Review

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Developmental pathways to functional brain networks: emerging principles

V. Menon[1,2,3]

[1] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94304, USA
[2] Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA 94304, USA
[3] Program in Neuroscience, Stanford University School of Medicine, Stanford, CA 94304, USA

The human brain undergoes protracted developmental changes during which it constructs functional networks that engender complex cognitive abilities. Understanding brain function ultimately depends on knowledge of how dynamic interactions between distributed brain regions mature with age to produce sophisticated cognitive systems. This review summarizes recent progress in our understanding of the ontogeny of functional brain networks. Here I describe how complementary methods for probing functional connectivity are providing unique insights into the emergence and maturation of distinct functional networks from childhood to adulthood. I highlight six emerging principles governing the development of large-scale functional networks and discuss how they inform cognitive and affective function in typically developing children and in children with neurodevelopmental disorders.

Cognitive development from the perspective of functional brain networks

The emergence of complex cognitive functions, such as language, reasoning, and cognitive control, is a hallmark of human development [1]. These extraordinary and uniquely human abilities are made possible by a protracted trajectory of brain development and learning over the first two decades of life [2]. Understanding how the developing brain achieves such abilities ultimately depends on knowledge of how functional interactions between distributed brain regions mature with age to produce sophisticated cognitive systems. Brain network analyses are increasingly being used to characterize the developing brain and to understand the dynamic maturation processes that engender complex human cognitive abilities [3]. New research is beginning to demonstrate how functional brain networks emerge from childhood to adulthood, providing fundamental new insights not only into the ontogeny of complex brain function in typically developing individuals, but also into the processes that can go awry in neurodevelopmental disorders. The perspective advanced in this review is that a thorough understanding of the functional architecture of the adult brain requires critical consideration of the developmental pathways by which plasticity and learning lead to the construction of dedicated large-scale brain systems.

Most, if not all, major psychopathologies, with the exception of the dementias, have a prominent origin in childhood or adolescence [4]. The onset and diagnosis of these psychopathologies vary greatly: some, like autism, are mainly diagnosed in early childhood, others such as attention deficit hyperactivity disorder and anxiety disorders are mainly diagnosed in middle childhood, whereas bipolar disorder, depression, and schizophrenia are predominantly diagnosed in late adolescence. For the past two decades, structural brain imaging, with an emphasis on gray matter volume, was the mainstay for identifying abnormalities in children and adolescents with these disorders. An important limitation of these studies is that they provide a relatively narrow window into the distributed functional systems impacted in psychopathology. A paradigm shift is now

Glossary

Attention deficit hyperactivity disorder: one of the most common childhood disorders that can continue through adolescence and adulthood. Symptoms include difficulty staying focused and paying attention, difficulty controlling behavior, and hyperactivity.
Autism: a neurodevelopmental disorder that appears in the first 3 years of life and affects normal development of social and communication skills. Individuals with autism have difficulties with social interaction, display problems with verbal and nonverbal communication, and exhibit repetitive behaviors or narrow, obsessive interests.
Central executive network (CEN): a brain network that is responsible for high-level cognitive functions such as planning, decision making, and the control of attention and working memory.
Default mode network (DMN): a large-scale network of brain areas that form an integrated system for self-related mental activity, including autobiographical, self-monitoring, and social functions. The DMN is typically deactivated during stimulus-driven cognitive processing.
Graph-theoretical measures: a graph is a mathematical structure comprising nodes and the edges that connect them. Expressing functional brain connectivity as a graph allows quantitative association of network properties such as path length, clustering, degree, modularity, and hierarchy.
Intrinsic functional connectivity: a measure of spontaneous synchronization of brain signals between two or more areas. It is computed using the statistical relation of temporal changes in different brain areas in the absence of external stimuli i.e., ('rest').
Salience network (SN): a large-scale brain network involved in detecting and orienting to salient external stimuli and internal events.
Small-world network: a network in which most nodes are not neighbors of one another, but most nodes can be reached from every other node with a small number of links. Small-world networks optimize wiring and efficiency.

Corresponding author: Menon, V. (menon@stanford.edu).

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emerging in the study of neurodevelopmental disorders in children, propelled by recent conceptual and methodological advances in characterizing brain networks and connectivity [5–10]. Critically, this research is also leading to a more thorough characterization of aberrant brain development and providing complementary biological markers for early detection and classification of neurodevelopmental disorders [11–13].

In this review, I outline a developmental perspective on functional brain networks and discuss how advances in our understanding of typical and atypical brain connectivity in children and adolescents are providing new insights into the construction of mature functional systems in adults. I first present a brief overview of methodological and conceptual issues involved in characterizing brain systems in typical and atypical development, pointing out the unique insights afforded by different analytic approaches. I then examine the global architecture of the developing brain, focusing on the development of a small-world organization, the changing landscape of subcortical–cortical interactions, and the emergence of segregated circuits as key features of the maturing functional architecture between infancy and adulthood. I describe several key intrinsic neurocognitive networks that play distinct roles in cognition, highlighting how they are reconfigured in typical development and the implications of these dynamic changes for understanding cognitive function. Aberrations in the development of these networks and how they contribute to psychopathology and clinical symptoms are then examined using examples from major neurodevelopmental disorders including autism spectrum disorders and attention deficit hyperactivity disorder. Candidate neural mechanisms underlying abnormal brain connectivity and its effect on task-related signaling are discussed in relation to the emergence of developmental psychopathology. I conclude by summarizing models and emerging principles of functional network development (Box 1) and identifying avenues for future work.

Box 1. Six emerging principles of functional brain network development

(i) Small-world, hierarchical organization and formation of hubs. Functional brain networks are constructed from an anatomical backbone that is mature by age 2. Key topological features of global functional brain architecture are mature by age 8, but large-scale functional brain connectivity continues to undergo significant restructuring during late childhood and adolescence, leading to the emergence of a hierarchical brain organization and formation of functional hubs that integrate complex exogenous and endogenous mental processes.

(ii) Segregation of functional circuits. Development is characterized by increased segregation of functional brain circuits, with a shift from stronger short-range connections in children to stronger and more distinct patterns long-range connections in adults. This pattern is observed at multiple spatial scales, including global architecture, functional subsystems, and individual cytoarchitectonically distinct nuclei.

(iii) Changing landscape of subcortical–cortical functional connectivity. Reconfiguration of subcortical–cortical connections is a major hallmark of functional brain network development. In particular, basal ganglia–cortical circuits important for motivation, reward- and incentive-based learning, and habit formation undergo significant changes between childhood and adulthood. Aberrant development of subcortical–cortical connectivity plays an important role in several major neurodevelopmental disorders including autism and attention deficit hyperactivity disorder.

(iv) Dynamic pruning of functional circuits. The dynamic process of over-connectivity followed by pruning, which rewires connections at the synaptic level, also operates at the systems level, helping to reconfigure and rebalance connectivity in the developing brain.

(v) Reconfiguration of large-scale functional networks. Functional connectivity within and between spatially independent large-scale functional networks undergoes significant changes with development. The salience network and insula show weak cross-network signaling in the developing brain and are a source of vulnerability for developmental psychopathology.

(vi) Physiological basis of aberrant functional brain networks. Changes in excitatory–inhibitory balance over development not only impact local circuit excitability but also alter large-scale brain connectivity in typical and atypical development. A general developmental principle proposed is that this imbalance underlies aberrant brain connectivity in many developmental psychopathologies.

Characterizing brain networks in typical and atypical development

With ever-increasing sophistication, advanced computational methods [5–10] are being used to: (i) characterize the developmental stages and processes by which global functional brain architecture, neurocognitive networks, and region-specific functional circuits emerge and mature from infancy to adulthood; and (ii) understand how these changes influence information processing in the developing brain. These methods are also relevant to the study of developmental psychopathology, where the overarching goals are to: (i) uncover differences in global brain architecture, neurocognitive networks, and region-specific connectivity that distinguish children with specific neurodevelopmental disorders from typically developing children; and (ii) link features of aberrant brain organization to phenotypic behavioral features.

Early structural neuroimaging research first provided foundational knowledge regarding the gray matter volume of the brain and these methods were applied to the study of brain development with a focus on charting region-specific trajectories of gray matter volume from infancy to adulthood [2,14,15]. Collectively, these studies have revealed that the human brain undergoes extensive, heterogeneous, and heterochronous changes in gray and white matter structure between childhood and adulthood. Overall brain volume [16], volume of individual brain areas [17], regional cortical thickness [18,19], and regional and global gray matter density [14,15,20] all go through significant changes from infancy to adolescence. A common finding from this literature is that gray matter volume initially increases in early childhood and peaks in adolescence with a subsequent decline in adulthood [2], commonly referred to as an 'inverted-U' pattern of development.

Moving beyond this localization approach, advances in structural image acquisition and analysis have provided additional tools for characterizing brain networks, allowing researchers to build on these early structural findings to address important questions regarding the development of brain networks. For example, recent work has examined the development of white matter pathways that facilitate brain connectivity between distal regions of the brain.

Results from this body of work have shown that white matter undergoes a much more extended pattern of change over the lifespan relative to gray matter [21], suggesting that the strengthening of brain connections, which relies on the maturation of white matter tracts, also undergoes a protracted period of development. Additionally, more detailed studies of gray matter covariance across the brain have suggested that regional changes in gray matter thickness, rather than being isolated or random, follow a pattern of coordinated global change [22–24]. Thus, local synaptic pruning [14,15,25], microstructural changes in white matter [26,27], and the strength of long-range white matter pathways all undergo significant and extensive changes from infancy to adulthood [21,28], contributing to widespread and coordinated change in brain connectivity across much of the brain during the first two decades of life.

A thorough characterization of the development of large-scale brain networks requires the integration of multiple structural and functional measures [28–31]. The complexities of this effort, including linking brain structure, anatomical connectivity, task- and context-specific functional connectivity, and characterizing their dynamic maturation with age continue to present unique methodological and scientific challenges. As a result, researchers have increasingly focused on intrinsic 'resting-state' connectivity measures for characterizing the development of functional brain networks. Recent findings using this approach are the primary focus of this review.

Intrinsic functional connectivity, as considered here, is based on spontaneous synchronization of functional MRI (fMRI) signals between two or more brain areas [32]. It is typically measured using one of three methods: (i) full or partial correlation analysis of multiple regions of interest [33]; (ii) independent component analysis of the entire brain, which identifies spatial nodes with a common temporal profile [34]; or (iii) regression analysis using a seed region of interest [35]. Each of these measures can then be used to characterize different aspects of the architecture and connectivity of large-scale brain networks. Critically, studies of intrinsic functional connectivity are not only providing important new insights into the development of specific functional circuits, but, more generally, are also revealing fundamental organizing principles underlying brain development.

Three approaches for describing brain networks using intrinsic functional connectivity are highlighted in this review. The first approach views the whole brain as a single network and uses graph-theoretical analysis of functional or structural connectivity to characterize the topology, modularity, and hierarchy of this network across all brain regions. The advantage of this approach is that it provides a global account of the functional architecture of the entire brain. The second approach examines the organization and development of spatially independent neurocognitive networks that underlie distinct aspects of cognitive function, an approach that facilitates targeted exploration of circumscribed brain systems. A third approach examines developmental changes in the connectivity patterns of specific regions of interest to all other regions of the brain, providing a relatively unconstrained method for examining functional circuits associated with localized brain regions. These approaches have yielded complementary knowledge about the principles of brain network development.

Global functional brain architecture in development

The global functional architecture of the developing brain has been examined most comprehensively using graph-theoretical approaches that have identified several major results [36–39]. The first key result to emerge from these studies is that, early in development, the brains of children have a stable, non-random, small-world organization characterized by optimal connectivity for synchronization and information transfer with minimal rewiring cost [36] (Figure 1A,B). In graph theory, small-world architecture refers to a network in which constituent nodes exhibit a large degree of clustering as well as relatively short distances between any two nodes of the system and is thought to reflect a balance between local processing and global integration of information [40]. Graph-theoretical analyses of intrinsic functional connectivity have shown that the brain possesses a small-world topology immediately after birth [39]. By age 7, most gross measures of network topology, such as path length, degree, and clustering coefficient, reach levels similar to those observed in young adults aged 19–22 years [36] (Figure 1B). The second major finding is that, early in development, cortical hubs and their associated cortical networks are largely confined to primary sensory and motor brain regions [38]. With age, these hubs shift to the posterior cingulate cortex and insula [41], heteromodal regions that integrate complex exogenous and endogenous mental processes in more mature ways [5,29,42].

The third major finding from these studies is that children also differ in the hierarchical organization of functional brain networks (Figure 1C). Graph theory defines hierarchical networks according to the presence of small, densely connected clusters of brain regions that combine to form large, less-interconnected clusters, which combine again to form larger less-interconnected clusters [43]. Hierarchical networks are optimally connected to support top-down relationships between nodes and minimize wiring costs, but are vulnerable to impairments in major hubs that can substantially impact the performance and efficiency of the entire network. Several such hubs have been identified in adults and include the posterior cingulate cortex and the insula [41]. The age at which such functional hubs are formed is currently unknown, but hubs that integrate multimodal information are largely absent in infancy [38]. Lower levels of hierarchical organization and altered organization of functional hubs in children may therefore be protective against such vulnerability, allowing for more flexibility in network reconfiguration on the basis of individual differences in learning, cognitive experience, and reserve.

The fourth key result to emerge from studies of global brain architecture is that the development of large-scale brain connectivity is characterized by weakening of short-range (less than ~50 mm) and strengthening of long-range connections from middle childhood to adulthood [36,37,44] (Figure 1D). These developmental changes to the strength

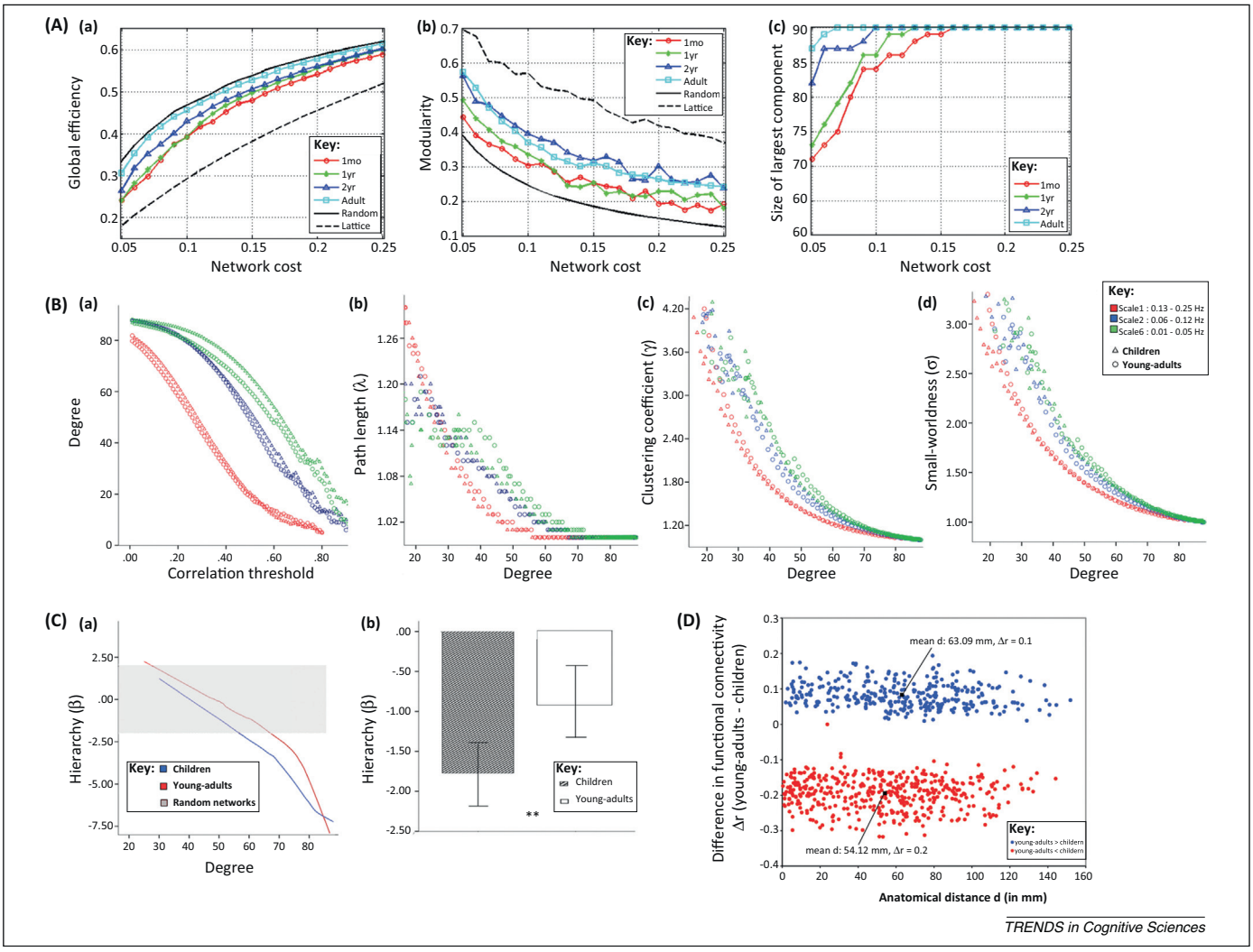


Figure 1. Global functional brain architecture in development. **(A)** Global structural topological metrics are stable by age 2. (a) Global efficiency, (b) modularity, and (c) size of the largest connected component as a function of network cost in 1-month-, 1-year-, and 2-year-old children and adults. For each measure, the comparable random graphs and regular lattices show non-randomness at the earliest stages of development. **(B)** Global functional topological metrics are stable by age 8. (a) Degree, (b) path length, (c) clustering coefficient, and (d) small worldness do not differ between children aged 7–9 years (Δ) and adults aged 19–22 years (○). Each color reflects a different frequency scale in the functional MRI (fMRI) signal. **(C)** Hierarchical organization of functional connectivity increases with age. (a) Hierarchy (β) for children (blue) and young adults (red) at scale 3 (0.01–0.05 Hz). The β values for both groups are high (β *z*-scores ranged from −7.5 to 2.5) and are significantly greater than the β values obtained from random networks (β for random *z*-scores ranged from −1.96 to 1.96, indicated in gray). (b) Mean β values are significantly higher in adults. **(D)** Developmental changes in functional connectivity with tract-based wiring distance. The wiring distance (d) of all connections that differed significantly between children and adults is plotted against developmental change in functional correlation values (Δ*r*) of those connections. Short-range connections (less than 54 mm) are significantly stronger in children (shown in red) whereas adults show stronger long-range connectivity (shown in blue), reflecting increased segregation and integration with age. Adapted from [36,48].

of short- and long-range connections have been observed at the global level [36,37], in circumscribed attentional control networks [45], and within proximal cytoarchitectonically defined nuclei [46] and are thought to underlie the formation of tightly linked functional modules connected by hubs that together promote the segregation and integration of neural information [47]. Specifically, reductions in short-range connections are thought to contribute to increased segregation of neural information, whereas strengthening of long-range connections is thought to facilitate the integration of information.

An important principle highlighted by these findings is that large-scale functional brain connectivity undergoes significant restructuring over development, even as global topological features are preserved. The relative stability of several key topological features from middle childhood suggests that changes in functional brain networks are subject to significant constraints and are likely to arise from an established pattern of small-world topology and the modular organization of structural brain networks. Consistent with this view, a longitudinal study in pediatric subjects, using structural MRI data collected at ages 1 month, 1 year, and 2 years, has demonstrated that a core anatomical network characterized by small-world topology and modular organization of brain networks is established early in brain development by age 2 [48]. These data indicate that the anatomical backbone of fundamental network characteristics seen in the brains of older children and adults are established by the age of 2 and suggest that these network features represent critical organizational principles of both the developing and mature central nervous systems. These findings provide new insights into the development and maturation of human brain networks and new avenues for future research on neurodevelopmental disorders such

as autism, schizophrenia, and attention deficit hyperactivity disorder.

Although graph-theoretical methods have provided useful metrics for characterizing the gross architecture of the developing brain and for identifying hot spots of typical and atypical developmental change, they are less useful in relating the maturation of specific brain systems to learning and cognitive development. Alternate approaches that examine specific large-scale intrinsic brain networks and the connectivity of individual brain regions have filled this gap.

Changing landscape of subcortical–cortical interactions as a major hallmark of the developing brain

A major developmental principle to emerge from whole-brain connectivity studies is that there are heterogeneous patterns of changes across functional systems that map the external world onto the brain's sensory, attentional, mnemonic, emotional, and motivational systems [49]. In particular, subcortical regions appear to be a primary locus of developmental changes in functional connectivity compared with primary sensory, paralimbic, limbic, and association areas [36]. Subcortical structures that feature prominently in these developmental results include the basal ganglia, which are important for adaptively sequencing and mapping sensory input and cognitive operations into behavior [50,51]. The basal ganglia are also important for reward- and incentive-based learning and habit formation, processes that undergo significant changes in childhood and adolescence.

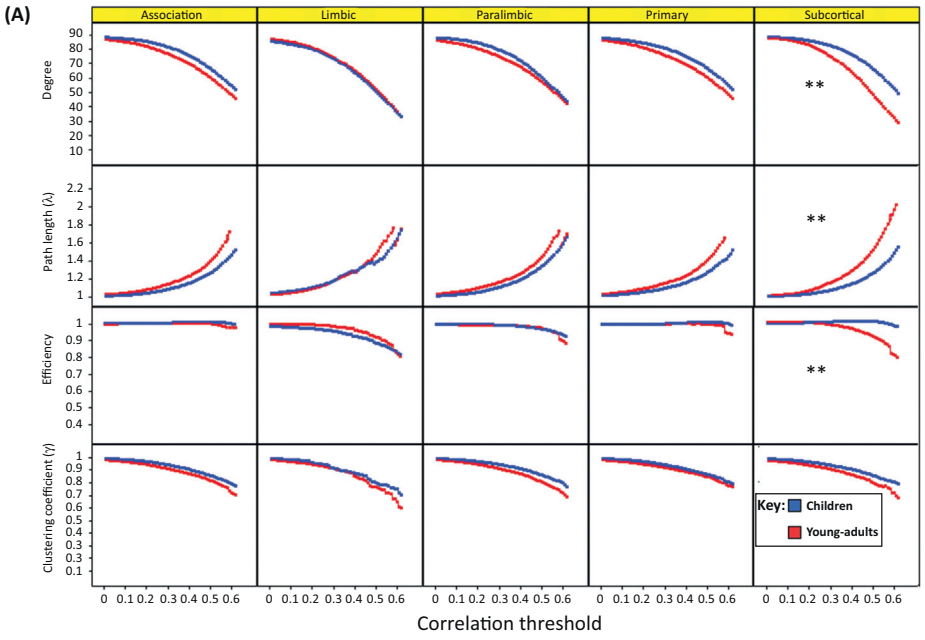
The degree, path length, and efficiency of wiring within subcortical regions showed prominent developmental changes (Figure 2A). Notably, these differences were large enough that subcortical–cortical connectivity patterns distinguished children from adults with a high level of accuracy (Figure 2B). The direction of differences in connectivity strength between functional systems is also noteworthy: subcortical regions were more strongly connected with primary sensory, association, and paralimbic areas in children. By contrast, adults showed stronger corticocortical connectivity between paralimbic, limbic, and association areas (Figure 2C). A crucial aspect of developmental change highlighted by this finding is that although the development of large-scale brain connectivity is characterized by weakening of short-range functional connectivity and strengthening of long-range functional connectivity, the reconfiguration of subcortical–cortical connections is a major exception to this rule. Brain regions that are connected more strongly in children, compared with adults, include the basal ganglia.

More broadly, these findings also suggest that the dynamic process of initial over-connectivity followed by pruning, which rewires connectivity at the neuronal level, also operates at the systems level, helping to reconfigure and rebalance subcortical connectivity in the developing brain. The changing landscape of subcortical connectivity with multiple functional systems further suggests a mechanism by which the integration of motivational systems with sensory, attentional, mnemonic, and affective systems undergo radical changes with development [50–52]. It is likely that the most significant changes are manifested during adolescence, a period characterized by marked changes in hormonal levels and reward seeking [53–55]. How plasticity in basal ganglia–cortical functional brain circuits influences motivational behaviors in adolescence is a major question for future research. Another important area for further research will be to determine how connectivity patterns across different functional systems are affected in children with behavioral disorders such as autism and attention deficit hyperactivity disorder, in which accumulating evidence points to disruptions of subcortical–cortical connectivity (Figure 2D) and impaired interactions between attentional, cognitive control, and reward pathways [56–59].

Reconfiguration of functional brain networks with development

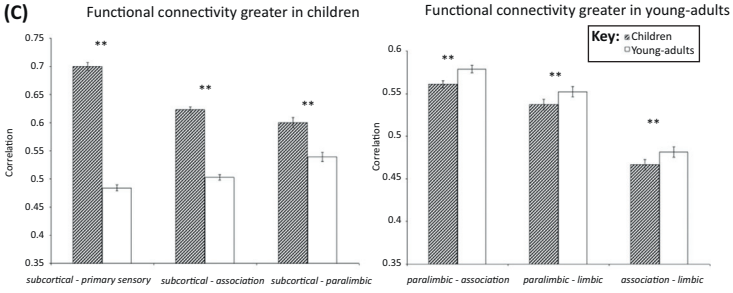
The discovery that the adult brain is intrinsically organized into about twenty independent functional networks [60] has opened new avenues for investigating the developing brain. Among these, the three most prominent networks to be examined from a development perspective are: (i) the frontoparietal central executive network (CEN) anchored in the dorsolateral prefrontal cortex and supramarginal gyrus; (ii) the salience network (SN) anchored in the anterior insula and anterior cingulate cortex; and (iii) the default mode network (DMN) anchored in the posterior cingulate cortex, medial prefrontal cortex, medial temporal lobe, and angular gyrus [35,61,62] (Figure 3A). Activation of the key nodes of these three networks can be readily identified across a wide range of cognitive tasks and the strength of their responses increase and decrease proportionately with task demands [35,63,64]. Studies in adults suggest that these core networks play distinct roles in cognition. Briefly, the CEN is critical for actively maintaining and manipulating information in working memory and for judgment and decision making [65,66], the SN plays an important role in orienting attention to salient stimuli and facilitating goal-directed behavior [67], and the DMN plays an important role in self-referential mental activity and autobiographical memory [68].

Given the importance of these three core networks in distinct aspects of human cognition [36,67], considerable efforts have been made to characterize their developmental trajectories [37,45,69]. These networks can be readily identified by age 2 [70] but undergo protracted changes in node distribution and connection strength throughout childhood and adolescence. Between the ages of 7 and 20, the CEN, SN, and DMN undergo significant developmental changes, spanning both within- and across-network links [69]. Analysis of these links provides unique insights into the maturation of core neurocognitive systems. Specifically, compared with adults, children show significantly weaker functional connectivity between the anterior insula and anterior cingulate cortex (within the SN), the posterior cingulate cortex and ventromedial prefrontal cortex (within the DMN), the anterior insula and dorsolateral prefrontal cortex (between the SN and CEN), and the anterior insula and posterior cingulate cortex (between the SN and DMN) (Figure 3B). Notably, the anterior insula is the only node that showed significant differences in within- and between-network functional



(B)

Interregional functional connectivity	Accuracy Percent
Subcortical - Primary sensory	91
Subcortical - Association	90
Subcortical - Paralimbic	83
Paralimbic - Association	80
Paralimbic - Primary sensory	78
Association - Primary sensory	78
Association - Limbic	78
Limbic - Paralimbic	76
Limbic - Subcortical	64
Limbic - Primary sensory	44



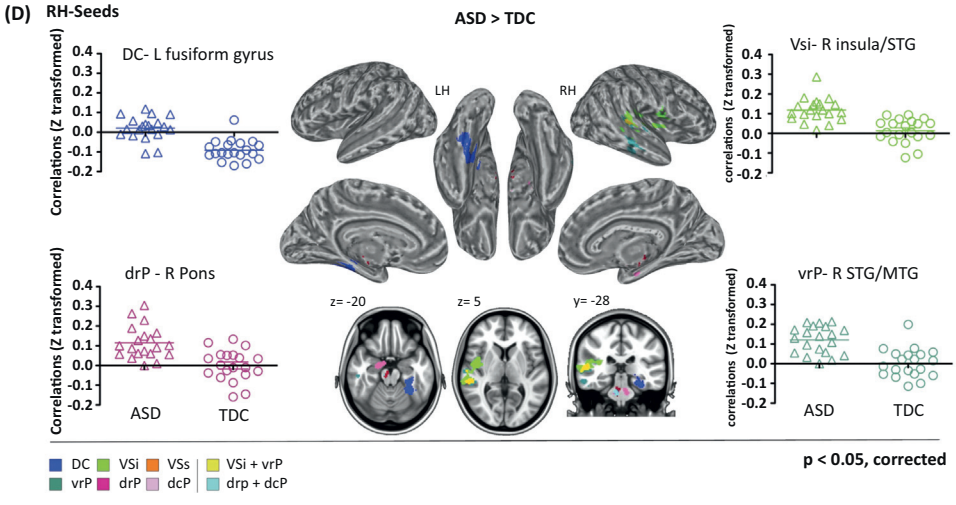


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Figure 2. Changing landscape of subcortical–cortical connectivity in typical and atypical development. **(A)** Subcortical regions are a major locus of developmental changes in functional connectivity. Degree, path length, efficiency, and clustering coefficient within each of the five major functional systems – association, limbic, paralimbic, primary, and subcortical – are shown in blue for children and in red for adults, as a function of the correlation threshold. Children and adults differ only in the subcortical division; degree and efficiency of connectivity are significantly higher and path length is significantly lower in children. **(B)** Subcortical connectivity is a distinguishing feature in children. Support-vector machine classifiers identify subcortical regions as the major locus of differences in connectivity patterns with each of the four other functional systems. **(C)** Developmental changes in subcortical functional connectivity. Children show significantly greater subcortical–primary sensory, subcortical–association, and subcortical–paralimbic and lower paralimbic–association, paralimbic–limbic, and association–limbic connectivity than adults. **(D)** Functional hyperconnectivity of the basal ganglia in autism spectrum disorder (ASD). Cortical and subcortical clusters with significantly greater functional connectivity in children with ASD relative to typically developing children (TDC) are shown for multiple regions of interest in the right hemisphere. Abbreviations: DC, dorsal caudate; dcP, dorsal caudal putamen; drP, dorsal rostral putamen; L, left; MTG, middle temporal gyrus; R, right; RH, right hemisphere; STG, superior temporal gyrus; vrP, ventral rostral putamen; VSi, ventral striatum inferior; VSs, ventral striatum superior. Adapted from [36,59].

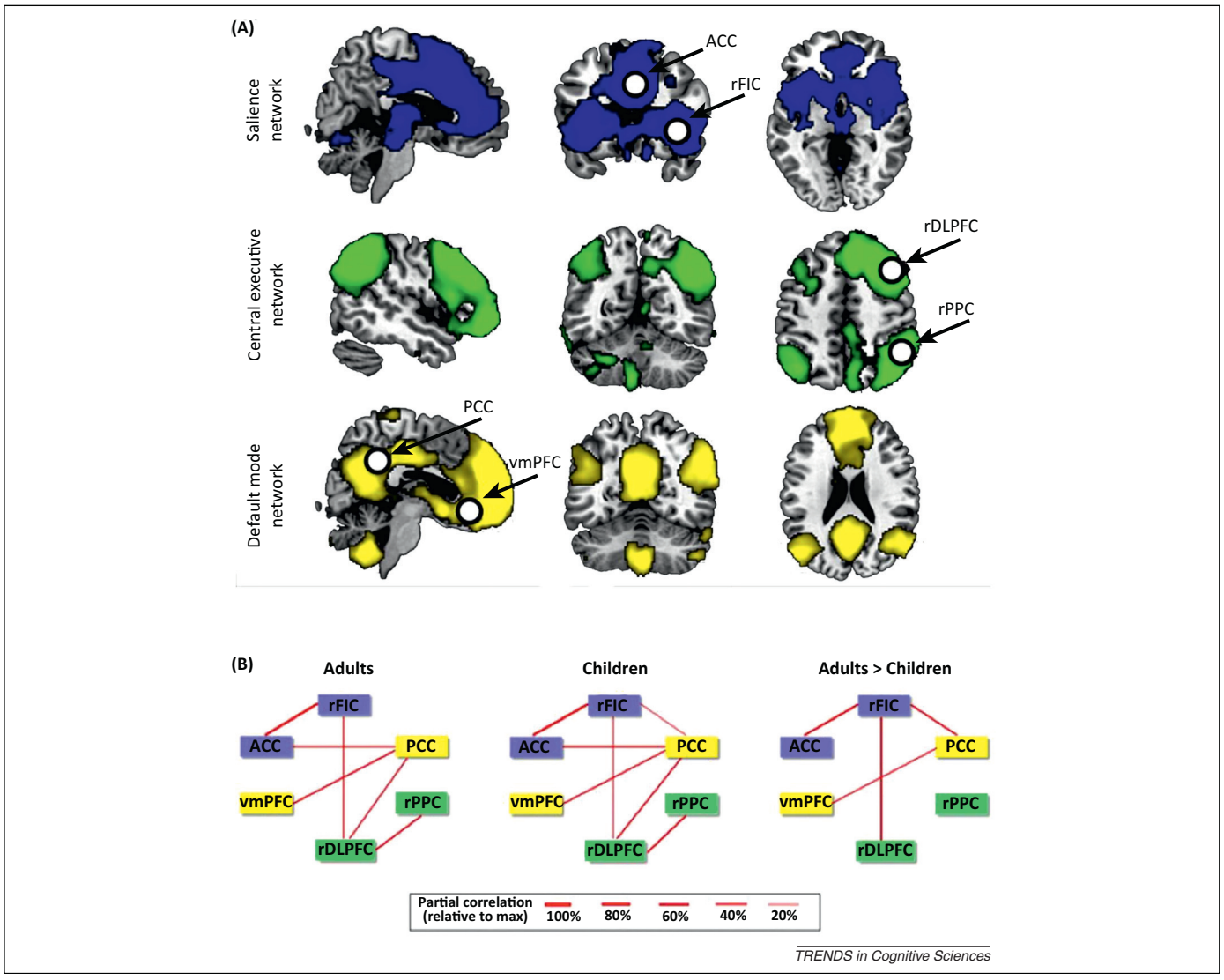

Figure 3. Reconfiguration of brain networks with typical development. **(A)** Three core neurocognitive networks identified using independent-component analysis. The salience network (SN) (shown in blue) is important for detection and mapping of salient external inputs and internal brain events. The frontoparietal central executive network (CEN) (shown in green), anchored in the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex (PPC), plays an important role in working memory and attention. The default mode network (DMN) (shown in yellow), anchored in the posterior cingulate cortex (PCC) and ventromedial prefrontal cortex (VMPFC), is important for self-referential mental processes including autobiographical memory. **(B)** The anterior insula is a locus of weak intrinsic functional connectivity in children. Instantaneous functional connectivity, as measured by partial correlation, of the six key nodes of the SN (blue), CEN (green), and DMN (yellow) in adults and children. Adapted from [69].

connectivity, suggesting that this region is a locus of weak signaling in children. Consistent with this view, the right anterior insula also showed weaker causal influences on the CEN during problem solving and weaker signaling also contributed to lower levels of behavioral performance in children [71]. The anterior insula plays an important role in saliency detection, by switching between other large-scale networks to facilitate access to attention and working memory when a salient event occurs. Moreover, the insula has access to the motor system via strong functional connections with the anterior cingulate cortex and the interaction of the anterior and posterior insula facilitates physiological reactivity to salient stimuli [42,72]. These observations suggest that the functional maturation of anterior insula pathways is a critical process by which human brain networks reconfigure and mature during development to support more flexible cognitive control processes in adulthood [69].

Deficits in engagement and disengagement of the SN, CEN, and DMN, and other neurocognitive networks, play a significant role in many psychiatric and neurodevelopmental disorders [5]. Because these networks can be consistently identified in children with neurodevelopmental disorders (Figure 4A), their careful characterization offers a principled approach for defining core features of developmental psychopathology. For example, characterization of large-scale brain networks, including the SN, CEN, and DMN, has been particularly promising for identifying atypical development in children with autism [13,73] (Figure 4B,C). Autism is a disorder with early-life onset and a variable developmental trajectory [74]. It affects nearly 1 in 88 children and is characterized by a complex phenotype that includes social, communicative, and sensorimotor deficits. Autism has been linked with atypical connectivity across multiple brain systems and numerous approaches have been used to examine these deficits, often

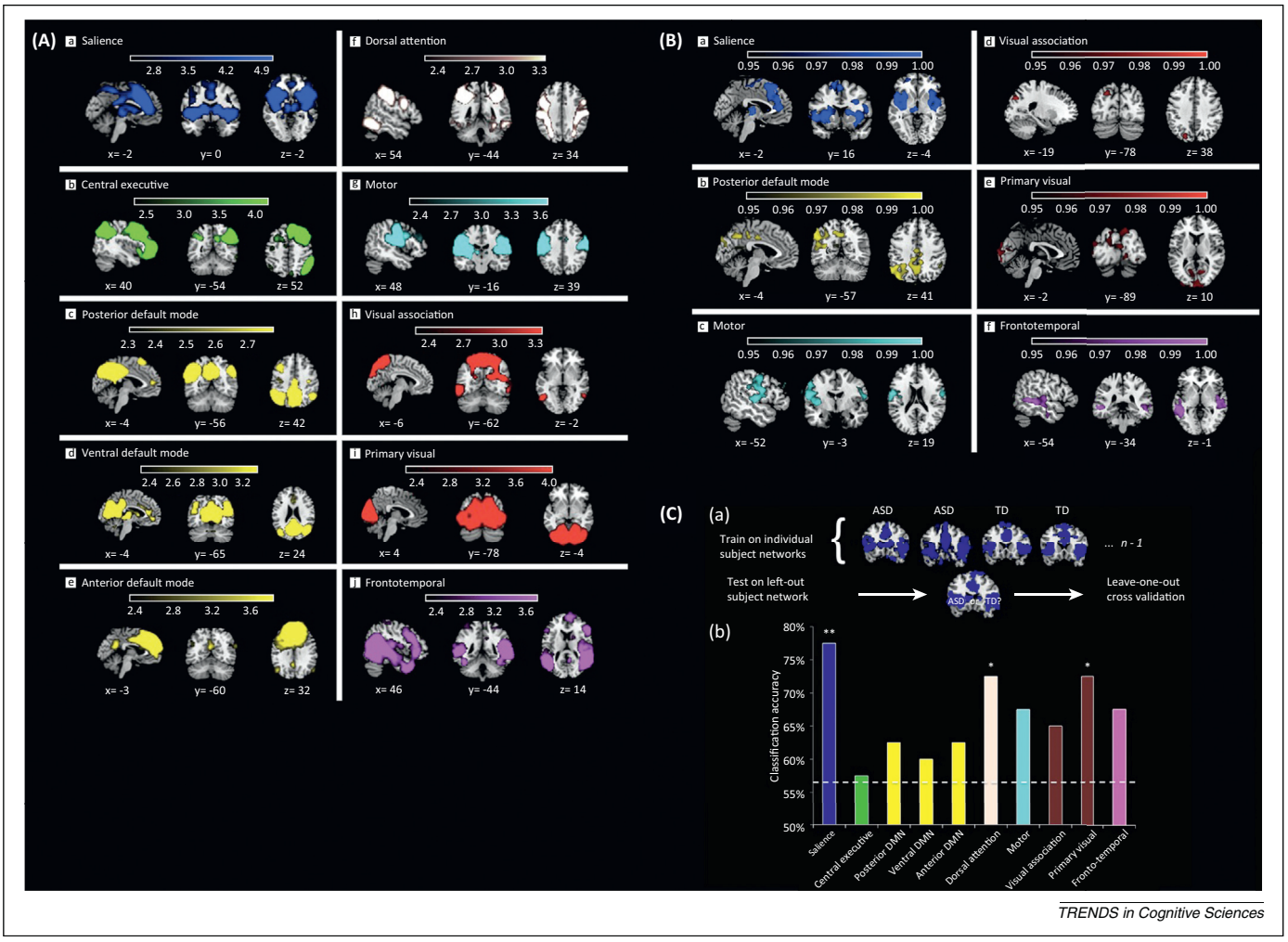

Figure 4. Aberrant brain networks in atypical development. **(A)** Large-scale brain networks in 7–12-year-old children identified using independent-component analysis. They include: (a) salience; (b) central executive; (c) posterior default mode; (d) ventral default mode; (e) anterior default mode; (f) dorsal attention; (g) motor; (h) visual association; (i) primary visual; and (j) frontotemporal networks. **(B)** Brain network hyperconnectivity in children with autism spectrum disorder (ASD). Children with ASD showed greater functional connectivity in six of the ten networks examined: (a) salience; (b) posterior default mode; (c) motor, (d) visual association; (e) primary visual, and (f) frontotemporal. **(C)** Classification analysis distinguishes children with ASD from typically developing children (TDC). (a) Classification-analysis flowchart. The ten components identified from each participant served as features to be input into classification analyses. (b) Features from each network were used to distinguish children with ASD from TDC. The salience network has the highest classification accuracy. Adapted from [13].

with conflicting findings [75,76]. Surprisingly, the SN and DMN as well as other, independent frontotemporal, motor, and visual networks show significant hyperconnectivity in children with autism (Figure 4B). Critically, connectivity in these networks can be used to distinguish children with autism from typically developing children (Figure 4C). Among all networks examined, the connectivity patterns of the SN show the highest classification accuracy between children with autism and typically developing children and its functional organization predicted restricted and repetitive behavior scores, one of the core symptoms of autism. Identification of the SN as a particular locus of aberrant connectivity is consistent with the hypothesis that inappropriate assignment of saliency to external stimuli or internal mental events by the SN plays a prominent role in autism [42]. More specifically, aberrant detection of saliency linked to weak development of signaling from the anterior insula to key nodes of the SN and DMN may be a particular source of vulnerability for psychopathology in the developing brain [5,77,78]. The application of this model and general approach holds great promise for the principled investigation of autism and other developmental psychopathologies.

Taken together, findings to date suggest that network-identification approaches can inform our understanding of the neurobiology of childhood disorders in fundamentally new ways, making links to cognitive and affective dysfunction while facilitating the development of biomarkers for early detection and classification of developmental psychopathologies.

Emergence of segregated functional circuits with development

Analysis of the connectivity fingerprint of anatomically distinct nuclei affords complementary and unique insights into the development of functional circuits. Here the goal is to illustrate the general principles of functional circuit development that are beginning to emerge using this approach, drawing on an example from analysis of developmental changes in the connectivity of cytoarchitectonically distinct nuclei within the amygdala [46] (Figure 5A). The amygdala is a brain structure that plays a pivotal role

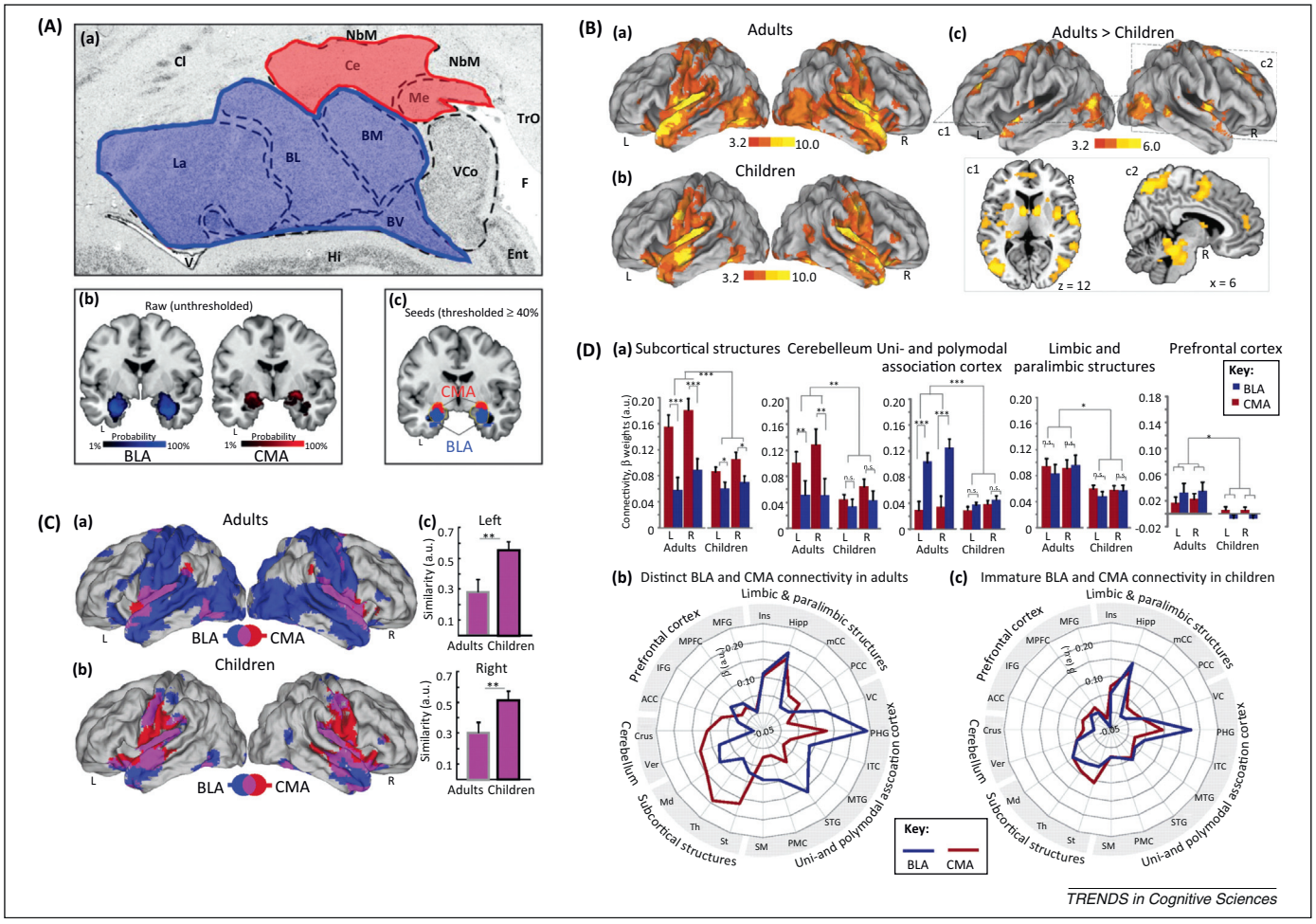

Figure 5. Emergence of segregated amygdala circuits. **(A)** Cytoarchitectonic maps of the basolateral amygdala (BLA) and central medial amygdala (CMA) nuclei. (a) The CMA is coded light red and the BLA is coded light blue. (b,c) Unthresholded and thresholded maps of the BLA and CMA. **(B)** Weak functional connectivity of the amygdala in children compared with adults. Amygdala connectivity in (a) adults and (b) children. (c) Cortical and subcortical areas where adults showed greater connectivity than children. Children did not show greater amygdala connectivity with any brain area. **(C)** Similarity between BLA and CMA functional connectivity in adults and children. Brain regions showing significant connectivity with the BLA (shown in blue) and CMA (shown in red) in (a) adults and (b) children. Overlap between BLA and CMA connectivity is shown in pink. (c) Children show greater overlap between BLA and CMA connectivity than adults. **(D)** Differential patterns of CMA and BLA functional connectivity in adults and children. (a) Parameter estimates represent the strength of functional connectivity between the BLA (shown in blue) or CMA (shown in red) with target networks of interest, including subcortical structures, cerebellum, polymodal association areas, limbic and paralimbic structures, and prefrontal cortex. (b) Schematic representation of weaker segregation of BLA and CMA connectivity in children (right panel) compared with adults (left panel). In adults, the BLA has stronger functional connectivity with polymodal association areas (shown in light blue with broken lines connected), whereas the CMA showed stronger functional connectivity with subcortical structures (shown in orange with broken lines connected). In children, these differential patterns are significantly less pronounced (shown in lighter color with thinner lines). Adapted from [46,108].

in emotion-related functions. Although the gross structure of the amygdala is mature by age 5 [79], its role in emotion and cognition undergoes protracted development, with dramatic changes in expression and regulation of emotion from childhood to adulthood. The amygdala is a major hub for processing affective and biologically salient cues [80–82] and investigating its functional circuits in children is important not only for understanding the maturation of emotional processing in the typically developing brain, but also for examining how aberrant amygdala circuits result in selective vulnerability to affective disorders. The basolateral and centromedial amygdala nuclei were first characterized in animal studies; these two major nuclei contribute to distinct functions via their dedicated networks and unique pattern of interactions with cortical and subcortical regions [80,83,84]. The centromedial amygdala is essential for controlling the expression of fear responses, such as freezing behaviors, through projections to other subcortical structures including the thalamus, hypothalamus, striatum, brainstem, and cerebellum [80,83–85]. The basolateral nucleus, by contrast, plays a critical role in the perception, evaluation, and regulation of emotionally salient stimuli via its abundant projections to widely distributed cortical regions. Functional connectivity analysis has recapitulated these findings in both adults and children with some important developmental differences [46] (Figure 5B). Compared with adults, the functional connectivity of the amygdala with subcortical, paralimbic, and limbic structures, polymodal association, and ventromedial prefrontal cortex is significantly weaker in children. Importantly, target networks associated with the basolateral and centromedial nuclei exhibited greater overlap and weaker dissociation in children (Figure 5C). Furthermore, children also show greater intra-amygdala connectivity between the basolateral and centromedial nuclei and this profile underpins the weak segregation of large-scale

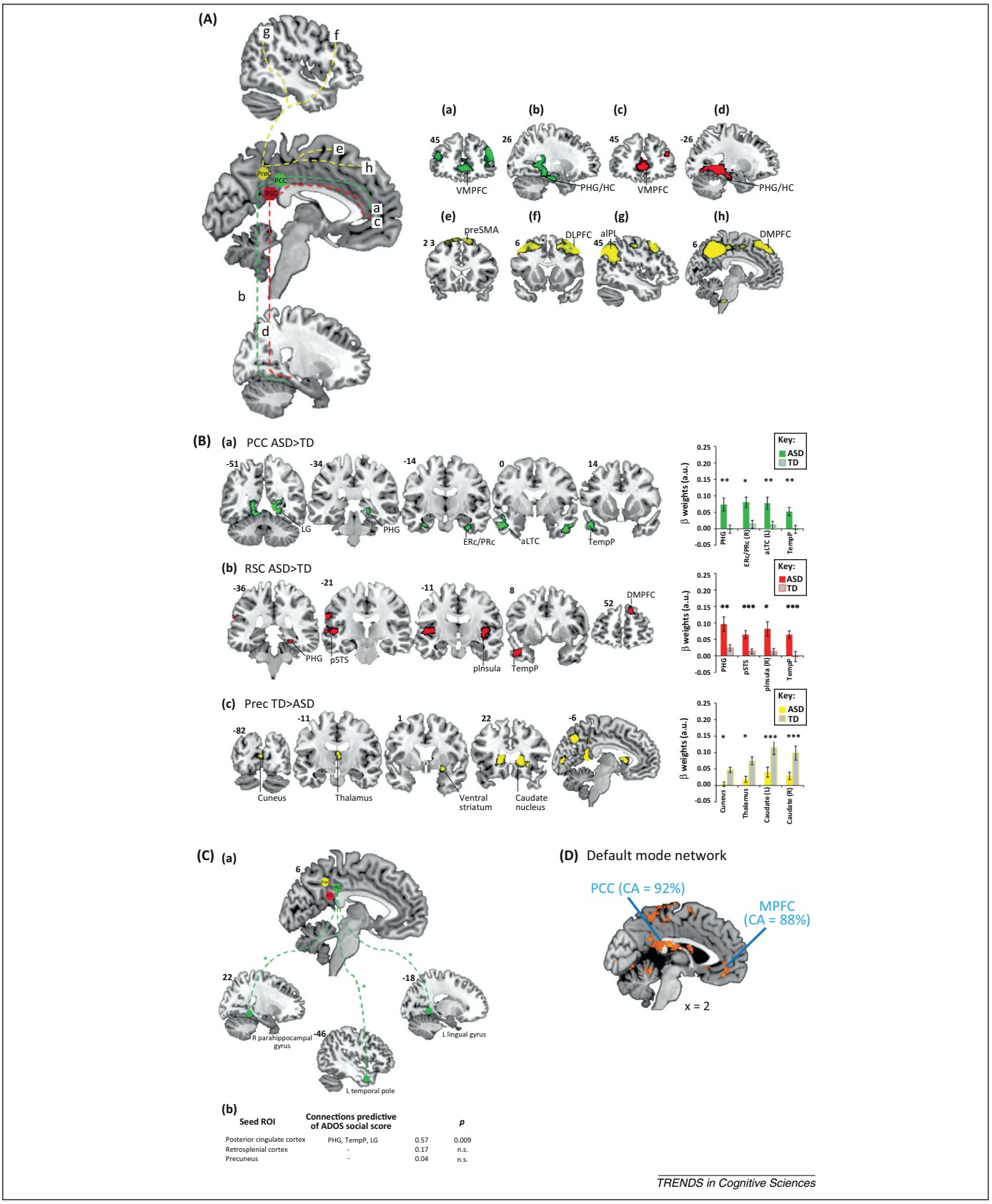

Figure 6. Heterogeneous patterns of hyper- and hypoconnectivity in atypical development. **(A)** Heterogeneous profiles of posteromedial cortex connectivity in children with autism spectrum disorder (ASD). Compared with the precuneus (PreC), the posterior cingulate and retrosplenial cortices show stronger connectivity with the ventromedial prefrontal cortex (VMPFC) and medial temporal lobe (a,b,c,d). The PreC was more strongly connected with the presupplementary motor area (preSMA) (e), the dorsolateral prefrontal cortex (DLPFC) (f), the anterior inferior parietal lobule (aIPL) (g), and dorsomedial aspects of the medial prefrontal cortex (DMPFC) (h). Posterior cingulate cortex connectivity most closely resembled the default mode network (i). **(B)** Children with ASD show both hyperconnectivity (ASD > TD) and hypoconnectivity (TD > ASD) of individual posteromedial cortex regions. The posterior cingulate cortex (PCC) and retrosplenial cortex (RSC) are hyperconnected in ASD whereas the precuneus (PreC) is hypoconnected. **(C)** Posterior cingulate cortex hyperconnectivity predicts social deficits in childhood ASD. Connections between the PCC seed region of interest (ROI) and

(Figure legend continued on the bottom of the next page.)

functional circuits associated with the nuclei in children [46] (Figure 5D). Aberrant maturation of these pathways is likely to have major implications for the study of aberrant brain circuitry in anxiety disorders and depression, both of which have prominent developmental origins [86]. How aberrant development of these circuits contributes to affective disorders such as anxiety, phobia, and depression remains an important topic for future research [86–88].

More generally, this pattern of maturation illustrates how segregation of local circuits facilitates the development of mature large-scale functional circuits capable of differentially mapping input and output streams. A prediction based on these results is that the development of large-scale functional circuits associated with other brain regions will follow a similar principle, with major consequences for typical and atypical development of specialized functional subdivisions within both subcortical and neocortical structures.

Linking functional hyper- and hypoconnectivity with the physiological basis of neurodevelopmental disorders

One approach to examining common and divergent networks targeted by individual neurodevelopmental disorders is to examine the connectivity of brain regions whose function is closely associated with a disorder's behavioral impairment [89,90]. Although the pattern of aberrations varies considerably with regions of interest and clinical phenotype, an important feature highlighted by recent studies is that neurodevelopmental disorders such as autism and attention deficit hyperactivity disorder involve a complex profile of hypo- as well as hyperconnectivity [58,91–94]. Surprisingly, even adjacent brain areas can differ in their profile of hyper- and hypoconnectivity, a pattern that is important for understanding the physiological basis of neurodevelopmental disorders. For example, within the posteromedial cortex, children with autism show hypoconnectivity of the precuneus and hyperconnectivity of the posterior cingulate cortex with target brain areas [92] (Figure 6A,B). Similarly, in children with attention deficit hyperactivity disorder, the substantia nigra and ventral tegmental area show enhanced connectivity within limbic reward-motivation regions and decreased connectivity with regions in the default mode and dorsal attention networks [58]. The physiological mechanisms underlying functional hyper- and hypoconnectivity in neurodevelopmental disorders are at present poorly understood, but such heterogeneity may arise from an interplay between local circuit properties and differential patterns of anatomical connections; that is the 'connectional fingerprint' that distinguishes the function of one cortical area from another [95].

Local circuit abnormalities can contribute to abnormal signaling and temporal interactions between brain regions even in the presence of normal structural connectivity and computational models have provided insights into how pathology at the level of intrinsic node-level properties can alter network function [96]. Similar mechanisms are likely to underlie the heterogeneous pattern of brain connectivity in atypical development, because local circuit abnormalities are a prominent feature of many neurodevelopmental disorders [97,98]. Neurophysiological studies have revealed that excitatory and inhibitory synaptic plasticity and synaptogenesis are impaired in many neurodevelopmental disorders [99,100]. In particular, alterations in the expression of excitatory and inhibitory neurotransmitters play a major role in sculpting local circuit properties [101]. This in turn is likely to impact the development of segregated and specialized large-scale functional circuits, as described in the previous section. Consistent with this view, one recent study found that global functional hyperconnectivity between regions is associated with high-amplitude, low- fluctuations within these regions [93]. Neuronal migration deficits can also alter local circuit properties. In autism, for example, posterior cingulate cortical cytoarchitecture is characterized by irregularly distributed neurons, poorly demarcated cortical layers IV and V, and the presence of ectopic white matter neurons [102]. Neuroanatomical irregularities in this same region have also been identified in children with autism using multivoxel pattern analysis of gray matter volume measured with structural MRI [12] (Figure 6D). For highly connected hub regions, such as the posterior cingulate cortex and precuneus [103], these localized aberrations can greatly influence signal propagation and functional connectivity with many anatomically connected regions, causing significant deficits in social cognition and behavior (Figure 6C).

A general developmental principle suggested by these observations is that the fluctuating excitatory–inhibitory balance over development not only impacts local circuit excitability but also sculpts large-scale brain connectivity [104–106]. How this complex pattern of intrinsic connectivity influences the saliency of sensory inputs and mental processes over development is an important topic for future research. An important methodological issue here is that because the fMRI signal is blind to excitatory and inhibitory processes in local circuits [107], complementary approaches using animal models [97,105] and computational methods [96] will be needed to better understand the complex pattern of hyper- and hypoconnectivity that characterize typical and atypical development of functional brain networks.

Concluding remarks

Understanding the development of human brain organization is critical for gaining insight into the function of the adult brain and for characterizing the biological basis of cognitive disorders in which normal developmental processes are disrupted. This review has surveyed how complementary methods for probing typical and atypical functional connectivity are providing novel and unique insights into fundamental aspects of brain and cognitive

associated ASD hyperconnected target regions were found to be predictive of social impairments. No significant relationships were observed in the RSC or precuneus (PreC). **(D)** The PCC is a locus of structural abnormalities in ASD. Multivoxel patterns in PCC gray matter distinguish children with ASD from typically developing children (TDC) with an accuracy of 92%. Aberrations were also observed in the medial prefrontal cortex (MPFC) node of the default mode network (classification accuracy 88%). Abbreviations: aLTC, anterolateral temporal cortex; ERc, entorhinal cortex; LG, lingual gyrus; PHG, parahippocampal gyrus; pInsula, posterior insular cortex; PRc, perirhinal cortex; pSTS, posterior superior temporal sulcus; TempP, temporal pole. Adapted from [12,92].

development. It has highlighted several key principles governing the development of functional brain systems that are emerging from recent studies (Box 1). First, as evidenced by graph-theoretical studies of whole-brain connectivity, building on an anatomical backbone that is mature by the age of 2, key topological features of global functional brain architecture are mature by age 8. However, large-scale functional brain connectivity continues to undergo significant restructuring for many more years, leading to a more hierarchical organization and the formation of hubs in heteromodal cortex. Second, development is characterized by increased functional segregation and integration, with a shift from stronger short-range connections in children to stronger long-range connections in adults. This pattern is observed at multiple levels, including global architecture, functional systems, and individual nuclei with distinct cytoarchitectonic features. Third, the changing landscape of subcortical–cortical connectivity is a major hallmark of brain development. An important locus of developmental changes in connectivity is the basal ganglia, which are important for reward- and incentive-based learning and habit formation, processes that undergo significant changes in childhood and adolescence. Aberrant development of subcortical–cortical connectivity is also implicated in several major neurodevelopmental disorders including autism and attention deficit hyperactivity disorder. Fourth, the dynamic process of over-connectivity followed by pruning, which rewires connections at the neuronal level, also operates at the systems level, helping to reconfigure and rebalance connectivity in the developing brain. Fifth, functional connectivity within distinct and independent brain systems undergoes significant reconfiguration with development [36,37]. The anterior insula and SN are loci of weak signaling and vulnerability in the developing brain and are likely to be a major source of the deficiencies in saliency assignment and goal-directed behavior that characterize many developmental psychopathologies. Sixth, changes in local circuit properties and the relative balance of excitation and inhibition in local circuits may play a key role in altering global brain connectivity in neurodevelopmental disorders. It is proposed that changes in local circuit properties arising from synaptic pruning and alterations in excitatory–inhibitory balance will emerge as a key physiological mechanism underlying aberrant brain connectivity in developmental psychopathology.

The study of functional brain network development is still in its infancy. Significant methodological and scientific challenges remain to be addressed. From a methodological viewpoint, increasing sample size and statistical power, replication, studies of awake infants and children under 6 years, longitudinal modeling of growth trajectories, and devising techniques for assessing and removing physiological and non-physiological artifacts on brain connectivity remain priorities for the future.

A significant scientific challenge for future research is to understand how intrinsic functional networks constrain maturation of task- and context-specific modulation of brain activity, connectivity, and dynamic causal interactions between brain areas and how this in turn impacts cognitive development, learning, and skill acquisition (Box 2). The limited progress made in this direction, mainly in the context of attention and cognitive control networks [45,71], suggests that intrinsic functional networks impose tight constraints on information processing in the developing brain. Further elaboration of the principles of functional network development highlighted here may contribute to a deeper understanding of cognitive development, the ontological basis of normal adult brain organization and cognition, and the contributions of aberrant connectivity in specific pathways to phenotypic features of individual neurodevelopmental disorders. In this context, it is noteworthy that functional connectivity profiles incorporating hyper- and hypoconnectivity are beginning to yield sensitive and specific systems-level biomarkers of individual neurodevelopmental disorders. It is hoped that progress in these areas will lead to improvements in the early identification, classification, and treatment of neurodevelopmental disorders that afflict 10–15% of children worldwide.

Box 2. Linking functional brain networks and cognitive development: outstanding questions

- How does the maturation of white matter connectivity influence functional network development? Conversely, do changes in functional networks alter structural connectivity?
- How do developmental changes in intrinsic functional networks influence signaling, task-related connectivity and dynamic causal interactions between distributed brain areas?
- How do developmental changes in intrinsic functional networks influence the emergence of cognitive control and higher-order cognition?
- How does learning and academic skill development alter functional brain networks?
- Are there critical periods for plasticity in individual functional brain networks?
- How do changes in brain connectivity influence learning, reward seeking, cognitive control, and motivational behaviors in adolescence?
- How do intrinsic hyper- and hypoconnectivity alter signaling, task-related connectivity, and dynamic causal interactions in neurodevelopmental disorders? How do these aberrations in signaling contribute to cognitive dysfunction?
- What functional systems go awry in children with learning disabilities such as dyslexia and dyscalculia?
- How do aberrations in subcortical–cortical connectivity affect behavior, learning, and motivation in children with neurodevelopmental disorders such as autism and attention deficit hyperactivity disorder?
- How does aberrant development of amygdala circuits result in affective disorders such as anxiety, phobia, and depression?
- How does the changing balance of excitation and inhibition over development impact large-scale brain connectivity, cognition, and the course of developmental psychopathology? How do specific genetic and epigenetic factors influence these processes?
- How can aberrant functional connectivity measures be used to facilitate early detection and classification of developmental psychopathologies? Can functional brain network measures be used to develop predictive biomarkers of treatments in developmental psychopathology?

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