Emergence of system roles in normative neurodevelopment

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Adult human cognition is supported by systems of brain regions, or modules, that are functionally coherent at rest and collectively activated by distinct task requirements. However, an understanding of how the formation of these modules supports evolving cognitive capabilities has not been delineated. Here, we quantify the formation of network modules in a sample of 780 youth (aged 8–22 y) who were studied as part of the Philadelphia Neurodevelopmental Cohort. We demonstrate that the brain's functional network organization changes in youth through a process of modular evolution that is governed by the specific cognitive roles of each system, as defined by the balance of within- vs. between-module connectivity. Moreover, individual variability in these roles is correlated with cognitive performance. Collectively, these results suggest that dynamic maturation of network modules in youth may be a critical driver for the development of cognition.

neurodevelopment | graph theory | network science | modularity | brain network

The human brain is composed of large-scale functional networks that are coherent at rest, forming identifiable modules that support specific cognitive functions (1–3). These modules include well-known subsystems, such as the default-mode, visual, motor, auditory, attention, salience, and cognitive control systems. Prior research has shown that this modular structure evolves considerably during development in youth (4, 5) and across the life span (6, 7). Network modularity, a measure of the segregation between modules, is high during young adulthood and decreases across the latter life span (6, 7). Other features of network reorganization accompany development (8), including a growing preference for interactions between hubs and nonhubs (9), and between regions separated by large physical distances (10).

Although prior research has explored such changes in gross network features, it remains unknown how the relationships between specific types of cognitive systems evolve during adolescent development. Ongoing developmental changes in connectivity between cognitive systems are suggested by known differences in how these systems are organized in the adult brain: Primary motor and sensory systems display a high degree of segregation with limited connections to other modules, whereas higher order cognitive systems have more between-module connectivity (1). Moreover, the disparate connectivity profiles of such systems may be critical for optimal cognitive functioning (11). Differentiation of specific network modules may thus support the burgeoning cognitive, emotional, and motor capabilities seen during adolescence (12). Furthermore, abnormalities in functional network organization are a ubiquitous finding in major neuropsychiatric conditions (11), which are increasingly considered disorders of neurodevelopment (13). Thus, a quantitative characterization of the modular maturation of functional networks in youth is critical to understanding the development of both normal and abnormal brain function.

Here, we tested the hypothesis that the brain's functional network organization changes in youth through a process of modular evolution that is governed by the specific cognitive roles of each system. Specifically, we predicted that the development of the functional organization of the brain is driven, in part, by changes in the balance of within- vs. between-module (henceforth "system") connectivity. To address this hypothesis, we quantify the formation of putative functional network systems (1) in a sample of 780 youth (aged 8–22 y) who were studied as part of the Philadelphia Neurodevelopmental Cohort. Critically, we adapt a previously defined approach to role determinations used in other complex systems, such as airline transportation networks and the Internet (14). This approach allows network systems roles to be defined based on their position in a 2D plane mapped out by their within- and between-system connectivity. In this framework, modules with high between-system connectivity are designated connector systems, whereas modules with low between-system connectivity are provincial systems. Similarly, modules with high within-system connectivity are cohesive systems, whereas modules with low within-system connectivity are incohesive systems. Using this approach, we define intuitive network roles for network modules in the early life span and delineate changes in these roles over development.

As described below, our results demonstrate that network modules, initially less disparately sized and highly integrated, become increasingly differentiated in a manner that matches the organization of the adult brain. Moreover, we observe that the

Significance

The human brain is a complex system displaying intricate, dynamic functions. In a multidisciplinary effort, the recent application of tools from network science to characterize the interconnected nature of the brain has enabled a tremendous advance in our understanding of cognition. Here, we develop and apply an extension of these tools to define and characterize the role of cognitive systems in the larger scale brain network, and to map how these roles change during adolescent development, providing an important context for understanding psychopathology. Our results are also consistent with the hypothesis that individual variation in network configuration implies differential vulnerability to cognitive abilities or deficits.

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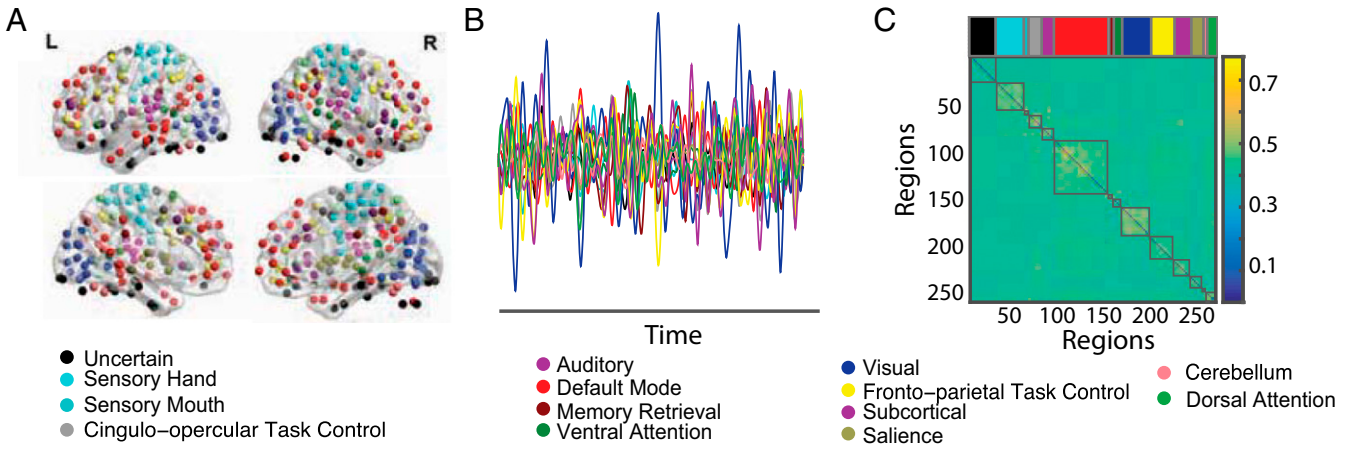

Fig. 1. Construction of functional brain networks. (*A*) We examined $N = 264$ cortical and subcortical regions of interest previously defined by Power et al. (1). L, left; R, right. (*B*) We calculated the pairwise coherence r_{ij} between the wavelet scale two coefficients of mean regional blood oxygenation level-dependent signals. (*C*) We represented the set of pairwise coherence values in an $N \times N$ adjacency matrix **A** whose elements $A_{ij} = r_{ij}$. This procedure was applied to each subject.

within- vs. between-network connectivity profile of each network module falls into one of four categories that correspond to their functional role in the brain: Roles are defined as functional hub (connectors) vs. nonhub (provincial) systems and as functionally cohesive vs. incohesive systems. Finally, we find that individual variability in the between-network connectivity of the sensorimotor and default mode networks is correlated with cognitive performance. Collectively, these results suggest that dynamic maturation of network modules in youth may be a critical driver for the development of cognition and provides an important context for understanding psychopathology.

Results

Using resting-state functional MRI (fMRI) data acquired from 780 children aged 8–22 y, we estimated functional connectivity (network edges) between 264 functionally defined regions of interest (network nodes) across cortical, subcortical, and cerebellar structures (Fig. 1). We identified network communities or modules using a modularity-based community detection algorithm (*Materials and Methods*); this technique provided a partition of brain regions into communities (putative cognitive modules) for each subject in the cohort (Fig. 2*A*). We examined the network roles of four major system types, consistent with prior literature: higher order cognitive (dorsal attention, ventral attention, frontoparietal, cinguloopercular, salience, and memory), default mode network, sensorimotor (hand, mouth, auditory, and visual), and subcortical (cerebellum and basal ganglia).

Formation of Cognitive Systems During Development. If cognitive systems form during development, we hypothesized that network modules would change in anatomical extent, and hence community size (number of regions constituting the community). We therefore tested whether the communities identified in single subjects were similarly sized in young vs. older subjects (Fig. 2*B*). Younger subjects showed more similarly sized communities than older adults (Fig. 2*C*, *Upper*; the Pearson correlation coefficient between variance of community size and age was $r = 0.67$, $P = 0.032$ for binned data; consistent results in nonbinned data and smaller bins are

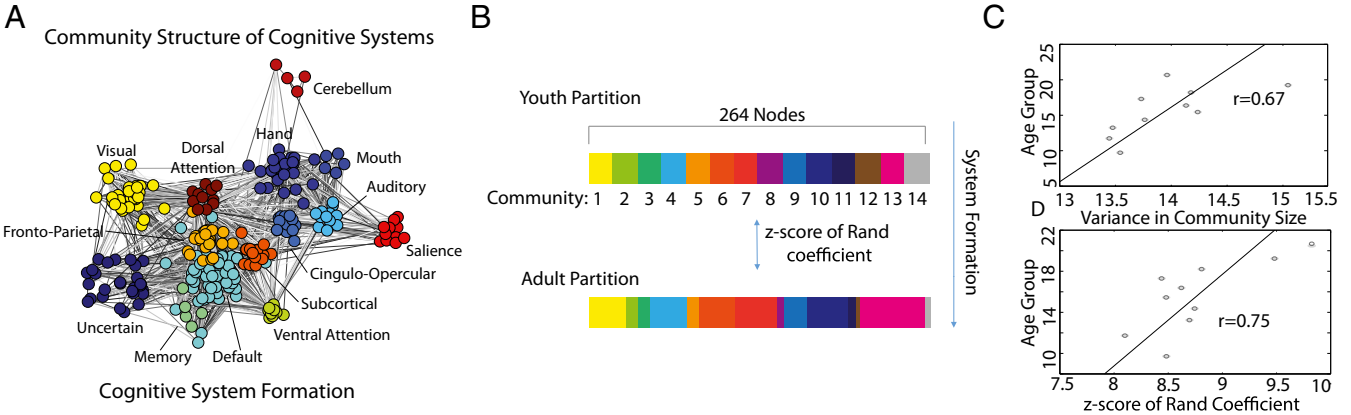

Fig. 2. Formation of cognitive systems. (*A*) We plot a representative average functional connectivity matrix from the adults in our sample (18 y or older) using a spring-embedding algorithm to illustrate the segregation of network communities, or putative cognitive systems. (*B*) We hypothesized that as systems form, initially similarly sized modules would differentiate in size and become more similar in constitution to 13 cognitive systems identified in a separate adult population (1). (*C*) Consistent with our hypothesis, variance in community size is lowest in the youngest subjects and highest in the oldest subjects: The Pearson correlation coefficient between variance of community size and age was $r = 0.67$, $P = 0.032$. Furthermore, the similarity between the adult partition of brain regions into cognitive systems and the subject-specific partition of brain regions into network communities is lowest in the youngest subjects and highest in the oldest subjects: The Pearson correlation coefficient between the *z*-score of the Rand coefficient (15) and age was $r = 0.75$, $P = 0.013$. In *C*, data from all individuals are averaged within 10 age-based deciles of 78 subjects each; results are robust to bin size (*SI Appendix*).

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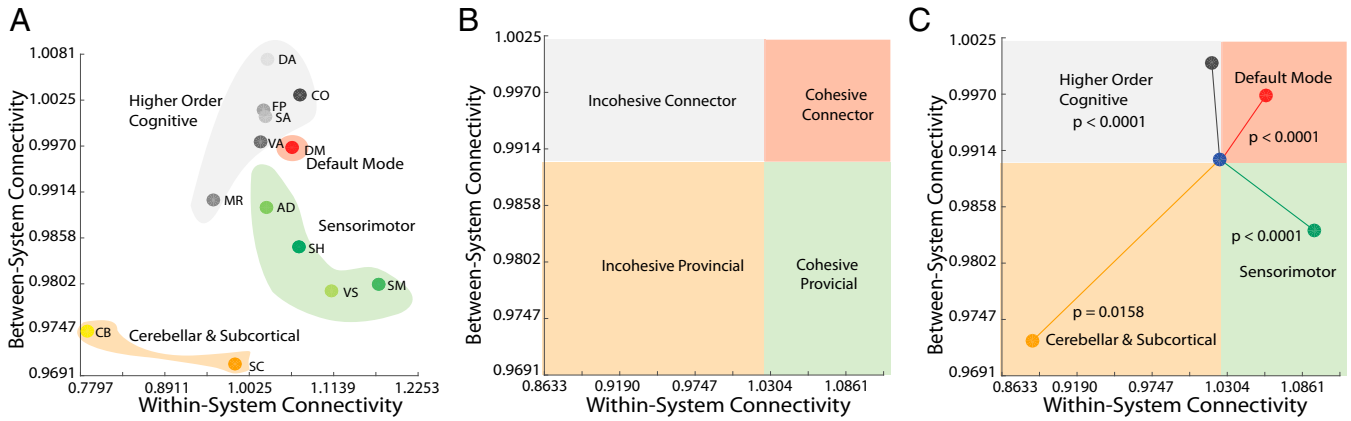

Fig. 3. Network roles of cognitive systems. (*A*) We compute the average within- and between-system connectivity over all subjects for 13 putative cognitive modules defined in a separate adult population (1). AD, auditory; CB, cerebellum; CO, cingulo-opercular; DA, dorsal attention; DM, default mode; FP, fronto-parietal; MR, memory; SA, salience; SC, subcortical; SH, sensorimotor hand; SM, sensorimotor mouth; VA, ventral attention; VS, visual. We highlight the following four types of systems using different color clouds: higher order cognitive (gray), default mode (red), sensorimotor (green), and cerebellum and subcortical (orange) systems. (*B*) We subdivide the 2D space mapped out by within- and between-system connectivity. We define systems whose within-system connectivity is greater/lesser than the average to be connector/provincial systems; we define systems whose between-system connectivity is greater/lesser than the average to be cohesive/incohesive systems. (*C*) Using a 2D permutation test (*Materials and Methods*), we show that the separation of the four types of systems into the four distinct network roles is not expected under the null hypothesis ($P < 0.016$).

provided in *SI Appendix*). These results are consistent with the notion that network modules are less well differentiated in early childhood, with each community being composed of a more similar number of nodes. In contrast, systems in later development are characterized by both large and small modules, suggesting a process of network differentiation whereby different systems grow or shrink according to evolving cognitive demands.

We next investigated how the community structure seen in children becomes more similar to the community structure seen in adults as development progresses. We use the *z*-score of the Rand coefficient (*Materials and Methods*) to estimate the similarity between each subject's partition of nodes into network communities and an adult partition of nodes into 13 cognitive systems, defined in a separate adult population by Power et al. (1) (Fig. 2*C*, *Lower*). The Pearson correlation coefficient between *z* and age was $r = 0.75$ ($P = 0.013$), indicating that as children age, network communities become more similar to the modules seen in adults. More generally, these results demonstrate that commonly described network modules dynamically emerge during adolescent development.

Network Reconfiguration Accompanying Module Formation. The network reconfiguration that we observe to accompany module formation in neurodevelopment could be driven by a change in the connectivity within or between modules. To clarify the nature of this reconfiguration, we therefore calculated the within-system connectivity (mean strength of the functional interactions within a community) and the between-system connectivity (mean strength of functional interactions between communities). We observed a global decrease in between-system connectivity during development (Pearson correlation coefficient between age and between-system connectivity: $r = -0.79$, $P = 0.0007$), suggesting a steady segregation of cognitive systems. No global relationship was observed between age and within-system connectivity ($r = 0.21$, $P = 0.46$).

Roles of Functional Modules in the Brain. Although the above results suggest that functional network structure matures predictably toward an adult configuration, they do not specify how the functional roles of specific systems change during adolescence. As a first step, we defined the average functional role for each system across all ages in our sample, drawing inspiration from procedures allowing the determination of modular roles in other complex systems (14). In this approach, the functional role of each module is mapped in a 2D space according to the within- and between-system connectivity. We separate this space into four quadrants; each quadrant represents a different network role, and the lines demarcating the boundaries of the quadrants are defined by the average within- and average between-system connectivity (Fig. 3). Qualitatively, one can initially observe that functional systems cluster together into four system types: Higher order cognitive systems (including cognitive control, salience, memory, and attention systems), sensorimotor systems, subcortical and cerebellar systems, and the default mode system each reside in a different quadrant, suggesting that they each play different roles within the larger scale brain network.

Both the default mode and higher order cognitive systems tend to have high between-system connectivity, indicating their roles as connector systems. The strong ties between these systems and the rest of the brain could form a mechanistic explanation for their utility in myriad complex cognitive processes. However, the default mode system and other higher order cognitive systems can be discriminated from one another based on their within-system connectivity. The default mode, a cohesive connector, shows high within-system connectivity, indicating that all brain regions within this system display similar activity profiles, together forming a cohesive driver of intrinsic brain function. In contrast, higher order cognitive systems, incohesive connectors, show weak within-system connectivity, indicating that brain regions in these systems show inherently dissimilar activity profiles, potentially enabling a complex set of functional drivers.

In contrast to the higher order cognitive systems that act as connectors, the sensorimotor, subcortical, and cerebellar systems tend to have low between-system connectivity, indicating their roles as provincial systems. The weak ties between these systems and the rest of the brain indicate that they display distinct profiles of neurophysiological activity, and may perform more segregated functions. However, these systems can be differentiated based on their within-system connectivity. Sensorimotor systems show high within-system connectivity, forming cohesive provincial systems, whereas subcortical and cerebellar systems show weak within-system connectivity, forming incohesive provincial systems.

Although the location of each system provides a descriptive visualization of the relevant connectivity profile, it does not provide a quantitative statistical hypothesis test. To do so, we developed a 2D permutation test in which the assignment of brain regions to systems was permuted uniformly at random (*Materials and Methods*). This

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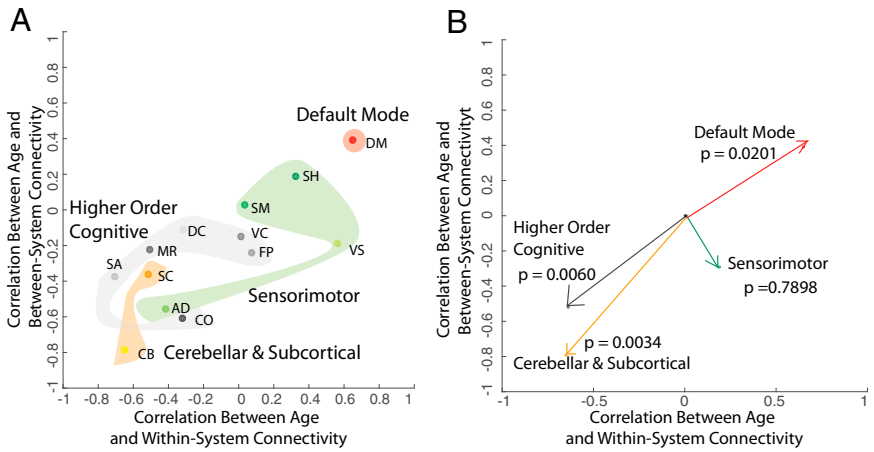

Fig. 4. Emergence of functional roles of cognitive systems during neurodevelopment. (*A*) We computed the correlation between age and average within- and between-system connectivity for 13 putative cognitive modules (same as in Fig. 3*A*) (1). We highlight the following four types of systems using different color clouds: higher order cognitive systems (gray), default mode network (red), sensory systems (green), and cerebellum and subcortical systems (orange). (*B*) Using a 2D permutation test (*Materials and Methods*), we show that the network role of the default mode, subcortical/cerebellar, and other higher order cognitive systems developed significantly ($P < 0.001$, uncorrected). In both panels, data from all individuals are averaged within 15 equisubject age bins (with each bin containing 52 subjects); results are robust to bin size (*SI Appendix*).

test allowed us to assess whether the separation of the four types of systems into the four distinct network roles was expected under the null hypothesis of no difference between system types. We observed that the distance of each system type from the origin was significantly greater than expected ($P < 0.018$ for each system type; Fig. 3*D*), indicating that each system type plays a statistically distinct role in the wider brain network.

Emergence of Module Roles During Development. After determining typical roles of each network module across all ages in our sample, we next investigated how these roles developed from childhood through young adulthood. For each cognitive system, we calculated the correlation between its within- or between-system connectivity and age, and we map these results into the 2D space defined by these correlations (Fig. 4*A*).

We observe that some system types grow in their developmental roles, whereas others decline (Fig. 4*B*). For example, the default mode network displays increasing within- and between-system connectivity, showing that its role as a cohesive connector grows with age. Subcortical and cerebellar systems display a decrease in both within- and between-system connectivity, indicating that their role as incohesive provincial systems also grows with age. In contrast, sensorimotor systems display an increase in between-system connectivity and a decrease in within-system connectivity, indicating that their role as cohesive provincial systems declines with age. Notably, higher order cognitive systems show differentiation in their developmental roles, rather than simple growth or declination. These systems display an age-related decrease in both within- and between-system connectivity, indicating that their role as incohesive systems grows with age, whereas their role as connector systems declines. Both axes of this cross-sectional trajectory are consistent with a growing functional diversity of both brain regions (leading to incohesion) and network modules (leading to decreasing integration).

As previously, we used a 2D permutation test to confirm the statistical validity of network role development. In the 2D space mapped out by the correlation between age and within- and between-system connectivity, we observed that the distance of three system types from the origin (representing no network role development) was significantly greater than expected ($P = 0.006$ for the higher order cognitive systems, $P = 0.0034$ for the subcortical and cerebellar systems, and $P = 0.02$ for the default mode system; Fig. 4*B*). The cross-sectional trajectory of the sensorimotor systems was not significant ($P = 0.7898$), indicating that the network roles of these systems did not develop significantly. These observations are supported by a separate line of analysis based on subject-level partitions into cognitive systems (*SI Appendix*). Interestingly, when separating the data by gender, we observe that males displayed significant development in the network role of the higher order cognitive systems, whereas females displayed significant development in the network role of the subcortical and cerebellar systems; permutation testing demonstrated trends for age by gender interactions, providing preliminary support for the presence of differential trajectories of network role development (*SI Appendix*).

Drivers of Module Maturation Relate to Cognitive Variation. Although within- and between-system connectivity provides quantitative measurements of network roles and their maturation in the entire population, it is unclear whether these measurements are sensitive to cognitive performance, which improves dramatically over the age ranges studied (12) and differs appreciably across individuals. We hypothesized that between-system connectivity could explain individual differences in cognitive development because it, unlike within-system connectivity, was significantly modulated by age ($r = -0.79$, $P = 0.0007$). We performed a linear regression using between-system connectivity of the four system types to predict composite scores of general cognitive functioning (*SI Appendix*), controlling for age (additional results in mediation models are provided in *SI Appendix*). We found that the between-system connectivity of the sensorimotor systems was negatively correlated with general cognitive performance ($r = -0.07$, $P = 0.04$) and that between-system connectivity of the default mode network was positively correlated with cognitive performance ($r = 0.08$, $P = 0.03$).

Discussion

We examined the emergence of cognitive systems in the patterns of intrinsic functional connectivity in a large cohort of 780 subjects aged 8–22 y. We demonstrate that cognitive systems become increasingly disparately sized, functionally segregated, and similar in constitution to systems observed in a separate adult population. These systems play diverse roles in the larger scale brain network and display distinct trajectories of these roles during development. Sensorimotor systems tend to be cohesive provincial systems, and become increasingly segregated from other systems during development. Higher order cognitive systems, including cognitive control, salience, memory, and attention systems, tend to be incohesive

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connector systems, and become increasingly segregated from other systems during development. Uniquely, the default mode system tends to be a cohesive connector system, and becomes both increasingly cohesive and increasingly associated with other systems during development. Finally, subcortical and cerebellar systems tend to be incohesive provincial systems, and become increasingly differentiated during development. These results complement previous studies in development (*SI Appendix*) by providing unique insights into the neurophysiological changes in network architecture that accompany the emergence of cognitive functions characteristic of adulthood, and provide critical baseline parameters against which to examine altered network neurodevelopment in psychiatric syndromes.

Network Roles and the Evolutionary Hierarchy. Mammalian brain evolution follows a structured trajectory (16). The cerebellum and subcortical structures are some of the earlier formations, followed by sensorimotor systems and then higher order cognitive functions, including language in humans. We observe that both within- and between-system connectivity increases through the evolutionary hierarchy: The least connectivity is observed in the subcortical and cerebellar systems, followed by the sensorimotor systems, default mode, and higher order cognitive systems in that order. These results suggest that the cognitive functions characteristic of humans require not just new tissue but also a different network structure. This putative evolutionary process is potentially enabled by gross cortical thinning in the same phylogenetic order (17), albeit with some exceptions (18), and a decoupling of cognitive systems from tight molecular regulation (19).

Development of the Default Mode. The default mode network displays strong within-network connectivity (20) and strong links with salience (21), memory (22), and attention (23) systems. Our results extend these prior observations by defining this system's role within the wider brain network as a cohesive connector, a broadly influential role that is likely supported by the hub-like pattern of structural connectivity emanating from many default-mode regions (24). The connective nature of this system might underlie fluid thought processes that require interactions with other cortically based cognitive systems, such as mind wandering, internal trains of thought, and prospective imagination (25). Indeed, such a possibility is supported by our finding that the between-system connectivity of the default mode was significantly correlated with general cognitive performance.

Our results emphasize that the default mode's role evolves significantly during adolescence, with increasing internal coherence and interaction with other systems. This evolution likely facilitates the default mode's growing role in intrinsic functions. For example, its increasing integration with higher order cognitive systems might underlie a growing ability to maintain cognitive readiness and to control the movement of the brain to myriad cognitive states supporting task demands (26). If true, such a relationship would suggest that children display less network controllability than adults and, by extension, a decreased ability to move between cognitive states (27).

Higher Order Cognitive, Sensorimotor, Subcortical, and Cerebellar Systems. Several brain systems become less integrated with one another over the course of development; however, this segregation might have different functional implications in different subnetworks. For example, higher order cognitive networks might become less integrated to enable distinct functions. Such a hypothesis is supported by decreasing functional coherence between regions (increasing dissimilarity in neurophysiological time series), enabling a larger repertoire of functional dynamics. In contrast, the increasing segregation of subcortical and cerebellar systems may come from their distinct neural architectures, which differ significantly from cortical tissue, facilitating the development of distinct functional dynamics.

On average, sensorimotor systems do not display significant changes over neurodevelopment, consistent with Piaget's theory that gross sensorimotor functions develop earlier than other cognitive functions. However, controlling for age, individuals vary in sensorimotor integration considerably. Indeed, individuals with weaker sensorimotor integration tended to display better cognitive performance than individuals with stronger sensorimotor integration. We can speculate that these results support a competition in the relative development of cognitive systems. Such a hypothesis adds a developmental component to the dual-process account of sensorimotor–cognitive interactions that posits a competitive nature to cognitive vs. sensorimotor load (28). Increasing modularization of the sensorimotor systems might therefore be critical to efficient overall cognitive performance on developmental time scales.

Methodological Considerations. Here, we asked how adult systems developed during childhood, and comparison with the adult partition was therefore critical. This work could be complemented in the future by the examination of subject-specific systems and the role of individual brain regions within them. Atlases that parcellate subcortical and cerebellar regions more finely might provide additional insight (additional discussion is provided in *SI Appendix*). Finally, we did not identify strong correlations between the roles of higher order cognitive systems and overall cognitive performance, which may require complementary information from task-based fMRI data where these systems are actively engaged.

Implications for Neuropsychiatric Syndromes. The current results provide a context for understanding developmental neuropsychiatric processes. Normative cognitive development is characterized by system-specific network roles that change over time; deviations from these trends might predict conversion into pathological syndromes. Between-system connectivity explained significant individual differences in cognitive development. Collectively, our results are compatible with the hypothesis that individual variation in network configuration implies differential vulnerability to cognitive abilities or deficits.

Materials and Methods

Data Acquisition and Preprocessing. Data were acquired in a collaboration between the Center for Applied Genomics at the Children's Hospital of Philadelphia and the Brain Behavior Laboratory at the University of Pennsylvania. Study procedures were approved by the Institutional Review Board of both institutions. Adult participants provided informed consent; minors provided assent and their parent or guardian provided informed consent. Resting-state fMRI data were acquired from 780 healthy children aged 8–22 y [a description of the imaging methodology is provided by Satterthwaite et al. (29)]. Cognition was measured using the Penn Computerized Neurocognitive Battery (30). General cognitive performance was summarized by averaging across all cognitive domains.

Functional Network Construction and Organization. We extracted regional mean blood oxygenation level-dependent time series from $N = 264$ functional regions (nodes) (1) and estimated functional connectivity (edges) A_{ij} between any pair of regions i and j using a wavelet coherence in 0.06–0.12 Hz (31–33). The weighted adjacency matrix **A** represents the functional brain network for a given subject. Using modularity maximization, we identified network communities: groups of brain regions that were densely interconnected by strong functional connections.

Roles of Cognitive Systems. To examine the roles of cognitive systems within the network, we calculated within- and between-system connectivity. Within-system connectivity is the mean strength of the functional interactions within a community, $\mathcal{C}$: $R_i = \frac{\sum_{ij \in \mathcal{C}_i} \tilde{A}_{ij}}{|\mathcal{C}_i|^2}$. Between-system connectivity is the mean strength of functional interactions between a community and all other communities: $I_i = \frac{\sum_{i \in \mathcal{C}_i, j \notin \mathcal{C}_i} \tilde{A}_{ij}}{|\mathcal{C}_i| \cdot (N - |\mathcal{C}_i|)}$. Here, $\tilde{A}$ is the weighted adjacency matrix normalized by the mean to ensure maximal sensitization to topological structure.

Permutation Test. We performed a 2D permutation test in which the assignment of nodes to systems is permuted uniformly at random to examine the significance

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of (*i*) a system type's distinct role and (*ii*) a system type's distinct cross-sectional trajectory in light of the null hypothesis that all system types displayed the same roles and cross-sectional trajectories.

Effects of Gender and Motion. In this cohort, there were no significant differences in the mean age of males and females (two-tailed $t(778) = 0.65$, $P = 0.517$), indicating that gender is unlikely to drive our results demonstrating brain-based correlates of development. Following normalization by global connectivity at the level of the connectivity matrix, and regression of motion at the single-connection level, connectivity was not significantly related to in-scanner motion.

Additional methodological details are provided in *SI Appendix*.

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