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New ways of understanding brain neurocircuitry

Florence Thibaut, MD, PhD – Editor in chief

Abstract
Inside the brain, neural regions dynamically interact at multiple spatial and temporal scales through a highly structured and adaptive neurocircuitry. Comprehensive maps of brain connectivity have led to the emerging field of connectomics. Graph theory methods are interesting tools to improve our understanding of the brain as a complex interconnected system.

Keywords: neurocircuitry; connectome; graph theory method; mental disorder

The brain is definitely the most complex human organ. Neurons are linked by a large number of connections that can be analyzed across several orders of spatial, as well as temporal, magnitude. Indeed, functional brain networks are intrinsically dynamic on multiple timescales. To add another level of complexity, brain functional networks also spatially overlap and interact with each other. Moreover, such network interactions may temporally evolve. Even during the resting state, the brain undergoes dynamical changes in functional connectivity. The structural and functional study of these networks remains crucial to the understanding of brain organization, dynamics, and cognition or behavior by quantitative description of the temporal evolution of spatial overlaps/interactions of connectome-scale brain networks. For example, Kottaram et al (2018) have studied spatio-temporal dynamics of resting state brain networks in the prediction of schizophrenia diagnosis (see also Marek and Dosenbach in this issue, p 133).

An essential tool used to understand functional brain networks is functional magnetic resonance imaging (fMRI), which allows the indirect study of brain neural activity using the hemodynamic relationship between blood flow and neural firing. It is often used to examine contrasts between different cognitive conditions or changes in functional signal amplitudes and connectivity associated with different behaviors.

Comprehensive maps of brain connectivity have given rise to the emerging field of connectomics. Collin and Keshavan, in this issue (p 101), have explored how disruptions in these processes could lead to abnormal brain network architecture and organization and, thereby, give rise to mental disorders such as schizophrenia.

The connectome is the complete structural wiring diagram of the brain. A better knowledge of its organization is an important and challenging question. Interareal connectomes are wiring diagrams of white matter pathways (also called mesoscale or macroscale connectomes). Previous studies have described modules, hubs, module hierarchies, and rich clubs, as structural characteristic of these wiring diagrams. Modules are densely intraconnected areas which constitute functionally specialized systems; hubs are connected areas which integrate information between these systems. Module hierarchies are nestings of smaller modules within larger ones; while rich clubs are highly connected groups of hub nodes which reflect the dense connectivity between association areas. One important rich club is the structural substrate of the default-mode network (for review see Rubinov, 2016). In this issue, Griffa and Van den Heuvel (p 121) will review recent neuroimaging, computational, and cross-species comparative literature to provide an insight into the function and origin of rich clubs and the core brain architecture, while discussing the relevance of rich clubs to human cognition and behavior as well as vulnerability to brain disorders.

A number of emerging trends to identify central network elements that facilitate communication and signal transfer are the growing use of generative models, dynamic (time-varying) and multilayer networks, as well as the application of algebraic topology. The mathematical basis in which one can represent and study networks of nodes and connections is called graph theory which is crucial to study brain complexity. Using this latter theory, the analysis of brain resting state using fMRI has shown several interesting pathways of healthy and dysfunctional brain network organization. In this issue, Sporns reviews some of the most relevant graph theory methods and illustrated their application in various neurobiological contexts (p 111). Calhoun (p 87) will also discuss the synergistic relationship between brain structure and function to link together...
macrossoscopic structural and functional MRI data. This latter author will provide a selective review of data-driven approaches with a focus on independent component analysis approaches for capturing multivariate relationship both within and between brain structural and functional measure with multiple analytic examples.

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Data-driven approaches for identifying links between brain structure and function in health and disease

Vincent Calhoun, PhD

Introduction

Magnetic resonance imaging (MRI) data is a powerful tool which can provide us with detailed information about both brain structure and brain function. The use of high-resolution T1-weighted scans provides comprehensive anatomic information about brain tissue which can be used to estimate the volume of specific regions, cortical thickness, and networks of regions that covary together across individuals. Diffusion MRI (dMRI) gives information about white matter structure, and can be used to assess structural connectivity. While a variety of approaches have been used to study how brain structure informs function, the study of such relationships in living humans in most cases is limited to noninvasive approaches at the macroscopic scale. The use of data-driven approaches to link structure and function provides a tool which is especially important at the macroscopic scale at which we can study the human brain. This paper reviews data-driven approaches, with a focus on independent component analysis approaches, which leverage higher order statistics to link together macroscopic structural and functional MRI data. Such approaches provide the benefit of allowing us to identify links which do not necessarily correspond spatially (e.g., structural changes in one region related to functional changes in other regions). They also provide a “network level” perspective on the data, by enabling us to identify sets of brain regions that covary together. This also opens up the ability to evaluate both within and between network relationships. A variety of examples are presented, including several showing the potential of such approaches to inform us about mental illness, particularly about schizophrenia.

Keywords: brain function; brain structure; data driven; mental illness

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tivity by using approaches to estimate various diffusion parameters including anisotropy as well as probabilistic tractography using tensor-based models and higher-order connectivity through multi-shell imaging and modeling with orientation distribution functions. Finally, functional MRI (fMRI) provides information about brain function via blood oxygenation level-dependent (BOLD) imaging over time and has been used to perform exquisite mapping of intrinsic connectivity networks. All three of these techniques compile important information about brain function and structure and have been widely used in the study of mental illness.

The structure-function synergy

While the most obvious perspective is that structural information leads to subsequent functional changes, the plasticity of brain structure should also be kept in mind, as the functional activity may well reshape structure. It is also well known that structural sulcal/gyral boundaries definable at the macroscopic level do not necessarily correspond well to architectonic studies at the microscopic level. fMRI studies are improved if individualized functional boundaries are incorporated into the spatial normalization strategies. This complex synergy between structure and function increases the complexity of studying mental illnesses such as schizophrenia which are known to impact both structure and function. Figure 1 provides a simple illustration of these relationships; structure can be (and often is) claimed to be a fixed substrate onto which function operates. However, the reality is more complex as we know functional changes can also reshape brain structure, with such changes visible within days even at the macro level.

This then highlights the complexity of studying psychopathology, as illness can impact structure or function direction, or the directional relationships between these two modalities.

One of the challenges of complex mental illnesses such as schizophrenia is their highly intricate and diffuse presentation. That is, schizophrenia impacts much of the brain, and there are numerous examples of structural and functional deficits associated with the illness. The use of data-driven methods can be particularly useful in this regard, as one can analyze the whole brain with an unbiased lens allowing for weak contributions from many different brain regions. Likewise, the relationship between function and structure can be elucidated with flexible analysis approaches such as independent component analysis (ICA). ICA is a type of blind source separation which allows for the estimation of signals from complex data sets with minimal assumptions on their specific form. In particular, with ICA the goal is to extract maximally independent sources from the data, typically written \( X = AS \) where \( X \) is the data, \( A \) is an estimated mixing matrix, and \( S \) are the estimated maximally independent sources. In practice, the widely used ICA algorithms such as infomax and fastICA often include two complementary constraints, independence (ie, the maps are maximally independent of one another) and sparsity (ie, the maps have a small number of region with high values), which when combined provide for relatively well-behaved and interpretable results (eg, a component can be interpreted as a brain network) as demonstrated by the extensive number of studies using this approach.

Data-driven approaches like ICA can be used to extract brain networks from sMRI, dMRI, and fMRI data and also link together brain structure and brain function. Approaches that can capture all of the possible relationships illustrated in Figure 1 are needed as this is where data-driven approaches provide a distinct advantage. In addition, hybrid approaches that combine the flexibility of data-driven approaches with the ability to focus on specific networks and/or regions are also quite powerful in this context. There are a large number of studies to date which have used data-driven approaches such as ICA to study neuropsychiatric and neurological brain disorders. While the neuropsychiatry field is still very heterogeneous in findings, there is some evidence that the data-driven approaches are producing replicable and canonical results which reliably show...
differences in schizophrenia\textsuperscript{31} and show promise for the use of imaging to make diagnostic or treatment predictions.\textsuperscript{32}

In this paper, we briefly introduce data-driven approaches to study brain structure and function with an emphasis on ICA-based approaches. Then we provide examples of several specific variations that have been used to analyze sMRI, dMRI, and fMRI data and also to link together these structural and functional modalities to study the healthy and diseased brain.

**Data-driven approaches for analyzing brain structural and functional data**

A data-driven approach includes minimizing the upfront assumptions and allowing the data to be the primary driver of the results. This includes approaches such as clustering,\textsuperscript{33} principle component analysis (PCA),\textsuperscript{34} ICA,\textsuperscript{35} and more. In the context of brain imaging data, ICA has proven to be highly versatile and is now a widely used approach.\textsuperscript{36} One of the likely reasons for this is that the resulting maps tend to be relatively well-behaved and interpretable due to the incorporation of both independence (which emphasizes non-systematically overlapping networks) and sparsity (which encourages more focal networks) in the estimation of the components.\textsuperscript{37}

**Source-based morphometry**

The use of ICA for sMRI analysis, called source-based morphometry (SBM),\textsuperscript{3} can be considered a multivariate extension of voxel-based morphometry.\textsuperscript{38} Essentially, individual subject data are segmented, and gray-matter maps are organized into a matrix and entered into an ICA analysis that produces maximally spatially independent component maps. These maps include regions that show similar gray matter covariation across subjects. The degree to which they are “expressed” in the data is captured via their loading parameters (Figure 2). SBM has been studied with multi-site data and a number of the components have been found to be canonical, some consistently impacted by schizophrenia (such as the medial frontal/insular/temporal lobe component 1 in Figure 2).\textsuperscript{31}

![Source-based morphometry](image)

**Figure 2.** Source-based morphometry: input typically includes whole brain gray matter segmentation maps, output includes components (representing covarying gray matter regions) and their loading parameters (which can be tested for relationships with variables of interest such as age or group).
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SBM can also be applied to dMRI data. For example, SBM can be used to analyze fractional anisotropy (FA) maps, which are essentially providing information about the directionality of the diffusion within each voxel. Figure 3 shows results from an SBM of FA study of patients with schizophrenia and healthy controls. A number of the SBM components showed group differences, with all of these showing reduced FA in schizophrenia. This included primarily frontal white matter (thalamic radiation, inferior fronto-occipital fasciculus, and the cingulum bundle) and temporal white matter (left inferior longitudinal fasciculus and the left inferior fronto-occipital fasciculus) in addition to forceps major, forceps minor, corticospinal tracts and the superior longitudinal fasciculus. A key advantage to this approach is that one does not have to make strong assumptions associated with the use of tract atlases. The results for ICA of SBM however do not inform us about the directionality of the diffusion data (an approach for this will be discussed later39); rather they identify regions that show similar between-subject covariation in FA values.

Group ICA of fMRI data

In the era of the connectome, which is essentially a structural map of brain connectivity, resting fMRI has entered, and enabled us to estimate a “functional” connectome. Both of these, as measured by MRI, provide a “macro” view of the connectome, a domain in which multiple spatial and temporal domains overlap with one another in a complex manner, nowhere near a microscopic map of neuronal connectivity, and difficult to predict. Using group ICA, one can extract networks that are functionally coherent, that is, identify networks that are showing correlated activity. The output from group ICA24,41 allows one to evaluate each network separately, essentially to evaluate the within-network connectivity, as well as to study the between-network connectivity, also called functional network connectivity (FNC; Figure 4). Importantly, one can also leverage single-subject spatial maps and timecourses that are estimated from the group ICA through a process called back-reconstruction.42 Group ICA thus allows estimation of changes in functional connectivity at the voxel level within specific networks, changes in the relationship between pairs of brain networks, as well as other information such as spectral response, and in the case of a task, modulation by task stimuli. One can then evaluate changes in the within and between network connectivity which are related to symptoms, cognitive scores, individual subject prediction of diagnosis or treatment response.

Time-varying connectivity

Recent years have seen a rapidly growing interest in the analysis of brain connectivity which can capture transient changes in connectivity within a given experiment.43,45 Such chronnectomic information provides a more natural way to analyze fMRI data, especially resting fMRI data which is unconstrained and likely contains many different unmeasured “tasks.” While the field continues to develop,46 recent work in this

![Figure 3. SBM on dMRI data identifies a number of white matter components (highlighted in different colors) all of which show reduced fractional anisotropy in schizophrenia compared with healthy controls. SBM, source-based morphometry; dMRI, diffusion magnetic resonance imaging.](image-url)
Data-driven approaches and the brain - Calhoun

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area has found high replicability, increased sensitivity to individual subject classification, and evidence of multiple sources of variation including sleep/arousal, emotion, and even mind wandering. In one study, a sliding-window approach was used, followed by clustering, to estimate patterns of connectivity from which individual subjects move into and out of over time. When evaluating the relationship of these “states” with schizophrenia, we found the patients tended to spend more time in the more weakly connected states and vice versa for the healthy controls (Figure 5). This expands our perspective on schizophrenia beyond the commonly observed weaker connectivity patterns. Additional relationships between cortical and subcortical structures (e.g., putamen, thalamus) also showed strong state and group dependencies. Other work has identified the presence of “sticky states” whose presence is correlated with, e.g., negative symptoms in the patients. Extensive ongoing work from many groups continues in this area and undoubtedly, such work will provide further insights into brain connectivity and hopefully schizophrenia. In a later section, we will discuss links between time-varying connectivity and brain structure.

Structural networks subserving functional networks

Interestingly, if one compares the results from SBM of sMRI data and group ICA of fMRI data, it is clear that some of the SBM components are quite similar to the resting fMRI networks that are widely studied. The sMRI maps resemble the fMRI maps, but with less specificity (that is, typically multiple fMRI networks comprise a single sMRI network), as one might expect. Figure 6 shows an example of results from approximately 600 individuals comparing sMRI and fMRI networks.

The group ICA model can also be used to analyze probabilistic dMRI data in a data-driven manner which, in contrast to SBM of FA, preserves the directional information contained in the dMRI data. In that case, one computes a region-by-region (or voxel-by-

Figure 4. Examples of within and among network connectivity information. The left panel shows brain regions parcellated from resting fMRI data using group ICA and the right panel shows the functional network connectivity (FNC) matrix among these regions (cross-correlation). fMRI, functional magnetic resonance imaging; ICA, independent component analysis.
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voxel) matrix for each individual which contains the diffusion probabilities for traversing the space and enters these matrices into group ICA. This is called connectivity matrix ICA (cmlICA). The results from a subset of corpus callosum components output from a cmlICA analysis of almost 600 individuals are shown in Figure 7. This model provides a powerful way to decompose such data which is not restricted to specific regions of interest or specific atlases of tracts, allowing the data to speak for itself. Importantly, it also enables us to directly relate seed-based connectivity to group ICA results, and provides a computationally much faster way to compute these measures.39 Using the single-subject output from the back-reconstruction step allows calculation of group differences in the identified components.39 One can also combine both functional and structural information within a single analysis using such a model.

Deep learning

More recent models include the development of deep learning approaches which can be applied to neuroscience data.54 Deep learning refers to an approach in which multiple models are essentially combined together to create a more complex (deeper) model. Deep learning is typically implemented as a stacked neural network, and as such is closely related to ICA (ICA can be modeled as a single-layer neural network). This allows for the capture of more complex and nonlinear relationships within the data. Interestingly, the restricted Boltzmann machine (RBM), a building block of deep learning models, provides results that are highly similar to those of ICA.55 Figure 8 shows an example of the application of a deep belief network (essentially stacks of RBMs) to sMRI data from a range of patients including schizophrenia, schizoaffective disorder, and bipolar disorder, as well as healthy controls. Interestingly, as the depth of the model goes from one to two to three, the separation between the two groups increases. In addition, despite the more complex model, there continues to be overlap between some subjects, highlighting the complexity of categorizing these individuals who have disorders which share overlapping symptoms and for which we do not yet have an underlying cause. Such approaches can help us with potentially refining diagnostic criteria by characterizing the degree to which individuals are well separated using the biological data.56

Data fusion

Importantly, one can also study the relationship between brain function and brain structure more directly, allowing the data from multiple modalities to interact with one another, called data fusion.15 An approach called joint ICA provides a way to do this, by jointly extracting from multiple modalities maximally independent components that share a common covariation among subjects. The joint components share a common loading parameter which quantifies the degree to which each subject expresses the joint component (Figure 9; top). An example of joint ICA analysis of brain connectivity during an auditory oddball task and gray matter concentration is shown in Figure 9 (bottom). In this case, the analysis included patients with schizophrenia and healthy controls and the loading parameter associ-
### Basal ganglia networks

<table>
<thead>
<tr>
<th>s-IC</th>
<th>rs-IC</th>
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<tbody>
<tr>
<td>IC 51 (-26, +2, +4)</td>
<td>IC 21 (0.59) (-26, +3, +4)</td>
</tr>
<tr>
<td>IC 72 (-12, +16, +12)</td>
<td>IC 27 (0.53) (-12, +18, +12)</td>
</tr>
<tr>
<td>IC 17 (+5, -65, +57)</td>
<td>IC 72 (0.43) (+5, -65, +66)</td>
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### Posterior networks

<table>
<thead>
<tr>
<th>s-IC</th>
<th>rs-IC</th>
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<tbody>
<tr>
<td>IC 43 (+5, -41, +20)</td>
<td>IC 53 (0.45) (+5, -41, -20)</td>
</tr>
<tr>
<td>IC 55 (+5, -92, +3)</td>
<td>IC 46 (0.44) (+5, -92, +3)</td>
</tr>
<tr>
<td>IC 50 (0.40) (+5, -80, +51)</td>
<td>IC 45 (0.28) (+5, -80, +37)</td>
</tr>
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The diagrams illustrate the brain regions associated with basal ganglia and posterior networks, highlighting the anatomical locations and correlations with IC values.
Figure 7. cmICA components from an analysis of probabilistic diffusion captures regions that are showing similar orientation in their diffusion profiles. Both individual components (top) as well as a rendering for components that were traversing the corpus callosum (bottom) are shown. cmICA, connectivity matrix ICA.

Figure 8. Deep learning results from sMRI data from schizophrenia, schizoaffective, and bipolar patients as well as healthy controls. Each dot represents an individual subject. As the depth of the model increases, the separation between the groups increases, although there are still boundary cases, which may be useful to help refine the diagnostic categories.
ated with one of the components showed a significant group difference. Interestingly, parietal regions showing reduced gray matter in controls were implicated as associated with increases in task activation. Importantly, the (apparent) gray matter reductions were due to decreases in the white matter,\textsuperscript{57} further emphasizing the importance of incorporating sMRI, dMRI, and fMRI together.

There are a few approaches capable of combining more than two modalities including linked ICA,\textsuperscript{58} independent vector analysis,\textsuperscript{59} PCA,\textsuperscript{30} parallel ICA, and an extension of joint ICA, called multiset canonical correlation analysis/joint ICA (mCCA+jICA).\textsuperscript{60, 61} The mCCA+jICA model approach leverages the strength of mCCA, which identifies maximally correlated multimodal latent variables from the data, with joint ICA, which enables leveraging of the higher order statistical information in the data. These approaches provide a fully data-driven way to identify linked multimodal variables. An extension of this approach allows for the incorporation of prior knowledge to constrain the problem further by adding a reference function to the mCCA approach. This approach was used to identify multimodal patterns which are linked to a composite cognition score based on cognitive scores assessed with the MATRICS Consensus Cognitive Battery (MCCB).\textsuperscript{62} An extensive network of gray matter, white matter, and functional regions were identified and showed significant differences in schizophrenia patients versus healthy controls (Figure 10). The analysis and results replicated in a second cohort, underscoring the robustness of the resulting patterns. Interestingly, in addition to implicating specific structural and functional regions in the brain, one can also observe more similarity between individuals in the structural features and more variability in the functional features.

![Figure 9](image_url)

**Figure 9.** Joint ICA takes input features (e.g., gray matter segmentation maps and fMRI activation maps) and estimates maximally independent components from both modalities which share common covariation among subjects. Example of linked regions associated with an auditory oddball task and gray matter concentration.\textsuperscript{57} ICA, independent component analysis.
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Preprocessing

Features

MCCA with reference

Joint ICA

(fMRI) HC

(SZ) fALFF

(DTI) HC

Gray Matter

X1

X2

X3

DTI

sMRI

Reference

Canonical Variants $A_i$

Components

Joint component highly correlated with the reference in mixing profile and high spatial independence

$X_k = D_k \cdot S_k$

$D_k = A_k \cdot W^{-1}$

Correlation matrix between $A_k$ and $A_j$

$E(A_k^T A_j)$

$E(A_k^T A_2)$

$E(A_k^T A_3)$

FBIRN (CMINDS)

GM

UNM (MCBB)

FA

fALFF
reflective of the more state-like aspect of the fMRI measurement.

**Structural substrates for time-varying connectivity**

Another question of interest is to what degree, and in what ways, is the highly dynamic connectivity which has been observed in the past few years dependent on a structural substrate. This is especially important in the context of psychopathology, as there are known structural differences that have been observed. Further analyzing the same data set as summarized in Figure 5, we implemented a deep-learning model designed to capture nonlinear links between brain structure and dynamic state. For example, one can use a model that estimates both alignment between different sources of information (eg, the caption and figure in an image) and the sequential relationship between dynamic data (eg, translation of two text phrases). Using this model, we identified two covarying structural networks in temporal lobe, both showing significant differences in alignment between patients with schizophrenia and healthy controls. Interestingly, the structural links parallel the amount of time each group spent in a given state. That is, state 3 was occupied more often by the healthy controls and also showed a stronger structure/function alignment with insula/temporal lobe, whereas state 2 was occupied more of the time by schizophrenia patients and showed a stronger structure/function alignment with medial temporal lobe. Such results highlight the highly synergistic relationship between brain structure and brain function and the need for more work in this area.

**Conclusion**

In conclusion, this paper discussed the synergistic relationship between brain structure and function, provided a selective review of data-driven approaches for capturing multivariate relationship both within and between brain structural and functional measure, and presented

![Figure 10](image-url). (Opposite) Advanced fusion approach (mCCAR+jICA) which allows one to identify multimodal features that are linked to an external variable (top). Example showing multimodal features (for both original analysis and replication) linked to cognition and also showing group differences in schizophrenia versus healthy controls.; mCCAR, multiset canonical correlation analysis; jICA, joint independent component analysis

![Figure 11](image-url). Nonlinear alignment of brain structure regions to dynamic connectivity patterns (left) reveal significant changes in the alignment of structure in the temporal lobe region in schizophrenia versus controls.
multiple analytic examples from prior studies. There are still only a small number of studies that directly evaluate the relationship between brain structure and brain function; without this information we will undoubtedly be ignoring important information that can inform us about the healthy brain and the ways in which it is impacted by psychopathology.

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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. 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. Abnormalities at any stage of this process—from the initial formation of the brain’s network to its ongoing reorganization throughout the course of development—may underlie the evolution of neurodevelopmental disorders such as schizophrenia.

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. The first episode is typically preceded by a prodromal phase characterized by subthreshold psychotic symptoms, social withdrawal, cognitive dif-

Keywords: brain network; connectome; connectivity; critical window development; illness trajectory; neurodevelopmental model; schizophrenia

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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.

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 macroscale23 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. 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. 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.

A competing theory on hub formation from the field of network science is the preferential attachment or “rich-gets-richer” hypothesis. 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, 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 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. 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. 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 and with ongoing changes in the diameter and myelination of axonal connections underlying wide-spread changes in structural connectivity beyond the early postnatal phase.

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. 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 states that sensitive periods for seeing, hearing, speech production, and higher cognitive functions have been documented in developing children. 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.” 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. 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. 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. 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. 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. 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.

**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. 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. 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). 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.

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. With age, higher-order networks develop and take on an increasingly central role in the brain’s functional organization. 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. 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.

**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. 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, e.g., between frontal and parietal circuits—strengthens, suggesting a reorganization of the functional connectome during the transition from adolescence to early adulthood. 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. 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 include 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 functions68 and the failure of such maturation could lead to cognitive deficits in schizophrenia. More-

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**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-modal 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, leading to internal preoccupation, 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 disengagement 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. 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.

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 neuropathological 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. 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.

**Box 1. Hierarchical brain and cognitive development.**

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. 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.
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. 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. 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 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 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.

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, 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. 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 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.

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. These studies may help elucidate how and when risk factors for schizophrenia...
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Translational research


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Graph theory methods: applications in brain networks
Olaf Sporns, PhD

Introduction

Some of the most daunting scientific challenges of the 21st century involve complex social, technological, and biological systems—from the stability of global financial and economic networks to the spreading of epidemics, the web of biotic interactions in an ecosystem, and metabolic and transcriptional processes inside cells and tissues. An important theoretical foundation for understanding complexity is network science, which focuses on the structure and function of systems that are composed of numerous elements and their interactions. Over the past couple of decades, the network perspective has gained considerable ground in neuroscience.

Brain networks have become a fertile area of research, now called network neuroscience, ranging across different scales, from interacting biomolecules all the way to social behavior. A major driving force has been the application of mathematical and computational network science tools to neurobiological systems, especially models and measures of graph theory.

Graph theory is a branch of mathematics that dates back to the 18th century. Today, applications of graph theory pervade all scientific disciplines as well as many other aspects of our lives.
modern information and computing technologies. The brain is a natural fit for graph theory approaches as it is readily represented as a network (a graph) of elements and their pairwise interconnections, also called nodes and edges. Comprehensive maps of brain connectivity have given rise to the emerging field of connectomics, a central focus of which is the systematic and quantitative study of brain networks and graphs.

Graph theory methods, when applied properly, can offer important new insights into the structure and function of networked brain systems, including their architecture, evolution, development, and clinical disorders. This brief review surveys some of the most relevant graph theory methods and illustrates their application in various neurobiological contexts. Comprehensive coverage of the topic is beyond the scope of this article (see a recent textbook). Instead, the emphasis here is on highlighting some new methodological trends, discussing their application to brain data, and suggesting future avenues for graphical models and measures.

**Basic concepts**

Networks or graphs are collections of elements (nodes, vertices) and their pairwise links (edges, connections) which, in their simplest form, can be summarized in the form of a connection (or adjacency) matrix. The complete set of all pairwise connections defines the graph’s topology, providing a complete map of all relations among nodes and edges. Brain nodes may be individual neurons or entire brain regions, depending on the measurement technique. Edges can take on binary or weighted values, and they can be directed or undirected, depending on how interactions are estimated from empirical data. The selection of appropriate graph theory methods for modeling and analyzing empirical data requires that the nature of the edge representation is taken into account. Put differently, not all graph theory methods fit all purposes.

The two most common species of brain graphs describe structural and functional connectivity among neural elements. Structural graphs are generally sparse (most possible structural connections in a given nervous system do not exist) and temporally relatively stable (but subject to plasticity and development). In contrast, functional graphs record statistical dependencies among neuronal time series, and hence are often dense and highly variable across time. The dichotomy of structural and functional graphs is important to consider, as each domain draws on a specific subset of graph theory methods that are commensurate with the origin of the data.

The definition of nodes generally requires sophisticated data-processing pipelines and is the subject of much methodological discussion. In whole-brain networks acquired with neuroimaging, nodes are often derived from a parcellation of the original voxel-level data, designed to extract coherent brain “areas” that form the building blocks of structural or functional brain networks. Some approaches leverage anatomical templates, others pursue parcellation in a data-driven manner, eg, by boundary detection and clustering patterns of connectivity. A recent multimodal study employed machine learning to extract coherent brain regions on the basis of several different anatomical and functional criteria. Node definition is considerably more straightforward in studies of circuits and neuronal populations, where individual neurons are natural candidates for individual network nodes.

A major simplification inherent in most current applications of graph theory is the assumption that, within a given network representation, all nodes and edges are identical and homogeneous. Annotation of nodes and edges can address this limitation of simple graphs, by allowing additional layers of data to be linked to network elements, which can be useful for identifying biologically meaningful network communities. A further elaboration of simple graphs is the inclusion of multidimensional relationships which can be expressed in multilayer networks, composed of different layers that encode different types of interactions (eg, synaptic links, temporal correlations, transmitter systems, or gene coexpression).

Graphs can be investigated at different levels of scale, and specific measures capture graph attributes at local (nodal) and global (network-wide) scales. Nodal measures include simple statistics such as node degree or strength, while global measures express network-wide attributes such as the path length or the efficiency. Intermediate scales can be accessed via hierarchical neighborhoods around single graph elements, or by considering subgraphs or motifs. Motifs are defined as subsets of network nodes and their mutual edges whose patterns of connectivity can be classified into distinct motif categories. In empirical networks, these categories often occur in characteristic frequencies that
can be compared with distributions from appropriate (random) null models. In the brain, motif analysis has been applied to structural and functional graphs.21

Most highly resolved structural brain networks are not fully, or even densely, connected. In such sparsely connected graphs, the minimal topological distance between two nodes, ie, the length of the shortest path, often involves multiple steps. Network paths are composed of unique edges that are traversed only once, while the usually much more abundant walks between two nodes can use edges any number of times. Paths and walks are considered important for the flow of signals and communication, and are the basis for popular graph metrics such as the so-called efficiency which defines the global capacity of a graph to pass information via short paths. Importantly, concepts of path lengths and efficiency are most naturally applied to brain graphs that represent structural connectivity. In contrast, they have rather different (and potentially problematic) interpretations when applied to functional connectivity. The distinction derives from the nature of functional connectivity which reports statistical associations among neural time series rather than a web of physical links that propagates neural signals.

**Modularity**

Among the most widely encountered and biologically meaningful aspects of brain networks is their organization into distinct network communities or modules.6,10,23 (Figure 1). Modules are useful to partition larger networks into basic “building blocks,” ie, internally densely connected clusters that are more weakly interconnected amongst each other. Modular partitions have neurobiological significance as their boundaries separate functionally related neural elements, define critical bridges and hubs that join communities, channel and restrict the flow of neural signals and information, and limit the uncontrolled spread of perturbations.28

There are numerous computational techniques for extracting communities and modules from complex networks.24,28 One of the most widely used approaches in network neuroscience is modularity maximization which aims to divide a given network into a set of non-overlapping communities by maximizing a global objective function, the modularity metric.26 Originally, this metric was formulated to detect communities whose internal density of connections is maximal, relative to a degree-preserving null model. More recently, variants of the metric that can be applied to directed27 and signed networks have been proposed. Of special note are variants of the scheme that are designed to deal with correlation matrices, a data type that is often encountered in studies of functional connectivity.

Modularity maximization faces important methodological limitations that need to be addressed. One limitation refers to the existence of several, often quite numerous, distinct partitions that are almost equally optimal (ie, degenerate) under the modularity metric. Given the inherent noisiness of empirical estimates of the network topology, it seems arbitrary to pick a single “optimal” partition as the sole representative of the network’s community structure. Instead, multiple degenerate solutions should be aggregated into consensus partitions, for example by forming an agreement matrix that can then be reclustered until a single consensus partition emerges.30 The application of such a consensus approach can also reveal additional facets of community organization, including the degree to which individual nodes are affiliated with their host community.28,31

Another fundamental limitation is the inability of the original modularity metric to detect modules below a certain size. This resolution limit can be addressed in a number of ways. One common avenue is the inclusion of an additional resolution parameter into the modularity metric that rescales the intrinsic null model and allows the detection of smaller or larger communities.33 Varying the resolution parameter is important since many brain networks exhibit communities across different scales, which renders the selection of a single scale of analysis potentially problematic. The issue becomes of fundamental neurobiological importance when community detection methods are used to identify, for example, specific partitions of the brain into resting-state functional networks or “functional systems.” While several landmark studies have proposed canonical partitions of such networks that are now widely applied in the field, it should be noted that other partitions at both finer and coarser scales may represent additional levels of organization. Up to date, most studies circumvent full multiscale analysis by selecting one or a few settings of the resolution parameter, usually based on some criteria of partition stability.

One way to preserve and represent the full multiscale structure of brain networks is to perform consensus clustering across multiple spatial resolutions, an...
Module 1

Module 2

Edge
Node

H ub

Figure 1. Modularity. (A) Schematic network plot showing a set of nodes and edges interconnected to form two relatively distinct modules (communities). Note that the two modules are linked via a single hub node (black) that maintains two bridges between the two modules. Panels (B) to (E) use a 77-node data set from reference 74, representing the 77 areas and directed weighted projections of the rat cerebral cortex. (B) The plot at the top illustrates the varying number of modules as the value of the resolution parameter is increased from 0.1 to 4.0. The number of detected modules increases from 1 to 22 within this range. (C) The matrix plot represents the variation of information between all detected partitions within the range of the resolution parameter plotted above. Dark blue corresponds to a variation of information (distance) of zero, i.e., identity. The region around gamma=0.7 is the most homogeneous region within the range. (D) The rat cerebral cortex connection matrix (weights displayed on log-scale), reordered by module assignment for gamma=0.7. The three modules are indicated with white boundaries. (E) The multiscale co-assignment matrix, computed using the method described in ref. 37. Co-assignment varies between 1 (node pair in same module at all scales) to 0 (node pair never co-assigned at any scale). Tree plot at the bottom shows all hierarchically clustered solutions, with the top one corresponding to the same three modules shown in panel (C). Within each of the three modules, additional modular structure is detected.
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An approach that combines sampling the entire range of possible spatial resolutions with a hierarchical consensus clustering procedure. The approach returns a coassignment matrix that captures the probability that each node pair remains associated within the same community as the scale is varied, together with a hierarchy that illustrates their mutual relations. Multi-resolution consensus clustering delivers a more complete picture of community structure than is provided by single partitions, and avoids complicated and often rather arbitrary models for selecting relevant scales in brain networks.

Finally, many extensions of the above framework for detecting communities in brain networks should be noted. While modularity maximization detects non-overlapping communities, it may also be useful to define modules as overlapping communities (eg, see ref 38), ie, sets of nodes where some, or all, nodes maintain multiple affiliations. Other methods, eg, multislice modularity,\(^4^9\) are designed to track modular partitions, and their nodal memberships, across time. Yet another promising avenue, with deep historical roots in the social sciences, is the use of block models.\(^4^0\) Block modeling attempts to fit a statistical model for generating networks to empirical data to identify those model parameters that provide the best match. For example, those parameters may correspond to a number of blocks and the corresponding within and between block connection probabilities. Since block models are not limited to strictly modular arrangements (maximizing within-module density while minimizing between-module density) they can detect more complex block structure in networks,\(^4^1\) including the existence of a dense core and a more weakly connected periphery. In addition to versatility, block models offer the advantage of fitting a generative model to data (see below), which may offer insight into the processes that underlie the observed network topology.

### Centrality and communication

Empirical networks have architectures that differ significantly from those of classic random graph models – most importantly, their nodes and edges are not equal in the way they are connected with the rest of the network. Far from being “equipotential,” the ways in which nodes and edges are embedded within the overall topology play a major role in determining their specific contributions to network function. Thus, network theory reconciles functional specialization with distributed processing—a dichotomy that has in the past led to strongly polarized theories of brain function, to the detriment of scientific progress.

Indeed, a major rationale for mapping brain connectivity arises from the idea that connectivity drives the functional specialization of local network elements. This idea is inherent in the notion that different brain regions have unique connectivity fingerprints that are indicative of their network embedding and predictive of their functional roles.\(^4^2\) Similarities among connectivity fingerprints can be informative of functional groupings of areas and their mutual relations.

Numerous measures quantify the potential of individual nodes and edges to influence the global state of the network. Many of them allow the identification of network hubs,\(^4^3,4^4\) generally defined as highly central parts of the network. The number of connections maintained by a node (its degree) or the combined weight of these connections (its strength) often provides a strong indicator of influence or centrality. Other measures of centrality take advantage of the layout of the shortest paths within the network, and record the number of such paths that pass through a given node or edge, a measure called the betweenness. Yet another way to approach centrality is by referencing the relation of nodes and edges to a network’s community structure. The participation coefficient quantifies the diversity of a given node’s connections across multiple modules—high participation indicates that many of these connections are made across modules, thus linking structurally and functionally the distinct communities. This measure is particularly useful in brain networks, as it can be applied to both structural and functional network data.\(^4^5\)

Most measures of node centrality are mutually related (and hence statistically correlated); for example, in most (but not all) networks nodes with many connections (high degree) also serve as intermediaries on many short paths (high betweenness). Since different measures of centrality index different aspects of network organization, it can be beneficial to rank nodes by aggregating multiple centrality measures.\(^4^3\)

Centrality measures can be useful tools for charting the global architecture of a brain network. Of particular neurobiological interest is the mutual association among highly central (eg, high degree) nodes. If these nodes maintain interconnections that are found to be denser than expected by chance (ie, a suitable null
model) the network is said to exhibit so-called rich club organization \(46\) (Figure 2). Rich clubs have been found in virtually all structural connectivity data, from the connectomes of humans \(47\) to those of invertebrates. \(48,49\) Rich club organization tends to centralize network traffic, as the dense core formed by interconnected high-degree nodes attracts the bulk of short network paths that link lower degree nodes to each other. \(50\) This important role in network communication is thought to boost network communication and efficiency, thus trading off against the high wiring cost involved in linking spatially distributed hub regions.

While much of the interest in centrality is based on the putative role of hubs in network communication, it should be noted that the mechanisms by which brain networks communicate remain obscure. Most models and their associated graph theory metrics assume that communication unfolds along the most efficient and shortest paths available. However, this idea ignores the fact that these paths cannot be discovered by neural elements or signals in the absence of global information about the network topology. \(22\) Hence, alternative models based on spreading and diffusion \(51\) and path ensembles \(52\) are important to explore in future work.

Emerging trends

This final section briefly reviews several new directions that have great potential for future applications in brain networks.

Generative models

Most current graph theory methods applied to brain data deliver descriptive statistics that capture various aspects of network architecture. While such measures can be informative about the topological characteristics of a specific empirically measured network, their estimation should always be accompanied by some estimate of statistical significance or evidence. Every graph, even one generated by an entirely random process, will exhibit some graph attributes, including some chance level of clustering and modularity. Null models are important adjuncts of descriptive graph analysis as they allow discriminating which graph attributes are due to chance, and which exceed the expected values given by the null model. The choice of a proper null model is crucial for any descriptive analysis, as it will determine which graph features survive statistical comparison. Classic null models involve the rewiring of an empirical graph by swapping connections such that local degree is preserved while the global graph architecture is randomized. Other null models preserve subgraph frequencies to estimate the significance of larger subgraph distributions, or null models that preserve spatial locations of nodes.

Null models that fix a number of different factors such as local node measures, spatial locations, and wiring cost effectively become generative models of the empirical data. They generate graphs that may become indistinguishable from the empirical network, and in that sense can account for its topological properties. Hence, generative models can provide important insights into the factors that have shaped the emergence of specific architectural or performance characteristics. As such they are important reminders that not all graph attributes are the product of adaptation, and instead may have arisen as “spandrels” along the way. \(53\) a mere by-product of other more basic generative factors such as degree distributions or spatial embedding. Another important insight that can be gleaned from the design of generative models is that many graph attributes are mutually dependent and arise jointly from a common set of driving factors. For example, high clustering is invariably linked to particular statistics of subgraphs that favor triangles, and strongly favored by spatial embedding and wiring conservation.

Spatial embedding as an important generative principle behind the organization of brain graphs deserves special mention, as it is a fundamental constraint on brain architecture. \(54,55\) Much evidence points to distance-dependence as a major rule that governs the topology of anatomical brain connectivity within local circuits in single brain regions as well as for inter-areal projections. Generative models that combine spatial embedding with other, nonspatial, topological rules have suggested that their mutual trade-off may more fully account for characteristics of brain topology than any single (spatial or topological) factor alone. \(56\)

Generative models are also crucial for understanding the emergence of dynamic states and functional connectivity. \(57\) Many classic models explored in computational neuroscience are generative models, in that they attempt to generate neuronal activity and dynamics from simple biophysical and structural ingredients. In human neuroimaging, the relationship between structural and functional connectivity has been illuminated by the use
of computational models that can capture some of the patterns exhibited in brain dynamics. Some of these generative models are simple, as they can be computed analytically on top of structural graphs, or make minimal assumptions (e.g., linearity) about the nature of neuronal dynamics. Other models utilize detailed biophysical mechanisms to generate neuronal time series and population activity. Implementation of large numbers of generative models with varying model parameters combined with model selection are central to estimate variations in network parameters, including causal effects, in the course of varying conditions of stimulus and task.

**Dynamic networks**

Brain networks are not immutable, static constructs—rather, their structural and functional connectivity patterns change on multiple time scales. Data on time-varying brain graphs generally takes on the form of time series (or stacks) of graphs that form an ordered series of snapshots, for example recorded in the course of learning or across developmental stages. Changes in network topology can be tracked by computing graph measures on each time point followed by the subsequent examination of the resultant time courses of

![Figure 2. Paths and rich club organization. (A) Schematic network plot illustrating an optimally short path (length three steps) that links the two nodes shown in black; intermediate nodes are shown in gray. (B) Left: Using the rat cerebral cortex data set from ref 74, this plot shows the density of subgraphs, compared with a degree-sequence preserving null model, with subgraphs increasing in size from 1 to N (N=77) and with nodes arranged by total degree. Subgraph of size 1 comprises the single node with highest degree, subgraph size 2 the one comprising the two highest degree nodes, and so forth. Red data points indicate subgraphs for which the density is significantly above that of the null model (P<0.001, false discovery rate-corrected). Middle: Rat cerebral cortex connection matrix, with node arranged by total degree (highest degree node in the top row and left-most column). Note dense (nearly full) connectivity among the top 15 high-degree nodes (white lines). Right: Edge betweenness displayed in the same node ordering as middle panel. Note that there are numerous edges with high edge betweenness in upper left section of the matrix. These edges link high-degree nodes and they also participate in a large number of shortest paths across the network.](image)
graph metrics. Another analysis approach involves arranging this stack into a series of time slices that are mutually coupled and can be analyzed as a single graph construct.39 This allows the derivation of nodal measures of flexibility which can pinpoint parts of the network that are more variable across learning or development.61

Much effort has recently been expended to track fast changes in graph topology and organization of functional networks recorded with fMRI.62 Most commonly, a long time series of fMRI activations is partitioned into shorter “windows” that are then analyzed separately. Possible confounds are measurement artifacts such as physiological noise and increased uncertainty of estimating the magnitudes of functional connections on short samples.63 In resting state, fMRI networks appear to undergo fluctuations between states of higher integration and segregation,64 or modularity.65 Similar transitions between different network states occur during task switching66 and in the course of cognitively demanding spontaneous stimulation.67

Multilayer networks

The arrival of multiomic data has enabled the joint analysis of networks between elements of neurobiological systems at different levels of organization. Prime examples are recent studies that combine maps of anatomical and functional networks, as well as studies that combine large-scale brain connectivity data with spatially registered data on patterns of gene expression. The latter have yielded important insights into relations between the centrality of network elements, for example their membership in a dense core or rich club, and distinct genetic signatures in energy metabolism.68

In most studies so far, graph theoretic analysis proceeds through simple comparison or correlation of graph metrics across different levels (eg, anatomy and genetics). In the future, more explicit use of a multi-layer graphical framework is likely to occur. A few early examples are studies that place structural and functional connectivity into a multilayer model, eg, with data from human neuroimaging69 and magnetoencephalography.70

Algebraic topology

All graph theory approaches discussed so far build on networks that are composed of pairwise (dyadic) interactions. However, higher-order interactions can be highly informative for understanding non-random attributes of brain networks. Such higher-order relations can be represented with tools from applied algebraic topology, such as so-called simplicial complexes or simpli
ces.71 Simplices reframe the problem of relational data in terms of collections of vertices: a 0-simplex is a node, a 1-simplex is an edge, and a 2-simplex is a filled (connected) triangle. Simplices can be used to locate cliques (all-to-all connected subgraphs) or cavities. Recent applications of simplices to human connectome data have shown the utility of the approach for identifying both densely connected groups of nodes as well as other patterns of connectivity (eg loop-like paths) that would facilitate parallel processing.72 Finally, the related area of topological data analysis attempts to detect, quantify and compare mesoscale structure present in complex network data. Essentially, the approach attempts to embed the data in a way that provides an optimal summary of its global structure. A recent example used topological data analysis to reveal dynamical organization in multitask fMRI time series, by creating graphical representations of relations among single image frames at the level of individual participants.73 These representations allow a comparison of how individuals transition among multiple cognitive tasks and states and could provide useful markers for clinical diagnosis and treatment. Overall, the arrival of these topological methods capitalizes on higher-order and high-dimensional features in brain data that have so far been inaccessible with simple graph methods, and are therefore promising avenues for future investigation.

Conclusion

The growth of network neuroscience over the past decade or two has been nothing short of astonishing. A major driving force for this rapid expansion is the availability of relational data recording couplings and interactions among elements of neural systems. For now, most studies remain descriptive and focus entirely on pairwise interactions resulting in graphs composed of dyadic links. But graph theory is much more powerful than current methods applied to brain networks suggest. Generative models, dynamic networks, multilayer models, and algebraic topology are just a few of the promising directions that are currently pursued. With time, these new approaches will likely find applications...
not only in basic, but also in clinical and translational research. For years to come graph theory methods will remain indispensable tools to further our understanding of the brain as a complex interconnected system.

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Over the past decades, network neuroscience has played a fundamental role in the understanding of large-scale brain connectivity architecture. Brains, and more generally nervous systems, can be modeled as sets of elements (neurons, assemblies, or cortical chunks) that dynamically interact through a highly structured and adaptive neurocircuitry. An interesting property of neural networks is that elements rich in connections are central to the network organization and tend to interconnect strongly with each other, forming so-called rich clubs. The ubiquity of rich-club organization across different species and scales of investigation suggests that this topology could be a distinctive feature of biological systems with information processing capabilities. This review surveys recent neuroimaging, computational, and cross-species comparative literature to offer an insight into the function and origin of rich-club architecture in nervous systems, discussing its relevance to human cognition and behavior, and vulnerability to brain disorders.

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other (Technical box).6,7 This organizational property is of particular interest because it dominates network topology8 and influences dynamic interactions among network elements.9 In the brain, rich nodes and their axonal projections enable short communication pathways and mediate connectivity among segregated functional systems.10,11 Rich connections span long distances in the white matter and have distinctive myelination and microstructural properties.12 Rich regions exhibit high oxidative metabolism and microstructural complexity in pyramidal neuron architecture, indicative of sustained activity and large computational capacity (Figure 1).13,14 These attributes suggest that rich clubs play a distinctive role in sustaining efficient communication across the whole-brain network, contributing to higher-order functions. However, the high connectivity density and metabolic demand make rich clubs costly features of brain networks and likely to be vulnerable to pathogenic agents.2 As a result, rich clubs express a trade-off between functional value, biophysical cost and vulnerability.

How do rich clubs convey dynamic integration of brain processes? Why, and in response to which selection pressures, has rich-club architecture emerged in neural networks? What are the functional and evolutionary benefits and vulnerability drawbacks of the rich-club extra-connectivity? The field of network neuroscience offers an optimal framework to answer these questions. First, the conceptualization of nervous systems as networks of nodes (neurons, cortical columns, or gray-matter chunks) and connections (synapses, axons, or white-matter bundles) grants a sufficient level of abstraction for cross-scales and cross-species comparisons, allowing to integrate multimodal and multiscale data. Second, the mathematical graph-theoretical framework is well-suited to the study of collective dynamics of interlinked elements, both through mechanistic models and computational analyses. Third, network generative and developmental models enable uncovering the roots and the evolutionary aspects of nervous systems’ organization.

The aim of this review is to provide an insight into the function and origin of the rich-club architecture observed in the human brain, and more generally in nervous systems, from a network science perspective. In the first part of the review, we mainly reason on the concept of functional integration and survey a selection of recent neuroimaging and computational studies that directly or indirectly investigate the contribution of rich-club architecture to whole-brain integrative dynamics. Next, we examine neural-network organizational principles across a series of animal species and scales of investigation, questioning the principles that contribute to the origin and evolution of rich clubs. Considering the relevance of rich-club architecture to clinical neuroscience, we conclude the review with a discussion on pathophysiological factors contributing to the vulnerability of rich clubs to neurological and psychiatric disorders, including schizophrenia and Alzheimer disease.

The functional role of the rich club

The topological characterization of neural networks positions the rich club at the center of brain communication pathways. From a mechanistic perspective, the short distance separating rich nodes from any other (peripheral) node in the network, and the gathering of shortest paths through rich edges make the rich club a putative core of neural integration. This view fosters a deeper conceptualization of functional integration in the brain, by means of both functional neuroimaging and computational studies, and in relation to the underlying anatomical substrate.

Functional integration

In functional neuroimaging experiments, the concept of functional integration has been associated with
measures of statistical dependency (functional connectivity) between neural-related signals recorded across distinct locations in the brain. Interestingly, functional connectivity is partially predicted by structural connectivity, so that topologically close regions in the structural connectome also have the tendency to functionally connect. Paradoxically, the highly structurally connected rich club demonstrates low functional connectivity values at rest, questioning its role as an integrative core of the brain. While the shared structural connectivity, cytoarchitectural characteristics, and transcriptional profiles suggest a common function in the brain, it is not clear whether rich regions mainly act in concert or rather alternate over time to flexibly coordinate peripheral functional modules.

Figure 1. Rich-club curves. To assess whether a network demonstrates a rich-club architecture, a “richness” curve is drawn as a function of a nodal “richness” parameter (here, the nodal degree $k$) and compared with an equivalent curve drawn from a set of randomized networks. Panel A shows the rich-club curve of the cat structural connectome. Each point of the black curve represents the connection density $\Phi(k)$ between nodes of the cat connectome that have degree equal or larger than $k$. The “richness” red curve is derived from a series of randomized versions of the cat connectome, where the randomization procedure preserved the degree-sequence of the network. The pink area indicates the rich-club regime, where the connection density between high-degree nodes of the cat connectome is larger than expected in the randomized networks. The definition of network “rich-clubness” naturally selects nested rich subnetworks. Panel B sketches a whole-brain network (in blue) and rich-club subnetworks corresponding to two different values of the richness parameter $k$. Rich and peripheral nodes are represented in red and orange; rich, feeder, and peripheral connections are represented in red, orange, and yellow. Rich-club characteristics of the primate brain. Panel C: In the macaque connectome, the nodal richness parameter ($k$) significantly correlates with the dendritic tree size in layer III pyramidal neurons (right corner: color-coded macaque cortical map of dendritic tree size for 22 cortical regions). In humans, large proportions of rich and feeder brain connections span long distances in the white-matter. Panel D pictures the proportions of short- (<30 mm), middle- (30 to 90 mm) and long- range (>90 mm) connections belonging to the peripheral (yellow), feeder (orange), or rich (red) connection-classes. Figures A, C, and D have been adapted with permission from ref 6: Zamora-López G, Zhou C, Kurths J. Cortical hubs form a module for multisensory integration on top of the hierarchy of cortical networks. Front Neuroinform. 2010; 4:1 - ref 14: Scholtens LH, Schmidt R, de Reus, MA, van den Heuvel MP. Linking macroscale graph analytical organization to microscale neuroarchitectonics in the macaque connectome. J Neurosci. 2014; 34:12192-12205 - ref 10: van den Heuvel MP, Kahn RS, Gole J, Sporns O. High-cost, high-capacity backbone for global brain communication. Proc Natl Acad Sci U S A. 2012; 109:11372-11377.
To approach this question, it is necessary to consider a growing body of literature that investigates dynamical aspects of functional connectivity and time-dependent reconfiguration of brain states. During both resting and task conditions, the brain experiences time-varying functional connectivity and alternates periods of relatively localized activity/parallel processing (corresponding to low functional efficiency and high segregation) with periods of widespread synchronization (characterized by high functional efficiency). How does the rich club position itself within this dynamic landscape? As a first consideration, high-efficiency states consistently involve brain regions that partially overlap with the structural rich club and enable accurate performance of cognitive tasks requiring integration among multiple functional domains. As a second consideration, rich-club nodes and heteromodal cortices are particularly flexible over time, both at rest and in task settings. Flexibility refers to the property of some regions to frequently change their brain-wide functional connectivity profile, dynamically switching their allegiance to other functional communities. Structurally central regions, such as the frontoparietal system and default-mode-network areas, flexibly interact with other functional systems at rest and display variable patterns of functional connectivity across tasks, demonstrating high adaptability to changing demands.

Interestingly, most flexible connections during rest show near-zero time-average functional correlations, which might explain the low levels of functional connectivity observed within the rich club at a time-average scale. Another possible explanation might be that, during rest, the brain tends to be less integrated than in cognitively demanding tasks and to “fall apart” into separate functional modules, so that the rich club could partially lose its integrative role and synchronization during rest.

Taken together, these observations indicate that functional integration cannot be ascribed to a single brain region or subnetwork, but should rather be regarded as a more complex and dynamic process, where flexibility and cross-system allegiance emerge as fundamental features. Structurally rich regions and connections might mediate those time-dependent integrative processes, with rich clubs forming an anatomical workspace for integration.

**Computational underpinnings of rich-club function**

Computational studies simulate the unfolding of functional dynamics on top of structural connectivity architectures, allowing for the assessment of the impact that structural topologies, presence of cores, or connectivity alterations have on global network dynamics. In the framework of this review, we are particularly interested in how a rich-club topology relates to the dynamic integrative processes characterizing nervous systems, and how rich clubs might support optimal information integration/segregation balance and functional complexity of the brain.

An early computational study on the cat connecome investigated how whole-brain activity, and in particular rich-club synchronization, is perturbed by an external input targeted toward primary sensory areas. This study showed that only a subset of the rich nodes tends to synchronize as a consequence of sensory stimulation, while the activities of the other rich nodes remain relatively independent. This result is compatible with above-reviewed experimental findings on rich-club flexibility and suggests that the rich club can functionally separate in response to changing inputs. This functional diversification may also relate to partially heterogeneous topological features of rich nodes, such as diverse participation coefficients to structural communities.

Computational studies also show that a rich-club topology favors synchronization among peripheral areas (ie, integration of different and specialized brain units) and promotes complexity (richness) of brain dynamics. Structurally, single rich nodes tend to be (bidirectionally) connected with pairs of peripheral nodes not directly interconnected themselves, forming triadic resonant motifs. This particular topological configuration promotes synchronization between peripheral nodes through the central rich drivers. Moreover, rich nodes’ signals possess particular spectral properties when compared with peripheral nodes. Computational models that allow heterogeneous local dynamics (ie, heterogeneous spectral characteristics) across brain regions show that, during task execution, the rich club tends to shift from a noisy to an oscillatory behavior that brings peripheral areas into coherence.

Besides this integrative role, rich-club topology seems to promote dynamical complexity of networked systems. Complexity emerges when a dynamical system can access a large landscape of functional states that lie inbetween the two extremes of statistical independence (complete segregation) and global synchrony.
chronization (complete integration) of its constituent elements.\(^5\) When considering the brain system, a condition of high functional complexity would correspond to a large landscape of accessible brain states and “optimal” metastable balance between segregation and integration, allowing both specialized processing and integration into conscious perception and higher-order functions.\(^5\) Simulations demonstrate that a rich-club topology achieves dynamic complexity levels larger than scale-free networks (ie, larger than networks with hubs but no rich-club phenomenon)\(^36\) and matching observations are reported in human functional data.\(^32\) Moreover, selective lesioning of the rich club entails a reduction in the system complexity,\(^32\) suggesting that rich-club organization subserves complexity and integration/segregation balance. This evidence has possible implications for the understanding of pathological mechanisms linking structural connectivity alterations, brain dynamics, and symptomological/cognitive consequences.\(^5,37\)

Overall, rich clubs are characterized by flexible and adaptive functional profiles. Rich nodes tend to mediate communication among distinct functional systems in virtue of their topological characteristics and spectral properties; they promote dynamic complexity and enable the coexistence of diverse integrative and localized functional patterns. The high neural cost of the formation of rich clubs may thus be justified by bringing advantageous integrative and dynamic properties to nervous systems.

**An evolutionary and cross-species perspective**

The wiring architecture of the human brain, and more generally of nervous systems observed in nature, are expressions of evolution, a process where different and often competing biological constraints and selection pressures shape biological organization. Understanding the mechanisms involved in the evolutionary path of nervous systems could provide valuable insights into the origin and function of complex features characterizing neural networks. A first question we might ask is whether a rich-club organization is an early feature of nervous systems, or a relatively recent “entry” in the evolutionary line. Subsequently, one might consider which selection pressures are compatible with the formation of rich clubs and/or lead to cross-species evolution of rich nodes and connections.

**Rich clubs across species and neural scales**

Connectivity studies highlight the presence of rich-club topology in a range of different species, ranging from small invertebrates to primates.\(^3\) The mesoscopic connectome of the nematode *C. elegans* has been mapped with electron microscopy and demonstrates a hierarchical structure, with modules interconnected through a dense rich club of neurons that are important for worm coordination and behavior.\(^38\) Similarly, the neurocircuitry of the *Drosophila melanogaster*, a fruit fly, includes local processing units (LPUs) organized in modules interconnected through a rich club.\(^39\) Rich LPUs lie deep in the center of the *Drosophila* brain, are heavily innervated by giant neurons, and constitute the sensorimotor integrative center of the organism, favoring nervous signals’ spreading and coordination.\(^39,40\)

At a macroscopic scale, vertebrate connectivity estimated from histological, neural tracing and in vivo MRI methods demonstrates defining features of hierarchical modular networks with rich-club organization.\(^2,3,5\) In the rodent, high-degree regions forming rich-clubs mainly overlap with associative cortices,\(^41\) shape brain functional patterns\(^42\) and have high co-expression of genes associated with oxidative energy metabolism, learning and organism behavior.\(^22,43\) The cat connectome displays spatially dislocated but topologically central hubs, forming a rich club that is responsible for inter-modular communication.\(^10,11\) Equivalent global organizational features are evident across mammals in general, as in the ferret,\(^44\) the macaque, and the chimpanzee.\(^45\)

A comparative analysis of these findings demonstrates that functional specialization and integration are two fundamental aspects of neurocircuitry, preserved across species and scales of investigation.\(^2,3,5\) Interestingly enough, integration is consistently achieved through hierarchical rich-club architecture at different levels of network size and complexity, which makes “rich-clubness” a possible expression of convergent evolution. Furthermore, rich nodes correspond to functionally pivotal elements in the neurocircuitry of the different species, accomplishing tasks important for the survival and adaptability of the individual organisms (from sensory-motor coordination in the simplest invertebrates, to coherent perception and cognitive capabilities in mammals).
Finally, it is worthwhile to mention that rich clubs have been discovered in additional organizational scales of nervous systems. For example, in electrical recordings of spontaneous activity from in vitro mouse somatosensory cortex and in silico simulations of rat neocortical microcircuits, a minority of neurons forms rich clubs with high information transfer and a central role in shaping microcircuit synchronization patterns. “Rich-clubness” might be a scale-invariant organizational principle of natural systems with computational and information processing tasks.

Evolutionary and developmental principles

Rich-club formation thus emerges as a common organizational feature of nervous systems. This observation suggests that its formation might be driven by some fundamental evolutionary principles shared across different species. Generative models help elucidate this hypothesis by simulating network development under multiple constraints. In a generative experiment, network elements (nodes and/or connections) are progressively added to the system according to some predefined rule or to optimize some energy function. Alternatively, a real network can be progressively rewired according to some objective function. The resulting synthetic networks are then compared with real brain networks to identify possible evolutionary or developmental drivers.

A first evolutionary requirement shared by neural systems is the minimization of biological costs, which translates to limiting the overall number and length of connections. Cost-minimization is dictated by the finite spatial embedding, limited metabolic resources, and the necessity of bounding signal transmission delays in nervous systems. Generative experiments show that minimum-cost selection under geometrical constraints shapes highly clustered networks, but cannot reproduce long-distance connections, short path-length, and rich-club architecture. However, supplementing the model with additional rules, such as homophilic attraction (ie, the preferential formation of links between nodes that share a common neighborhood) results in cost-efficiency trade-off networks compatible with rich-club architecture.

These considerations indicate that few simple generative rules can fairly reproduce a range of brain network properties, but the developmental/evolutionary interpretation of these results deserves further attention. It has been proposed that, at a microscopic scale, the homophily rule is compatible with Hebb’s law for synaptic plasticity, so that neurons with common inputs (such as rich nodes) are more likely to be activated together, consolidating their interconnectivity and favoring rich-club formation in the long term. Other factors, such as the timing of the formation of nodes and connections, could also be a determinant for the resulting network architecture. In nonlinear growth models, new nodes are progressively added to the network, in numbers that increase exponentially with time. Nodes that develop early in the model tightly link together (as there are no other nodes for establishing connections), forming a dense core that contributes to shape the final network topology across later developmental stages. This exponential growth-model reproduces the same rich-club topologies observed in *C. elegans* and monkey, with no need for additional rules, such as preferential attachment or homophily. In the model, rich nodes appear early in the development of the network, similarly to what is observed in *C. elegans* and in the human brain.

In general, complex organizational features of nervous systems, such as a rich-club topology, might emerge as byproducts of simpler and (spatially or temporally) local developmental rules, which globally fit competing constraints and natural selection pressure. On the one hand, the fact that different species are subject to comparable developmental rules, dictated by comparable biological constraints, might partially explain the cross-species ubiquity of rich clubs. On the other hand, the subsistence of such constraints might limit the landscape of possible evolvable neural networks, questioning the mechanisms underlying cross-species differentiation and divergent evolution.

Cross-species differentiation

Rich nodes of nervous systems relate to crucial functions in the life of the organisms. In humans, rich regions have been associated with behavioral variability among individuals, including cognitive and intellectual performance. These functions are particularly developed in, or specific to, humans compared with their primate relatives. A fundamental question is therefore whether rich regions preserve their function among related species or whether they develop new or improved functions. Reasoning that brain functions are supported
by the underlying cortical characteristics and white-matter wiring, one will also be interested in understanding whether rich regions and connections are spatially and morphologically preserved among related species, or whether they undergo substantial structural modifications.

Comparative studies of primate neuroimaging data show a significant overlap of rich regions among primate species, including the macaque, chimpanzee, and the human. Hubs have consistently been found in the insular, medial-parietal/precuneus, and ventro-lateral prefrontal cortices in all three species. However, hubs in the polar and medial prefrontal cortices are present in macaque and chimpanzee, but absent in human. Prefrontal regions undergo important morphological and microstructural changes between these species. Human brains have an expanded and more convoluted cortex and a larger white-matter volume in prefrontal areas, with lower neural density and higher number of dendrites. These structural variations suggest a functional specialization of the prefrontal cortex in human compared with other primates. This process might entail a partial reorganization of the brain-network topology, with a potential displacement of some network hubs (eg, the prefrontal hubs) and a possible reinforcement of other network hubs to achieve an adequate level of integration in a progressively more complex network. For example, the precuneus hub demonstrates an important expansion from chimpanzee to human and an altered connectivity pattern from macaque to human, which might suggest a topological reinforcement of this region. Further studies targeted to cross-species rich-club characterization might elucidate these aspects.

Rich clubs demonstrate cross-species structural variations. Many studies investigating primate-brain evolution have focused on cross-species morphological changes of the cortical mantle, highlighting a spatially nonuniform expansion centered on a few hot spots in frontal, parietal, and temporal areas. It remains to be understood whether rich regions are particularly involved in such morphological changes, and how these changes might relate to gray-matter microstructural reorganization (eg, increased/decreased neural density or arborization) and white-matter connectivity alterations (eg, reinforcement or diversification) in these regions. Moreover, it will be crucial to link cross-species structural differences with specific functional traits and increasing behavioral complexity across primates. Indeed, regions with the highest rates of cortical expansion from macaque and chimpanzee to human are involved in complex cognitive functions, such as relational thinking, and form resting-state networks that are present in humans, but absent in macaque, suggesting a relationship between cross-species morphological evolution and functional development.

Finally, it should be noted that an expanding brain with increasing complexity and growing intelligence is also expected to be progressively more biologically expensive and susceptible to genetic and environmental insults. In particular, an evolving rich club, composed of highly active and functionally “stressed” cortices with long axonal projections, might reach large, and at worst unsustainable, biophysical costs. This aspect could have important evolutionary consequences, on the one hand impeding unlimited development of human intelligence, and on the other hand favoring disease susceptibility or the onset of human-specific brain disorders. For example, schizophrenia, a human-specific disorder, has been suggested to result from a “costly trade-off” between an increased connectivity complexity in humans compared with their ancestors and the development of valuable functions, such as social cognition.

Rich-club vulnerability in pathological conditions

Over the last decades, the connectionist approach has caught on in the investigation of neurological and psychiatric disorders. Accordingly, symptoms and cognitive deficits can be read as faulty connectivity among brain areas. As already discussed, the rich club plays a distinctive role in sustaining overall functional coordination and is associated with higher-order cognitive abilities, which are impaired in the majority of brain disorders. One can therefore expect the rich club to be involved in a large number of pathologies. A recent meta-analysis, including 392 studies on 26 different disorders (Alzheimer disease, schizophrenia, and epilepsy, among others) indicates that gray-matter lesions are more likely to occur in brain hubs than in peripheral regions. MRI studies on large cohorts suggest that white-matter impairments also converge on rich and feeder connections in schizophrenia and other psychiatric and neurological disorders. Although different disorders may target different subsets of hubs, rich-club impairment and a parallel
loss of network efficiency seem to be a general feature of brain pathologies. On one hand, a cross-disorder, rich-club impairment might express overlapping psychiatric and cognitive comorbidities. For example, depression, a mood disorder associated with hub impairment, is a comorbid factor of diverse pathologies, including multiple sclerosis, dementia, and epilepsy. On the other hand, a rich-club impairment might produce more pronounced symptoms by virtue of the rich-club functional importance.

The reasons underlying the vulnerability of rich regions and connections can be multiple and depend on the specific pathology under investigation. Rich regions demonstrate a continuously high baseline activity and glucose metabolism compared with peripheral regions. This aspect exposes the rich club to harmful mechanisms, such as oxidative stress and neuroinflammation, in a possibly preferential or selective way. Oxidative stress arises from a failure to maintain a correct balance between oxidative species and can lead to synaptic malfunction, deficits in myelination, alterations in cellular processes, and neuronal death. Different pathophysiological mechanisms, such as antioxidant system failure, metabolic alterations, and redox-species accumulation can jointly cause oxidative stress and ultimately converge on a rich-club vulnerability. For example, schizophrenia, a neurodevelopmental disorder characterized by a disruption of rich connections, has been associated with a deficit of glutathione synthesis, a major cellular antioxidant, and related to oxidative stress. In general, patients in the early stages of neurodegenerative disorders show increased compensatory brain activity, potentially concentrated in hub regions, which can lead to excitotoxicity and oxidative species accumulation. Among neurodegenerative disorders, Alzheimer’s disease is characterized by deposition of β-amyloid (Aβ) plaques. The processing of amyloid precursor protein (APP), whose proteolysis generates Aβ, is activity-dependent and may therefore result in a preferential accumulation of Aβ in high-metabolism rich regions. Furthermore, the topologically central rich club may mediate transneuronal spread of toxic substrate through axonal projections, accelerating disease progression or causing hub disruption as a secondary effect of unrelated pathological mechanisms. Indeed, different forms of brain dementia have been associated with “prion-like” transsynaptic propagation of pathogenic agents, such as Aβ and other misfolded proteins. In those pathologies, the longitudinal spreading of brain lesions is highly predictable based on structural connectivity patterns, centralized through the rich-club circuitry.

The vulnerability of rich clubs may also relate to genetic factors. Patterns of similar gene expression in brain subnetworks can contribute to subnetworks’ susceptibility to brain disorders in the context of transcriptional alterations or genetic risk factors. Notably, brain hubs demonstrate highly similar transcriptional profiles, enriched with genes relating to oxidative metabolism, synaptic signaling, and axonal structure. Hubs’ transcriptional profiles are also enriched for schizophrenia-related genes, and the cortical expression patterns of those genes correlate with brain connectivity disruption in schizophrenia.

The rich club also demonstrates characteristic developmental features. Rich regions and connections form early in the prenatal life: long-range corticocortical connections are established during the second and third semester of gestation, while feeder and peripheral connectivity develops over the third semester of gestation. After birth, long-range projections connecting associative hubs continue their maturation (myelination) longer than other peripheral connections, and until adolescence and adulthood. In parallel, cortical shrinkage and intracortical myelination rates are particularly high in hub regions during adolescence and early adulthood. Considering that hierarchical patterns of maturation in brain functional circuits relate to the development of specific cognitive functions, and that the timing of brain circuit maturation may determine windows of selective vulnerability, the developmental signature of the rich club, in combination with genetic and environmental adverse factors, could partially account for the involvement of the rich club in neurodevelopmental disorders.

In summary, these observations demonstrate how different vulnerability factors (including biophysical and metabolic cost, topological centrality, genetic signature, and long maturational trajectories), combined with different pathological mechanisms (eg, primary vs secondary pathological pathways), can converge on a common end result, namely changes in rich-club characteristics. Large-scale, cross-disorder studies are required to elucidate cross-disorder differentiation from a network perspective.
Summary and perspectives

The research reviewed in this article identifies “rich clubness” as a scale invariant feature of nervous systems, an expression of convergent evolution, and a characterisation feature of biological systems with information processing capabilities. The rich club forms a flexible substrate promoting functional complexity and coordination among brain regions, ultimately supporting multisensory integration, coordination, and cognition. Further insights into the functional value of a rich club topology will require a better comprehension of brain dynamics and their cognitive and behavioral counterpart. Computational and neuroimaging studies able to explicitly model (directional) information flow through the structural network substrate might help clarify these aspects. This may require methodological development at multiple levels, including (i) multimodal and multiscale integration methods (eg, functional and structural neuroimaging modalities); (ii) advanced network formalism (eg, multilayer and temporal networks for cross-frequency dynamics tracking); and (iii) high-complexity computational models (eg, including fine-grain intracortical characteristics, such as chemo-architecture and dynamics heterogeneity). Furthermore, it should be acknowledged that the “rich clubness” remains, per se, an abstract mathematical property of networks, which needs further validation and biological interpretation in the context of nervous systems’ organization. On the one hand, this could be accomplished through animal studies where rich-club connectivity can be structurally and functionally manipulated or physically perturbed, for example with genetic or optogenetic techniques. On the other hand, future research could merge multiple fields of expertise, integrating genetic, neurobiological, and microstructural data with functional recordings and multiscale analyses of in vivo and ex vivo brain connectivity information. Finally, the ascertained functional value of rich clubs comes at the price of a high biophysical cost that contributes to the vulnerability of rich-club resources to pathogenic agents. An intriguing hypothesis is that an increasing complexity of brain networks and (possible) expansion of rich clubs across primate species, might relate not only to the development of more sophisticated intellectual abilities, but also to the inception of human-specific brain disorders. Cross-species and cross-disorder network analyses on large datasets will help elucidate these aspects.

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The frontoparietal network: function, electrophysiology, and importance of individual precision mapping
Scott Marek, PhD; Nico U. F. Dosenbach, MD, PhD

The human brain is unique among other species in its ability to accurately and rapidly learn new concepts and switch between states, while maintaining complex rule sets. We engage in countless goal-directed tasks throughout a given day, adopting task sets that flexibly configure information processing in response to changing task demands. In cognitive psychology and neuroscience, this process of volitional goal-driven behavior is referred to as cognitive control. Cognitive control is not executed by a single brain region or single brain network, but rather by several largely non-overlapping brain networks, each consisting of a relatively large set of anatomically distributed regions, including the frontoparietal, cingulo-opercular, and salience networks.

There is now abundant evidence that these networks are anatomically separate from downstream processing or attention networks, both during task states and

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Introduction
the resting state. Each network plays a unique role in cognitive control, including its implementation, maintenance, and updating. Networks related to attention vs cognitive control map onto those outlined by Petersen and Posner, with the dorsal and ventral attention networks supporting orienting and the frontoparietal and cingulo-opercular networks supporting cognitive control. For the duration of this review, we will be focused on the control networks, with emphasis on the frontoparietal control network.

We begin our review by summarizing evidence for the frontoparietal network as distinct from other control and attention networks, including its privileged role as a flexible hub of cognitive control. We then move into a discussion of the oscillations underlying frontoparietal network interactions, during both resting and task states. Following this, we will discuss the importance of densely sampling individual subjects. There is compelling evidence that while core regions of the frontoparietal network are present across individuals, critical variants in this network’s topography exist. We conclude by briefly reviewing evidence for frontoparietal dysfunction in several forms of psychopathology that emerge during adolescence, a time when the frontoparietal network is refining many of its interactions with other brain networks. Given the anatomical heterogeneity of the frontoparietal network across individuals, we argue a complimentary shift towards densely sampling individual subjects in both normative and diseased states is of paramount importance to understanding the frontoparietal network in typical and atypical cohorts.

**Evidence for parallel, segregated control networks**

The original focus on the anatomical substrate of cognitive control was within the anterior cingulate cortex and to a lesser extent the anterior insula. This is because the anterior cingulate demonstrates reliable activation in response to many forms of control, including, but not limited to, task switching, novelty detection, focal attention, and error commission. This early work led Botvinick and colleagues to conclude that the anterior cingulate facilitates outcome monitoring by evaluating the result of an individual’s actions, and facilitating the resolution of conflict during task (ie, conflict monitoring). Thus, it was proposed that the anterior cingulate acts to alert regulatory regions, such as the dorsolateral prefrontal cortex, which in turn exert top-down control. Since this time, the conflict monitoring hypothesis has evolved, prescribing a role of dorsal anterior cingulate in signaling the expected value of control. Working closely in conjunction with this region and comprising the core of the brain’s salience network, the anterior insula is thought to detect salient features for additional processing and is thought to act as a switchboard to direct other brain networks.

Although the conflict-monitoring hypothesis ascribes the anterior cingulate a central role in control, a separate dual network’s view holds that cognitive control is supported by multiple, anatomically distributed brain networks. This model is the result of studies specifically aiming to delineate distinct control signals. Though the detection of salient stimuli and conflict resolution are essential features of cognitive control, humans also need to maintain and adapt control. Thus, there are three main signals related to cognitive control: (i) a transient signal resulting from the realization of the need to instantiate control; (ii) a sustained signal supporting the maintenance of control; and (iii) a transient signal supporting performance feedback. An early attempt to disentangle brain regions supporting different modes of control was executed by Braver and colleagues using a mixed block/event related design in functional magnetic resonance imaging (fMRI). Results from this study concluded that the anterior prefrontal cortex was most reliably activated during the maintenance of control, while the superior parietal lobes were involved in transient control. Several years later, Dosenbach and colleagues executed a cross-studies analysis on 10 mixed block/event-related fMRI studies to tease apart regions contributing to the main signals contributing to cognitive control. These tasks included visual and auditory stimuli, with many different decision criteria, such as semantic, timing, and similarity judgments. They discovered a set of regions including the anterior prefrontal, anterior insular, and anterior cingulate cortices that showed preferable activation for the maintenance of control, whereas the bilateral intraparietal sulcus and lateral prefrontal cortex showed preferable activation for task-set initiation. Lastly, performance feedback seemed to be supported by the inferior parietal lobe, dorsolateral prefrontal cortex, and lateral cerebellum.

During the mid-2000s, fMRI analysis was shifting from a focus on regional contributions to brain function to a broader network-level focus. With respect to
this network-level approach, a key observation is that co-fluctuations during the resting-state largely recapitulate patterns of activation during task.\textsuperscript{14} Capitalizing on this observation, Dosenbach and colleagues implemented resting-state fMRI to delineate a whole brain network's view of the brain's control architecture.\textsuperscript{15,16} During the resting state, two largely parallel control networks emerged. These two distinct networks were coined the frontoparietal and cingulo-opercular networks. The original putative role of the cingulo-opercular network was in the flexible control of goal-directed behavior through the stable implementation of task sets in downstream sensorimotor processors across trials, while control needed to be maintained. Conversely, the frontoparietal network was prescribed the role of supporting control initiation and provide flexibility by adjusting control in response to feedback.

Currently, there is an abundance of evidence for both a unified framework of control (conflict monitoring) and for parallel control networks. However, we and others\textsuperscript{13} argue that the latter is more likely. First, investigations of lesions in lateral PFC have shown these patients have deficits in the ability to switch tasks; however, they retain the ability to maintain a task set.\textsuperscript{17} Conversely, lesions of midline prefrontal cortex, including the anterior cingulate, have resulted in the ability to switch tasks, but not maintain a set. Second, there is little to no evidence for any temporal lag between the anterior cingulate cortex and lateral prefrontal cortex. In a study by Ploran and colleagues,\textsuperscript{18} noisy images were slowly revealed to track the rate of sensory evidence accumulation. Activity in the frontoparietal network slowly increased as evidence was accumulated, but the cingulo-opercular network was activated in the periresponse period. These data suggested that the cingulo-opercular network has a more prominent role in motor control, rather than in higher-order control. Third, electrophysiological studies also point to segregated control networks, using a working memory paradigm in which cues were presented either before the memory array or during the maintenance period to assess prospective and retrospective control of working memory.\textsuperscript{19} The frontoparietal network showed increased activity for both prospective and retrospective cues, while the cingulo-opercular network only showed increases in activity for retrospective cues during working memory maintenance. Furthermore, a cross-correlation analysis revealed frontoparietal network activity modulated $\alpha$-band activity in downstream visual association cortices, whereas there was no evidence for top-down modulation of the visual network by the cingulo-opercular network, supporting a role for the frontoparietal network in bias sensory information in processing networks.\textsuperscript{20,21}

**Role of the frontoparietal network: a flexible hub for cognitive control**

Humans are unique and quite remarkable in their degree of flexibility and speed when instantiating cognitive control. How the human brain is capable of doing this given its rigid anatomical backbone is an area of ongoing research. Given its role in task adaptation and implementation, a reasonable hypothesis is that the frontoparietal network, or at least a subset of it, is a functional hub (ie, it engages in strong co-fluctuations with many other brain networks). Indeed, not only does the frontoparietal network share a high degree of functional connectivity without considering functional network organization,\textsuperscript{22,23} but it also demonstrates a large degree of connectivity to many diverse brain networks, meaning that the frontoparietal network is a functional hub both globally, and specifically in terms of distributed connectivity.\textsuperscript{24-25} Moreover, fluid intelligence is positively correlated with the degree to which the frontoparietal network’s coupling is distributed to other brain networks\textsuperscript{26}; in particular, greater connectivity between the frontoparietal and default mode networks during resting state was correlated with higher intelligence scores.\textsuperscript{27} Furthermore, there is a significant positive correlation between functional integration of the frontoparietal network and overall cognitive ability, indicating that the strength of functional integration of the frontoparietal network and the rest of the brain is crucial for supporting superior cognitive functioning.\textsuperscript{28} Given previous evidence for its role in task adaptation and implementation, the frontoparietal network was hypothesized to play a role in instantiating and flexibly modulating cognitive control.

To test this hypothesis, Cole and colleagues used a rapid instructed task learning paradigm,\textsuperscript{29} which refers to the ability to immediately perform novel instructed procedures accurately after the first instance a new instruction (rule) is given.\textsuperscript{30} Twelve task rules were randomly permuted to achieve 64 different task “states.” The 12 task rules were created to assess three distinct cognitive
domains (logical decision, sensory semantics, and motor response) with four rules per domain. The frontoparietal network’s pattern of coupling shifted significantly more throughout the rapid switching of tasks than any other network, including other control networks, providing evidence that the frontoparietal network is a functional hub for influencing brain-wide communication to meet task demands. Moreover, the pattern of functional connectivity was specific, such that the individual task being completed was predicted by the pattern of connectivity of the frontoparietal network to other networks. Lastly, these predictive patterns held even when the tasks were practiced. Thus, the frontoparietal network (and not the cingulo-opercular network) is a flexible hub amongst other brain networks for the flexible coordination of cognitive control, providing further evidence in favor of dissociable and parallel control networks. Taken together, the frontoparietal network is highly integrated with other brain networks, providing a functional backbone for rapid and flexible modulation of other brain networks.

**Electrophysiology of the frontoparietal network**

fMRI has been the primary tool used to understand the role of the frontoparietal network, which is only sensitive to slow oscillations (0.005 Hz to 0.1 Hz; ie, approximately 1 cycle per minute). However, the cognitive constructs that the frontoparietal network supports, including flexible integration of other networks supporting cognitive control, occur at much faster timescales (ie, 1-100 Hz). For example, consider a simple task in which you are instructed to make a left finger motor response to a green crosshair and a right finger motor response to a blue crosshair as quickly and accurately as possible. In the task, the presentation of blue and green cues is mixed, such that the sequence is random. At each switch in cue color (eg, from blue to green), the frontoparietal network must signal the instantiation of control and recruit downstream networks, such as the motor network, for a correct response. The reaction time on any given switch trial would be less than 1 second, faster than one full cycle of a blood oxygen level-dependent (BOLD) oscillation. Thus, there is great interest as to how control networks recruit other networks for rapid accurate responses to task switching, including temporal precedence.

Much of the work characterizing specific contributions of neural oscillations to brain function in this faster range (1Hz to 100 Hz) has been done in task-state analyses. The correlation between electrophysiology and BOLD has been studied in both human and non-human primates, with a consistent finding of correlations between modalities in broadband γ activity (40 Hz to 100 Hz). Oscillations in this frequency range play a critical role in enabling local neuronal synchronization, whereas slower θ/α (4Hz to 14Hz) band oscillations have been shown to be critical for long-distance integration. Inter-areal synchronization of θ/α band oscillations within the frontoparietal network are associated with cognitive control, and have been shown to improve behavioral performance on control tasks, most prominently when switching rule sets. Additionally, θ/α power has been shown to intensify when control demands are increased. Hence, slow-frequency oscillations across control regions may underlie top-down modulation of sensory networks. For example, long-range frontoparietal interactions during working memory retention and mental imagery evolved most strongly in the θ and α (4 Hz to 14Hz) frequency range, and the prefrontal cortex has been shown to lead the posterior parietal cortex in sustained visual attention tasks in theta band oscillations. Slower frequency oscillations, often in the θ band (4 Hz to 10 Hz) have been shown to organize local neural activity in the γ band, such that neurons tend to have greater firing rates in the trough of an ongoing slow-frequency oscillation. As such, the phase of slower-frequency oscillations may be critical for coordination of neural activity over long distances, perhaps acting as an organizing mechanism for downstream sensorimotor function.

In contrast to task states, less is known about the electrophysiological correlates of control networks defined by BOLD fMRI during the resting state. There is some evidence that resting-state BOLD networks correlate to the α and β band, as measured with magnetoencephalography. However, there is evidence that correlations with BOLD may be greater at even slower frequencies (4 Hz to 13 Hz). More recently, Hacker and colleagues characterized the spatial correspondence in humans of resting state BOLD fMRI and band-limited power using electrocorticographic recordings. They found that γ band correlation was high throughout the brain. In addition to this, they uncovered a dissociation between the frontoparietal control...
network and dorsal attention network, such that the frontoparietal network demonstrated greater coupling of θ band power (3 Hz to 8 Hz) to BOLD, whereas the dorsal attention network had greater coupling between band-limited power and BOLD in the α band (8 Hz to 12 Hz). In sum, the frontoparietal network seems to map onto slower-frequency oscillations (4 Hz to 14 Hz), critical for supporting its role as a flexible hub for coordinating the activity of other brain networks.

**Precision mapping and its implication for the frontoparietal network**

fMRI data has a notoriously low signal-to-noise ratio. To overcome this issue, the standard paradigm of fMRI imaging in humans has been to collect small quantities of data (5 to 10 mins of resting state) per subject and to then average them over tens, hundreds, or sometimes thousands of individuals to identify central tendencies of both healthy and diseased cohorts. This paradigm has been fruitful in helping investigators understand regional and network-level brain organization and function. While group averaging has revealed many basic principles of functional brain organization, it has been understood for centuries that individual brains differ in their functional neuroanatomy. The current lack of emphasis on understanding individuals limits the utility of fMRI to characterize and understand normative and atypical cohorts.

To begin understanding individual differences in functional neuroanatomy, a single individual was scanned for a total of 200 minutes of resting-state data across 10 different sessions, known as precision mapping. Several crucial observations were made. First, high reliability of resting-state correlations can be achieved with long enough data acquisition (~45 minutes), overcoming the low signal-to-noise nature of fMRI in a single individual subject. Second, individuals exhibit measurable variants in functional network organization compared with a group average. Third, in the individual brain, part of the lateral prefrontal cortex bilaterally contained a variant belonging to the cingulo-opercular network, which belongs to the frontoparietal network in group studies.

As an extension of densely mapping a single individual, 10 individuals were scanned for a total of 300 minutes of resting state data over 10 sessions, referred to as the Midnight Scan Club (MSC). In addition to the motor, visual, and cingulo-opercular variants observed in a single individual, several new types of spatial and organizational variability in brain networks emerged. These included unique network features and topologies that corresponded with structural and task-derived brain features. For example, even a well-defined network, such as the somatomotor hand network, demonstrated measurable variability between subjects, especially in the degree of their task/rest overlap on a block design motor task. Moreover, there was significant heterogeneity in network assignments in frontal and parietal association cortices. Specifically, with respect to the frontoparietal network, areas of high overlap between subjects were in the intraparietal sulcus, ventral inferior temporal lobe, and localized regions of the lateral prefrontal cortex. However, across the prefrontal cortex, there were substantial deviations between subjects, with variants of other control and attention networks located in regions of frontal cortex affiliated with the frontoparietal network in other subjects (Figure 1). Thus, there is substantial individual variation in the precise anatomical distribution of the frontoparietal network.

**Development and clinical implications of the frontoparietal network**

Both cognitive control and the functional brain networks that support it show a protracted development through adolescence and early adulthood. Children and adolescents are able to exert cognitive control. Thus, development is not characterized by the emergence of cognitive control, but rather the refinement of it. Paralleling this notion, there is evidence that the brain’s control networks are apparent by 2 years of age. Control networks are observable in infants younger than 2 years of age, and are thought to be immature forms of control networks identifiable later in development. Throughout childhood and adolescence, the brain’s control networks become more integrated with other brain networks, potentially laying the early groundwork for greater flexible engagement later in development. For example, the increased integration of the cingulo-opercular and salience networks supports the maturation of inhibitory control engagement. Recently, Chai and colleagues showed that the expression of the frontoparietal network increased in both strength and flexibility throughout development. As such, the developmental
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trajectory of the control networks parallels advances in cognitive control abilities.

Cognitive control is commonly comprised in many forms of psychopathology, many of which emerge during adolescence while control is being refined. It is likely that there exist shared mechanisms in the dysfunction of neural networks resulting in these different forms of psychopathology. The abnormal developmental of a flexible brain network, such as the frontoparietal network, may be a common feature across many diseases,

![Figure 1. Individual frontoparietal network assignments (yellow patches) displayed on the left hemisphere cortical surface from the Midnight Scan Club (outer ring). The central montage depicts the number of subjects having a frontoparietal network assignment on the left and right lateral and medial cortical surface. Yellow arrows indicate exemplar patches where there is a high degree of overlap in frontoparietal assignment across subjects. Conversely, red arrows show exemplar areas where a minority of subjects contains frontoparietal network patches, highlighting the relatively large degree of heterogeneity in frontoparietal network topography. Only 52 vertices out of the 19,074 (0.3%) vertices had overlap across all 10 subjects, and 1,171 of 19,074 vertices (6.1%) had overlap across eight subjects. This high degree of heterogeneity is especially prominent across large swaths of the lateral prefrontal cortex.](image-url)
including schizophrenia, depression, and anxiety. For example, patients with schizophrenia consistently exhibit relatively low levels of cognitive control, often apparent as early as childhood. Patients with schizophrenia demonstrate reduced BOLD activity and connectivity within and between regions of both the frontoparietal and cingulo-opercular networks across many cognitive tasks. These findings underscore the notion that schizophrenia may be characterized by a generalized cognitive deficit implicating similar neurobiological mechanisms across cognitive domains.

Disorders involving cognitive control can be broadly broken into primary and secondary control disorders. Primary control disorders directly impact control networks, such as schizophrenia, in which substantial cellular and molecular alterations occur within the lateral prefrontal cortex, possibly underlying changes in global connectivity of the lateral prefrontal cortex observed in humans. Secondary control disorders, such as anxiety and depression, are those that manifest in such a way as to not directly impact control networks. For these disorders, cognitive control is thought to act as a buffer, such that high control abilities ameliorate symptoms, whereas lower control abilities cannot compensate for downstream abnormalities. As such, lower cognitive control capacity evident early in development may be a risk factor for schizophrenia and other forms of psychopathology. It has been proposed that frontoparietal connectivity could be augmented through cognitive training, such as in psychotherapy. Future research should focus on the contributions of modulations within frontoparietal interactions through cognitive training to ameliorating symptoms of psychopathology. Moreover, accurately characterizing frontoparietal network topography in individual subjects may be critical for treatments targeting these regions, as is often done using transcranial magnetic stimulation.

**Conclusion**

The frontoparietal network is a control network, distinct from the salience and cingulo-opercular networks, serving to rapidly and instantiate new task states by flexibly interacting with other control and processing networks. The slow-frequency BOLD components that define it are correlated with relatively slow oscillations in the frequency range sensitive to electrophysiological recordings (θ/α band), likely supporting its role in coordination of whole-brain network activity. Along with the other control networks, the frontoparietal network demonstrates a protracted development, perhaps lending it to vulnerability to various forms of psychopathologies linked to cognitive control deficits, such as schizophrenia. Due to its heterogeneity in anatomical location within individual subjects, future studies should seek to densely sample individuals, mapping frontoparietal networks individually, and subsequently comparing and contrasting normal and diseased states to further our understanding of the neural basis of psychopathology.

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and task-evoked network architectures of the human brain. 

Basic research


Evolving a new neuropsychiatry
Gregory L. Fricchione, MD

“A I would say that the future of psychiatry from my vantage point remains uncertain until it identifies a solid foundation.”

Samuel Gershon
Australian and New Zealand Journal of Psychiatry 2016;50:1020

An evolutionary neuropsychiatry

Academicians debate the utility of the Diagnostic and Statistical Manual (DSM)-5 when it comes to validly diagnosing mental disorders.1-4 The Research Domain Criteria (RDoC) aim to develop a more valid dimensional framework.5-7 However, questions remain.8,9 Perhaps the biggest challenge comes when clinicians must understand and treat patients with idiosyncratic multidimensional blends of neuropsychiatric disorders.10-11

Keywords: attachment solution; attachment theory; basal ganglia-thalamocortical circuit; brain evolution; neuropsychiatry; neurocircuitry; separation challenge; Tinbergen’s Four Questions

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Clinical neuroscience struggles with poor scientific validity of neuropsychiatric diagnosis and its negative impact on management. Sydenham’s ancient conformity of type approach to nosology with its assumption that the symptom cluster and course of a disorder are due to a common etiology, has proven no match for the complicated comorbidities faced in neuropsychiatry. In the absence of accurate pathological biomarkers there is a challenge in finding a solid foundation for modern neuropsychiatry. We find standard psychiatric nosology to be of limited benefit at the general hospital bedside in evaluating and treating neuropsychiatric disorders. Consequently, we have developed over the years a neurocircuitry-based training for our psychosomatic medicine fellows. In this commentary, we will introduce a strategy for understanding patients with neuropsychiatric disorders that may advance our ability to diagnose and treat them in accordance with neuroscientific evidence anchored in evolutionary neurocircuitry and attachment neurobehavior.
Brief report

findings.10-12 Psychiatric nosology is of limited benefit in evaluating and treating neuropsychiatric disorders in the general hospital. This realization led us to develop a neurocircuitry training program for fellows based on the science of brain evolution.

Tinbergen urged scientists interested in understanding any biological or psychological process to ask four questions.15 How does the process work? How did it develop? What is it for? How did it evolve? By asking Tinbergen’s four questions and combining two foundational principles that emerge in the course of answering them, we may build a neuropsychiatric nosology capable of providing greater diagnostic understanding regardless of complex comorbidities.

Evolutionary brain biology depicts life’s unfolding as a sensory-motor analyzer-effecter entity.14 Because fitness may be defined in terms of attachment solutions to separation challenges, natural selection has sculpted a specialized organ to focus functions on human life’s four attachment-based objectives (metabolic energy, sexual, social, and future objects).15 These functions are manifested through neurocircuitry allowing for discernment of brain form and function.

While wrestling with Tinbergen’s questions, two foundational principles emerge. The first recognizes what the brain’s workplan is and how it developed. In the brain, we see evidence of the sensory-motor analyzer-effecter bauplan (body plan) in the corticostriato-thalamo-cortical loops that are segregated yet integrated for the purpose of deciding whether to avoid or approach, separate or attach.16 This first foundational principle also hints at how the brain evolved its bauplan to accomplish what it is for. Indeed, the performance demands of brain function as prescribed by natural selection gave rise to brain form.

In a meta-analysis based on voxel-based morphometry (VBM) studies, six major neuropsychiatric disorders—schizophrenia, bipolar illness, depression, obsessive-compulsive disorder, anxiety and addiction—showed a common defect called the VBM psychiatric core, centered in the dorsal anterior cingulate cortex (dACC)/anterior insula network.17 This network is central to analyzer-effecter functioning and is key to response selection. The brain actively constructs inferences based on sensory data to predict future rewards leading to approach or avoidance response selections via the dACC and other PFC zones.18 The VBM researchers suggest that this psychiatric core “concordance provides an organizing model that emphasizes the importance of shared neural substrates across psychopathology, despite likely diverse etiologies, which is currently not an explicit component of psychiatric nosology.”17 In another recent study, conjunction analysis showed smaller VBM psychiatric core volumes in subjects with major depression and bipolar disorder, lending support to this notion.19

Some of the sensory-motor neural networks are confined to primary sensory and motor cortex terminal zones. Analyzer-effecter networks spread out across many brain regions, allowing for more integrative functioning. Several lines of integration are postulated. There is convergence of terminals from functionally proximate cortical areas onto increasingly more confined basal ganglia structures resulting in an interpenetration of signals.20,21 In addition, information from the motivational system can reach the motor system through a series of interconnections. Information in the “paralimbic” and “limbic” basal ganglia-thalamo-cortical circuits and information within the “motor” basal ganglia-thalamo-cortical circuit come together to enable the organism to effect an appropriate avoidance-approach response to sensory stimulation. This occurs when the ventral striatum receives input from the paralimbic medial prefrontal cortex (mPFC) and in turn projects to a midbrain region that feedforwards to the central associative striatum. The central striatum then projects in part to a section of the substantia nigra, which connects with the dorsolateral motor striatum.20,22 Haber and Calzavara23 conclude that cortex “exploits” basal ganglia as an additional processor forming a central selection-effecter mechanism that enhances decision-making in the service of attachment goal-directed behaviors and habits.

One important integrative neural network is the default-mode network (DMN).23,24 It has nodes in mPFC, posterior cingulate cortex (PCC), precuneus, and lateral parietal cortex. The DMN mediates self-focused introspective and prospective thinking. Another network looks outward and is known as the task-positive network and includes the frontoparietal central executive sub-network (CEN), which is important for working memory and attention. Another task-positive subnetwork is the anterior cingulo-insular network (ACIN) or salience network, which overlaps with the VBM psychiatric core (left and right insular cortex and dACC also known as the midcingulate [MCC]).25 Much of neuropsychopathology emerges from dissolution of...
aCIN (implicit) and CEN (explicit) emotion regulation pathways, which emanate from the ventral ACC and medial orbital frontal ventromedial PFC in the former case and from the dACC/MCC and the dorsolateral PFC (dlPFC) in the latter case, to provide circuit-based control of the amygdalar fear conditioning separation stress pathway. This dissolution may come from disruptions in point-to-point channel connectome functions leading to neurological defects in informational content flow and/or from state shifting modulatory system psychiatric dysfunctions leading to deficits in the state of information processing. Modulatory systems include neurotransmitter, neurohormone, and neuroimmune cytokine impacts on these neural node terminals via the brain reward and motivation circuitries in the medial forebrain bundle (MFB) as well as frontocerebellar and dorsal diencephalic habenular tract influences. A strategy for assessing loop channel and state functioning at the bedside or in the clinic becomes an integral part of the neuropsychiatric exam. For example, interrogating MFB dopamine tracts entails monitoring eye blink rate and speech latency.

The second foundational principle defines the relationship between separation challenge and attachment solution. Because fitness can be defined in these terms, the brain has been sculpted to focus its form and structure on the four attachment-based objectives of life mentioned above. This understanding helps us assess how individuals perform when experiencing amygdalar stress.

Bowlby contended that human evolutionary adaptability was sourced in an environment of secure base attachment. Recently a transdiagnostic model of psychopathology based on Bowlby’s attachment behavioral system has emerged. There are mechanisms through which epigenetically developed attachment dispositions serve as transdiagnostic risk factors when insecure attachment, be it attachment anxiety or avoidance, becomes the residual internal working model for self and the world perhaps reflecting DMN and aCIN disconnection. MacLean cited the ACC as the hub for what he called the mammalian behavioral triad comprised of key attachment sustaining behaviors—the separation cry, maternal nurturance, and play. This may tie in the VBM psychiatric core in the first foundational principle with the second foundational principle. Thus, attachment-based transdiagnostic risk factors may mediate pathways that set the stage for so-called “multifinality” in which the attachment risk factor leads to multiple disorders.

Analyzing separation stress and implementing attachment solutions is integral to caregiving. If we examine anxiety based in separation threat and depression based in attachment loss according to these principles, we discover particular subset neural network dysfunctions. The DMN may contribute to maladaptive rumination and negative thinking as an endophenotype; the aCIN salience circuit may produce social anxiety and panic as well as depression; the cingulo-opercular sub circuit may play a role in anxious avoidance; the negative affect circuit (mPFC, ACC, vmPFC, hippocampus, insula, and amygdala) may mediate negative bias and implicit separation threat dysregulation; the positive affect circuit (mPFC, mOFC, nucleus accumbens, ventral striatum, VTA) may mediate an anhedonia endophenotype when dysfunctional; the attention circuit (medial superior frontal cortices, anterior insula, anterior inferior parietal lobe, and precuneus) may contribute to inattentiveness; and a disordered cognitive control circuit (dlPFC, dACC, dorsal parietal cortex, and precentral gyrus), may lead to an explicit inability to dampen default mode rumination. A similar analysis can be made for a wide variety of neuropsychiatric diseases. These sensory-motor analyzer-effector malfunctions disturb a patient’s ability to separate or attach expeditiously, efficiently, and effectively. In this dysfunctional matrix, we can begin to see analyzable biological markings that correlate with the dimensions of neuropsychiatric disorders.

By using our own segregated yet integrated analyzer-effector capacity, we neuropsychiatrists can endeavor, with our patients, to effect an attachment solution to their illness separation challenge.

Conclusion

Embedding neuropsychiatry in the dual principles of evolutionary neuroanatomy and attachment theory should be a priority. Our diagnostic tasks require attention to two foundational principles, ie, neurology anchored in an understanding of brain evolution and psychiatry based on the concept of separation challenge and attachment solution decision-making. Building the capacity of neuropsychiatrists to ask the Tinbergen questions and to link up foundational principles with the mechanisms on which they are based can create brain doctors capable of
anchoring their diagnoses in a scientific safe harbor and of providing healing care. It is the evolution of the brain’s neurocircuitry that has led to the meaningful experience of separation stress and attachment loss that fuels neuropsychiatric dysfunction and distress.

After decades studying brain evolution, MacLean concluded in an inscription in his magnum opus, The Triune Brain, that separation is “the most painful mammalian condition.” We would do well to take heed in developing a solid foundation for neuropsychiatry.

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REFERENCES

**An interface between clinical neuropsychiatry and neuroscience, providing state-of-the-art information and original insights into relevant clinical, biological, and therapeutic aspects**

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| 2004 | Predictors of Response to Treatment in Neuropsychiatry  
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  Parkinson’s Disease  
  Mild Cognitive Impairment |
| 2005 | Early Stages of Schizophrenia  
  New Psychiatric Classification based on Endophenotypes  
  Pharmacology of Mood Disorders  
  Sleep Disorders, Neuropsychiatry, and Psychotropics |
| 2006 | Diagnosis and Management of Schizophrenic Disorders  
  Depression in Medicine  
  Drug Discovery and Proof of Concept  
  Stress |
| 2007 | Neuropsychiatry and Cardiovascular Disease  
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