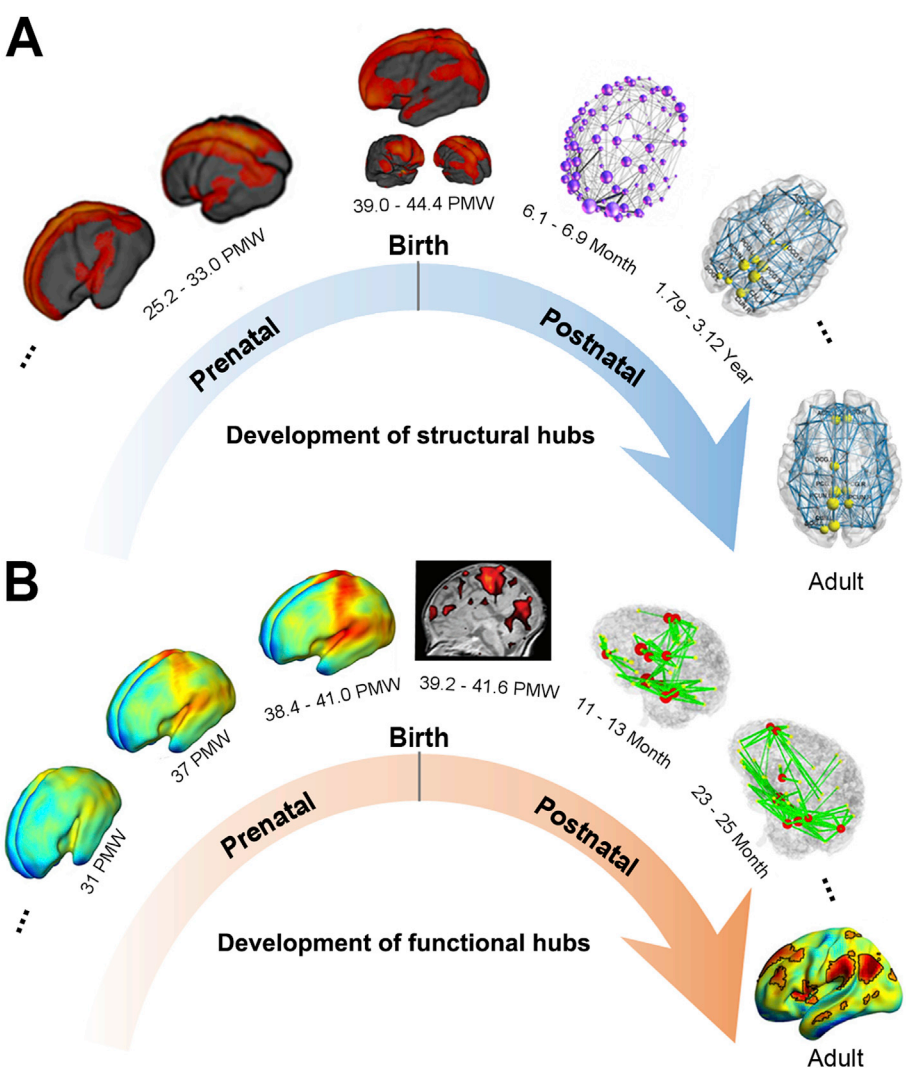

Fig. 3. The development of human brain hubs at the early stage of life. (A) The collected findings of the development of structural hubs in the human cerebral cortex, derived from diffusion imaging data. The structural hubs are largely overlapped with those in adult at the time of birth, including the superior and medial frontal, superior parietal, sensorimotor, posterior-medial cortices, insula regions, and inferior frontal cortex. (B) The collected findings of the development of functional hubs in the human cerebral cortex, derived from resting-state functional imaging data. The functional hubs of infant brains are primarily located in the sensorimotor and visual cortices at birth and move toward the areas involved in high-order cognitive functions, such as the medial superior frontal gyrus and some default mode network regions, in 2-year-olds.
Source: reproduced from (Ball et al., 2014; Cao et al., 2017a; Fransson et al., 2011; Gao et al., 2011; Huang et al., 2015; Liu et al., 2016; Tymofiyeva et al., 2013).

Functional networks

To date, three studies have used the graph theoretical model to reveal prenatal functional network development (Cao et al., 2017a; Thomason et al., 2014; Toth et al., 2017), including two functional MRI studies and one EEG investigation. In the fMRI brain network studies, prominent small-world and rich-club structures in preterm brains were found at approximately 30 PMW (Cao et al., 2017a), and significant modular organization was observed at approximately 20 weeks in gestational age (GA) in fetal brains in utero (Thomason et al., 2014) and at 30 PMW in preterm brains (Cao et al., 2017a) (Fig. 2). Using minimum spanning tree graphs, an EEG investigation has also reported the early presence of an optimal hierarchical architecture over different frequency bands in infants at 36 weeks in GA (Toth et al., 2017). These results revealed that similar to structural network, the initial functional network also presents a high efficient and organized topology. With development, the clustering coefficient of the functional network increased significantly with age, indicating an enhanced segregation process (Cao et al., 2017a). This growth of the network segregation was also reflected by the deceased participation coefficient and deceased number of connectors with age in preterm brains (Cao et al., 2017a), resulting in separation of the modular system during the prenatal period. The EEG study found that the network topology was changing toward a less centralized and hierarchical organization with age in infants at the theta- and alpha-bands, which also indicates a segregation enhancement (Toth et al., 2017). The age-related decrease in global efficiency and increase in diameter (similar to the characteristic path length) were found in preterm and infant brains in the fMRI and EEG studies, revealing decreased network integration. However, some inconsistent results were also observed. Decreased modularity and increased inter-module connection strength with age were detected in the fetal fMRI study (Thomason et al., 2014), showing enhancement of the network integration process. Methodological differences, such as the choice of network thresholding method or brain node definition, may explain this discrepancy.

Notably, even though it exhibits prominent topological structure, the functional network of the brain is still in an incomplete state at the beginning of the third trimester. Primary networks, such as the sensorimotor, visual and auditory networks, can be detected in preterm brains; however, higher-order networks, such as the default mode network and salience network, are still in the formation process (Fransson et al., 2007; Smyser et al., 2010). Thus, functional hubs (Fig. 3B) are also immature and largely confined to the primary regions, including the supplementary motor areas and visual regions (Cao et al., 2017a), which are distinctly different from adult brain hubs located in the superior parietal and superior frontal cortex and anterior and posterior cingulate gyrus, as well as insula regions (Buckner and Krienen, 2013; Liang et al., 2013; Liu et al., 2016; Zuo et al., 2012). With development, hub members spread into primary sensorimotor, visual regions and Wernicke's area, corresponding to the functional hubs in full-term neonates (Cao et al., 2017a; Fransson et al., 2011), and this growth is dominantly affected by the enhancement of short-to-middle range primary cortex connections (Cao et al., 2017a). Meanwhile, the size of rich-club organization expands with age, and dramatic changes in the connections were detected, including increases in the number and strength of the feeder connections, and a decreased number but increased strength of local connections (Cao et al., 2017a). These regional changes suggest that the development of functional hubs during the prenatal period primarily concentrate on specific primary functional systems that may function as an urgent infrastructure to establish before birth. These enhancements in certain functional communities may promote the functional specialization and information segregation of the brain.

Early postnatal brain network development

Structural networks

Compared to the topological changes that occur before normal birth, the reconfigurations of structural network occurring during the postnatal period show different developmental patterns (Fig. 2). Specifically, decreased modularity in 6-month-old infants (Tymofiyeva et al., 2013), as well as decreased modularity and an increased number of inter-module connectors in 2-year-old toddlers, were observed compared with those in term neonates (Huang et al., 2015). Meanwhile, decreased characteristic path length in 6-month-old infants (Tymofiyeva et al., 2013) and increased global efficiency in 2-year-old toddlers were found compared with those in term neonates (Huang et al., 2015; Yap et al., 2011). These results indicate that the structural segregation is decreasing while the structural integration is increasing with age during the early postnatal period. The decrease in network segregation was also confirmed by the findings that the normalized clustering coefficient and small-worldness decreased monotonically in term neonates, 2-year-old toddlers and adults (Huang et al., 2015; Tymofiyeva et al., 2013). The growth of network integration may be closely associated with the increasing proportion of long fiber connections linking distant areas with development (Tymofiyeva et al., 2013). Additionally, the local efficiency of the structural network was found to be increased in one-year-old and two-year-old toddlers compared with that in neonates, indicating the improvement of the fault-tolerant ability of networks (Huang et al., 2015; Yap et al., 2011).

Relatively dynamic regional reshaping also occurs in the structural network during early postnatal life. As a whole, the brain network retains a degree distribution of truncated power law in the early postnatal period and demonstrates some refinements (Huang et al., 2015; Yap et al., 2011). Toddlers exhibit age-dependent upgrades in network robustness against both random and targeted attacks compared with those in neonates (Huang et al., 2015). The hub distribution (Fig. 3A) identified by nodal efficiency still presents an adult-like pattern and primarily remains unchanged (Huang et al., 2015; Tymofiyeva et al., 2013), except for the left anterior cingulate gyrus and left superior occipital gyrus, which become hubs in toddler brains compared with neonate brains (Huang et al., 2015). However, the topological roles of brain regions change with age by accessing age-related classifications, according to their intra-modular degree and participation coefficient (Yap et al., 2011). The centrality of the posterior-medial regions, such as the precuneus and cuneus, was observed to be increased before pre-adolescence (Huang et al., 2015; Yap et al., 2011), while the importance of some brain regions, such as the left Heschl's gyrus and bilateral precentral gyrus, are reduced with age due to their decreased normalized regional efficiency (Huang et al., 2015).

In addition to individual structural connectivity network modeling, studies have also used the anatomical covariance network model to capture regional co-variation patterns during early development (Fan et al., 2011; Nie et al., 2014). The efficient small-world topology and nonrandom modular organization of the morphological covariance connectome were discovered in infants ranging in age from 1 month to 2 years (Fan et al., 2011) (Fig. 2). In the same study, the global efficiency, local efficiency and modularity of the anatomical network all increased with age, demonstrating the increase of both network segregation and integration with development (Fan et al., 2011). Another study has also found increased local efficiency and decreased global efficiency from birth to 2 years of age (Nie et al., 2014) using a cortical curvedness correlation network model, indicating a reinforcement of network segregation. This study also found that different anatomical characteristics of network edges exhibit distinct development patterns. The local efficiency of the cortical-thickness correlation network and fiber-density correlation network decreased with age before 2 years old, while the global efficiency remained stable (Nie et al., 2014). These inconsistent results may reflect different regional synchronized maturation in anatomy during cortex development. Different growth patterns between the anatomical covariance network and structural connectivity network are conceivable because unlike white matter connectivity, the regional anatomical covariance is not a real biological pathway of information transfer but a comprehensive index of both brain structure and function

(Evans, 2013).

Functional networks

At the time of a full-term birth, neonatal functional brain networks maintain highly efficient small-world and modularity structure (De Asis-Cruz et al., 2015; Fransson et al., 2011; Gao et al., 2011); however, they are still largely immature. Only some primary functional networks, such as the sensorimotor network, show an adult-like pattern at birth (Gao et al., 2011; Pendl et al., 2017). The dorsal attention network and default mode network emerge in a mature architecture at one year of age, while high-order cognitive networks, such as the salience network and bilateral frontoparietal networks, are still incomplete at the end of year one (Gao et al., 2015a). Four articles have explored the early postnatal functional brain network; two concerned the network configuration of term babies (De Asis-Cruz et al., 2015; Fransson et al., 2011), and two investigated age-related topological developments (Berchicci et al., 2015; Gao et al., 2011). Gao and colleagues (Gao et al., 2011) conducted an investigation of age-related changes in network topologies in infant brains in a large cohort of 147 naturally sleeping healthy infants at the age of three weeks, one year and two years. They found that the global efficiency and local efficiency of the brain functional network increased in 1-year-old infants compared to neonates, while remaining stable during the second year of life (Gao et al., 2011). They verified the results in a wide rage network threshold and further revealed that the development of long-distance connections contributes greatly to the increase of global efficiency. Another MEG study concerning the development of sensorimotor network topology through infancy to adult period found marked increases of local efficiency and global efficiency after the first year of life (Berchicci et al., 2015). These changes reveal an increase of both network segregation and integration processes during early postnatal development (Fig. 2).

After birth, the evolution of functional hub distribution continues through dynamic regional configurations. Nodal local efficiency was found to be increased in the temporal and occipital regions, as well as several subcortical regions, and decreased in the frontal regions during the first year of life. The increased nodal global efficiency was distributed in an extensive regional pattern during the first year and concentrated in the default mode network regions during the second year (Gao et al., 2011). The functional hubs of infant brains (Fig. 3B) are primarily located in the sensorimotor and visual cortices at birth (De Asis-Cruz et al., 2015; Fransson et al., 2011; Gao et al., 2011), and move toward the areas involved in high-order cognitive functions, such as the medial superior frontal gyrus and some default mode network regions, in 2 year olds (Gao et al., 2011). Connection analyses also found that the anterior and posterior cortical regions are connected with each other through long functional connectivity by the age of two, while most primary sensorimotor regions are already functionally connected at birth (Fransson et al., 2007; Gao et al., 2011, 2015b; Smyser et al., 2010). Task-based fNIRS brain connectivity analyses revealed that the adult-like neural activation in infants during object and socioemotional processing increase over the first year of life (Wilcox and Biondi, 2015). Together, these studies showed a clear evolution of brain hubs maturing from segregated primary regions to integrated higher-order function cortices, which is consistent with the behavior observation during this period (Gao et al., 2017). Additionally, although it has incomplete regional components, the functional network at birth is more resilient than simulated scale-free networks in targeted attacks (De Asis-Cruz et al., 2015). The early postnatal development of network integration through increased long-distance functional connections brings age-dependent improvements in network resilience in random and targeted attacks (Gao et al., 2011).

Developmental rules of baby brain networks

In general, the early development of the human brain network, which occurs during the mid-gestation period before birth through approximately the first 2 years of life, involves a shift bias in growth processes from segregation to integration (Fig. 4). Before birth, the well-connected structural network and the fragmentized functional network form a highly efficient small-world topology and distributed modules. During development, the structural network enhances the local information transfer ability and global integration capacity but tends to be more segregated. Meanwhile, the functional network primarily enhances connections between the local primary clusters and short-range edges, resulting in a more separated network. After birth, the structural and functional brain networks become more efficient in global and local information transfer but gain more improvement in the integration capacity. Long-range connections linking distributed brain regions enhance their strength in the network and join new members in the functional network. One possible explanation for the shift of development from segregation to integration is that in preparation for delivery before birth, the brain more actively strengthens within-neuron clusters to build an excess localized foundation of specific functions. After birth, the abundant environmental stimuli may require a great deal of cooperation between disparate functional circles to achieve finely tuned responses and high-order cognitive abilities. This hypothesis is supported by the "local to distributed" developmental pattern of the human brain, which is proposed as an interactive specialization framework initially and further extended to brain network modeling studies (Fair et al., 2009; Johnson, 2000; Vértes and Bullmore, 2015).

Note that the structural supports are far ahead of the functional emergences. The structural network has established pathways between high-order regions and forms adult-like hubs at the time of birth. While the adult-like functional networks involved with complex cognitive abilities, such as self-awareness, attention or execution (Damoiseaux et al., 2006; Smith et al., 2009), require cooperation among multiple distant regions, these networks are largely incomplete in the infant brain (Fransson et al., 2007; Gao et al., 2015a, 2015b; Smyser et al., 2010). However, large co-owned edges and strong coupling of connection strength between neonatal structural and functional network have been observed (van den Heuvel et al., 2015). Studies have shown that the functional organization of the adult brain is sculpted by the underlying anatomical structure (Park and Friston, 2013; Wang et al., 2015). Further studies are urgently needed to reveal how the initial structural topological basis supports the development of functional networks.

The early development of the brain network provides an opportunity to investigate when the prominent topological attributes emergence as the network is forming. An interesting phenomenon is that the small-world and modularity architecture emerge in the earliest probe in brain structural and functional network in the mid-trimester stage (Song et al., 2017; Thomason et al., 2014). Most white matter fibers and functional connectivity have not yet emerged during this period. It is reasonable to infer that these topological architectures are intrinsically preconfigured to drive the later network layouts. Considering the high efficient and high information capacity of small-world and modularity structure, these topologies may minimize the wring-costs when adding new edges in brain network (Bullmore and Sporns, 2012) and may serve as a substructure for network growth in structure and function. A computational modeling study have found that with the constraints of low wiring costs and high processing efficiency, topological architectures such as modules and hubs will present in neural systems (Chen et al., 2013, 2017). Further studies should confirm the brain topologies in the earlier period in combination with certain predictive models to uncover the mechanisms underlying the formation of network organization in baby brain.

Linking brain network development to microstructural maturation

The brain network models used in current infant development studies are all on a large scale level, and the significant topological changes are derived from varieties of microstructural maturation. Most prenatal

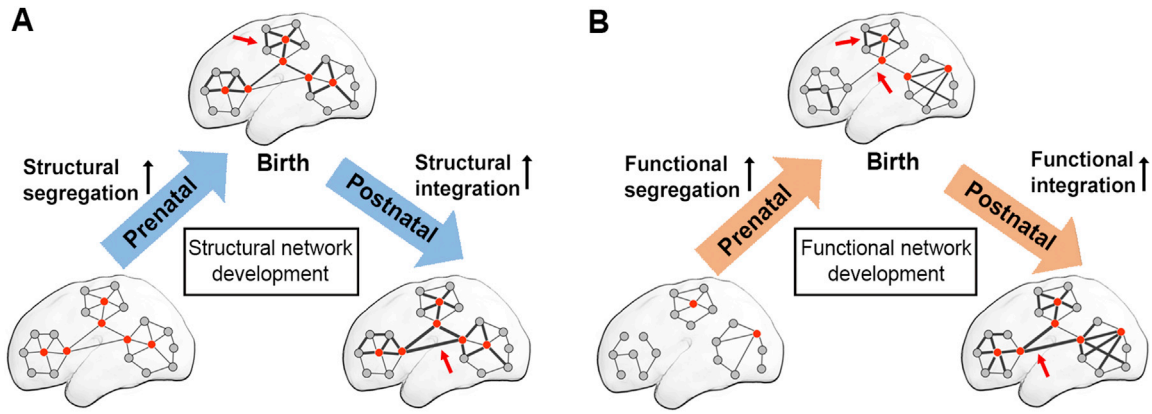

Fig. 4. Hypothesis model of the topological development of the baby brain network. (A) The development of topological architecture in the brain structural network. The hypothesis here states that the structural network is well-established at the time of birth, with abundant local connections within modules and several major distant connections between modules. With development, the network becomes more segregated with enhancement of local clusters during prenatal development and then becomes more integrated with increasing inter-module connections during postnatal development. (B) The development of topological architecture in the brain functional network. The hypothesis here indicates that the functional network is still immature and incomplete at the time of birth. With development, the network shows enhanced segregation during prenatal development and then the emergence and increase of long connections intensify the integrated ability of networks.

investigations of brain networks are conducted in the middle and last trimester of pregnancy, which are the periods where most of the neurogenesis and neuronal migration has occurred (Stiles and Jernigan, 2010). Meanwhile, exuberant synaptogenesis and axonal growth result in billions of new synaptic junctions and the overproduction of macroscopic connections at around birth (Bruer, 1999; Huttenlocher and Dabholkar, 1997) (Fig. 5A). A reasonable inference is that the observed prenatal network growth is primarily caused by axonal growth and synaptogenesis. The dMRI-based tractography is a bridge linking micro-structural features to macro-network connections, which can indicate both the axonal bundles and radial glial scaffold (Huang and Vasung, 2014; Huang et al., 2009; Takahashi et al., 2012; Vasung et al., 2010) during development. An interesting study using postmortem fetal brains has found that the efficiencies of structural network at 20 PMW may be primarily affected by the glial pathways that are responsible for guiding axonal growth rather than by real white matter fibers (Song et al., 2017). In the following third conception period, the majority of cortico-cortical association white matter tracts can be reconstructed through dMRI (Huang et al., 2006, 2009; Takahashi et al., 2012); therefore, the adult-like structure and related changes of the neonatal brain network may be primarily contributed by these fibers.

After birth, although new synapses continue to form, synaptic and axonal pruning, which are accompanied by progressive myelination, become predominant processes during postnatal life (Huttenlocher and Dabholkar, 1997; Huttenlocher and De Courten, 1987; Innocenti and Price, 2005; Stiles and Jernigan, 2010) (Fig. 5A). The coherently consolidated synaptic pruning may speed and enhance the precision of information processing (Luna et al., 2004). Meanwhile, axonal myelination dramatically increases the conduction speed of nerve impulses (Baumann and Pham-Dinh, 2001) and is assumed to improve the functional efficiency of brain (Knaap et al., 1991). These micro-structural changes could be partly captured by dMRI data (Giedd, 2008; Suzuki et al., 2003). Dubois and colleagues have proposed a model (Fig. 5B) in which several maturation stages are described for white matter and are associated with corresponding changes in diffusion indices, such as fractional anisotropy (FA) (Dubois et al., 2014a; Qiu et al., 2015). Neuroimaging assessments may provide some indications for tracing increased anisotropy in the cortical areas and white matter tracts of the infant brain (Dubois et al., 2014a; Huppi and Dubois, 2006; Miller et al., 2012). Importantly, the nodal efficiency of structural networks and the corresponding regional FA values were significantly correlated across individuals from the neonatal to preadolescent periods (Huang et al., 2015), indicating that the topological structure was reshaped by microstructural changes (Fig. 5C). Studies have also found that specific microstructural changes such as neurite density were particularly useful for identifying the changes in local connections due to prematurity (Batalle et al., 2017). However, it is worth noting that macro-scale brain structural networks are derived from image voxels containing millions of neurons at a millimeter scale, which makes it difficult to explain the accurate relationship between micro- and macro-level connections. Further combination of cellular-level neurofilament immunohistochemistry and *in vivo* neuroimaging (Belcher et al., 2013; Bourne et al., 2004), or new chemical transformation technology of non-human mammalian baby brain (Chung et al., 2013; Murakami et al., 2018) may be the feasible approaches to fill in the gap between cellular development and macro-scale network evolution.

Macro-scale functional brain networks are thought to partly reflect communication between distant micro-neuronal clusters (Lichtman et al., 2014), although with different biological significance. One way to link the formation of functional networks in these two scales is to investigate the gradual maturation of neuronal networks *in vitro*. The correlated spontaneous activities of neuronal cultures can be recorded using multi-electrode arrays (MEAs) to estimate micro-scale functional networks (Blankenship and Feller, 2010). Studies have found that a significant small-world architecture with high nodal clustering and a well-organized modular organization at the micro-scale of neuronal cultures can be observed *in vitro* after a minimum of approximately 14 days (Bettencourt et al., 2007; Downes et al., 2012; Gerhard et al., 2011; Pajevic and Plenz, 2009; Schroeter et al., 2015). A rich-club organization is also established at the same time based on a "rich-get-richer" developmental rule (Schroeter et al., 2015). By observing developmental topological properties in different stages, researchers have found functional networks that spontaneously transform from a random topology to an organized small-world structure exhibiting increasing small-worldness until approximately 28 days *in vitro* (Downes et al., 2012). These studies have greatly enriched our understanding of the intrinsic wiring paradigms underlying the functional activation of neurons and suggest that functional networks, when viewed at different scales, may share the same rules of formation that drive a similar basic topological layout.

The baby brain network organization predicts later cognition

The initial wiring observed in the infant brain creates a blueprint for the development of cognitive abilities. The brain network topology observed during the early phase has been found to be significantly

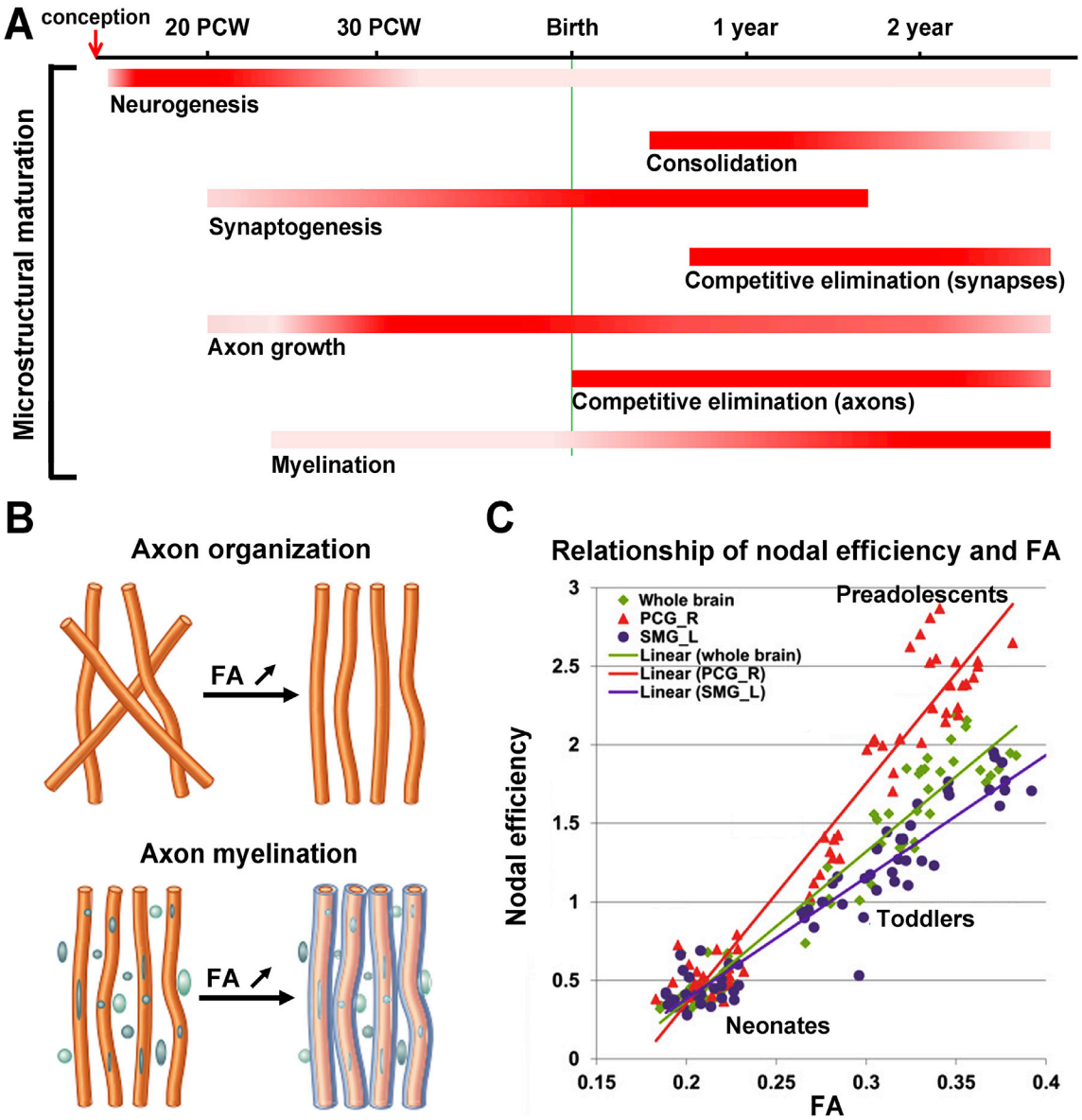

Fig. 5. Microstructural maturation and its relationship with macro-scale network topological development. (A) Gantt chart of the sequence of microstructural events during brain maturation. (B) The hypothesized changes in diffusion indices caused by the maturational processes. (C) The relationship between regional FA and nodal efficiency in a neurodevelopmental cohort.
Source: reproduced from (Dubois et al., 2014a; Huang et al., 2015; Qiu et al., 2015; Vértes and Bullmore, 2015).

correlated with cognitive performance later in life. In structural network studies, network integration and segregation measurements of the neonatal network, including global efficiency and the clustering coefficient, can serve as predictors of Performance IQ and processing speed at 5 years of age (Keunen et al., 2017). The regional clustering coefficients of several brain regions in the neonate brain were found to be significantly associated with internalizing and externalizing behaviors (Wee et al., 2017) assessed in early childhood (24 and 48 months of age, separately). The connection strength of preterm white matter pathways that run between the thalamus and the whole cortex could explain 11% of the variance in cognitive scores in two-year-old children (Ball et al., 2015). The altered global and regional network topology observed in 1-year-old infants with intrauterine growth restriction (IUGR) was associated with abnormal performance in later neurodevelopmental abilities, such as socio-emotional and adaptive behaviors, at two years of age (Batalle et al., 2012).

Studies have also revealed significant relationships between wide neonatal functional networks and later behavior development. Specific functional connectivity in the ventral attention and default mode networks in neonates have been associated with behavioral inhibition at two years of age (Sylvester et al., 2017). A longitudinal study has reported that the immature thalamus–salience functional network of 1-year-old children was predictive of working memory performance at two years of age (Alcauter et al., 2014). The well-established functional connectivity originating from neonatal amygdala was associated with the emergence of fear and other cognition issues (including sensorimotor, attention, and memory abilities) at 6 months of age (Graham et al., 2016) and could predict internalizing symptoms at two years of age (Rogers et al., 2017). EEG studies have also revealed that there is a significant correlation between coherence in the left hemisphere at 14 months of age and individual epistemic language skills at 4 years of age (Kühn-Popp et al., 2016). These results indicated the potential of network attributes serving as early markers of cognitive development. However, how these separated functional connectivity cooperate with each other in a network form to determine the high-order functions of baby brain in future life remains unknown. Studies are urgently needed to investigate the

relationship between early functional topological architectures and later cognitive abilities.

Atypical early development of the brain network

The most common type of atypical growth in the early stage is preterm growth, which involves the sudden interruption of typical development processes as a result of complex genetic and environmental factors (Simmons et al., 2010). It is also a high-risk factor for specific psychiatric disorders, such as attention deficit/hyperactivity disorders (ADHD) (Linnet et al., 2006), and autism spectrum disorder (ASD) (Burd et al., 1999; Larsson et al., 2005). Under the graph theoretical modeling assessment, the abnormal brain topology caused by preterm can be identified in the infant stage. Structural investigations have found that preterm infants show significant disruptions in cortical–subcortical connectivity and short-distance cortico-cortical connections (Ball et al., 2014; Batalle et al., 2017). Additionally, the observation of reduced edge strengths in widespread tracts was associated with premature birth (Pandit et al., 2014). Preterm brains showed an increased clustering coefficient and increased nodal clustering coefficients located at the lateral parietal, ventral and lateral frontal cortices, as well as the regions around the Sylvian fissure, compared with term cohort brains (Ball et al., 2014). More importantly, the alterations in brain network caused by preterm birth continue into later life. Very preterm children showed reduced density and global efficiency but increased local efficiency compared with full-term children, and the reduced connectivity was predictive of impaired IQ and motor impairment (Thompson et al., 2016). Very preterm adults exhibited reinforced rich-club architecture compared to term adults (Karolis et al., 2016). Interestingly, the structural alterations observed in preterm white matter networks look similar to those observed during the prenatal brain development trajectory, including enhanced segregation (increased local clustering) and rich-club configuration, suggesting a possibility that preterm infants go through an overgrowth or compensatory brain maturation during later development. Notably, some inconsistent results have been reported. A preadolescent structural network study has observed that longer gestation preferentially enhanced rich-club connections and strengthened global and local network efficiency in the brain (Kim et al., 2014). A functional network investigation has found that while preterm neonates preserved the rich-club organization of the brain, they exhibited reduced core connections and decreased functional segregation, with significantly reduced clustering coefficients, assortativity, and modularity at term (Scheinost et al., 2016). The cumulative lifelong effects and the impairments of different modalities of a preterm birth on the brain connectome require further multi-modality investigations performed over a wide age range to cover an entire lifespan of changes.

Another adverse condition in early development is the IUGR, which has been considered a candidate brain disorders (Rubinov and Bullmore, 2013). Studies have found that the structural and functional networks of IUGR infants exhibit decreased global and local efficiency and several altered regional properties (Batalle et al., 2012, 2016). School-age IUGR infants maintain their modularity, small-world and rich-club attributes but have different underlying network community structures (Fischi-Gómez et al., 2014). These results indicate a relative vulnerability of network integration and segregation as a result of IUGR.

Meanwhile, many developmental psychiatric disorders show high genetic or pathological risks at the origin of brain development. Maternal schizophrenia produced decreased global efficiency, longer connection distance and less hub regions of structural covariance network in high-risk infants (Shi et al., 2012). At the age of 2, autistic infants exhibit significantly lower local and global network efficiencies in brain structural connectivity network than those observed in healthy babies (Lewis et al., 2014), and infants at high-risk for autism spectrum disorder can be identified with an accuracy of 76% by multi-parameter and multi-scale analyses of their structural connectivity networks (Jin et al., 2015). Additionally, disrupted topological organization of structural connectivity network in the corpus callosum agenesis has also been observed in the fetal stage in 20 PMW showing locally increased nodal strength and reduced centrality (Jakab et al., 2015). These findings reveal high sensitivity in detecting developmental abnormalities from graph theory measurements and emphasize the significance of early intervention in patients with brain disorders.

Technical considerations and future directions

Baby brain image acquisition

Multi-modality neuroimaging approaches are powerful for detecting structural and functional layouts of the baby brain in *vivo*. Each modality has its own advantages and drawbacks. For the structural brain network, sMRI and dMRI techniques provide distinct cortical and white matter anatomical details of the brain at a millimeter level. However, owing to the small head of neonates, a refined spatial resolution is needed to offer an equal representation as that of the adult brain. For the functional brain network, different modalities capture synchronized functional activities at different frequencies. Functional MRI offers a high spatial resolution but a relatively low temporal resolution on a second level. EEG and MEG can detect neural activities directly on a millisecond time scale but are lack of whole brain coverage. FNIRS provides a portable measuring equipment and can be collected in the various behavioral states of babies and has high electromagnetic compatibility. However, the effect of changes in the optical properties of different brain tissues during early development needs to be further considered. Researchers should be aware of these characteristics of each imaging modality and select an appropriate method according to their study aims (for a review, see Mohammadi-Nejad et al. (2018)).

Of note, to perform an accurate network modeling of infant brains, high quality neuroimaging data are necessary. However, due to the inherently uncontrollable behavior of babies, specific measures should be taken during image acquisition. The motion-resistant imaging acquisition method should be promoted in MRI studies of fetuses and newborns (Ferrazzi et al., 2014) to control for the effect of head movement. Using portable cameras to record the subject's movements and the surrounding scene might be useful for the identification of artifacts in the EEG/MEG collection process (Puce and Hämäläinen, 2017). Importantly, it is well worth acquiring an imaging system developed specifically for infant scans, such as the recently proposed neonatal brain imaging system (NBIS) in the Developing Human Connectome Project, which adopts a set of new designs to achieve a 2.4-fold increase in the SNR of images (Hughes et al., 2017). It should also be noted that to minimize the uncontrollable factors, infant brains are usually scanned during natural sleep or a medically sedated state. The observed state-related changes in functional networks (Fransson et al., 2009; Greicius et al., 2008; Horovitz et al., 2008, 2009) may confuse findings of early brain functional network development. Simultaneous EEG-fMRI data acquisition that can monitor the sleep stages may resolve these difficulties but still require technology refreshing (Gao et al., 2017). Furthermore, highly optimized multi-band EPI sequences allowing for the acquisition of high quality MRI data at fine spatial and temporal resolutions (Hutter et al., 2018; Makropoulos et al., 2017; Price et al., 2015). To delineate network refinements related to certain maturation processes, advanced imaging sequences, such as magnetization transfer (MT) imaging (Vavasour et al., 2011) or neurite orientation dispersion and density imaging (NODDI) (Zhang et al., 2012) should be adopted.

Baby brain network construction

The constant changes of the baby brain in early development highlight several issues in the definition of brain nodes and connections during network construction. In terms of node parcellation, adopting widely used adult brain atlases on baby data may induce methodological biases. The rapidly growing baby brain needs age-specific templates in

fine age intervals to offer an accurate reference for image registration and segmentation. Infant-specific brain parcellations are also needed to provide appropriate definitions of brain nodes in different developmental stages. Notably, several baby-specific brain templates (Oishi et al., 2011; Zhan et al., 2013) and atlases (Oishi et al., 2011; Shi et al., 2011, 2017; Wright et al., 2015) have been created. In terms of the edge definition, dMRI-based tractography of infants is challenging owing to the dynamic water content, low anisotropy and increased risk of motion artifacts of neonatal brain imaging. Several technical improvements including the application of large diffusion encoding directions, advanced diffusion models, and integrated subject movement correction methods may facilitate the estimation of the white matter microstructure in the baby brain (Dubois et al., 2014b; Ouyang et al., 2018; Pannek et al., 2014). Meanwhile, regularization tractography algorithms can be used in the low anisotropy voxels of baby brain images (Perrin et al., 2005). Improved tractography strategies such as spherical-deconvolution informed filtering (SIFT) or convex optimization modeling for microstructure informed tractography (COMMIT) could be adopted to filter the tractography results, consequently reducing the local bias in the streamline density (Daducci et al., 2015; Smith et al., 2013). Additionally, the low fractional anisotropy of the cortical regions of the baby brain and the dense axons running parallel to the cortical surface (Reveley et al., 2015) impede the detection of potential white matter connections based on dMRI data. Dilation of cortical gray mattter atlases into white matter voxels when obtaining network connections may ameliorate this bias. However, caveats should be kept in mind that the reconstructed fiber streamlines are highly dependent on the methodological parameters and may contain many invalid fiber bundles (Maier-Hein et al., 2017). For functional connections, several baby-specific issues also exist. The frequency profiles of functional bold signal fluctuations exhibit individual differences that are related to behavioral performance in 1-year-old infants (Alcauter et al., 2015). Meaningful functional connectivity patterns can be derived using frequency bands that are different from adults (Smith-Collins et al., 2015). The infant brain exhibits age-specific changes in neurovascular coupling (Hagmann et al., 2012). The detailed effects of these changes on the resting-state functional connectivity of the baby brain require future studies (Graham et al., 2015).

Baby brain network analysis

Several issues caused by thresholding methods, the growth of the brain size and the effect of head motion should be addressed in baby brain network analyses. Before obtaining the brain network, the edges included in the network model should be defined (see the "Network thresholding" section for details). Cares should be taken when adopting different threshold methods to generate the brain network. During the construction of a binary network, a loose threshold may induce a high density of the network, which could lead to the invalidation of specific network metrics, especially for functional and structural covariance networks. Adopting a weighted network model and new network measurements appropriate for fully connected models may avoid this issue (Bolanos et al., 2013; Sporns and Betzel, 2016). One study has also showed that when adopting the proportional thresholding, the overall functional connectivity of the network should be controlled (van den Heuvel et al., 2017). Regarding to the difficulty in selecting a suitable threshold, empirical evaluations indicated that edge specificity is at least twice as important as edge sensitivity when selecting the thresholding (Zalesky et al., 2016). When performing the dMRI-based tractography, the growth in size of the brain may result in an increasing number of seed voxels. These extra seed points may increase the number and weights of the edges in the structural network (Brown et al., 2014). Controlling for the total weights of the network edges or considering the brain size effect when accessing age related changes in network topology may reduce these biases (Brown et al., 2014; Huang et al., 2015). Importantly, although preventive measures for movement are applied during image collection, the head motion effect cannot be neglected in baby brain structural and functional network analyses, especially for the neurodevelopmental cohorts (Baum et al., 2017; Roalf et al., 2016; Satterthwaite et al., 2012). Methods proposed to reduce head motion effects in adult brain studies should be applied to studies of early brain development, although the effect is difficult to completely remove (Ciric et al., 2017; Power et al., 2012, 2017).

Notably, cares should be taken when interpreting the developmental changes of the topological metrics. First, when comparing the network metrics, the dependence of the metric values on the network size should be considered (Van Wijk et al., 2010). Second, due to a lack of information on neuronal currents, the large-scale brain network model is not a direct measurement of how the brain transforms information. Future studies combining multi-modality collections (e.g., EEG/MEG/ECoG) to directly detect neural activities of the human brain may solve this issue. Nonetheless, the specific topological architectures of brain structural and functional networks are thought to reflect the physiological basis for information processing (Avena-Koenigsberger et al., 2018; Bullmore and Sporns, 2009). Adopting a weighted network model may improve the representation of information transfer in brain structure and function. The intrinisc differences in weights between cortical connections are extraordinarily huge (Ercsey-Ravasz et al., 2013), with a large weights indicating wider bandwidth bundles or denser axons (Bassett and Bullmore, 2017). Meanwhile, the most strongly weighted connections own the shortest physical distance across cortical areas (Ercsey-Ravasz et al., 2013; Klimm et al., 2014; Rubinov et al., 2015), which may facilitate the functional segregation process (Rubinov et al., 2015; Ypma and Bullmore, 2016). Third, the same changing pattern of a topological metric derived from different edge weights may underlay different brain developmental processes. For instance, in white matter networks, an increase of network efficiency may be induced by the myelination or the growth of size in white matter tracts (Collin and van den Heuvel, 2013), which relates to an increase in diffusion anisotropy. However, for structural covariance networks, the regional covariance of the cortical thickness across a typical developing cohort is proposed to reflect the synchronized growth of homologous anatomical and functional systems over the course of development (Evans, 2013; Zielinski et al., 2010). The increasing efficiency of structural covariance networks is likely to reflect the synchronized maturation of distributed axonal connected and functionally related cortical regions.

Baby brain network modeling

One of the most challenging questions in the baby brain research is understanding how the brain network forms and evolves within a limited biological condition. Studies have found that the pressures of the wiring economy and topological complexity play important roles in the organization of networks in both human and non-human mammalian brains (Bullmore and Sporns, 2012). Computational modeling results in monkey brains suggest that the trade-offs between the wiring costs and network efficiency are important for the organization of brain structural connectivity, which support the formation of key topological features including modules, hubs and most brain network connections (Chen et al., 2013, 2017). Recently, the generative modelling framework has exhibited great values in revealing the generative rules of large scale non-human or human connectomes. Importantly, generative models with timescales corresponding to a developmental stage may uncover specific realistic growth mechanisms of the brain at that period (Betzel and Bassett, 2017). Vertes and colleagues concluded that a model considering distance penalty factors and topological favors could generate topological characteristics of brain networks using functional MRI data (Vértes et al., 2012). Betzel and colleagues found that a combination of geometric constraints with a homophilic attachment mechanism can create network models that match many of the topological features of the human brain white matter network and that these model parameters undergo progressive adjustments across the lifespan (Betzel et al., 2016). Over the development period from 8 to 22 years old, the human brain white

matter network becomes optimized with a set of growth rules including increased average controllability, increased modal controllability and decreased synchronizability (Tang et al., 2017). Current neuroimaging data on the baby brain provides a unique opportunity to reveal the early developmental rules of the human brain network architecture. The application of generative models to these baby data would make irreplaceable contributions to future studies on early brain development.

Several additional directions are valuable for the investigations on baby brain network modeling. In the adult brain, dynamic functional connectivity captures the detailed temporal features of brain topology (Allen et al., 2014; Jones et al., 2012) and is found to be largely constrained by the structural pathways (Liao et al., 2015). The existence and development of these fine functional fluctuations and their structural constraint in the early developmental stage is still unknown. The impact of spatial embedding on network topology has been found in adults (Roberts et al., 2016). Considering the dramatic changes in brain size across early life, how such contributions affect brain networks during the early development period is still an open question. The variant complex behavioral abilities of humans are largely derived from individual differences of the brain. Studies have also revealed the initial pattern of individual difference in the functional brain network during the prenatal (Xu et al., in preparation) and postnatal periods (Gao et al., 2014). However, the potential neural mechanisms underlying these differences and the later cognitive correlations may need further interpretations. The rapid growth of the brain network at early stage is determined by both genetic and environmental modifications. How these factors model the brain network topology or abnormally induce mental or behavioral problems is still largely unknown (Gao et al., 2017). Additionally, one study has shown that the topology of brain networks such as small-world architecture can improve the classification accuracy of artificial neural networks (Erkaymaz et al., 2014). Further studies are needed to investigate whether early formation principles of the human brain network can provide references for the evolution of artificial neural or engineered networks (Navlakha et al., 2018).

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