Biological Psychiatry: CNNI

Review

Understanding the Emergence of Neuropsychiatric Disorders With Network Neuroscience

Danielle S. Bassett, Cedric Huchuan Xia, and Theodore D. Satterthwaite

ABSTRACT

Major neuropsychiatric disorders such as psychosis are increasingly acknowledged to be disorders of brain connectivity. Yet tools to map, model, predict, and change connectivity are difficult to develop, largely because of the complex, dynamic, and multivariate nature of interactions between brain regions. Network neuroscience (NN) provides a theoretical framework and mathematical toolset to address these difficulties. Building on areas of mathematics such as graph theory, NN in its simplest form summarizes neuroimaging data by treating brain regions as nodes in a graph and by treating interactions or connections between nodes as edges in the graph. Network metrics can then be used to quantitatively describe the architecture of the graph, which in turn reflects the network's function. We review evidence supporting the utility of NN in understanding psychiatric disorders, with a focus on normative brain network development and abnormalities associated with psychosis. We also emphasize relevant methodological challenges, such as motion artifact correction, which are particularly important to consider when applying network tools to developmental neuroimaging data. We close with a discussion of several emerging frontiers of NN in psychiatry, including generative network modeling and network control theory. We aim to offer an accessible introduction to this emerging field and motivate further work that uses NN to better understand the normative development of brain networks and alterations in that development that accompany or foreshadow psychiatric disease.

Keywords: Adolescence, Connectivity, Development, MRI, Network, Psychosis

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The human brain is a complex organ whose function still defies explanation. Among the myriad genetic, molecular, cellular, and anatomical drivers of this complexity, a key component that has recently received increasing attention is the elaborate and heterogeneous pattern of connectivity between large-scale brain regions (1,2). Complementing our understanding of regional function from lesion and brain-mapping studies, this pattern of connectivity between regions is thought to provide critical information about how information is processed, transmitted, and transformed in the service of cognition (3,4). Our understanding of brain connectivity has been facilitated by recent advances in mathematics, physics, computer science, statistics, and engineering, which have culminated in the formalization of an interdisciplinary field of inquiry referred to as network science (5). Intuitively, a network is a simplified representation of a system in terms of its components and a pattern of connections between them. Network science offers a mathematical language in which to quantitatively characterize such interconnected architecture, model the impact of network structure on observed function, and predict the nature, growth, and dynamics of such systems. As applied to the brain, the emerging discipline of network neuroscience (NN) encompasses the invention, application, and extension of network-based tools to address pressing questions related to the structure, function, and development of the brain (6).

The purview of NN extends to molecular and cellular biology, spans across species, and bridges data science and clinical translation. Yet despite this broad applicability, one of its most well-developed contributions has stemmed from studies of large-scale brain networks measured using noninvasive human neuroimaging techniques (7). Here, one studies the connectivity between large-scale brain areas, with volumes on the order of several centimeters cubed. Such areas can be connected by white matter (WM) tracts (structural connectivity) (8) or by statistical similarities in activity time series (functional connectivity [FC]) (9).

In addition to offering insights into the general principles of brain network architecture across the population (10), this approach also allows a quantification of individual differences, including brain development. Developmental associations with brain network structure and function provide a unique opportunity to understand both normal brain development and how abnormal brain development is associated with major neuropsychiatric syndromes such as psychosis. This potential is underscored by the increasing recognition that disorders such as psychosis are fundamentally disorders of connectivity (11–13), with changes in network properties evident in youth

who either have the disease or are at elevated clinical or genetic risk. Critically, network markers may provide intermediate phenotypes for psychiatric disease, provide features for early diagnosis, and inform interventions to "bend the curve" of brain development during the plastic period of childhood and adolescence (14).

In this review, we offer a broad overview of the utility of NN in understanding normal network development and developmental network abnormalities associated with psychosis. We begin with a primer on NN methods, move to a brief discussion of applications of NN techniques to questions posed by the study of normative development, and address the extension of these applications to abnormal development and its relevance for psychosis. In addition, we provide a thorough discussion of the most pressing methodological challenges in applying network tools to neuroimaging data, including the pervasive impact of motion artifact on estimated connections. We close with a description of emerging frontiers in applying new network methods to developmental psychiatry.

PRIMER ON NN

Here we provide a brief primer on NN, beginning with its theoretical foundations and computational toolkit, before moving on to its relevance for developmental psychiatry (Figure 1). The two canonical roots of network science are graph theory, a field of mathematics that offers a formal way in which to represent interconnected systems (15), and statistical

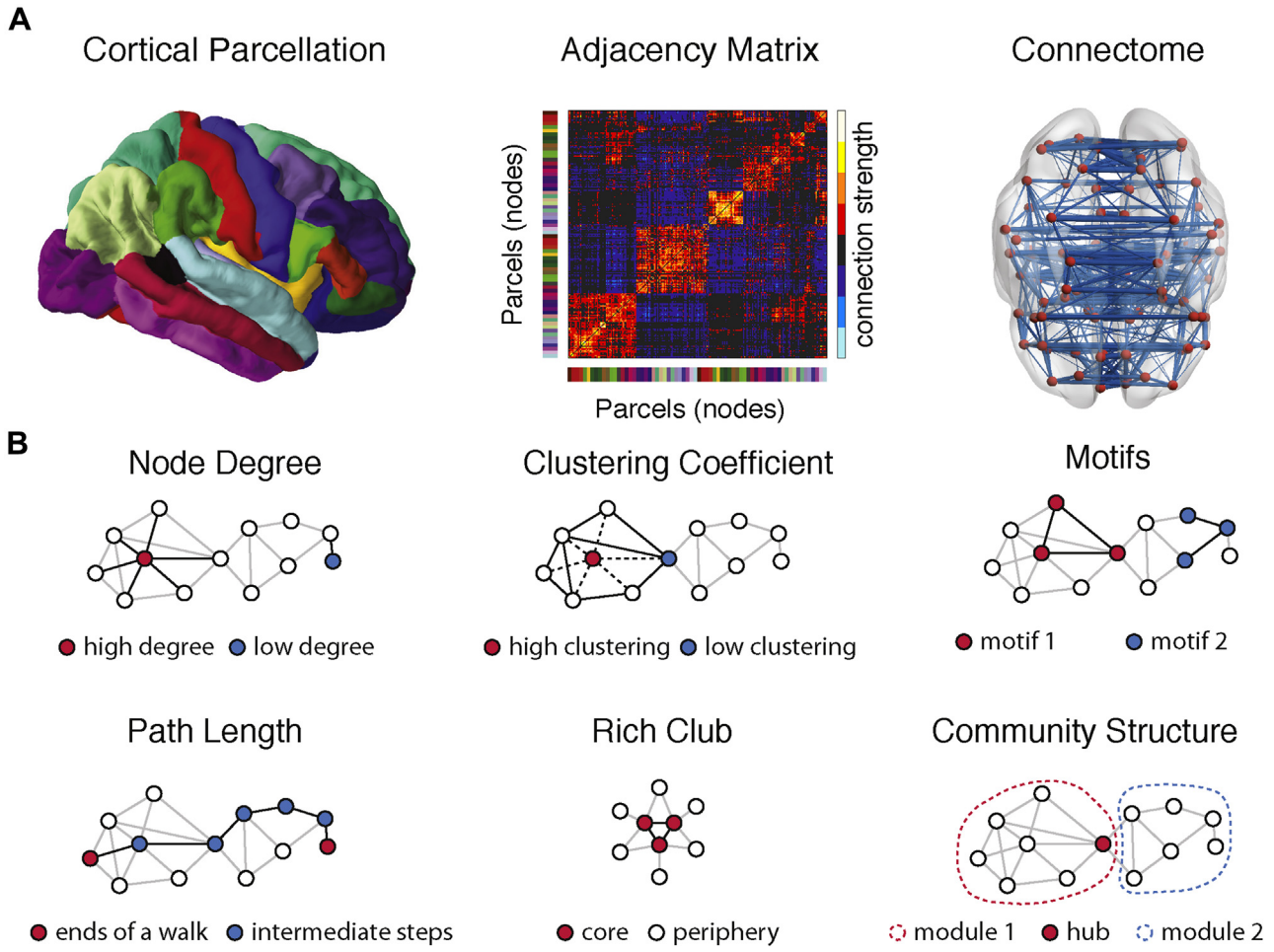

Figure 1. A brief network primer. **(A)** The process of building a brain network begins with a parcellation of imaging voxels into regions of interest. Next, connections between those regions (estimated via functional connectivity, white matter tractography, or cross-subject covariance in morphometric variables) are summarized in an adjacency matrix, which in turn can be represented by a network or graph. **(B)** A simple schematic of a few common graph metrics used to characterize human brain networks. First, node degree is defined as the number of edges of a given node. The clustering coefficient of a node in a binary graph can be defined as the number of triangles containing that node divided by the number of connected triples containing that node. Motifs are subgraphs with a fixed pattern of connectivity: a triangle is an example of a motif, and a connected triple is another example of a motif. The shortest path length between two nodes is given by the smallest number of edges that must be traversed to get from one to the other. Core–periphery structure in a network is present when high-degree nodes are also densely connected with one another (sometimes called a "rich club"), and when a periphery of low-degree nodes preferentially connects to the core. Community structure in a network is present when the graph can be decomposed into modules, where nodes in one module are densely connected to one another but sparsely connected to nodes in other modules. Panel **(B)** is inspired by Sporns (137).

mechanics, a field of physics that offers methods to infer how collective dynamics can emerge from ensembles of many interacting parts (16). In its simplest instantiation, network science represents a system in terms of a graph, where quintessential elements of the system are represented as nodes and where relations or interactions between elements are represented as edges (5). When edges take on weights of either 0 or 1, the graph is said to be a binary graph; when edges take on nonbinary weights, the graph is said to be a weighted graph. Graphs are called signed graphs if their edges can be either positive or negative, and they are called directed graphs if the edge from node i to node j need not have the same weight as the edge from node j to node i. Although not yet commonplace in NN, other network representations are being developed in the mathematics community that have shown initial promise in probing brain function (17,18). Examples include temporal graphs containing time-varying edges, multilayer graphs containing distinct layers that can each code for a different edge type, annotated graphs containing quantitative features assigned to nodes, and simplicial complexes accounting for nondyadic interactions.

In brain networks, nodes are usually chosen to be large-scale areas defined by cytoarchitecture, anatomical boundaries, functional responses, or a combination of multiple features (19). Parcellations of the brain into network nodes typically segregate cortical and subcortical areas into between 100 and 1000 regions of interest. It is also possible to construct more fine-grained graphs in which individual voxels constitute network nodes, although analysis of such networks can be computationally demanding. Irrespective of the spatial resolution at which nodes are defined, edges connecting nodes are commonly chosen to reflect estimates of structural connectivity (e.g., WM tracts) (8), FC (statistical similarities in time series, such as a correlation or coherence) (9), or morphometric similarity (across-subject correlation in, for example, cortical thickness, gray matter volume, or surface area) (20–22). Such graphs representing interregional connectivity are the standard in the field, although recent efforts have also demonstrated the utility of other representations. For example, so-called time-by-time graphs represent inter-time similarities in brain state (23), defined as a pattern of activation across all regions, and can be useful in assessing brain state variability both at rest and during the performance of cognitively demanding tasks (24).

As the reader likely appreciates at this point, there are many types of brain networks that one can construct from neuroimaging data. Despite this variability, several architectural features are consistently observed across structural and functional brain networks and across various spatial scales at which nodes can be delineated. Perhaps the earliest feature to have been observed—and the most broadly validated—is that of small-worldness, in which the nodes to which a region is connected also tend to connect to one another (leading to high clustering) and in which a few long-distance connections exist (leading to a short average path length, or the mean number of connections that must be traversed to get between a given pair of nodes) (25–28). Small-world architecture is often accompanied by a heavy-tailed degree distribution, where most nodes have few connections (low degree) and a few nodes have many connections (high degree); when the degree distribution is well-fit by a power law, the network is sometimes referred to as scale-free. Importantly, small-worldness is thought to support a balance between the local processing of information and the global transmission of information. Such a balance between segregation and integration is also supported by the architectural principles of modularity and core–periphery structure (29,30). Intuitively, a module is defined as a set of brain regions that are more densely (and strongly) interconnected with other regions in the same module than expected in a random network null model. The segregation enabled by modularity is complemented by the integration enabled by core–periphery structure, where a set of densely interconnected hubs (often called a rich club) extend pervasive connections to the remaining areas of the brain (31). Notably, this topological richness is maintained in a physically embedded system that also displays relatively minimal anatomical connection lengths, suggesting pervasive evolutionary, developmental, energetic, and/or metabolic constraints on wiring (10,32).

STUDIES OF NORMAL BRAIN DEVELOPMENT

An adequate description of normative brain network development is a prerequisite for any account of how abnormal development of brain networks might be associated with psychopathology. While an increasing array of network statistics have now been examined in studies of brain development, there is particularly convergent data supporting the evolution of two specific properties of brain networks: core–periphery structure and network modularity. Here, we review the extant literature on how these topological features evolve in youth.

While multiple methods to quantify core–periphery structure are available (33), in NN the most common has been the rich club approach (34). A rich club is a set of densely interconnected hubs that also connect to the remaining (peripheral) nodes in the network. These hubs tend to extend disproportionally high-cost, long-distance connections, which are critical for efficient information flow across the network. Previous work has shown evidence for rich club topology in the human brain using both structural and functional networks estimated from noninvasive imaging (31,35,36). Notably, this topology is present early in life and can be identified in human infants (37). Rich club organization is not unique to human brain networks and is also observed in the neural networks of species as diverse as *Caenorhabditis elegans* (38), cats (39), and macaques (40). Rich club regions have been shown to have elevated coupling of expression of genes involved in oxidative metabolism, emphasizing their importance for the brain's energy consumption (41). Critically, rich club architecture is not static, but evolves with age. Indeed, no fewer than seven independent studies have shown that the core–periphery architecture measured by the rich club consolidates and strengthens over childhood, adolescence, and young adulthood in humans (40,42–47).

In addition to such development of the core–periphery structure, there is ample evidence that network modularity is a critical property of brain networks that is refined during youth (48). Like many other types of networks, brain networks have been shown to have a clear modular structure, being made up of groups of nodes that are strongly connected to each other

and more weakly connected to other modules (49). Several network measures have been typically used, including modularity quality, which describes the modularity of the overall network (48). Similarly, the participation coefficient quantifies the degree to which a specific node (or set of nodes) has connections to multiple communities (50). The spatial distribution of brain network modules derived from human imaging data shows remarkable consistency across methods (51–53) and aligns with data from animal models (54), lesion studies (55), and task-based functional magnetic resonance imaging studies.

During childhood and adolescence, modules become more distinct: connectivity within modules increases while connectivity between modules declines (Figure 2A). In a classic series of studies, Fair *et al.* (56) initially described how the cognitive control system evolved into adult structure through segregation of the frontoparietal and cingulo-opercular elements (56); a follow-up study documented that a similar process occurs in the default mode network (57). Convergent results have subsequently been provided by independent efforts (58,59). Notably, studies that initially appear to provide discrepant results can be easily reconciled by noting differences in network edge definition (60): when anticorrelated time series in the default mode are considered functionally connected via the use of a positively signed edge measure such as coherence, increased between-module connectivity can be detected due to an enhancement of that anticorrelation. (In networks constructed from a signed edge measure such as a Pearson correlation coefficient, the effect of increased anticorrelation in time series is to enhance segregation between networks.) Complementing these data on functional networks, a large recent study by Baum *et al.* (61) using diffusion imaging similarly demonstrated increasing modularity within structural brain networks (Figure 2B).

Overall, these findings suggest a refinement of the modular structure of brain networks during adolescence through strengthening of within-network connectivity during adolescence and weakening of between-network connectivity. This process is frequently called modular segregation. It should be emphasized that evidence of increased modular segregation during youth is not at odds with the evidence for enhanced connectivity within rich clubs surveyed above. Despite a global decline in between-network connectivity, modular subnetworks do not become isolated. Indeed, recent evidence suggests that the opposite is true: brain networks simultaneously display greater modular segregation and enhanced global integration during adolescent development (61). Development of such unique topology occurs via targeted strengthening of hub edges that link modules, even while most between-module edges weaken. This profile of development is potentially consistent with the strengthening of a rich club module, which is apparent in certain hierarchical models (62).

The modular yet integrated topology that is refined during development may allow for both functional specialization within modules and coordination across modules. Such a configuration may potentially reduce interference among systems and facilitate cognition. Indeed, previous work suggests that greater modular segregation during adolescence is related to improvements in executive performance (Figure 2C) (61). Furthermore, as described in the next section, emerging evidence suggests that the disruption of such normative developmental processes may be associated with vulnerability to neuropsychiatric illness.

DEVELOPMENTAL NETWORK ABNORMALITIES ASSOCIATED WITH PSYCHOSIS

Severe neuropsychiatric disorders such as schizophrenia are increasingly conceptualized as developmental disorders of brain connectivity (63). This paradigm shift has been driven by the lack of evidence for a single focal "lesion" in psychosis, in concert with mounting evidence for the disruption of large-scale brain networks (64). Many aspects of brain networks that evolve during development are also disrupted in

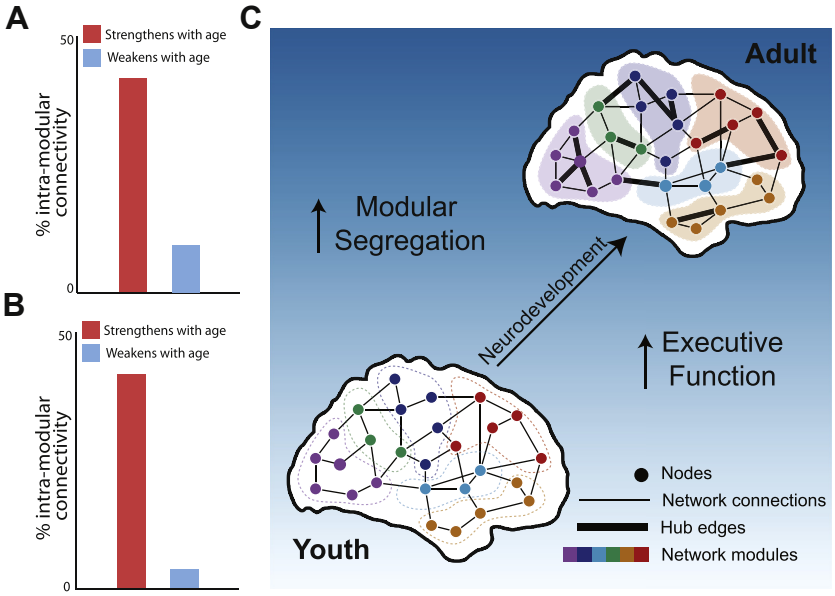

Figure 2. Modular segregation during adolescent development. Consistent effects of neurodevelopment are apparent in both functional networks **(A)** and structural networks **(B)**. Notably, connections that strengthen with age are much more likely to be within a network module, whereas connections that weaken with age predominantly span across modules. These edge level changes result in increased modular segregation of the network. **(A)** Adapted with permission from Satterthwaite *et al.* (97); **(B, C)** adapted with permission from Baum *et al.* (61).

psychosis, prompting focus on the developmental antecedents of network-level abnormalities in schizophrenia (SZ) (65,66). As described below, there is accumulating evidence that the network abnormalities that are present in adults with frank psychosis are also present in youth at clinical risk (Figure 3).

Studies of adults with SZ have consistently documented disruptions of many aspects of both structural and functional brain networks (67,68). However, the available evidence indicates that the impact of psychosis may be particularly prominent in a network's core, frequently defined via the rich club metric. For example, van den Heuvel *et al.* (69) found evidence for reduced rich club connectivity in both a discovery and replication dataset, in particular impacting hubs in the frontal cortex. Similar results were reported in two subsequent independent studies (70,71). In light of evidence for strengthening of the rich club in normal development (see above), the results of these studies are consistent with a developmental abnormality of connectivity within the network core. The downstream functional impact of such abnormalities is suggested by a recent meta-analysis of task functional magnetic resonance imaging studies in SZ, which found that activation abnormalities were enriched within rich club nodes (72). Intriguingly, alterations of connectivity within the network core have also been documented in youth at high risk for conversion to psychosis (73), as well as first-degree family members of those affected by psychosis (71,74,75). Thus, collectively these changes within the network core may constitute a stable endophenotype for psychosis risk that is independent of disease state. Based on such evidence, investigators are increasingly attempting to map specific genetic risk loci (76) or SZ polygenic risk scores (77) to abnormalities observed in the network core in psychosis.

Along with such abnormalities within the network core, multiple studies have documented a broader disruption of network modularity in association with psychosis. Two studies by Alexander-Bloch *et al.* (78,79) reported reduced modular segregation and alterations of community structure in patients with childhood onset SZ. Similar results were provided by an important cross-diagnostic study by Baker *et al.* (80) that provided evidence for reduced segregation between the frontoparietal control system and the default mode network in a large sample of adults with psychotic disorders (SZ and bipolar disorder) (80). However, it should be noted that several of the most consistent findings associated with psychosis—including increased connectivity within the default mode network (81) and abnormalities within frontostriatial and frontothalamic networks (82–85)—are distinct from both abnormalities within the network core and disruption of network modularity. Together, these results emphasize the complex, multifocal patterns of dysconnectivity that occur in psychosis.

Finally, while the results reviewed here are broadly consistent with an abnormality of the normal process of modular segregation in development, it should be noted that it remains unclear whether the observed alterations of network topology are specific or result instead from a more nonspecific network randomization process (86)—Váša *et al.* (87) address best practices in detecting randomization processes. Furthermore, it remains unclear whether reported network deficits are specific to psychosis. For example, abnormalities of the network core are a common feature of multiple disorders, although the specific regional distribution may vary across disorders (88). Moving forward, studies that use data-driven strategies to delineate network "biotypes" of psychosis may allow profiles of symptoms to be linked to specific patterns of dysfunction both within and across heterogeneous neuropsychiatric disorders.

METHODOLOGICAL CHALLENGES: DATA QUALITY

Methodological challenges of studying the normal and abnormal development of brain networks can be substantial (89,90). While methodological issues including acquisition protocol and atlas choice are important (91), data quality is frequently the largest obstacle to studying the development of brain networks and has recently attracted substantial attention from the field (92–94). Data quality is most commonly driven by in-scanner motion, which is frequently correlated with major variables of interest, including age and group (95). Thus, motion has the potential to systematically confound inference (96,97).

Motion may be particularly problematic for studies of functional networks: in 2012, three independent groups demonstrated that motion artifacts have a marked impact on measures of FC (96,98,99). The predominant effect of motion is a large drop in intensity across all network nodes (93,100,101), which tends to increase the observed FC across the network (101). However, when functional time series preprocessing includes global signal regression (GSR), these widespread changes are largely removed (102). However, the residual

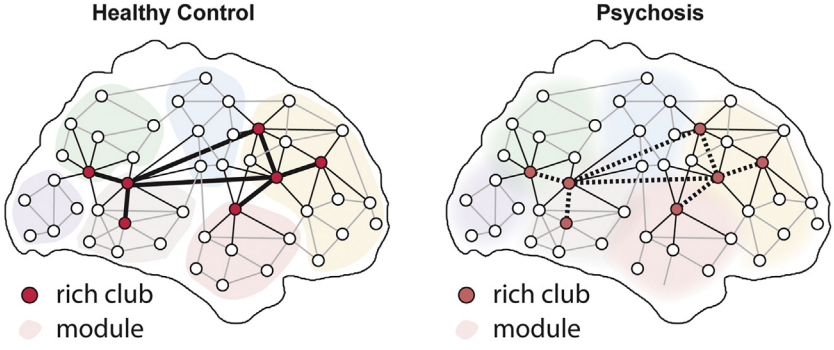

Figure 3. Psychosis is associated with alterations of network topology. Convergent evidence across studies suggests abnormalities of normal developmental processes, including reduced connectivity within the network core and diminished segregation of network modules.

impact of motion after GSR tends to have a substantial distance dependence, with motion being associated with an increase in connectivity between spatially adjacent nodes and diminished connectivity between distant nodes (96,99).

Such distance-dependent effects can confound developmental inference, with dramatically inflated appearances of weakened short-range connections and strengthened long-range connections (97,103). Such results have led to an acceleration of methodological studies that seek to limit the impact of motion artifact (104–106). Two recent benchmarking studies provide a framework for comparing denoising approaches (102,107). Specifically, both GSR and temporal censoring (scrubbing, spike regression, and despiking) remain a highly effective mechanism for controlling motion artifact (Figure 4). Critically, effective denoising approaches have also been shown to enhance the ability to detect modular subnetworks in graphs constructed from time series impacted by motion (101,102). However, it should be noted that denoising techniques can consume many temporal degrees of freedom, and aggressive denoising procedures may not be practical with time series of limited duration [for a recent review, see (92)]. While previous guidelines suggest that 4 to 6 minutes of usable data are required for network estimation (108), more recent evidence suggests that longer acquisitions improve reliability (109) and are a prerequisite for specific advanced analytic procedures [e.g., functional parcellations; see (110)].

There is substantially less research regarding the impact of motion on structural networks estimated through diffusion imaging (111). One important study demonstrated that motion systematically reduces the fractional anisotropy of major WM tracts (112). Furthermore, recent results suggest that motion artifact can have a variable impact on structural connectivity that is largely determined by connection consistency (113). Similar to the distance-dependent effects of motion on FC, in-scanner motion results in diminished connectivity in long-range, highly consistent structural connections in tandem with elevated connectivity in inconsistent (primarily short-range) network connections (113). Techniques that seek to control for motion in diffusion imaging have undergone rapid evolution, and the existing data suggest that recently introduced motion correction techniques can substantially reduce the impact of motion (114). Specifically, FSL's *eddy* procedure now has the capability to build a generative model in order to make nonparametric predictions about the expected signal in each slice of diffusion encoded volumes and replaces signal outliers attributed to head motion using this prediction (115).

Whether studying functional or structural networks, together these studies emphasize that investigators should evaluate and transparently report associations between motion and both subject-level variables (e.g., age, group status) and network measures of interest (e.g., modularity, rich club statistics). When significant associations are present, controlling for in-scanner motion during hypothesis testing is often warranted (93). Finally, it should be noted that acquiring data with less motion is far preferable to extensive postprocessing. This can be facilitated by use of videos during acquisition (116) and new online monitoring solutions (117).

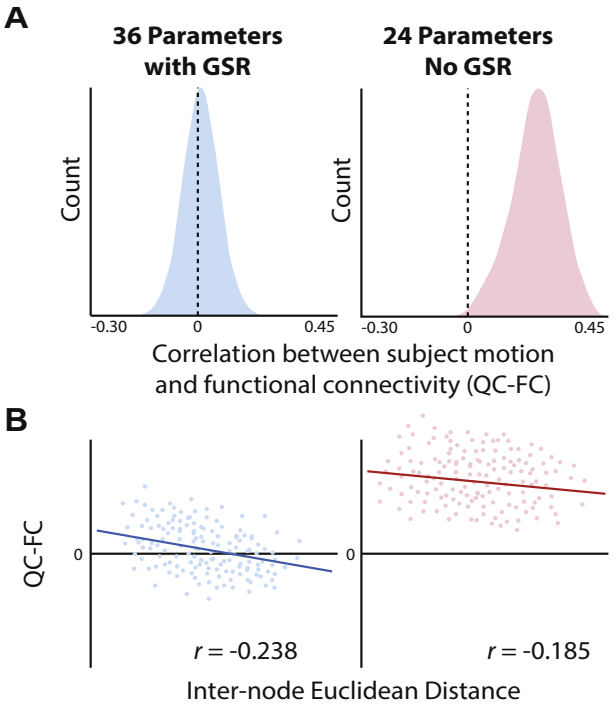

Figure 4. Effective denoising limits associations between functional connectivity and in-scanner motion. **(A)** When global signal regression (GSR) is included in confound regression, the distribution of correlations between motion and functional connectivity (QC-FC) are markedly reduced and centered around zero. **(B)** However, inclusion of GSR does result in a mild increase of distance dependence, which is quantified as the slope of the relationship between QC-FC correlations and the internode Euclidian distance. The confound regression model without GSR included 24 parameters, including six realignment parameters (three rotations and three translations), as well as their temporal derivative, square, and square of their temporal derivatives. The confound regression model with GSR included 36 parameters, which included not just the six realignment parameters but also the mean global signal, the mean white matter signal, and the mean cerebrospinal fluid signal. These nine base parameters were expanded as described above via their temporal derivative, square, and square of the temporal derivative. All data are drawn from a sample of 393 youths ranging from 8 to 22 years of age who were imaged as part of the Philadelphia Neurodevelopmental Cohort. All analyses include age and sex as covariates. Adapted with permission from Ciric *et al.* (102).

EMERGING FRONTIERS

As in most young fields, NN has begun by describing the organization of brain networks in health and disease: collating observations, categorizing phenotypes, and cataloging network measures. Yet descriptions do not amount to explanations, and categories do not amount to mechanisms (118). Gaining insight into such mechanisms and offering such explanations requires the development of theories that can be explicitly tested with perturbative experiments. An important initial step toward theory is the development of generative network models, where biologically grounded wiring rules are computationally implemented to produce synthetic network architectures with the same properties as those observed in empirical data (119,120). Generative network models (Figure 5) can be used to posit and test the principles (wiring rules) by

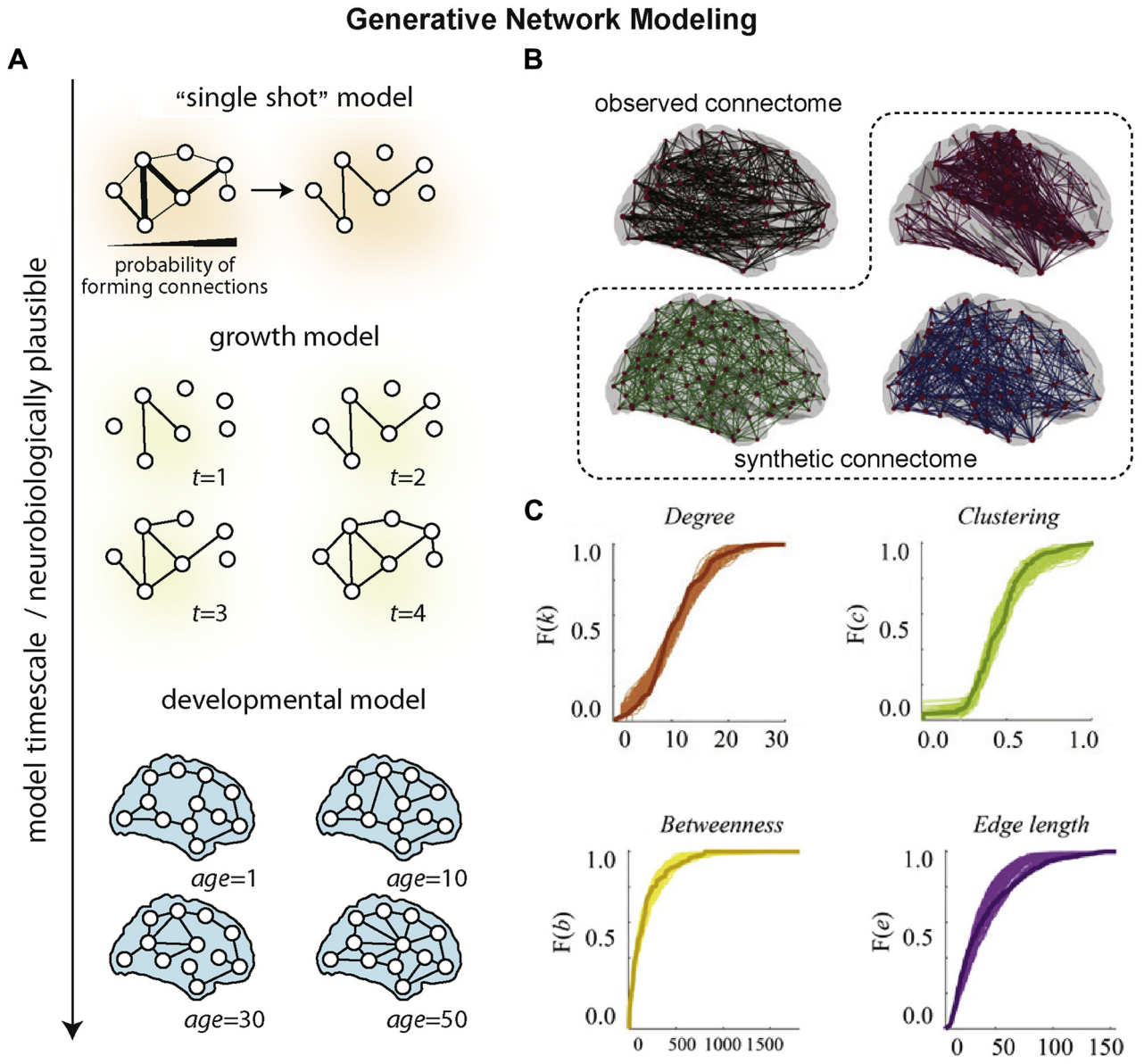

Figure 5. Emerging frontiers: generative network modeling. **(A)** The space of generative models. Generative models can be differentiated from one another along several dimensions, one of which is the timescale over which they operate. A model's timescale is related to its neurobiological plausibility. Models whose timescale is nearer to that of development can incorporate more realistic and interpretable features and, in turn, have the chance of uncovering realistic growth mechanisms. At the opposite end of the spectrum are "single shot" models, where connection probabilities are initialized early on and all connections and weights are generated in a single algorithmic step. Situated between these two extremes are growth models that exhibit intrinsic timescales over which connections and/or nodes are added to the network, but where the timescale has no clear biological interpretation. **(B)** Summary of a geometric model for human white matter networks estimated from diffusion imaging. Observed (black) and synthetic (colors) networks generated at different points in a predefined parameter space of interest. Each of the model-generated synthetic networks was created using an edge addition algorithm, in which connections were added probabilistically and one at a time according to a set of parameterized wiring rules. **(C)** Cumulative distributions of degree (orange), clustering coefficient (green), betweenness centrality (yellow), and edge length (purple) for the observed connectome (darker line) and best-fitting synthetic networks (lighter lines) for a representative participant. Panel **(A)** is adapted with permission from Betzel and Bassett (119); **(B, C)** adapted with permission from Betzel *et al.* (120).

which large-scale human brain networks are organized, and offer possible mechanisms for network development (121–125). Examples of such wiring rules include distance penalties based on the cost of maintaining long-range connections (120) and preferences for links between regions sharing similar inputs (25). Furthermore, generative network models can be used to predict network architectures from mechanisms and future network architectures from growth rules. Such capacities have already proven useful for understanding dysconnectivity syndromes in psychiatry. For

example, childhood onset SZ has been shown to be consistent with networks produced by a less economical clustering rule (25). Generative modeling approaches could also prove particularly powerful in forecasting the future networks of specific individuals, potentially identifying those with psychosis risk.

However, the capacity to identify those individuals at risk for psychosis begs the question of how we can intervene, either to correct existing alterations in connectivity or to stem the future emergence of abnormal connectivity. While a definitive answer to this question remains unknown, one novel approach that has considerable theoretical potential is network control theory (NCT) (Figure 6) (126). Unlike graph theory, which provides descriptive statistics of a network, NCT offers a dynamical systems model to explain how alterations in the activation of a single node in a network can lead to spatially distributed and systemwide effects whose exact pattern depends on the structure of the anatomical WM network interconnecting all nodes (127). Originally developed in the field of systems engineering, NCT describes how key nodes, or control points, can exert disproportionate influence over system function (128). Control points are identified with metrics that assess the ability of specific nodes to alter a system's state, based on the underlying network topology. The application of NCT has revolutionized the understanding and design of complex networks in contexts as diverse as financial markets, fire-control systems, and aircraft and automobile design (129).

Critically, the capabilities of NCT match the rationale for administering brain stimulation (130), a treatment approved by the U.S. Food and Drug Administration for major depression and a candidate treatment for other psychiatric disorders, including cognitive dysfunction in psychosis. Previous work applying NCT to neuroimaging data has offered initial evidence that control points can be identified and that their anatomical location differs depending on the type of brain state transition that is desired (131). These intuitions are built upon an energy landscape constructed directly from the pattern of WM architecture and a model of network dynamics that defines the patterns of regional activity that are expected to occur nearby in time. Regions that are theoretically predicted to effectively move the brain into states nearby on the energy landscape tend to be located in the default mode, while regions that are theoretically predicted to effectively move the brain to distant states tend to be located in frontoparietal areas implicated in executive function (132). Striking individual differences in the magnitude of regional controllability are observed, particularly in youth, and that variability is correlated with overall cognitive function as assessed with a broad neurocognitive battery (133). It is interesting to speculate that focal pathology in regional controllers early in development could lead to the later dysfunction in cognitive control observed in SZ, and—if such a

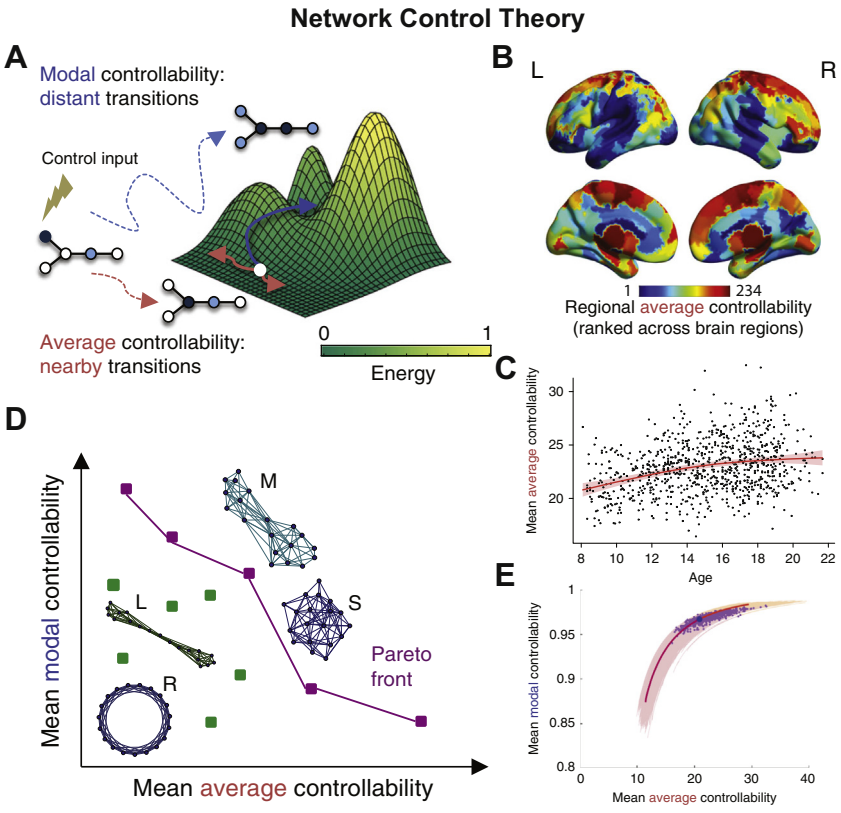

Figure 6. Emerging frontiers: network control theory. **(A)** Network control theory provides statistics that can be calculated from a dynamical systems model of activity propagation along a fixed structural (or anatomical) network. Here we illustrate the notion of average controllability, which provides structural support for moving the brain to easy-to-reach states nearby on the theoretically constructed energy landscape, and the notion of modal controllability, which provides structural support for moving the brain to difficult-to-reach states far away on the theoretically constructed energy landscape. **(B)** Applying these notions to structural networks estimated from diffusion tractography applied to diffusion spectrum imaging data acquired in 882 youths 8 to 22 years of age, Tang *et al.* (133) observed a heterogeneous spatial distribution of average controllability values across 234 cortical and subcortical regions defined by the Lausanne atlas. L, left; R, right. **(C)** In the same data set, Tang *et al.* (133) observed that average controllability increases appreciably with age, as did modal controllability, while synchronizability decreased with age (not shown). **(D)** To determine whether these statistics were sufficient to explain the observed developmental arc of white matter maturation, Tang *et al.* (133) performed a game theoretic rewiring procedure in which edges were rewired to advance the Pareto front (either increasing controllability and decreasing synchronizability or keeping these statistics constant). Letters beside the networks indicate their topology: ring lattice (R), regular lattice (L), modular (M), and small-world (S). **(E)** The authors observed that the simulated evolutionary trajectories track the human brain data points well, suggesting that one mechanism of human brain development is the reconfiguration of white matter connectivity to increase the human's ability to flexibly move between diverse brain states. Panels **(A-E)** adapted with permission from Tang *et al.* (133).

speculation were supported by empirical observation—it would be interesting to consider designing early-stage interventions to reduce the probability of conversion to psychosis from an at-risk state.

Despite the theory's important contributions to cognitive and developmental neuroscience, to date NCT has not been used to explain the impact of neuromodulation on brain networks. Particularly in the context of focal perturbation, efforts to test such a theory are critical, as validation could provide a generalizable mechanism of clinical interventions that would prove essential for choosing the target of stimulation, titrating stimulation dose, and personalizing stimulation to the subject's intrinsic brain network architecture. Notably, NCT can also be used to predict the effects of multipoint control, where the activity of multiple control points is altered to affect a change in brain state, and therefore also has potential as an approach for understanding and optimizing pharmacological interventions (118).

More generally, a key approach to understanding the brain is to perturb it (134). Brain stimulation, pharmacological manipulations, and cognitive behavioral therapy all constitute such perturbative approaches and therefore will be critical for a comprehensive understanding of the mechanisms of psychopathology. Preliminary studies have used pharmacological manipulations to test a hypothesis regarding a neurotransmitter-level mechanism of psychosis, demonstrating that an *N*-methyl-D-aspartate receptor antagonist alters dynamic reconfiguration of functional brain networks during *n*-back performance, an intermediate phenotype for SZ, consistent with a posited role of disrupted excitatory–inhibitory balance in the disease (135). Others have demonstrated that individual differences in network architecture can be used to predict who will respond to brain stimulation as a treatment of anhedonia (136). We envision that in the future it will be important to combine such experimental approaches with assessments of individual differences in genotype, cognition, and psychopathology to provide a more comprehensive, cross-scale view of psychiatric conditions and the subject-specific brain networks that accompany them, and to inform next-generation personalized interventions that maximize clinical impact.

CONCLUSIONS

We have reviewed emerging evidence supporting the utility of NN in understanding psychiatric disease, particularly in relation to the differences between normal and abnormal brain network development. We envision that the elegant mathematical approaches of network science will serve to support the goals of computational psychiatry, providing not only biomarkers and predictive phenotypes, but also fundamental insight into the systems-level processes of psychopathology. As this young field continues to grow, we anticipate that it will accelerate advances in our understanding of psychiatric disease and its developmental origins.

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ARTICLE INFORMATION

From the Departments of Bioengineering (DSB), Electrical and Systems Engineering (DSB), Neurology (DSB), and Psychiatry (CHX, TDS), University of Pennsylvania, Philadelphia, Pennsylvania.

Address correspondence to Theodore D. Satterthwaite, M.D., M.A., Brain Behavior Laboratory, Hospital of the University of Pennsylvania, 3400 Spruce Street, 10th floor, Gates Pavilion, Philadelphia, PA 19104; E-mail: sattertt@pennmedicine.upenn.edu.

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