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Review

Developmental Connectomics from Infancy through Early Childhood

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The human brain undergoes rapid growth in both structure and function from infancy through early childhood, and this significantly influences cognitive and behavioral development in later life. A newly emerging research framework, developmental connectomics, provides unprecedented opportunities for exploring the developing brain through non-invasive mapping of structural and functional connectivity patterns. Within this framework, we review recent neuroimaging and neurophysiological studies investigating connectome development from 20 postmenstrual weeks to 5 years of age. Specifically, we highlight five fundamental principles of brain network development during the critical first years of life, emphasizing strengthened segregation/integration balance, a remarkable hierarchical order from primary to higher-order regions, unparalleled structural and functional maturations, substantial individual variability, and high vulnerability to risk factors and developmental disorders.

Trends

Following the development of advanced neuroimaging techniques and an emerging developmental connectomic framework, the elaborate and complex reorganization of structural and functional connectomes during the early period of life has been recently explored.

Network neuroscience demonstrates the value of a global balance between integration and segregation in developmental connectome models during early development.

Explorations in pediatric populations at risk of or with developmental disorders reveal disrupted connectomic properties; these have important potential clinical applications in probing and identifying vulnerability during early development.

Early Development of the Human Brain from a Connectome Perspective

The structure and function of the brain undergo a highly dynamic and elaborate maturational process from 20 postmenstrual weeks to 5 years of age, corresponding approximately to the period from infancy to early childhood. These precisely regulated changes during this critical phase largely shape subsequent cognitive and behavioral development and lay foundations for essential skills in later life. The history of research in early brain development begins as early as the 1900s, primarily through postmortem histological exploration by neuroanatomists of human fetuses, neonates, and non-human primates [1]. A large amount of information has been obtained from histological sections, and this has provided the basic knowledge about early brain development. Advanced neuroimaging and neurophysiological techniques together with the newly emerging developmental **connectomics** (see Glossary and Box 1) framework provide unprecedented opportunities to delineate how the human brain develops from a circuitry or network perspective through non-invasive mapping of structural and functional **connectome** patterns [2–4]. These advances have led to exciting new insights into the early development of the brain in both healthy and pathological populations, and have paved the way for a better understanding of the origin of complex neural architecture and dynamics as well as of the mechanisms underlying developmental neuropsychiatric disorders. Notably, two large-scale projects, the Developing Human Connectome Project and the Baby Connectome Project (Box 2), have recently been launched, reflecting the urgent demand for a better understanding of how brain networks develop from infancy to early childhood, and of how they shape the development of important cognitive and behavioral skills in later life. Despite these advances, the developmental patterns and mechanisms of the human brain connectomes during this period remain to be fully uncovered.

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This review surveys the recent cross-sectional and longitudinal studies (Figure 1) on typical and atypical development in the human brain connectomes from 20 postmenstrual weeks to 5 years of age based upon diverse experimental modalities including **structural MRI** (sMRI), **diffusion MRI** (dMRI), **functional MRI** (fMRI), **functional near-IR spectroscopy**, **electroencephalography** (EEG), and **magnetoencephalography** (MEG). Specifically, we highlight five fundamental principles of brain network development during the most important first years of life. Technical challenges and potential questions in this field are also discussed.

Towards an Optimal Global Balance between Information Segregation and Integration

The ontogeny of **topological organization** of baby brains has recently been explored with **graph** theory modeling methods (Box 1). During the early development period a non-trivial **small-world** configuration has consistently been demonstrated in baby brain networks, which is one of the most influential findings regarding brain network development. Specifically, the small-world connectional architecture refers to a network with a high **clustering coefficient** and a small **shortest path-length** between nodes, which facilitates efficient information segregation and integration with low wiring and energy costs [5,6]. Following the first demonstration of small-world structure in the brains of full-term newborn babies [7], this unique organization principle has been also shown in structural and functional brain networks as early as in the last trimester of pregnancy through analyses in preterm infants [8,9]. With development, the network segregation/integration balance tends to be optimized with remarkable reorganization, resulting in the transformation of the connectomic architecture from a relatively randomized configuration to a well-organized one [8–16]. Notably, the most-rapid global and local reconfigurations could occur before 1 year of age [8–11], with more stable changes taking place after then [10,11].

Small-world brain networks are generally supported by the presence of **hubs** and **modules** which ensure integrated and specialized information transfer [6]. Specifically, hubs are usually densely connected or highly centralized, and occupy a crucial position for coordinating global communication [17]. Notably, hubs were already present in the brain of babies at ~30 postmenstrual weeks through analyses in preterm infants, indicating the early emergence of diversity in the communication roles of brain regions [8,9]. Interestingly, the hubs were found

Box 1. Brief Introduction to Human Connectomics

The human connectome is a recently emerging scientific concept that refers to a comprehensive description of the patterns of structural and functional connectivity in the human brain [3,4]. With the progression of advanced neurophysiological and neuroimaging techniques, researchers can map the brain as a complex network at the macro-scale; this map consists of a set of nodes (representing voxels, regions, sensors, or magnetometers) and a set of connections between the nodes (representing white matter pathways, morphological or functional correlations). After the construction of brain networks based on multi-modality imaging data, the properties of nodes, edges, and the entire network can be measured with respect to factors involving age, genes, and the environment (a 3D illustration is given in Figure IA). Brain network topology is a core element in connectomics. Network properties can be examined with various metrics based on network science using the principles of topological organization. Specifically, the global integration capacity of a network can be estimated through calculating the averaged shortest path-length across all the pairs of nodes. For example, the shortest path between nodes *a* and *b* in Figure IB is indicated by the red lines, the length of which is 3. Global segregation capacity can be computed with the average clustering coefficient of a network across nodes, representing the extent of local interconnectivity among neighbors. In Figure IB, node *c* has a total of three neighbors (yellow nodes) that are fully connected, and therefore its clustering coefficient is 1. By contrast, the clustering coefficient of node *d* is 1/3, which was calculated by the existing edge (i.e., 1) divided by the maximal number of possible edges (i.e., 3). Human brain networks exhibit clusters with short-distance local connections between spatially adjacent nodes, and these are often aggregated topologically and anatomically as modules/communities (Figure IC). Hub regions are usually highly connected or centralized, and exhibit long-distance short-cuts linking different modules, which increase the global efficiency of information processing (Figure IC). Furthermore, the hubs are densely interconnected, generating a rich-club organization (Figure IC). In a nutshell, brain networks exhibit an optimized balance between the global integration and local segregation of information transformation.

Glossary

Clustering coefficient: quantifies the extent of local cliquishness or local efficiency of a network.
Connectome: a complete set of neural elements (e.g., neurons, brain regions) and their interconnections (e.g., synapses, fiber pathways, temporal correlations).
Connectomics: a framework or methodology for the study of the connectome.
Diffusion magnetic resonance imaging (MRI): non-invasively maps the diffusion of water molecules in biological tissues and generates contrast in MR images, which can be used to infer white matter tracts based on deterministic or probabilistic tractography approaches.
Electroencephalography (EEG): an electrophysiological monitoring method to non-invasively record electrical activity of the brain.
Functional connectivity: refers to the synchronizations of neural activity in spatially remote brain areas, which can be estimated through computing the statistical dependences in fMRI, EEG/MEG, or functional near-IR spectroscopy data.
Functional MRI (fMRI): non-invasively measures blood oxygenation level-dependent (BOLD) signals which reflect the hemodynamic response to transient neural activity caused by external stimuli or spontaneous activity in the resting state.
Functional near-IR spectroscopy: non-invasively images brain activity by quantifying temporal or phasic changes in the chromophore concentration resolved from measuring near-IR light attenuation.
Graph: a simple network model that comprises a set of nodes and edges linking different nodes.
Hub: a network node with dense connections or a centralized position, as defined by one of several measures including degree centrality, nodal efficiency, or betweenness centrality.
Magnetoencephalography (MEG): a brain-mapping technique that uses magnetometers to record magnetic fields produced by electrical currents occurring naturally in the brain.
Module: a network module represents a set of nodes with denser links among them, but that

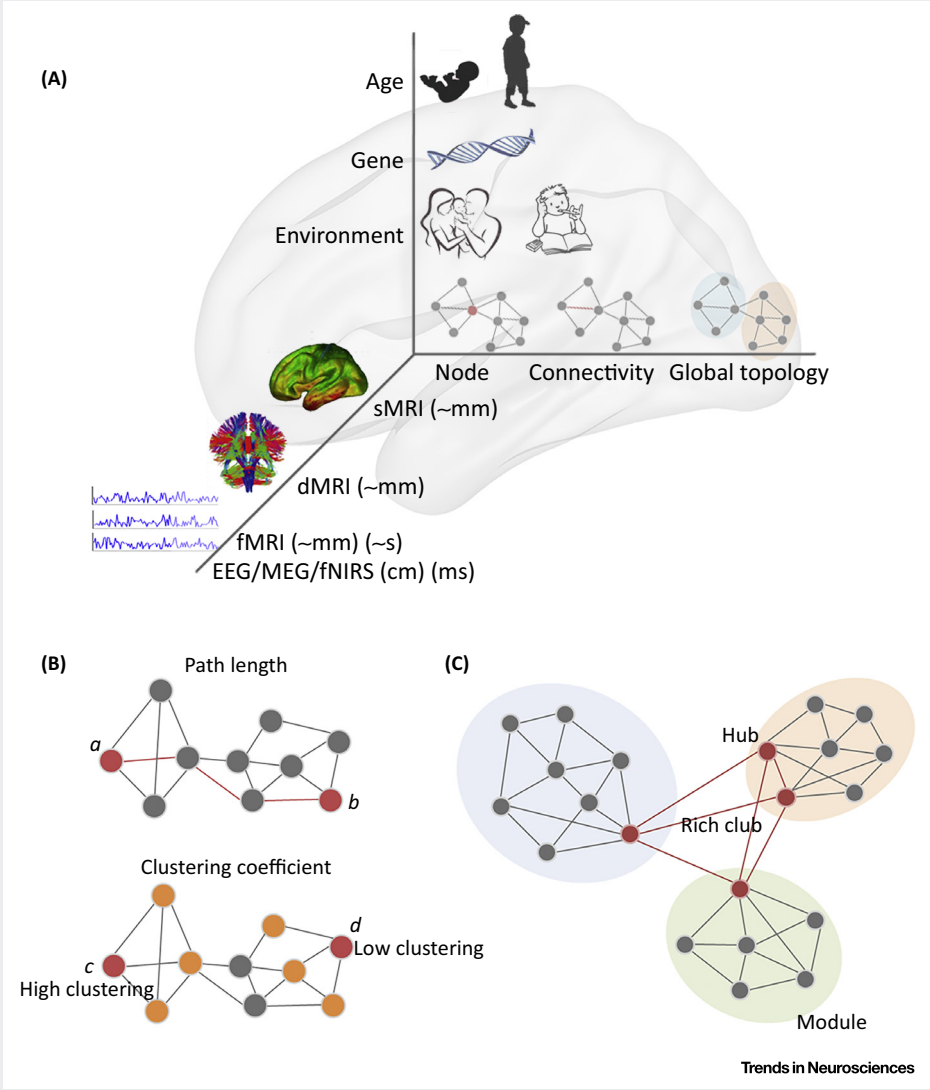

Figure I. Connectome Construction and Topological Analyses of the Brain.

are less connected with the rest of the network.

Rich club: a network structure comprising of a set of hubs that are more densely interconnected to one another than would be expected by chance.

Small world: a network model with a combination of both random and regular properties; that is, high global efficiency (short path-length) and high local efficiency (local clustering), respectively.

Shortest path-length: quantifies the global efficiency (in terms of inverse path-length) or the capacity for parallel information integration of a network.

Structural connectivity: the structural covariance of white matter tracts, which can be calculated by estimating inter-regional morphological correlations with sMRI data or by tracing the white matter fibers with dMRI data.

Structural MRI (sMRI): a technique to non-invasively examine structural morphology of the brain such as gray matter volume, thickness and surface area.

Topological organization: the layout pattern of interconnections of a network in terms of the relations of nodes and edges.

to be densely interconnected, forming the **rich-club** structure in the brain of both preterm babies [9] and newborns [18], and composing the crucial backbone for efficient neuronal signaling across the brain [19,20]. Notably, they experienced remarkable connectivity increases and spatial expansions with age, which greatly benefits global integration and makes the regions more heterogeneous and hierarchical [9,13,14,18]. Modular organization was also detected in *ex utero* [8,9] as well as fetal [21] baby brains, which comprise densely intra-connected clusters with sparse inter-cluster connections through hubs to promote efficient local specialization and global integration. With development, an integrative evolution process takes place in brain modular structure, with connectivity increasing within and across modules/communities. Specifically, modularity continuously increased with age before parturition, which might reflect a strengthening of modular specialization [8,13]. After then, postnatal development experienced decreases in modularity, primarily driven by enhancement of inter-module integration [12,16]. Collectively, the modular structure was reorganized from an anatomically

Box 2. The Developing Human Connectome Project and The Baby Connectome Project

Open resources with large samples of the human brain acquired using high-resolution MRI techniques are essential for a developmental brain study. Datasets focused on the early development period combined with a developmental connectomic framework may rapidly accelerate the science of human connectomics and yield deeper understanding of the origin of complex brain mechanisms. This need is increasingly addressed through two promising open resources for baby brain connectomic studies, documented in detail below.

The Developing Human Connectome Project (dHCP)

The dHCP project, led by King's College London, Imperial College London, and Oxford University, aims to make major scientific progress by creating a 4D connectome from 20 to 44 weeks of post-conceptional age. The dynamic connectome will be linked with imaging, clinical, behavioral, and genetic information. This project will provide crucial insights into both fundamental neural processes and the mechanisms underlying developmental neuropsychiatric disorders such as autism. To date, the dHCP has successfully collected 600 neonatal scans and further data acquisition is still ongoing, including fetal brain imaging (imaging babies before birth). The first release of dHCP dataset consists of 40 representive term neonatal scans, including sMRI, dMRI, and resting-state fMRI data (more details can be found at www.developingconnectome.org).

The Baby Connectome Project (BCP)

The BCP project, led by the University of North Carolina and the University of Minnesota, aims to collect the brain MRI scans of 500 typically developing children, age 0–5 years, over the course of 4 years. Biological (e.g., genetic markers) and environmental measures (e.g., family demographics) will be also collected and examined. Importantly, the BCP project will include both cross-sectional groups, where children will be scanned once at distinct ages, and longitudinal groups, where children will be scanned 4–6 times at distinct points during their development. The objective of this project is to provide a better understanding of how brain connectivity develops from infancy through early childhood, how the connectivity patterns shape behavioral development, and the factors that contribute to healthy brain development (more details can be found at www.med.unc.edu/bric/slide-pages/featured-study/baby-connectome-project).

local proximity-based pattern to a more functional distribution pattern over the development period [22,23].

Notably, the connectome development is constrained to a limited anatomical space. Thus, the wiring (or anatomical) patterns of brain connectivity have important implications for the speed of signal transmission as well as for energy consumption. Presumably actuated by the trade-off between minimizing cost and maximizing topological efficiency, human brain networks were confirmed to exhibit dominating short-range connections coexisting with a few long-range connections preferentially linked to hub regions [6]. During early development the brain connectomes experienced ordered strengthening of short-range connectivity followed by further growth of long-range connections. Specifically, a dominant enhancement of short-to-middle range connections was discovered during the prenatal period (through MRI of preterm babies), and this may largely benefit the specialization of local communities [9]. After birth, decreases in both short-range connectivity and local clustering have been reported which may reflect the underlying synaptic pruning process [24]. However, the long-range connections, which were less developed during the prenatal period, primarily appear in 1-year-olds and strengthen in 2-year-olds, making the brain networks more globally integrated [9,10,24,25]. Interestingly, an EEG study reported the existence of intermittent long-range connections during prenatal development in preterm babies, and these provide endogenous guidance for the development of long-range connectivity in an activity-dependent manner [26]. These dynamic changes in short- and long-range connections provide ancillary support to the optimization processes of global segregation/integration balance during early development.

We propose that a strengthening global balance between local and global information processing from infancy to early childhood drives the brain networks towards an organized and optimized configuration with an efficient and hierarchical architecture (Figure 2A, Key Figure).

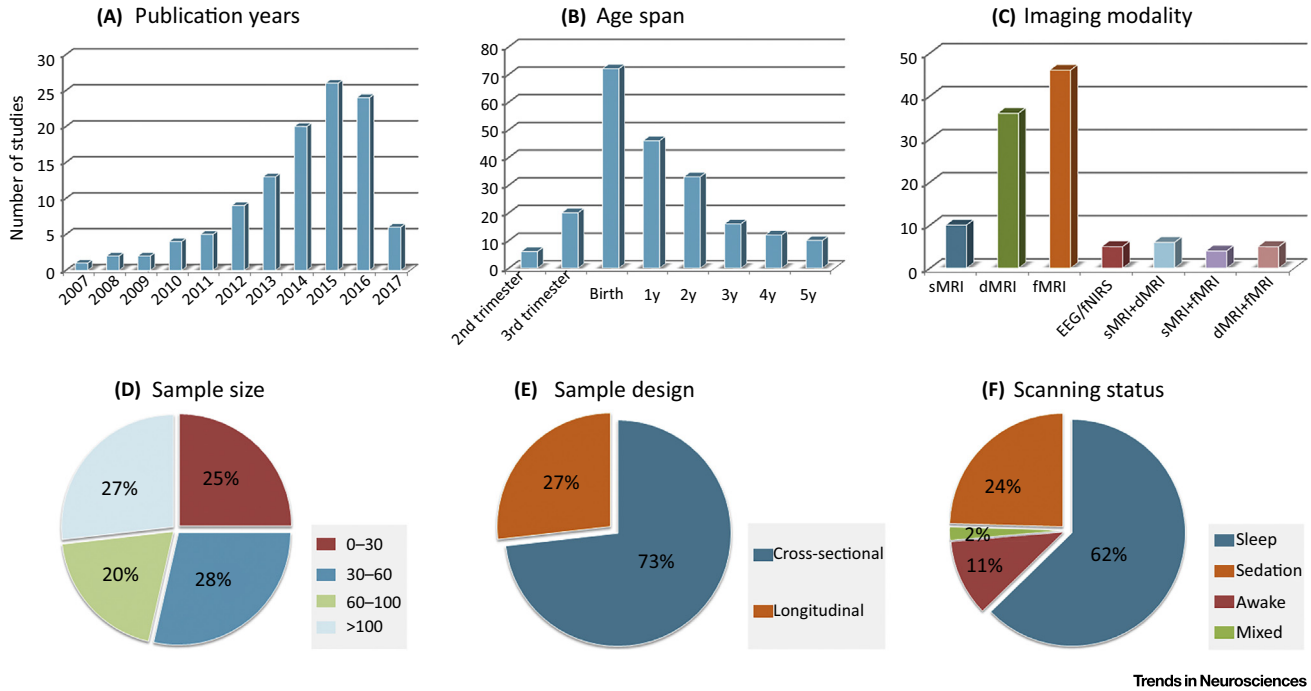

Figure 1. Research Summary of Developmental Connectomics from Infancy to Early Childhood. Summary of developmental brain connectomic studies from early infancy to childhood with advanced neuroimaging and neurophysiological techniques. This figure represents results of a literature search on PubMed (www.ncbi.nlm.nih.gov/pubmed) using with keywords 'connectivity' OR 'network' OR 'connectome' combined with 'early development' OR 'infant' OR 'baby'. A total of 112 relevant studies published between 2007 and 2017 are included here. The publications are summarized and plotted as distribution histograms according to their (A) publication year; (B) age span (y = years of age); and (C) imaging modality; as well as pie charts regarding sample size (D); sample design (E); and scanning status (F). Abbreviations: dMRI; diffusion MRI; EEG; electroencephalography; fMRI; functional MRI; fNIRS; functional near-IR spectroscopy; sMRI; structural MRI.

Further empirical and computational modeling studies will be necessary to explore how the economic and efficient brain networks form and which factors drive this complex process.

Elaborate Development Order from Primary to Higher-Order Functioning Regions

The maturation of brain regions can be described in regard to several aspects such as white matter, grey matter and functional activity. Specifically, white matter development involves sequential stages including fiber organization, membrane proliferation, and fiber myelination [27,28]. Generally, the onset of axonal growth is early during the prenatal period and most rapid during the first 5 postnatal months. The limbic fibers develop before the second trimester and the association fibers until early childhood [29–31]. During this interval the commissural and projection fibers form from the core to the periphery and from the anterior to the posterior regions of the brain [29–31]. All main fiber bundles were found to be in place by the time of birth [31,32]. Myelin maturation begins at ~2.5 months postnatally and proceeds until the end of adolescence, with peaks during the first year of life [27]. Myelination follows a sequence from caudal to rostral, proximal to distal, central to peripheral, and primary to association brain regions [28,33]. Graph theory analysis revealed that the nodal connectivity of all regions in the structural brain networks increased with postnatal development, with the most significant increases taking place in hubs located in the association regions, especially the precuneus [14]. Such a macro-scale topological reorganization might reflect the underlying micro-structural changes [14].

For grey matter, dendritic arborization and synapse formation increase within the cortical plate from mid-gestation, resulting in the dramatic changes in morphological properties.

Key Figure

Hypothetical Models of Brain Connectome Development from Infancy to Early Childhood

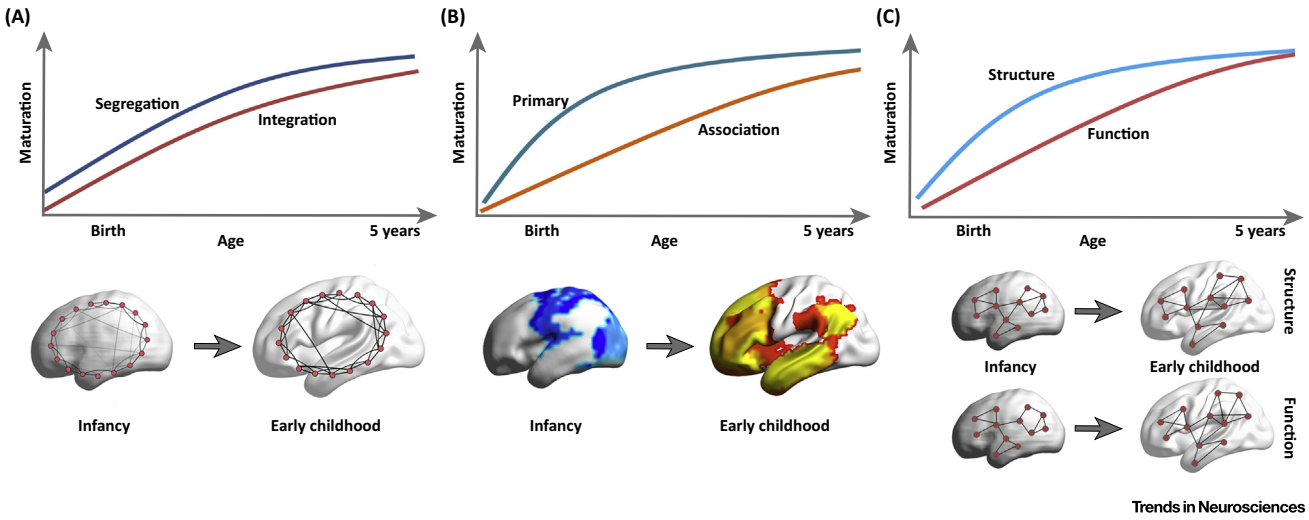

Figure 2. (A) A hypothetical developmental model of information segregation and integration in the brain networks. (C) A hypothetical developmental model from primary regions to higher-order association regions. (C) A hypothetical developmental model of structural and functional brain connectomes.

Specifically, cortical microstructure maps from dMRI-inferred progressive processes of dendritic arborization from primary sensorimotor cortex to higher-order cortex [34–36], consistent with the findings of synaptogenesis by neurohistology [37]. sMRI studies suggested that robust changes in brain morphology occur in the first year after birth, with association regions expanding larger and faster than primary regions, which had nearly matured by the time of birth in diverse measurements including grey matter volume [38], cortical thickness [39,40], surface area [40,41], cortical folding [42], and gyrification [43]. Structural covariance analysis further indicated that, although the primary visual and sensorimotor networks were more mature at birth, the default mode and dorsal attention network configuration remained immature by the age of 2 years [44]. Notably, late-maturing cortical regions such as the lateral temporal, parietal, and frontal cortices, as well as white matter tracts such as the superior longitudinal fasciculus, are closely related to evolution because they are better-developed in human brain than in monkey and chimpanzee brain, supporting the hypothesis that normal development mirrors the process of evolution [45,46].

Several previous resting-state **functional connectivity** studies based on blood oxygenation level-dependent (BOLD) fMRI data have highlighted the emergence of primary functional systems (e.g., sensory motor and auditory) in preterm and term babies [9,47,48], as well as the rapid development of higher-order functional systems (e.g., default-mode) after birth [49]. Specifically, a fetal fMRI study reported that the intrinsic functional connectivity increased before birth in the order of occipital, temporal, frontal, and parietal regions [50]. After birth, the functional subnetworks of the brain could follow the maturation sequence as follows: (i) the primary sensorimotor and auditory networks mature first, achieving mature network configurations by the time of birth; (ii) the visual areas then dramatically enhance their connectivity during the first 3 months postnatally; (iii) the attention and default-mode regions mature next, in

which dramatic increases in functional connectivity strength are observed across the first 6 months after birth; (iv) finally, the executive control network matures, and continues to develop during the first year, with rapid changes between 9 and 12 months of age [51,52]. Notably, the important role of the thalamus in transforming the peripheral sensory information to the cortex, as well as diversely associating with higher-order cognitive functions, has led to increasing interest in the development of thalamocortical connectivity. Specifically, thalamus–sensorimotor and thalamus–salience functional connectivity are already present in neonates, while specialized thalamus–medial visual and thalamus–default mode connectivities emerge later at 1 year of age [9,53,54].

In summary, while dramatic growth of the human brain takes place from infancy to early childhood, the developmental patterns of brain structure and function are most likely to follow the rule that the primary cortex develops before higher-order regions (Figure 2B). This principle allows prenatal resources to be focused on the regions/networks that are most important for early survival, while enabling enriched development of higher-order association regions/networks through prolonged postnatal gene-by-environment interactions. Notably, further work should establish more refined and accurate developmental curves for all regions, with diverse brain measurements being based on multi-modality data.

Different Maturation Modes of Structural and Functional Connectomes

Although the order of development is generally consistent between the structural and functional connectomes of the brain, they could mature at different timepoints (Figure 2C). Specifically, structural hubs emerge early within dorsal medial frontal, parietal, and hippocampal regions, emulating an adult-like distribution pattern at around the normal time of birth [8,14]. These hub regions, together with precuneus/posterior cingulate cortex and insula, form a rich-club architecture which serves as the communication backbone of structural brain networks in newborns [18]. Although hub and rich-club organizations are also observed early in functional networks during infancy, their configurations are largely different from those in adult brains [7,9]. Functional hubs were demonstrated to be largely confined to primary visual, auditory, and sensorimotor areas at around the time of birth [7,9]. By the age of 2 years, although bilateral superior medial frontal regions emerged as hubs, which may indicate a gradual shift of developmental focus to higher-order cognitive functions during this period, the functional hub distribution remained far from adult-like [10]. Intriguingly, in infants these functional hub regions displayed a relatively high metabolic rate, likely rendering them more vulnerable to deficits in energy supply [55–57].

While different developmental modes are observed for brain structure and function, empirical and computational modeling studies suggest that the functional network organization is shaped by the underlying structural network but exhibits more diverse and flexible configurations in human adults [58,59]. Specifically, while regions linked by dense **structural connectivity** tend to exhibit strong and stable functional connectivity, they do not exhibit a simple one-to-one mapping [58,60]. Studies on brain development reported that the coupling between structural and functional networks increased continuously from 30 weeks of gestational age until approximately 20 years of age [8,12]. This indicates that the non-parallel developmental patterns of structural and functional brain networks in infancy to early childhood merge to be in conformity in later life. Based on current findings, we postulate that the early-maturing structural networks may serve as an initial foundation that allows functional connections to develop diverse configurations. Ongoing functional coactivation between different regions, either evoked or intrinsic, is important for the subsequent strengthening/weakening of existing structural connections in a Hebbian sense of plasticity [61]. Nevertheless, how exactly the development of structural networks tailors functional network maturation, as well as how the changes in functional network further sculpt and reshape the underlying

anatomical substrates, are of great importance and warrant intensive future research. Specifically, model-based theoretical and computational studies will be necessary to uncover the possible mechanisms underlying this complex interaction process. Along these lines, new tools for empirical analyses of the relationship between structural and functional connectomes are urgently needed.

Remarkable Individual Variability in Structural and Functional Connectomes

Although most studies have focused on elucidating the general principles of brain development through group-level analysis, the importance of fully personalized investigations into this developmental phase has received considerable attention. Specifically, the structural and functional connectomes of the human brain vary between subjects, and these differences potentially underlie individual differences in cognition and behavior [62–64].

Individual variability in the functional connectivity architecture of healthy adults showed heterogeneity across regions, with significantly higher variability in the heteromodal association cortex and lower variability in the unimodal cortices, which was potentially rooted in evolution and predictive of individual cognitive differences [62,64]. Prenatal exploration showed that, although functional inter-subject variability values were relatively high and homogeneous across regions at the age of 30 weeks, non-uniform decreases occurred with development as the adult-similar pattern appeared at approximately 37 weeks (in preparation). After birth, the variability patterns remained relatively consistent, with the magnitude of variability values progressively decreasing until age 1 year and then increasing again to 2 years of age [65]. The changing patterns in functional variability after birth are not purely driven by genetic influences [65]. However, genetic effects in neonates were detected in nearly all white matter tracts [66]. In addition, gender effects on white matter networks were explored, and males exhibited generally higher global and local efficiency than did females from birth to 2 years of age [22]. These findings indicate that the brain maturation process is likely to experience a predominantly genetically determined growth first, in line with diminishing inter-subject variability during the first year of life, and is then followed by a more-plastic gene–environment interaction period that underlies the increasing inter-subject differences during subsequent development.

Notably, there is growing evidence that individual connectomic differences in pediatric populations are predictive of behavioral performance and cognitive capacity in later life. For example, the functional connectivity of the amygdala in newborn babies was related to emerging fear and cognitive development (including emerging sensorimotor, attention, and memory skills) at 6 months [67]. Thalamo–salience network connectivity in 1-year-olds was shown to be predictive for general cognitive development at 2 years of age [53], and the frequency profile of functional fluctuations in brain networks has also been linked to behavioral performance in 1-year-old infants [68]. In addition, EEG coherence in the left hemisphere of infants correlated significantly with epistemic language skills at 4 years of age [69]. Structural connectomic analysis showed that the connectivity strength between the thalamus and extensive cortical regions in neonates explained 11% of the variance in cognitive scores at 2 years of age [70]. Moreover, the segregation capacity of information transformation in the structural networks of neonates correlated significantly with their behavioral profiles assessed using the maternally reported Child Behavior Checklist at 2 and 4 years of age [71]. Collectively, identifying individual brain connectomic ‘fingerprints’ during early development is not only important for understanding cognitive and behavioral development but also has potential implications for monitoring normal development in cognitive capacity and mental health, which require more detailed exploration and clarification.

The High Plasticity and Dynamics of Brain Networks Presents High Vulnerability

With rapid maturation, highly dynamic connectomic changes make the brain not only highly plasticity but also vulnerable to risk factors leading to developmental problems and/or disorders. Simulation analysis revealed that brain network robustness, which measures resilience to attack, gradually increased with development but remained lower than in adults, indicating the immature status of the human brain in the early stages of life [10,14].

Premature birth is an identifiable risk that has a significant influence on brain development even in the absence of focal brain injury. Specifically, accumulating literature converges on pervasively disrupted thalamocortical structural connectivity as a result of preterm birth in neonates, and that this correlates significantly with cognitive variance in later life [70,72]. Reduced interhemispheric functional connectivity and impaired lateralization of language areas were also observed in preterm infants compared to healthy term controls [73]. While the overall layout of brain network organization remained similar, including small-world, modular, hubs, and rich-club structures, reduced local clustering and global network complexity were detected in both the structural and functional connectomes of preterm groups [18,74–77]. Moreover, preterm birth damage was noted to persist through childhood, leading to impaired global integration and segregation capacity, as well as impaired connectivity of hub regions in the brain networks of preadolescent populations, and these were predictive of impaired IQ scores and motor performance [74,78].

The next major risk factor is maternal substance exposure, an ever-increasing problem worldwide. Specifically, maternal exposure to cocaine disrupts the amygdala–frontal and insula–sensorimotor functional circuits in infants [79], as well as amygdala–frontal structural connectivity in adolescents [80]. Prenatal marijuana exposure was associated with disrupted functional connectivity of caudate and insula in neonates [81]. Interestingly, prenatal cortisol exposure exhibits sex-specific associations with network properties in children, and network segregation was only impaired in girls [82]. Disrupted network connectivity is thought to play important roles in arousal regulation and reward processing, and alterations may lead to adverse developmental consequences such as drug abuse in later life. Other factors, such as early-life stress, can also have significant effects on brain connectome development. For instance, postnatal exposure to inter-parental conflict was significantly associated with increased integration among default-mode regions in infants, potentially leading to higher negative infant emotionality [83]. Maternal depression significantly altered the functional connectivity of the amygdala in 6-month-old infants [84] and of the frontal regions in infants aged 18 months [85].

Last but not least, emerging data indicate that major psychiatric disorders have a prominent origin in early childhood development, such as in autism (onset at ~2 years of age) [86]. For instance, the early developmental curves of autism (or autism-risk) populations and healthy controls were observed to cross over in both the functional and structural connectomes. Specifically, a functional near-IR spectroscopy study reported that infants at high risk for autism exhibited increased overall functional connectivity strength at 3 months of age compared to subjects at low risk [87]. The differences diminished with development and reversed in the 12-month-old infants, in other words functional connectivity decreased in the high-risk autism group compared to the low-risk group [87]. Structural connectivity analysis with diffusion imaging data also detected a similar crossover of the developmental curves of autism subjects and healthy controls from 2–7 years of age, with a crossover age at ~4 years [88]. The white matter networks of autism subjects aged 2 years exhibited significantly decreased local and global network efficiencies compared to healthy babies [89].

In summary, the effects of these risk factors on early brain development may be genetically programmed, epigenetically mediated, and environmentally influenced. Identifying the impairments of brain connectomics associated with these risks and disorders as early as possible is crucial for early identification and may provide a unique and important opportunity for early intervention and prevention.

Concluding Remarks and Future Perspectives

We highlight five fundamental principles underlying the highly dynamic development of brain networks from infancy to early childhood. In particular, we have emphasized developmental connectomics – which provides an unprecedented computational framework by effectively integrating multi-modal and multi-scale brain connectivity information, and this significantly contributes to our understanding of early brain development (Box 1). Notably, the study of baby brain development is still in its infancy. Significant scientific challenges remain to be addressed, including how the dynamic changes in brain networks, both structurally and functionally, reflect the underlying neural and metabolic developmental processes; how the changing patterns converge across different scales from the micro-scale of individual neurons to the macro-scale of whole-brain recordings; and how the structural and functional networks interact with each other; as well as how the developmental connectomic changes interact with genetic and environmental factors to impact on cognitive development, learning, and skill acquisition (see Outstanding Questions). Further elaboration of the principles of brain connectome development may contribute significantly to a deeper understanding of cognitive and behavioral development in later life and aid in uncovering the biological mechanisms of developmental disorders.

However, before delving deeper into developmental connectomic research, several methodological issues are priorities to be addressed in the near future. These include specific imaging-acquisition techniques for fetuses and infants, head motion and conscious states during scanning, the refinement of up-to-date baby brain templates and atlases, connectome construction, and big data analysis approaches. Novel techniques for baby neuroimaging acquisition should be developed, including hardware and imaging sequences, because most imaging methods widely applied in adults are inappropriate for immature brains. For example, owing to their small head circumference, specially made coils with a dedicated receiver array design will be necessary for studies on babies, and such a tailor-made device would increase the signal-to-noise ratio as well as reducing noise and motion artifacts during scanning [90]. In addition, although neonatal dMRI data have the same resolution as for adult MRI, the resolution is generally suboptimal given the smaller head size of neonates. Towards optimized baby brain MRI, a few recent studies have used a higher dMRI resolution (e.g., 1.5 mm isotropic or smaller voxel size [35]) and optimized tract-based spatial statistics [91]. For fMRI studies, research has demonstrated that the hemodynamic response function significantly changes with development [92]. Although this would not affect resting-state connectivity analysis, further task-based studies should take this into account. Finally, advanced fetal imaging, which could monitor fetal programming *in utero*, also faces several problems – including scanning heat and noise risk to the fetus, fetal movement, and the lack of a fetal template – which need to be resolved in the future.

The situation of the participant during scanning is another important issue for brain research. Notably, while baby subjects are commonly scanned during sleep, with or without medical sedation, they still exhibit increased motion compared to cooperative awake adults. Thus, adjustments specific for baby MRI, such as carefully placing the baby head in the center of the coil for improved B1 homogeneity and MRI data quality, and placing cushions in the space around the head (e.g., [9,35]), need to be implemented to minimize motion artifacts. In addition, although no methods are currently available to fully remove the impact of motion, significant

Outstanding Questions

How can we establish a set of reliable dynamic developmental brain atlases from infancy to early childhood that involve structural, functional, and genetic properties?

How do the structural connectome, functional connectome, and their relationship develop from infancy to early childhood? How do the developmental connectomic changes interact with genetic and environmental factors to impact on subsequent cognitive and behavioral development, learning, and skill acquisition?

What are the underlying neurophysiological, molecular, and biochemical substrates of macro-scale brain connectome maturation?

How do we integrate and bridge the mechanistic gaps between the developmental changes in macro-, meso-, and micro-connectomics? In particular, how do we establish and validate biophysical models that characterize multi-scale brain network changes during early development?

How does the aberrant development of brain connectomes correlate with risk factors as well as with neurodevelopmental disorders such as autism? How can the connectomic findings provide insights into biomarkers for early diagnoses, assessment, and intervention?

How can we take full advantage of the emerging big data comprising imaging, clinical, behavioral, and genetic information for the study of early brain development? Advances in novel analytical and statistical methods such as high-dimensional data analysis and multivariate statistics are urgently needed.

advances have been made to mitigate motion effects in adult studies, and these provide a potential strategic reference point for research on early brain development [93]. Moreover, to avoid unnecessary risks to baby participants, natural sleep MRI without sedation is now increasingly employed. However, researchers should be cautious when interpreting findings with sleep-based fMRI because of potential confounds arising from differences between wakefulness and sleep during scanning, as well as between different sleep stages [94].

During imaging analysis of baby brains, predefined pediatric brain templates are needed for MRI image processing, including registration, segmentation, and surface extraction. Because the brain changes rapidly during early development, age-specific templates should be constructed at high temporal resolution, such as gestational weeks or months, which remains challenging [95,96]. Furthermore, an accurate pediatric brain atlas to provide brain regional labels for connectomic analysis and interpretation of findings is urgently needed. Although baby brain atlases have recently been published (e.g., [97]), these still lag behind adult atlases now emerging from prominent megaprojects such as the Human Connectome Project [98].

The connectomic framework provides unique opportunities to extensively map early brain development; however, some crucial issues relevant to connectome construction and exploration must be taken into consideration. Specifically, it is challenging to map the developmental brain networks appropriately and precisely. Owing to the lack of gold standard for regional parcellation in the brain, the definition of network nodes is relatively arbitrary at present. Edge definition is another important issue. For example, an optimized tractography protocol with appropriate parameters tailored for baby brains (e.g., a fractional anisotropy threshold of 0.1–0.15 [99] instead of the threshold of 0.2 used for adult brain) is necessary because of the low level of myelination of baby brain white matter tracts. In addition, because of fiber-crossing, test–retest reliability examination should be considered in identifying edges in the baby brain structural network. Furthermore, caution should be taken in the analysis of network integration and segregation (e.g., through the choice of appropriate null models), in the selection of measurements for network organization assessment (on account of the reliability and reproducibility of metrics), and in the physiological interpretation of connectomic findings.

Given that the narrow age interval and small sample sizes will limit the credibility of any research findings, large volumes of developmental connectomic data ('big data') are urgently needed, and these would crucially improve statistical power and enable the generalization of findings across populations. Importantly, the Developing Human Connectome Project and the Baby Connectome Project are making great efforts in this direction (Box 2). Developing novel developmental connectomic analytical methods involving data-mining and multivariate statistical analysis strategies are also fundamental to advancing research within this framework [100].

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