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Developmental Connectomics from Infancy through Early Childhood

Miao Cao, Ph.D.[1,2,3], **Hao Huang, Ph.D.**[4,5], and **Yong He, Ph.D.**[1,2,3,*]

[1]National Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China

[2]Beijing Key Laboratory of Brain Imaging and Connectomics, Beijing Normal University, Beijing 100875, China

[3]IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing100875, China

[4]Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

[5]Department of Radiology, University of Pennsylvania, Philadelphia, PA 19104, USA

Abstract

The human brain undergoes rapid growth in both structure and function from infancy through early childhood, which 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-invasively mapping structural and functional connectivity patterns. Within this framework, we review recent neuroimaging and neurophysiological studies investigating the connectome development from 20 postmenstrual weeks to 5 years of age. Specifically, we highlight five fundamental principles of brain network development during the most critical first years of life, emphasizing strengthened segregation/integration balance, 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.

Keywords

Connectome; graph theory; segregation and integration; functional connectivity; structural connectivity; developmental disorder

Early Development of the Human Brain from a Connectome Perspective

The brain's structure and function undergo a highly dynamic and elaborate maturational process from 20 postmenstrual weeks to 5 years of age, approximately corresponding 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

*Correspondence: yong.he@bnu.edu.cn (Y. He).

development begins as early as the 1900s, primarily through postmortem histological exploration in human fetuses, neonates, and non-human primates by neuroanatomists [1]. A large amount of information has been obtained from histological sections, which has provided the basic knowledge about early brain development. Advanced neuroimaging and neurophysiological techniques together with the newly emerging developmental **connectomics** framework (see Glossary, Box 1) provide unprecedented opportunities to delineate how the human brain develops from a circuitry or network perspective through non-invasively mapping 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 paved the way for a better understanding of the origin of complex neural architecture and dynamics as well as 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 it shapes 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.

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**, **diffusion MRI**, **functional MRI**, **functional near-infrared spectroscopy**, and **electroencephalography/magnetoencephalography**). 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** theoretical modeling methods (Box 1). During early development period, a nontrivial **small-world** configuration has been consistently demonstrated in the 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 the 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 the critical position for coordinating global communication [17]. Notably, hubs were already present in the brain of babies at approximately 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 to be densely inter-connected, forming the **rich-club** structure in the brain of both preterm babies [9] and newborns [18] and composing the critical 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 occurred in the brain modular structure, with connectivity increasing within and across modules/communities. Specifically, the modularity continuously increased with age before the normal birth, which might reflect the strengthening of modular specialization [8, 13]. After then, postnatal development experienced decreases in modularity, which were primarily driven by the enhancement of inter-module integration [12, 16]. Collectively, the modular structure was reorganized from an anatomically 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 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), which 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 electroencephalography study reported the existence of intermittent long-range connections during prenatal development in preterm babies, which provides the 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.

Together, we propose a strengthening global balance between local and global information processing from infancy to early childhood that drives the brain networks towards an organized and optimized configuration with an efficient and hierarchical architecture (Figure 2a, Key Figure). Further empirical and computational modeling studies are needed 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 the interval, the commissural and projection fibers form from the core to the periphery and the anterior to the posterior regions of the brain [29-31]. All main fiber bundles were found in place at the time of birth [31, 32]. The following myelin maturation begins at approximately 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 occurring 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. Specifically, cortical microstructure maps from diffusion MRI inferred progressive processes of dendritic arborization from primary sensorimotor cortex to higher-order cortex [34-36], consistent to the findings of synaptogenesis by neurohistopathology [37]. Structural MRI studies suggested that the 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 while 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 cortex, as well as white matter tracts, such as the superior longitudinal fasciculus, are closely related to evolution as they are more well developed in the human brain compared to the monkey and chimpanzee brains, which supports the hypothesis that normal development mirrors the evolution process [45, 46].

Several previous resting-state **functional connectivity** studies based on blood oxygenation level dependent functional MRI data have highlighted the emergence of primary functional systems (e.g., sensory motor and auditory) at preterm and termed babies [47, 48] and the rapid development of higher-order functional systems (e.g., default-mode) after birth [49]. Specifically, a fetal functional MRI study reported that the intrinsic functional connectivity increased in an order of occipital, temporal, frontal, and parietal regions before birth [50]. After birth, the brain's functional sub-networks could follow the maturation sequences as follows: i) The primary sensorimotor and auditory networks matured first, which achieved matured network configurations by the time of birth; ii) Then, the visual areas dramatically enhanced the connectivity during the first three month postnatally; iii) The attention and default-mode regions matured next, in which dramatic increases in functional connectivity strength were observed across the first half year after birth; iv) Finally, the executive control network matured, which continually developed during the first year with rapid changes between 9 and 12 months [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 interests in the development of thalamocortical connectivity. Specifically, thalamus-sensorimotor and thalamus-salience functional connectivity were already present in neonates, while specialized thalamus-medial visual and thalamus-default mode connectivity emerged later at 1 year of age [53, 54].

In summary, while the dramatic growth of the human brain occurs from infancy to early childhood, the developmental patterns of both the brain structure and function are most likely to follow the rule that the primary cortex develops prior to higher-order regions (Figure 2b). This particular principle is beneficial to focus prenatal resources 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 works should establish more refined and accurate developmental curves for all regions with diverse brain measurements based on multi-modality data.

Different Maturation Modes of Structural and Functional Connectomes

Although the developmental orders are generally consistent between the brain's structural and functional connectomes, they could mature at different time points (Figure 2c). Specifically, structural hubs emerged early within dorsal medial frontal, parietal, and hippocampus regions, emulating an adult-like distribution pattern around the time of normal birth [8]. These hub regions, together with precuneus/posterior cingulate cortex and insula, formed the rich-club architecture, which serves as the communication backbone of structural brain networks in newborns [18]. Although the hub and rich club organizations were also observed early in functional networks during infancy, their configurations remained largely different from those in adult brains [10, 14]. The functional hubs were demonstrated to be largely confined to primary visual, auditory and sensorimotor areas around the time of birth [7, 9]. By the age of 2, 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, a relatively high metabolism was observed for these functional hub

regions in infants, likely rendering them more vulnerable to deficits in energy consumption [55-57].

While different developmental modes were 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 the simple one-to-one mapping [58, 60]. Studies on brain development reported that the coupling between structural and functional networks experienced continuous increases 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 the current findings, we postulate that the more early maturing structural networks may serve as an initial foundation for the functional connections to develop diverse configurations. The continuous functional co-activation 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 the 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 works are in critical needs to reveal the possible mechanisms underlying this complex interaction process. Along this line, new tools for empirical analyses on the relationship between structural and functional connectomes are urgently needed.

Remarkable Individual Variability in the Structural and Functional Connectomes

Although most studies have focused on demonstrating 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 across subjects, and these differences potentially underlie the 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]. Prenatal exploration showed that while the 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 continually decreasing until 1 year and then increasing to 2 years old [65]. The changing patterns in functional variability after birth were found to not

be purely driven by genetic influences [65]. However, genetic effects in neonates were detected in nearly all white matter tracts [66]. Additionally, gender effects on white matter networks were explored, and males exhibited generally higher global and local efficiency compared with females from birth to 2 years old [22]. These findings indicate that the brain maturation process is likely to experience a predominantly genetically determined growth first, in line with the diminishing inter-subject variability during the first year of life, and is then followed by a more plastic gene-environment interaction period, enrooting to increasing inter-subject differences during subsequent development.

Notably, there is growing evidence indicating that the individual differences in the connectomic measurements of pediatric populations are predictive of behavior performances and cognitive capacity in later life. For example, the functional connectivity of the amygdala in new born 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 performances in 1 year-old infants [68]. Additionally, electroencephalography coherence in the left hemisphere of infants was significantly correlated with epistemic language skills at 4 years old [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 old [70]. Moreover, the segregation capacity of information transformation in neonates' structural networks significantly correlated with the behavior profiles assessed with the maternal reported Child Behavior Checklist scores at 2 and 4 years old [71]. Collectively, identifying individual brain connectomic 'fingerprint' during the 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 high plasticity but also vulnerability to risk factors leading to developmental problems and/or disorders. Simulation analysis revealed that the brain network robustness, which measures the capacity against attack, gradually increased with development but remained lower compared to that in adults, indicating the immature status of the human brain at the early stage of life [10, 14].

Premature birth is an identifiable risk that has significant influences 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 significant correlation with cognitive variances in later life [70, 72]. Reduced inter-hemispheric functional connectivity and impaired lateralization of language areas were also observed in preterm infants compared with healthy term controls [73]. While the overall

layout of the brain network organizations, including small-world, modular, hubs and rich-club structures, remained similar, 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, which were predictive of impaired intelligence quotient scores and motor performance [74, 78].

The next major threat factor is maternal substances exposure, which is a world-widely problem continuously on the rise. Specifically, maternal exposure to cocaine disrupts the amygdale-frontal and insula-sensorimotor functional circuits in infants [79] as well as amygdale-frontal structural connectivity in adolescents [80]. 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, which only impaired the network segregation of girls [82]. This disrupted network connectivity is thought to play important roles in arousal regulation or reward processing, the alterations of which may lead to adverse developmental consequences such as drug abuse in later life. Other factors, such as early life stress, also have significant effects on brain connectome development. For instance, postnantal exposure to inter-parental conflict was significantly associated with higher 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 infants [84] and of the frontal regions in 18 month infants [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 of approximately 2 years old) [86]. For instance, the crossed early developmental curves between autism (or autism-risk) populations and healthy controls were observed in both the functional and structural connectomes. Specifically, functional near-infrared spectroscopy study reported that infants at high risk for autism exhibited increased overall functional connectivity strength at 3 months old compared with subjects with low risk [87]. The differences diminished with development and reversed in the 12-month-old infants, i.e., the functional connectivity decreased in the high risk autism group compared with the low risk group [87]. Structural connectivity analysis with diffusion imaging data also detected similarly crossed developmental curves of autism subjects and healthy controls from 2 to 7 years old, with the crossed age at approximately 4 years [88]. The white matter networks of autism subjects aged 2 years exhibited significantly decreased local and global network efficiencies compared with healthy babies [89].

In summary, effects of these risk factors on early brain development could 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 the unique and important opportunity for early intervention and prevention.

Concluding Remarks and Future Perspectives

We highlight the five fundamental principles behind the highly dynamic development of brain networks from infancy to early childhood. Particularly, we emphasized developmental connectomics, which provides an unprecedented computational framework by effectively integrating multi-modal and multi-scale brain connectivity information, which significantly contributes to our understanding of early brain development. 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 cognitive development, learning, and skill acquisition (Outstanding Questions Box). Further elaboration of the principles of brain connectome development may significantly contribute to a more deeply understanding of cognitive and behavioral development in later life and aid for uncovering the biological mechanisms of developmental disorders.

However, before diving deeper into the developmental connectomic research, various relevant methodological issues remain priorities to be addressed in the near future, including imaging acquisition techniques in fetuses and infants, head motion and conscious states during scanning, 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 of the imaging methods widely applied in adults are inappropriate for immature brains. For example, due to the small head circumference, specially-made coils with dedicated design receive array suit babies better than those for adults, for the benefits of increasing the signal-to-noise ratio and reducing noise and motion artifacts during scanning [90]. Besides, despite that neonatal diffusion MRI data has the same resolution as that of adult MRI, the MRI resolution is usually not high enough considering the smaller head size of the neonates. Towards optimized baby brain MRI, a few recent studies have been conducted using higher diffusion MRI resolution (e.g. 1.5mm isotropic or smaller voxel size [35]) and optimized tract based spatial statistics [91]. For functional MRI studies, research has demonstrated that hemodynamic response function significantly changes with development [92]. Although this would not affect resting-state connectivity analysis, further task-designed studies should take it into account. Finally, the advanced fetal imaging, which could monitor the fetal programming in utero without preterm exposure, also faces some problems including scanning heat and noise risks to fetus, fetal movement as well as the lack of fetal template, which need to be resolved in future.
- Participant situations 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 higher motions compared with cooperative awake adults. Thus, proper steps specific for baby MRI, such as carefully placing the baby head in the center of the coil for improved B1 homogeneity and resultant high quality of the MR data and putting cushions in the space around the head (e.g. [9, 35]), need to be taken to minimize the effects of motion artifacts. Besides, although no excellent methods to fully remove the motion impacts exist currently, significant advances have been made to mitigate the relevant influences in adult studies, providing potential strategy references for early developmental research [93]. Moreover, to avoid unnecessary risks to baby participants, natural sleep MRI without sedation is now been more and more employed. However, researchers should be careful when interpreting their findings with sleep-based functional MRI, considering the confounds from difference between wakefulness and sleep as well as different stages of sleep during scanning across subjects [94].

- During imaging analysis of baby brains, predefined pediatric brain templates are needed for MRI image processing including registration, segmentation and surface extraction. Since 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]. Besides, sufficient pediatric brain atlas is also in urgently needed to provide brain regional labels for connectomic analysis and finding interpretation. Although several baby brain atlases have been published by recent studies (e.g. [97]), it is still far behind the new atlas in adults from prominent megaprojects such as the Human Connectome Project [98].
- Connectomic framework provides unique opportunities to extensively mapping the early brain development, however, some critical issues relevant to connectome construction and exploration should still be aware of. Specifically, it is challenging to map the developmental brain networks appropriately and precisely. Due 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 with considerations. For example, optimized tractography protocol with appropriate parameters tailored for baby brains (e.g. fractional anisotropy threshold 0.1 to 0.15 [99]), instead of 0.2 used in adult brains) due to poorly myelinated baby brain white matter tracts as well as test-retest reliability examination due to fiber-crossing should be considered for identifying edges in baby brain structural network. Besides, cautions should take in the network integration and segregation calculation (such as appropriate null models choosing), measurements choice for network organization assessment (on account of the reliability and reproducibility of metrics) as well as physiological interpretation of connectomic findings.
- Considering the fact of narrow age interval and little sample size would largely limit the credibility of studies' findings, developmental connectomic big data sets is in urgent needed, which would crucially benefit statistical power improvement and enable the generalization of findings across populations. Importantly, the

Developing Human Connectome Project and Baby Connectome Project are making great efforts towards this direction (Box 2). Developing novel developmental connectomic analytical methods involving data mining and multivariate statistical analysis strategies are also fundamentally required to advancing research within this framework [100].

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Glossary

Clustering coefficient
It 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 correlated correlations)

Connectomics
A framework or methodology for the study of the connectome

Diffusion MRI
It non-invasively maps the diffusion of water molecules in biological tissues and generating contrast in MR images, which can be used to infer white matter tracts based on deterministic or probabilistic tractography approaches

Electroencephalography
It is an electrophysiological monitoring method to noninvasively record electrical activity of the brain

Functional connectivity
It refers to the synchronizations of neural activity in spatially remote brain areas, which can be estimated through computing the statistical dependences in functional MRI, electroencephalography/magnetoencephalograph or functional near-infrared spectroscopy data

Functional MRI
It non-invasively measures blood oxygenation level dependent signals which reflect the hemodynamic response to transient neural activity caused by external stimuli or spontaneous activity in a resting state

Functional near-infrared spectroscopy
It non-invasively images brain activity by quantifying the temporal or phasic changes in the chromophore concentration resolved from measuring near-infrared 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
It recordes the magnetic fields produced by electrical currents occurring naturally in the brain with magnetometers for mapping brain activity

Module
A network module represents a set of nodes with denser links among them, but less connected with the rest of the network

Rich club
A network structure comprised of a set of hubs that are more densely interconnected to one another than 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
It quantifies the global efficiency (in terms of inverse path length) or the capability for parallel information integration of a network

Structural connectivity
It refers to the structural covariance or white matter tracts, which can be calculated by estimating inter-regional morphological correlations with structural MRI data or tracing the white matter fibers with diffusion MRI data

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

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Box 1

Brief Introduction to Human Connectomics

The human connectome is a recently emerging scientific concept that refers to a comprehensive description of the structural and functional connectivity patterns of 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 macroscale level; 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 (for a three-dimensional illustration, see Figure IA). The examination of brain network topology is a core element in connectomics. Network properties can be examined with various metrics based on network science on the topological organization principles. Specifically, 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 in total of three neighbors (yellow nodes) that are fully connected,and therefore its clustering coefficient is 1. Whereas, 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, which 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). Besides, the hubs are densely interconnected, forming the rich club organization (Figure IC). In a nutshell, brain networks exhibit an optimized balance between the global integration and local segregation of information transformation.

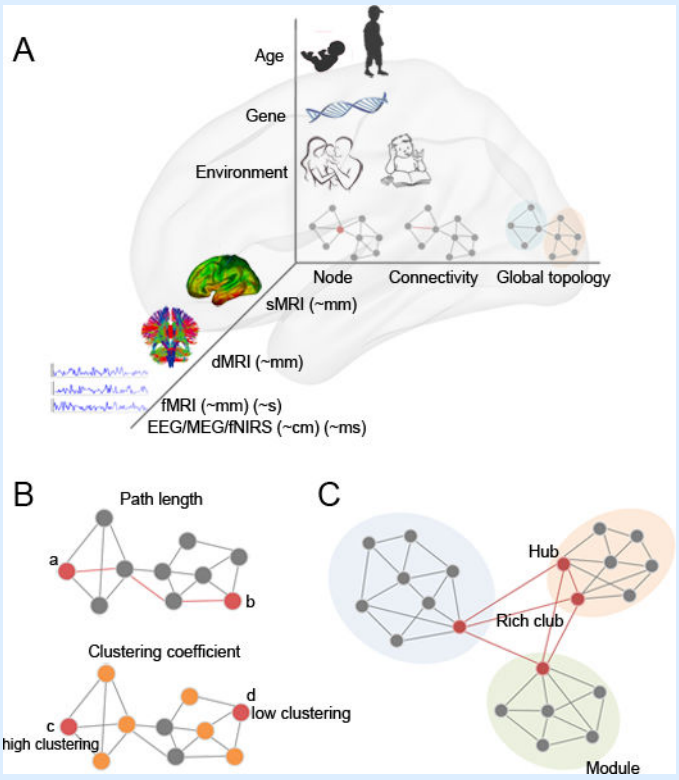

Figure I.

Box 2

The Developing Human Connectome Project and the Baby Connectome Project

Open resources with large samples of the human brain acquired with high-resolution MRI techniques are essential for a developmental brain study. Datasets focused on the early development period combined with the developmental connectomic framework may rapidly accelerate the science of human connectomics and yield deeper understandings of the origin of complex brain mechanisms. This need is increasingly addressed through two promising open resources for baby brain connectomics 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 4-dimensional connectome from 20 to 44 weeks post-conceptional age. The dynamic connectome will be linked together with imaging, clinical, behavioral, and genetic information. This project will provide crucial insights into both fundamental neural processes and the mechnism of 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 structural MRI, diffusion MRI and resting-state functional MRI data. For more details, please see http://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, ages 0-5 years, over the course of four 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 four to six times at distinct points during their development. The objective of this project is to provide a better understanding of how the brain connectivity develops from infancy through early childhood and how the connectivity patterns shape behavioral development as well as the contributing factors about healthy brain development. For more details, please see http://www.med.unc.edu/bric/slide-pages/featured-study/baby-connectome-project.

Outstanding Questions Box

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 subsequent cognitive and behavior development, learning, and skill acquisition?

What are the underlying neurophysiological, molecular and biochemical substrates of macroscale brain connectome maturation?

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

How does the aberrant development of brain connectomes correlate with risk factors as well as 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 sets comprising imaging, clinical, behavioral, and genetic information for the study of early brain development? Developing novel analytical and statistical methods such as high-dimensional data analysis and multivariate statistics are urgently needed.

Trends Box

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 or with developmental disorders reveal disrupted connectomic properties, which are important for potential clinical applications in probing and identifying vulnerability during early development.

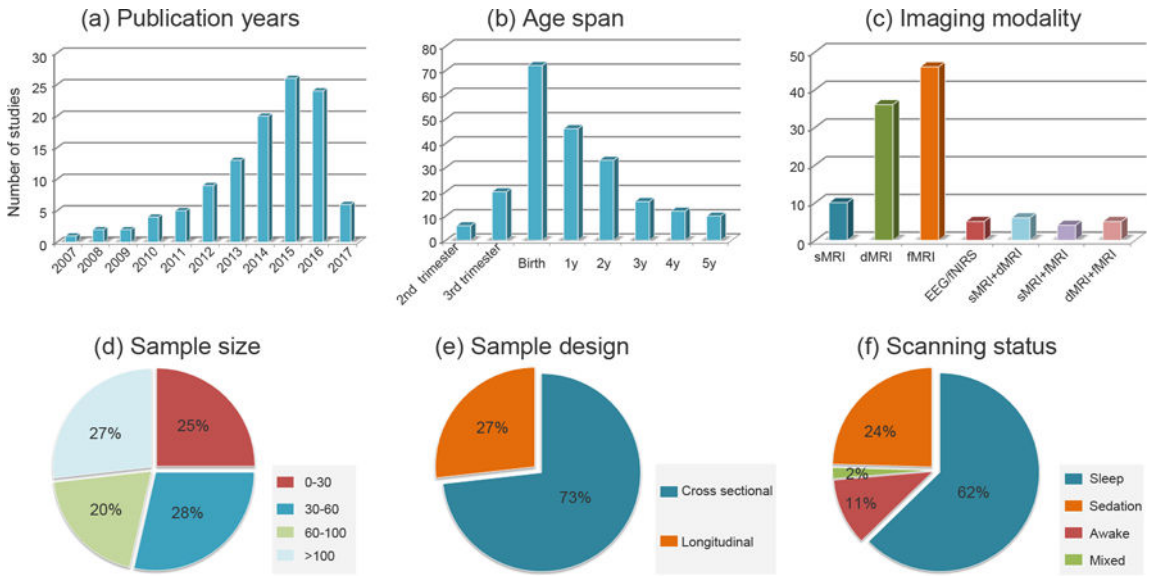

Figure 1. Research summary of developmental connectomics from infancy to early childhood

Summary of the developmental brain connectomic studies from early infancy to childhood with advanced neuroimaging and neurophysiological techniques. This figure represents the literature search results on Pubmed (www.ncbi.nlm.nih.gov/pubmed) 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 publication years (a), age span (b), imaging modality (c) as well as pie charts regarding sample size (d), sample design (e), and scanning status (f). sMRI, structural MRI; dMRI, diffusion MRI; fMRI, functional MRI; EEG, electroencephalography; fNIRS, functional near-infrared spectroscopy.

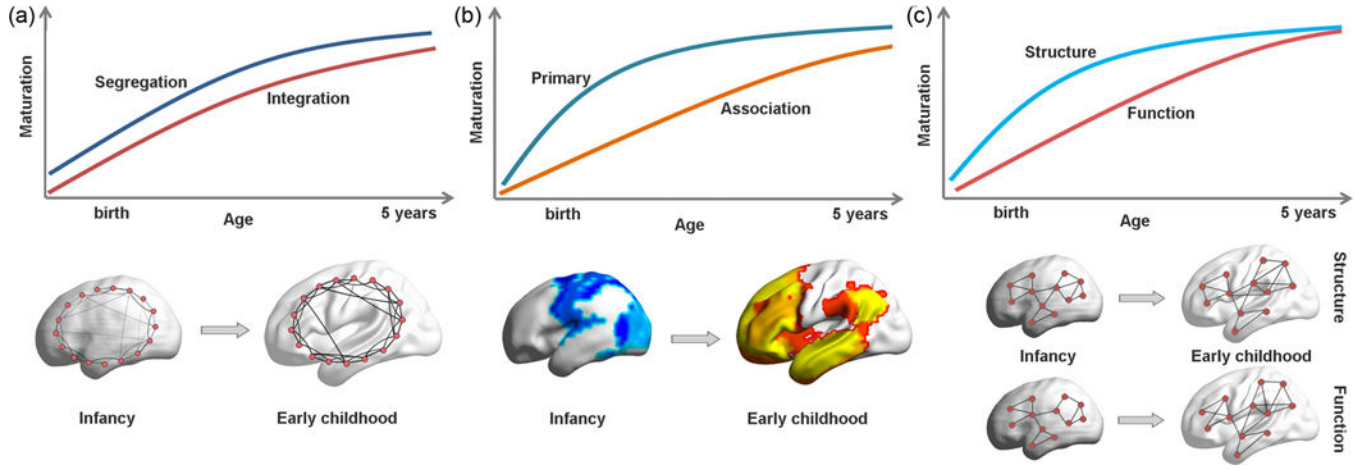

Figure 2. Hypothetic models of the brain connectome development from infancy to early childhood

(a) Presenting the hypothetic developmental model of information segregation and integration in the brain networks. (b) Presenting the hypothetic developmental model from primary regions to high-order association regions. (c) Presenting the hypothetic developmental model of structural and functional brain connectomes.