Translational research

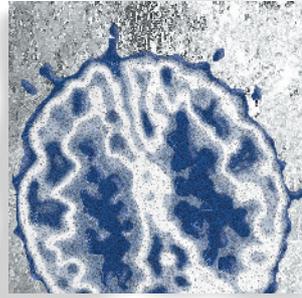# Connectome development and a novel extension to the neurodevelopmental model of schizophrenia

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The brain is the ultimate adaptive system, a complex network organized across multiple levels of spatial and temporal resolution that is sculpted over several decades via its interactions with the environment. This review sets out to examine how fundamental biological processes in early and late neurodevelopment, in interaction with environmental inputs, guide the formation of the brain's network and its ongoing reorganization throughout the course of development. Moreover, we explore how disruptions in these processes could lead to abnormal brain network architecture and organization and thereby give rise to schizophrenia. Arguing that the neurodevelopmental trajectory leading up to the manifestation of psychosis may best be understood from the sequential trajectory of connectome formation and maturation, we propose a novel extension to the neurodevelopmental model of the illness that posits that schizophrenia is a disorder of connectome development.

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Introduction

Human brain development involves a protracted sequence of events that starts in utero and extends into adulthood. During this time, the brain develops from a simple tubular structure to arguably the most complex system in biology; an intricately folded organ comprising a vast network of interconnected neurons known as the human connectome.[1] The connectome is sculpted over many years by genetically mediated processes and environmental inputs that exert an especially potent influence over the developing brain network during circuit-specific windows of developmental plasticity.[2,3] Abnormalities at any stage of this process–from the initial formation of the brain's network to its ongoing reorganization over the course of development–may underlie the evolution of neurodevelopmental disorders such as schizophrenia.[4,5]

Schizophrenia is a psychiatric disorder that manifests early in life and derails social, cognitive, and academic development. The first psychotic episode marks the formal onset of the illness, but converging evidence suggests that psychosis is a relatively late stage in illness development.[6,7] The first episode is typically preceded by a prodromal phase characterized by subthreshold psychotic symptoms, social withdrawal, cognitive dif-

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ficulties, and functional decline.[8,9] Preceding even this phase, children that will develop schizophrenia later in life have been noted to show subtle and nonspecific deviations from normal neuromotor, language, and socioemotional development.[10,11] The slow progression from early risk markers to the first psychotic episode represents both an extended window of vulnerability for schizophrenia and an opportunity for preventive or therapeutic intervention.[6]

This review examines connectome development in relation to the neurodevelopmental trajectory of schizophrenia. Following an overview of key features of brain network architecture, the first section of our review focuses on connectome formation and examines how fundamental properties of connectome organization may stem from biological processes in early brain development. The second section addresses mechanisms driving connectome maturation in childhood and adolescence. In the third section, we discuss connectome maldevelopment, and ask how this could give rise

to the neurodevelopmental trajectory of schizophrenia. Drawing from developmental neurobiology, neuroimaging, and brain network analysis, we put forward a novel extension to the neurodevelopmental model of schizophrenia. Arguing that schizophrenia is ultimately a disorder of connectome development, we propose that the sequential trajectory in which the illness develops may best be understood from the neurodevelopmental mechanisms guiding connectome formation and maturation.

Connectome architecture: key features

Graph theoretical analyses of brain connectivity data have demonstrated a number of key organizational properties of the connectome (for review, see ref 1). One central feature of brain network architecture is that it combines a high level of clustering with short average path length (*Figure 1A, B*). In other words, most connections link nearby neighboring neurons or neuro-
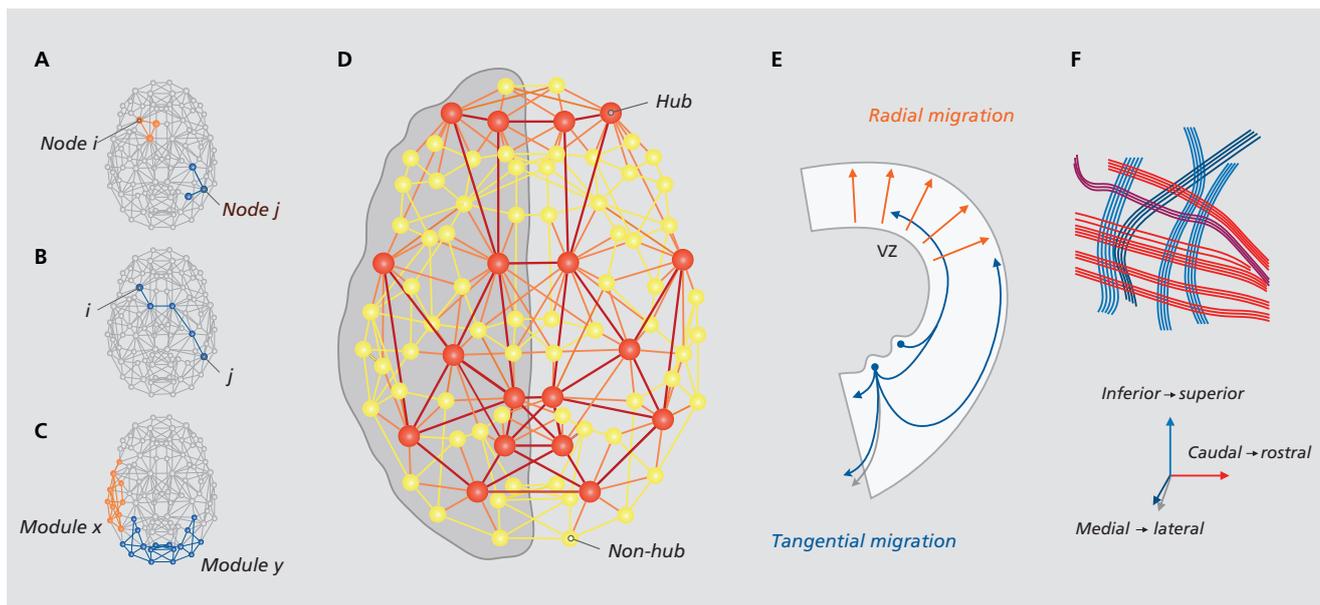

Figure 1. Connectome organization and formation. (**A**) The neighbors of node i are mutually connected, reflecting local clustering. In contrast, the neighbors of node j are not connected. A network with many triangular motifs (in orange) is highly clustered. (**B**) The shortest path from node i to node j is four steps. A network's average path length is the average number of steps along the shortest path between each node pair. Lower path length is consistent with a more efficient network. (**C**) shows connectome modules, with module x reflecting a left lateralized language module, and y a posterior visual module. (**D**) The brain's network contains hubs that are tightly interconnected into a rich club system (in red). (**E**) illustrates the two main forms of neuronal translocation: radial and tangential migration (VZ = Ventricular Zone). (**F**) depicts the potential grid-like microstructure of the brain's fiber pathways consistent with three primordial gradients of early embryogenesis.
(F) reproduced from ref 26. Wedeen VJ, Rosene DL, Wang R, et al. The geometric structure of the brain fiber pathways. *Science*. 2012;337:1628-1634. Copyright © Amercian Association for the Advancement of Science, 2012

nal populations, while a small number of long-distance connections make it easy to traverse the whole network in just a few steps. In addition to this "small-world" topology, the connectome has a modular organization, meaning that it can be decomposed into modules or communities (*Figure 1C*). Modules are thought to allow for specialized processing by limiting interference from brain regions processing other types of information.[12] Another characteristic feature of connectome topology is that it contains a small subset of brain regions with a disproportionately high level of connectivity. These highly connected "hub" regions (*Figure 1D)* have been identified across the heteromodal association cortex.[13] Hubs are especially tightly connected to other hubs, forming a "rich club" system that spans different modules (*Figure 1D*).[14,15] This feature of connectome organization may thus enable tasks requiring the collaboration of multiple specialized systems such as the integration of multisensory information or higher-order cognitive tasks.

Connectome formation

The establishment of these key features of connectome organization – ie, high-clustering, short path length, a modular organization, and the existence of highly connected hubs – may depend on fundamental processes in early neurodevelopment.

Clustering and path length

Early in prenatal life, neuronal precursor cells migrate into the cortical plate by one of two main forms of neuronal migration: radial migration and tangential migration (*Figure 1E*).[16,17] Radially migrating neurons move towards the pial surface of the cortex,[18] while tangential migration occurs in a parallel direction, allowing neurons from distant origins to intermingle in a common destination.[19,20] To connect to other neurons, neurons extend axons that navigate the developing brain, guided by molecules emitted by target cells or intermediate "guidepost" cells that serve as stepping stones along axonal trajectories.[21,22] Radial migration contributes to this process by providing patterning information that guides the appropriate arrangement of axon guidance cues, while tangential migration results in the formation of "permissive corridors," which are used by growing axons to bypass regions that

they could otherwise not traverse.[20] The emergence of high local clustering and short global path length in the brain's network may relate to these processes. As radial migration is the primary form of neuronal translocation, axons connect primarily to nearby neurons of similar origins, thereby promoting local clustering. Tangential migration is less frequent, and may thus drive the formation of a smaller number of long-distance connections between spatially distributed neuronal populations as a result of parallel migration patterns and permissive corridor formation. As cross-level studies of brain connectivity indicate that microscale architectonic features of a brain region relate to its network profile on the macroscale[23] the resulting connectivity patterns on the cellular scale may translate into concurrent patterns of connectome wiring on the whole-brain level.

Modular topology

The formation of modules of spatially distributed neuronal populations or brain regions may also relate to fundamental neurodevelopmental processes. The cortex is a patchwork of anatomically and functionally distinct regions, but these areas originate from a single neuroepithelial sheath through gradients in extracellular signals and transcription factors that operate across the field of cortical stem cells.[24] These stem cells use the spatial information encoded by gene expression gradients together with temporal information to generate differentially patterned neuronal progeny at different times in development.[24] Considering findings in *Drosophila* that neurons within the same module tend to be born around the same time,[25] differentially patterned generations of neurons may contribute to the formation of different brain network modules at different times in human brain development. There may be an additional mechanism by which primordial gradients could contribute to module formation, as these gradients are also thought to contribute to pathway formation in the brain. Indeed, recent diffusion spectrum magnetic resonance imaging (MRI) findings indicate that cerebral fiber pathways form a highly curved three-dimensional grid continuous with the three principal axes of development (*Figure 1F*).[26] This grid-like connectivity structure may serve as a scaffold for early functional collaboration in the brain and only develop into a more modular system over time in order to tune brain wiring

in accordance with functional communication patterns. A synthesis of these mechanisms may also be in place, with the cortex itself having an early modular organization conferred by cortical stem cells, and the early "proto-network" refining into a modular system with ongoing development.

Hub and rich club organization

Insights into potential mechanisms supporting hub formation in brain development come from the field of brain evolution. Specifically, studies on the origins of evolutionarily recent additions to the brain suggest that new cortical areas evolved from older regions via a process of "descent with modification." This implies that as a new area develops from an evolutionary older region, it inherits a large degree of the parent structure's design and organization.[27] If something similar occurs in ontogenetic neurodevelopment–ie, that later-developing brain regions develop via separation from earlier developing areas–this could mean that late-developing regions largely inherit connectivity patterns of earlier developing areas.[28] Such a mechanism would give rise to increasingly well-connected regions with ongoing development and may thus explain the hub-role of late-developing heteromodal regions. This hypothesis fits with observations that both in evolution and in brain development, expansion is non-uniform across the cortex. Prefrontal, parietal, and temporal association cortices, which house the brain's most highly connected hubs, expand about twice as much as, for example, primary visual cortex.[29]

A competing theory on hub formation from the field of network science is the preferential attachment or "rich-gets-richer" hypothesis.[30] This theory states that newly developing nodes in a network preferentially attach to nodes that already have high levels of connectivity. In terms of connectome development, this implies that early developing neurons and cortical regions would tend to accumulate more connections and thus become hubs. Indeed, such a mechanism has been shown for the 302-neuron nervous system of *C. elegans*,[31] but whether this contributes to hub formation in the human brain is currently unknown. If a similar mechanism is indeed in place, it could potentially explain the hub-role of early developing regions such as hippocampus and insula[14] in lieu of the mechanism described above.

Connectome maturation

Neuroimaging studies in infants suggest that the gross connectivity and organization of the structural connectome is largely established by the time of term birth.[32,33] The neonatal cortex displays an adult-like gyrification pattern, major connection pathways are in place, and the connectome shows many of the fundamental properties characterizing the adult connectome, including a small-world, modular topology with hubs and a central rich club system.[34,35] Despite this adult-like connectivity backbone, early postnatal neurodevelopment is known to involve a process of exuberant development, with an initial overproduction of connections that is gradually pruned back into a sparser, more efficient connectivity pattern[36–39] and with ongoing changes in the diameter and myelination of axonal connections underlying wide-spread changes in structural connectivity beyond the early postnatal phase.[39,40]

Molecular mechanisms

Developmental changes in brain connectivity and network organization are shaped by a combination of genes, environment, and their interaction. The extent to which experience–in the broadest sense, including sensory information, social interaction, and exposure to stress–is able to shape brain circuits changes greatly across the lifespan.[3] There are a number of highly regulated intervals known as critical periods, during which specific neural systems are intensely attuned to the outside world. A comprehensive review on critical periods[41] states that sensitive periods for seeing, hearing, speech production, and higher cognitive functions have been documented in developing children.[42] However, as the authors note, "the best understood critical periods are those controlling specific attributes of primary sensory modalities in animals, such as the representation of different tones in auditory cortex or of left versus right eye inputs in the visual cortex."[41] During these windows of high developmental plasticity, incoming information serves as a cue to establish appropriate patterns of connections, strengthening synapses between neurons that fire together and weakening those between neurons with "out-of-sync" firing patterns.[43] Over time, this process results in a connectivity pattern that is optimally attuned to the surroundings in which we grow up.

The field of critical window biology is starting to offer a glimpse into the molecular machinery governing this process.[2,44] Early in life, neurotransmission is mainly excitatory, but as the brain matures, inhibitory transmission strengthens. When this inhibition reaches a certain threshold, it triggers a period of heightened developmental plasticity.[45] Crucial to this process are a subset of γ-aminobutyric acid (GABA)-ergic inhibitory interneurons known as parvalbumin (PV) positive large basket cells. These cells are thought to quiet down haphazardly firing excitatory neurons and promote excitatory/inhibitory (E/I) balance, allowing the best neural representation to be selected from many inputs bombarding the maturing nervous system.[2] With ongoing development, the neural circuits that were sculpted by experience are stabilized by perineuronal nets, extracellular matrix structures that put a molecular brake on plasticity.[44] These processes have been noted to occur across increasingly more complex aspects of sensorimotor experience, suggesting a developmental sequence of critical periods from lower- to higher-order circuits.[46]

Systems-level findings

Developmental processes on the cellular and molecular level as referenced above may underlie findings of a systems-level reorganization of the connectome over the course of development. While the broad topology of the structural connectome appears to be largely established by the time of birth, the prominence of existing network features evolves throughout childhood and adolescence.[33] Recent findings from network analyses of diffusion-weighted MRI data indicate that from late childhood to early adulthood, the structural connectome becomes both more modular and more integrated.[47] This development is thought to stem from ongoing modular differentiation on one side and the strengthening of hub connections through the maturation of long-distance fiber pathways on the other *(Figure 2A)*.[47,48] Consistent with these findings, brain hubs become increasingly closely integrated and overall network efficiency goes up, while local clustering decreases with age from early childhood to young adulthood.[48–51]

Resting-state functional MRI (fMRI) studies are indicative of an immature functional organization of the connectome in infants. At this stage, the functional connectome is dominated by visual, auditory, and sensorimotor networks, consistent with an emphasis on

primary functions.[52,53] With age, higher-order networks develop and take on an increasingly central role in the brain's functional organization.[54,55] One of the most widely studied functional systems is the default-mode network (DMN), a set of regions in medial prefrontal and parietal cortex that is highly functionally connected during rest and that largely overlaps with the hubs of the structural connectome. DMN activity has been linked to self-referential processing, and its deactivation during goal-directed tasks is thought to be an important aspect of healthy DMN functioning. The extent to which the DMN is able to disengage from task-positive networks (TPN) subserving attention-demanding tasks goes up in childhood and adolescence, which may underlie improvements in cognitive control and working memory.[56] Moreover, network studies indicate changes in the modular organization of the functional connectome during development, with for example cingulo-opercular and frontoparietal networks evolving from one single network in childhood to the known separate systems in adulthood.[54,57,58]

Linking maturational mechanisms across levels of resolution

The link between neural circuit development on the molecular level and connectome maturation on the whole-brain scale is poorly understood, but findings from neurophysiological studies offer an intermediate model of brain circuit development that spans the two extremes of spatial and temporal resolution.[59] These studies indicate modifications in the synchrony and amplitude of neural oscillations across frequency bands (including γ-oscillations) during childhood and adolescence. With ongoing development, high-frequency oscillations increase and long-range synchronization–eg, between frontal and parietal circuits–strengthens, suggesting a reorganization of the functional connectome during the transition from adolescence to early adulthood.[60] Importantly, developmental changes in synchronous oscillations have been related to modifications in neurotransmitter systems and the interaction of excitatory glutamatergic and dopaminergic systems with inhibitory GABA-ergic interneurons.[61] This observation suggests that some of the molecular mechanism-controlling brain circuit maturation at the level of individual synapses during circuit-specific developmental windows are also important to the generation of high-

frequency oscillations. That play a crucial role in the activity-dependent self-organization of developing neural networks and large-scale functional reorganization of the brain network during late neurodevelopment.[62]

Connectome maldevelopment in schizophrenia

Studies of brain connectivity and network organization in schizophrenia have largely focused on adult patients with established illness (for review see ref 63). Well-replicated findings from structural connectome studies in-

clude increased path length and disruptions in brain hubs and the rich club system, reflecting a less efficient and less well-integrated network.[64] Among the most replicated functional findings are DMN abnormalities, including increased activity and connectivity within the DMN and weaker anti-correlations between DMN and TPNs reflecting reduced task-related DMN suppression.[65–67] The development of anti-correlations between self- and task-oriented networks may support the emergence of executive functions[68] and the failure of such maturation could lead to cognitive deficits in schizophrenia. More-
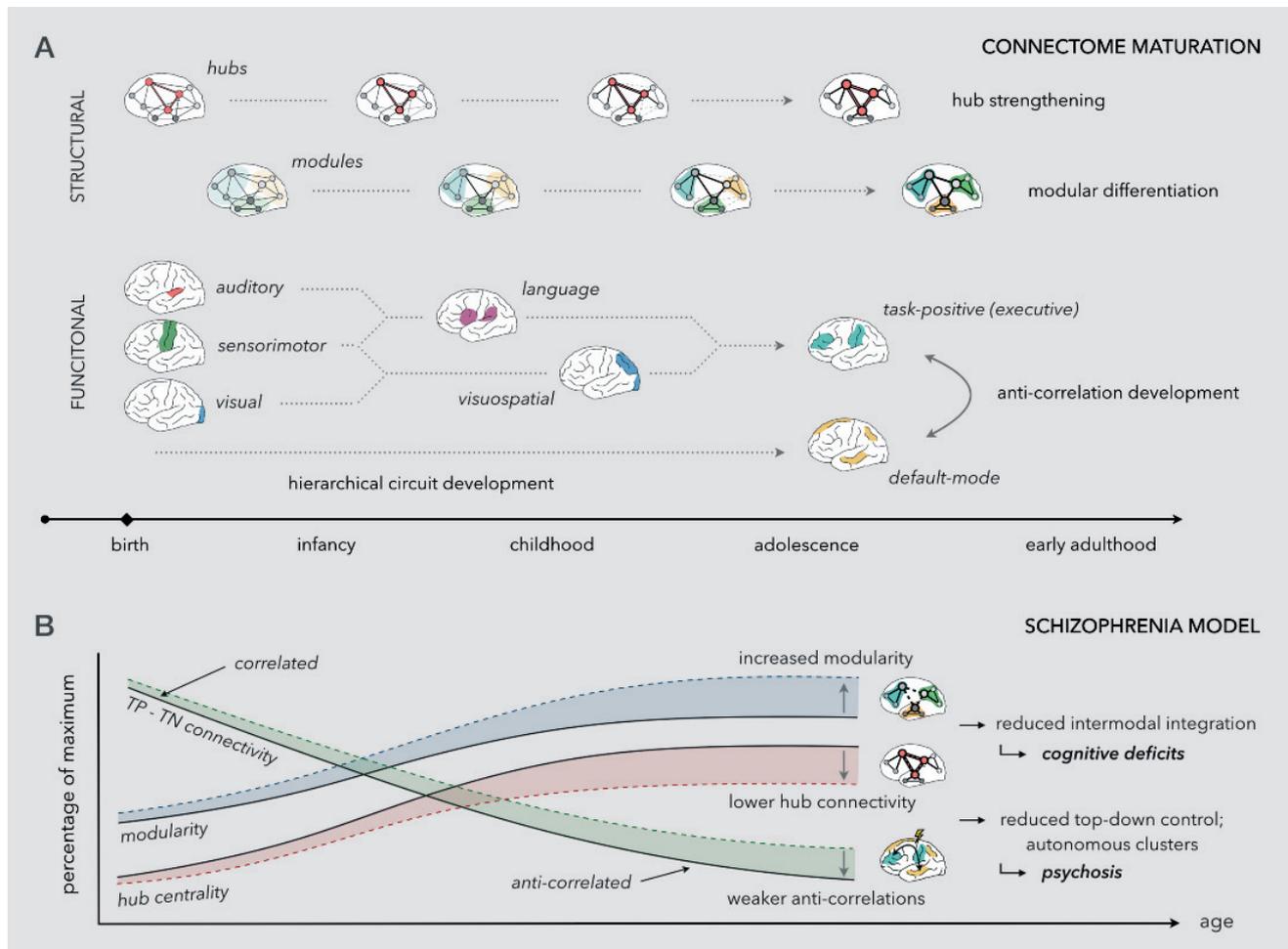

Figure 2. Connectome maturation and connectomic model of schizophrenia. (**A**) Structural and functional connectome maturation. The topology of the structural connectome is largely established at birth, but modular differentiation and the strengthening of hubs increase levels of modularity and integration. Functional circuits develop in hierarchical sequence; anti-correlations between task-positive and default-mode networks evolve. (**B**) Proposed connectomic model of schizophrenia. Reduced structural connectivity between hubs reduces inter-modular integration invoking cognitive deficits. Lower hub connectivity and weaker anti-correlations between task-positive (TP) and task-negative (TN) systems lead to reduced top-down control and autonomous 'runaway' activity of self-oriented (TN) networks giving rise to psychosis.

over, impaired control by late-developing task-positive networks over earlier developing circuits including DMN and primary sensory networks may cause them to function more autonomously,[69] leading to internal pre-occupation, psychotic symptoms, and social withdrawal (*Figure 2B*). Longitudinal connectomic studies in young individuals at risk for psychotic disorders may shed light on this hypothesis. Abnormal task-related DMN dis-engagement may also reflect difficulties in dynamically switching between functional connectivity patterns as a result of an affected central rich club structure, which fits observations in schizophrenia patients and offspring that rich club disruptions are accompanied by increased coherence between structural and functional connectivity.[64,70] An important open question is when, in the course of brain development, connectome disruptions arise and how this relates to the timeline of illness development in schizophrenia. In the next paragraphs, we discuss three broad ways in which connectome maldevelopment and the neurodevelopmental trajectory of schizophrenia may be related.

Affected connectome formation

First, schizophrenia may stem from abnormalities in the initial formation of the connectome leading to early deficits in brain network organization that become apparent in a sequential manner as affected functional systems come "online" throughout the course of development. Indeed, family and birth cohort studies indicate early developmental impairments in children that go on to develop schizophrenia, including delays in reaching developmental milestones such as the ability to sit, stand, and walk, and delays in speech and receptive language development (for review see ref 10). Developmental impairments in at-risk infants are consistent with an early deviation from normative connectome development.[10] In this model, scaffolds of brain circuits that will come to support higher-order cognitive functions may already be affected, but this may only become apparent when socio-emotional and cognitive functions develop. Alternatively, if cognitive functions are understood to develop in a hierarchical manner (*Box 1*), it could be that higher-order "proto-circuits" are unaffected at this stage and that deficits in early-developing circuits in and of themselves are the foundation for abnormalities in higher-order circuits. In addition to developmental delays, biological support for early connectome malformation includes neuro-pathological findings of a maldistribution of interstitial neurons in subcortical white matter and neuroimaging findings of reduced intracranial volume and abnormal cortical gyrification in schizophrenia patients.[71–73] These findings are all suggestive of disturbances in prenatal brain development, including abnormal neuronal migration and early connectivity deficits that may contribute to abnormal connectome formation.

Understanding neurodevelopment as a hierarchical process implies that basic skills and associated low-level circuits need to be established before more advanced functions can evolve. Before learning to speak, a child needs to be able to hear and produce sounds. This allows him or her to imitate caregivers, producing nonspecific babble at first, then speech-like vocalizations, and finally recognizable words. Next, the child learns to interpret and attach meaning to words and combinations of words through interactions with caregivers, thereby developing vocabulary and syntax. Through this process, children acquire a code or system of rules, that allows them to capture abstract representations of objects and events in the outside world and communicate ideas. As a result, language in itself is a building block for the development of higher-order functions. In his book *Seeing Voices: A Journey into the World of the Deaf*, Oliver Sacks argues that deafness is the most preventable cause of mental retardation. If deaf children do not learn sign language–as was common until the 18th century–other nonlingual cognitive abilities typically also fail to develop properly.[74] Due to the timing of developmental windows for various skills, these deficits typically cannot be corrected when sign language is learned at a later age. This suggests that development not only follows a hierarchical sequential pattern for specific functional domains (eg, with simple motor functions developing before more complex motor behaviors), but that this hierarchy extends across domains, with lower-level sensorimotor skills forming the building blocks for the development of higher-order cognition.

Box 1. Hierarchical brain and cognitive development.

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Abnormal connectome maturation

Second, schizophrenia development may stem from a disruption in the neurobiological processes governing the maturation of functionally specialized brain circuits, giving rise to cognitive and behavioral impairments that show up in a sequential manner consistent with the timing of their respective developmental windows. An important pathophysiological model for schizophrenia, of *N*-methyl-D-aspartate receptor (NMDAR) hypofunction, could fit in with such a mechanism.[75] NMDAR hypofunction has been hypothesized to disrupt PV-interneuron mediated inhibition, which is important to the opening and appropriate timing of developmental windows in infancy and childhood and the generation of high-frequency oscillations which are important to large-scale functional reorganization of the connectome during the transition from adolescence to early adulthood. NMDAR-hypofunction has been hypothesized to occur initially in cortical PV-cells during early postnatal development, with resulting maturational deficits causing GABAergic disinhibition and glutamate spillover, which may in turn elicit the dopamine dysregulation associated with psychotic development.[75–77] This hypothesis may not explain all molecular and pathological findings in schizophrenia, but it offers some interesting conceptual advantages. For example, given the role of PV-interneurons in quieting down excitatory activity to allow the brain to focus on external input, abnormalities in PV-cell-mediated inhibitory control over pyramidal cells[78] could result in neural circuits that remain overly attuned to internally generated activity. Such a mechanism could be consistent with findings that schizophrenia patients and relatives show reduced DMN disengagement during cognitive tasks[65,66] and ties in with theories relating psychotic symptoms to internally generated cues that are misinterpreted as external signals. In all, schizophrenia may involve abnormalities in the biological mechanisms governing critical window development, leading to abnormal timing (ie, premature or delayed onset), duration, or progression of critical periods and contribute to brain circuits that remain overly attuned to internal processing, and thereby predispose to psychosis development.[79]

Abnormal connectome integration

Third, schizophrenia development may relate to a failure to develop adequate integration between functional brain systems with ongoing development, due to deficits in anatomical connections linking connectome modules and associated abnormalities in synchronized oscillations. While cognitive and behavioral impairments in schizophrenia reach back as far as early childhood,[10] the characteristic expression of (subthreshold) psychotic symptoms typically occurs in the period from adolescence to early adulthood; a phase that is characterized by the integration of early- and late-maturing functional systems and in which precise temporal coding between large-scale brain networks needs to be established.[59,80] Although these processes are part of normal connectome maturation, we discuss them separately here to highlight the possibility that individual functional circuits develop normally, but that the integration between neural systems fails to develop properly. Such a mechanism may explain observations that hub-to-hub connections (ie, cross-linking modules) appear disproportionately affected in schizophrenia patients and at-risk relatives[64,70,81] and is in line with hypothesized abnormalities in corollary discharge mechanisms that ought to inform the brain of self-generated activity, as possibly underlying the generation of psychotic phenomena such as auditory hallucinations and delusions of control.[82]

Conclusion

We have proposed a novel extension to the neurodevelopmental model of schizophrenia, which asserts that abnormal connectome formation and maturation, including the establishment of adequate intermodal integration, is central to the etiology of the illness. We discussed three broad ways in which connectome maldevelopment may give rise to the typical neurodevelopmental trajectory of schizophrenia. These mechanisms need not be mutually exclusive and may not be the same for individual patients, but abnormal anatomical architecture and functional organization of the connectome may be a final common pathway to the manifestation of schizophrenia symptoms. Our model leads to a set of testable hypotheses that could be addressed in different experimental approaches, including connectivity analyses in vitro using induced pluripotent stem cells or brain organoids, experimental perturbations of the molecular mechanisms guiding critical window biology in animal models, or longitudinal connectomic imaging studies of developing children at risk for schizophrenia.[83,84] These studies may help elucidate how and when risk factors for schizo-

phrenia dysregulate connectome development. As such, these investigations may clarify the timing and sequence of connectomic abnormalities leading up to the manifestation of psychosis, and thereby promote prognostic, preventative, and therapeutic advances for schizophrenia. ❏

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