Spatial networks / Réseaux spatiaux

Spatial brain networks

Réseaux neuronaux spatiaux

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A R T I C L E   I N F O

A B S T R A C T

The human brain is a wonderfully complex organ characterized by heterogeneous connectivity between cellular and tissue units. This complexity supports the rich repertoire of dynamics and function that is characteristic of human cognition. While studies of brain connectivity have provided important insight into healthy cognition as well as its alteration in psychiatric disorders and neurological disease, an understanding of how this connectivity is embedded into the 3-dimensional space of the skull has remained elusive. In this article, we will motivate the importance of studying the brain as a spatially embedded network, particularly for understanding the rules of its development and alterations to those rules that may occur in neurodevelopmental disorders such as schizophrenia. We will review recent evidence for well-defined wiring rules in the brain, informed by notions of wiring minimization, spatially localized modules, and hierarchically nested topology. We will then discuss potential drivers of these rules in the form of evolution, genetics, energy, and the need for computational complexity. Finally, we will conclude with a discussion of emerging frontiers in the study of spatial brain networks, both in theory and modeling, and their potential to enhance our understanding of mental health.

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R É S U M É

Le cerveau humain est un organe merveilleusement complexe, caractérisé par une connectivité hétérogène entre les unités cellulaires et tissulaires. Cette complexité alimente le riche répertoire de dynamiques et de fonctions caractéristiques de la cognition humaine. Bien que les études sur la connectivité neuronale aient fourni des informations importantes sur la cognition saine ainsi que sur son altération observée dans les troubles psychiatriques et les maladies neurologiques, il reste difficile de comprendre comment cette connectivité est intégrée à l'espace tridimensionnel du crâne. Dans cet article, nous allons expliquer l'importance de l'étude du cerveau en tant que réseau spatialement intégré, en particulier pour comprendre les règles de son développement et les modifications de ces dernières

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qui peuvent intervenir dans les troubles neurologiques du développement tels que la schizophrénie. Nous examinerons la découverte récente de règles de câblage bien définies dans le cerveau, en nous appuyant sur les notions de minimisation du câblage, de modules spatialement localisés et de topologie imbriquée hiérarchiquement. Nous discuterons ensuite les moteurs potentiels qui gouvernent ces règles en matière d'évolution, de génétique, d'énergie et de nécessité d'une complexité computationnelle. Enfin, nous conclurons par une discussion des perspectives actuelles dans l'étude des réseaux neuronaux spatiaux, à la fois en matière de théorie et de modélisation, ainsi que leur potentiel pour améliorer notre compréhension de la santé mentale.

1. Introduction

The human brain is a complex organ that supports the rich set of behaviors, thoughts, and emotions that characterize our experiences. The tissue itself is far from homogeneous, crystalline, or completely disordered. Rather, it is segregated into areas, regions, or sectors each being characterized by a distinct set of attributes including cell types, gene expression profiles, and signaling chemicals [1–3]. Arguably even more striking is the intricate pattern of connectivity linking these areas with one another in a natural web [4–6]. Recent work has reported notable similarities between the architecture of this web or *brain network*, and the architecture of networks observed in manmade information processing and transmission systems [7]. Such similarities suggest the potential relevance of tools, models, and theories from network science for further developing our understanding of the brain [8].

In the contemporary landscape of scientific research, the treatment of the brain as a network has come to be formally known as *network neuroscience* [9] (Fig. 1). Common questions posed and addressed by this field range from the very basic to the highly translational. How does brain network architecture reflect a single human's cognitive abilities [10]? How do brain networks change as children grow or in old age [11]? How do brain networks differ between individuals who are healthy and individuals who are suffering from mental illness [12–14]? Progress in answering these and related questions has begun to provide intuitions regarding how information is transmitted throughout the brain's distributed circuitry. Yet such intuitions have also begun to motivate new questions regarding how the spatial locations of areas comprising the circuits, and the physical geometry of the edges connecting them, could impact the speed, precision, and veracity of information propagation and the complexity of the accompanying or ensuing dynamics.

The relevance of node location and edge geometry for system architecture and function can be naturally determined by considering the system to be a spatially embedded network, and by using tools developed explicitly for the analysis of spatial networks [15]. In an abstract (non-embedded) network, nodes form a set, and edges define pairwise relations or connections between nodes. In an embedded network, nodes are assigned a spatial location, such as coordinates in $\mathbb{R}^3$; then, edges are defined either as abstract connections between nodes, or as physical paths through $\mathbb{R}^3$. These notions can be simply mapped to brain networks by assigning 3-dimensional coordinates to nodes corresponding to their physical location within the volumetric constraints of the skull. Edges can then reflect (non-embedded) shared information between nodes, or can reflect (embedded) physical wiring architectures that support the propagation of action potentials.

In this article, we review the recent literature underscoring the importance of considering the brain as a spatially embedded network. To ensure that the exposition is as accessible as possible, we begin with a brief description of how brain networks are commonly constructed from imaging data, and we describe what topological features such networks tend to display (Fig. 1A). We then consider known neuroanatomy and neurophysiology to infer spatial constraints on the network's architecture and function, and how such constraints might change over the distinct time scales of evolution and of development (Fig. 1B). We then discuss statistics for quantifying these constraints, and a few generative models of brain networks that incorporate rules for spatial embedding. We close with a discussion of the relevance of these notions for understanding cognition and disease, and we highlight several important directions for future work.

2. Brain networks

Current efforts in the field of network neuroscience can be broadly categorized according to their study of three main types of brain networks: structural, functional, and morphometric [9]. In each case, we let $G = (V, A)$ be a network of N nodes, where $V = \{1, \cdots, N\}$ is the node set, and $A \in \mathbb{R}^{N \times N}$ is the adjacency matrix whose element A_{ij} gives the weight of the edge between node i and node j. Commonly, N ranges from 100 to 40,000. The three different types of networks have in common a fixed parcellation of the brain tissue into regions of interest, historically based on cytoarchitectonic boundaries and more recently also incorporating information about distinct functions [16]. Each region is then represented as a single network node. What differs across the network types is the metric used to define network edges. A *structural* brain network defines edges between nodes based on physical (rather than statistical) connections between brain areas. Commonly, these structural edges reflect estimates of synaptic connections or bundles of neuronal axons, or *white matter*
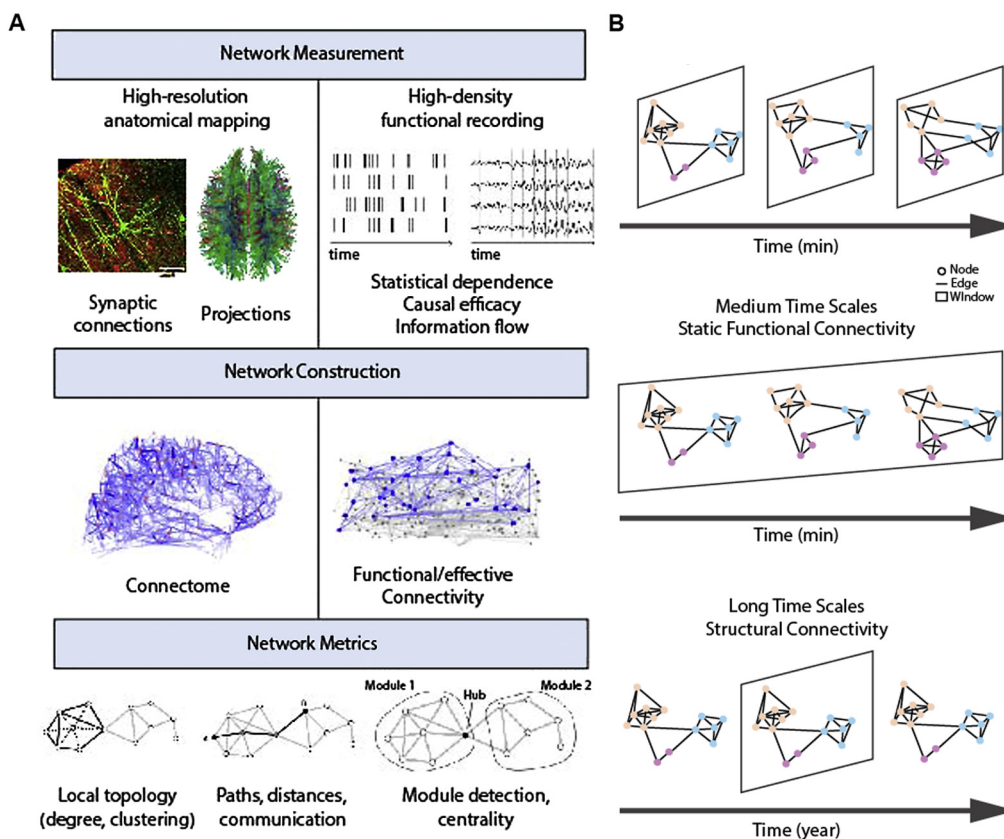
Fig. 1. Network science. (**A**) A schematic of the network neuroscience workflow from collection to analysis. First, either structural or functional data is collected (top), and then transformed into a network composed of nodes and edges (middle). From these networks, various statistics are calculated that measure different topological properties of interest (bottom). Local measures provide information about individual nodes in the network, paths and distances provide information about the patterns of edges, and mesoscale measures provide information about large-scale divisions of the network, for example into clusters, modules, or communities. (**B**) A schematic of different ways to sample networks over time, accomplished with different windows for network construction. (Top) Studies of dynamic functional connectivity can provide information about how brain network architecture changes over a series of short time windows spanning the course of an imaging experiment. (Middle) Static functional connectivity, on the other hand, can provide information only about features of the brain network architecture in a single time window. (Bottom) In contrast to both of the previous examples, structural connectivity does not change drastically after humans reach adulthood, except in relatively late age. Adapted with permission from [9].

tracts, that connect cell bodies, or *gray matter*, in distant regions of the brain. A *functional* brain network defines edges based on statistical relations between area activity time series, such as a correlation coefficient, coherence, synchronization index, or transfer entropy. Both structural and functional edges can be defined from imaging data collected from a single human, or a single non-human, animal. In contrast, a *morphometric* brain network is typically defined for a group of animals; here edges reflect cross-animal similarities in morphometric characteristics of brain regions, such as cortical thickness, surface area, gray matter volume, or curvature.

Brain networks can be defined across a range of spatial scales. The smallest scale commonly studied is that of individual cells, typically 4 microns (0.004 mm) in diameter. Each cell is represented as a node in the network, and synapses between cells are represented as structural edges, while correlations in cellular spiking activity are represented as functional edges. The most commonly studied cellular network is the connectome of the nematode *C. elegans*, which is reported to contain 302 neurons, 6393 chemical synapses, 890 electrical junctions, and 1410 neuromuscular junctions [17]. In contrast, the largest scale brain network commonly studied is constructed at the level of brain areas, which are typically a few centimeters in diameter. Each area is represented as a node in the network, and tracts composed of bundles of neuronal axons are represented as structural edges, while correlations in neuronal ensemble activity are represented as functional edges. The most commonly studied large-scale brain networks have been well mapped by invasive imaging techniques in the mouse [18], *Drosophila melanogaster* [19], rat [20], cat [21], and macaque [22], and by non-invasive diffusion-based imaging techniques in the human [23–26]. In future, concerted efforts in connectome mapping and dynamical modeling may benefit from emerging imaging techniques at intermediate spatial scales of measurement, a key focus area for current funding efforts across the globe [27].

Complementing this spatial diversity, brain networks can also be defined across a range of temporal scales, from microseconds to decades. At the smallest scale, structural edges represent physical connections and functional edges represent information-based relations that are true for the system over a period of a few microseconds [28]. At the largest tempo-

ral scale, brain networks can be studied whose edges represent functional connections that are characteristic of an entire imaging experiment, typically extending over an hour or more [29]. Similarly, brain networks can be studied whose edges represent structural connections that are maintained over a period of years [30]. These various time scales over which brain networks can be constructed also affect the sorts of biological processes that can be probed using the tools of network neuroscience, from the short time scales of synaptic plasticity to the long time scales of development and aging.

The flexibility and generalizability of the network approach ensures not only that neural systems can be studied over diverse spatial and temporal scales, but also that such systems can be studied across a range of animal species [31]. Some questions are arguably best addressed in a single system. For example, the nematode *C. elegans* has a relatively short lifespan (2–3 weeks), and is therefore particularly useful in the study of aging. In contrast, humans display a rich repertoire of complex behaviors that are not well replicated in other species, and those behaviors are therefore best studied in humans alone. Complementing species-specific questions, there exist open avenues of inquiry that require cross-species comparisons. For example, the study of evolutionary constraints on energy consumption [32], network complexity [7], or system control [33] is usefully complemented by considerations of and analytical evaluations across species.

3. Spatial embedding of brain networks: intuiting rules

All of the diverse sorts of brain networks described in the previous section are physically embedded into the 3-dimensional space of the organism (in the case of *C. elegans*), the exoskeleton (in the case of *Drosophila*), or the skull (in the case of mouse, rat, cat, macaque, and human). It is natural to suppose that such physical embedding occurs according to certain rules, which might be enforced by natural constraints on development and evolution. While it is impossible to identify such constraints directly, it is possible to seek to intuit them from the observation of conserved properties across species. In the recent literature in network neuroscience, three such properties have been identified that provide intuitions regarding the rules of spatial embedding for brain networks: wiring minimization, spatially localized modules, and physical Rentian scaling.

Arguably the most consistently reported feature of spatially embedded brain networks is the feature of unexpectedly short structural edges, often referred to as wires. In fact the distribution of edge lengths, l, tends to be heavy-tailed. In an intermediate range of l, whose exact values depend upon the resolution of the measurement, this distribution can be fit by a power-law of the form

$$P(l) \sim l^{-\psi} \tag{1}$$

where ψ is a parameter whose range of values is not yet well bounded, but is likely to become better known as the scaling phenomenon is assessed across multiple data sets [34]. The fact that the distribution of wiring lengths is heavily skewed to the left, with a markedly low average and long rightward tail, is suggestive of a preference for wiring minimization [35]. Observed quite early in the field in the context of tract-tracing studies of macaque cortex [36] and later in humans [34], this feature is also consistent with the near-optimal component placement hypothesis, which states that areas, ganglia, and even somata are laid out so as to nearly minimize the length of interconnections required [37]. Intuitively, wiring minimization allows for swift, precise, and veracious information transmission throughout the system. While long wires still exist, they are few in number, and appear to provide very specific benefits in terms of redundancy and dynamical complexity [38].

The second commonly observed property of physically embedded brain networks is spatially localized modules. In graphs and networks, a module is commonly defined as a set of nodes (and their connections with one another), where the nodes in the set are more densely connected to one another than expected under an appropriate random network null model [39]. Such modules are frequently identified in brain networks using community detection tools such as modularity maximization, InfoMap, k-means clustering, and others [39–41]. To enhance the reader's intuition for these methods, we note that modularity maximization seeks to maximize a modularity quality function, the most common of which is

$$Q = \sum_{ij} \left[\left(A_{ij} - \gamma P_{ij} \right) \right] \delta \left(C_i, C_j \right) \tag{2}$$

where A_{ij} is the ijth element of the adjacency matrix, node i is assigned to community C_i and node j is assigned to community C_j. The Kronecker delta $\delta(C_i, C_j)$ is 1 if node i and node j are in the same community and zero otherwise, γ is a structural resolution parameter [42], and P_{ij} is the expected weight of the edge connecting nodes i and j under an appropriate network null model [39]. Using this or a similar approach, it has been observed across many species that there is a clear tendency for modules in structural and functional brain networks to be composed of nodes that lie near one another in physical space [43]. In the human, functional brain networks – constructed from blood–oxygen level dependent (BOLD, a measure of metabolic activity in the brain) signals acquired with functional magnetic resonance imaging (fMRI) while the participant is resting – display between 7 and 17 modules at the largest topological scales in the network [16, 44]. Each module appears to be composed of regions that perform a similar function such as vision, audition, motion, or attention. Most modules are spatially localized, with the exception of the fronto-parietal module (thought to support executive function) and the default mode module (thought to support self-referential processes among others). The tendency for spatial localization of network modules is often interpreted as facilitating segregation of information processing.
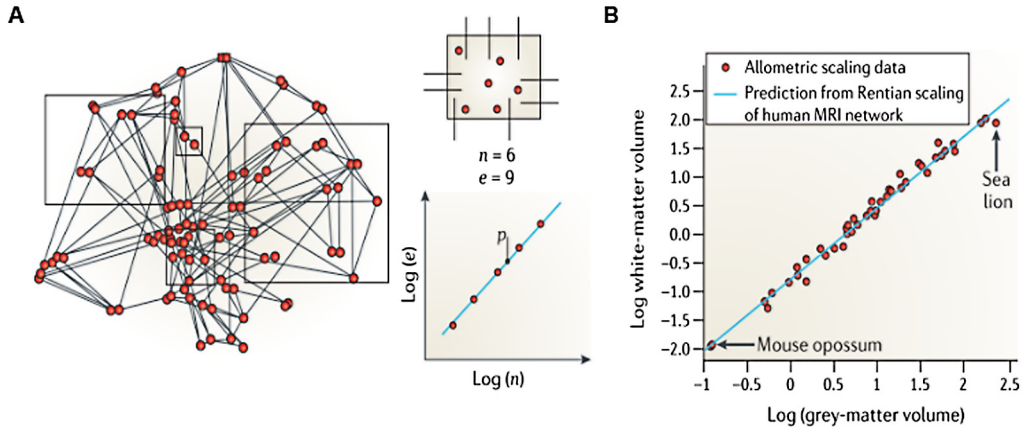
Fig. 2. Rentian scaling. (**A**) An illustration of the calculation of Rent's exponent, which quantifies the fractal scaling of the number of connections to or from a region of the brain (left). Regions in space that contain relatively more nodes (higher value of *n*) tend to have relatively more connections (higher value of *e*), and the relation between these two variables is well-approximated by a power law with exponent *p* (right). (**B**) The Rentian scaling exponent, *p*, calculated from human brains predicts the gray–white matter ratio across evolution, suggesting that the efficient embedding of brain networks in physical space is a conserved property across mammals. This figure is adapted with permission from [7].

The third and final commonly observed property of physically embedded brain networks that we will discuss here is physical Rentian scaling [7]. First observed in computer circuits in the 1960s by E.F. Rent, this scaling law stipulates that when an abstract topological architecture has been efficiently embedded into a physical space, the number of pins (terminals, *T*) at the boundaries of integrated circuit designs scales linearly in log–log space with the number of internal components (*g*), such as logic gates:

$$T = k\,g^p \tag{3}$$

where *k* is a Rent coefficient and *p* is the Rent exponent, which ranges from 0 to 1. Intuitively, this property suggests space-filling, fractal, hierarchically nested topology that has been efficiently embedded into physical space. In the context of brain networks, this property is examined by placing randomly sized rectangles (for approximately 2-dimensional systems like *C. elegans*) or randomly sized boxes (for approximately 3-dimensional systems like the human brain), and then by counting (i) the number of edges, *e*, crossing the boundary of a given box, and (ii) the number of nodes, *n* contained within that given box (Fig. 2A). If the system displays Rentian scaling, then

$$e \sim k\,n^p \tag{4}$$

where, as before, *k* is the Rent coefficient and *p* is the Rent exponent. Rentian scaling has been observed in distribution systems such as the London Underground [45], fungal chords, and rodent brain vasculature [46], and has also been observed in information distribution systems such as very large scale integrated circuits, the *C. elegans* connectome, and the human connectome [7,34]. In the context of neural systems specifically, these observations are consistent with the presence of wiring minimization and localized modules [47], but also further expand our intuitions by suggesting that the system can maintain highly complex topology (such as fractal hierarchically modular topology) in the face of heavy constraints on wiring (Fig. 2B).

4. Drivers of rules for spatial embedding

In the previous section, we described three properties of brain networks from which one can intuit the presence of heavy constraints on the manner in which topologies supporting information transmission and computation are instantiated in the physical volume of neural tissue. These constraints suggest the existence of rules for spatial embedding that ensure nearly-minimal wiring, spatially localized modules, and physical Rentian scaling. A natural next question is, "What mechanisms could drive these rules for spatial embedding?" The answer to this question is likely quite multiplicitous, and here we simply review a few candidate mechanisms that fall under the generic categories of either (i) those that are structural or (bio)physical, or (ii) those that are functional or relevant to dynamics and behavior.

Structural or biophysical constraints can range from small-scale molecular drivers to large-scale volumetric constraints. Perhaps the simplest and most obvious structural constraint on the spatial architecture of brain networks is the fact that, for many organisms, the network must be embedded into the fixed and rather small volume within the skull. The cranial capacity dictated by the skull has evolved by natural pressures, according to principles of morphological modularity, anatomical integration, and heterochrony [48]. The constraints imposed by its current size directly impacts the pattern of white matter connectivity that conserves both white and gray matter volume, leading to networks with nearly minimal wiring costs
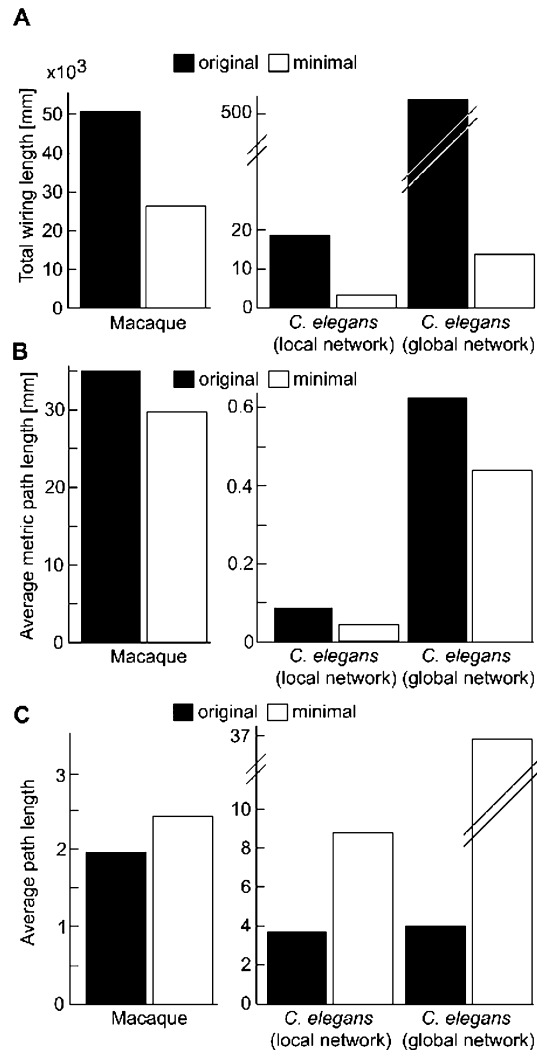
Fig. 3. Brain networks display near minimal wiring with enhanced efficiency. (**A**) Comparisons of wiring length between empirical connectomes, and those with node placement shuffled to minimize wiring length in macaque and *C. elegans*. The local *C. elegans* network refers to neurons within the rostral ganglion. (**B**) Similar to the information presented in panel (**A**), but instead comparing the average metric length of the shortest path. Here, metric shortest path is the physical distance that must be traversed to travel from any node to any other node in the network. (**C**) Similar to the information presented in panel (**A**), but instead comparing the average path length. Here, average path length refers to the average number of processing steps (not metric distance) between any two nodes in the network. Figure adapted with permission from [36].

(Fig. 3) [49]. Yet, to the degree that this pattern-embedding problem has degenerate solutions, it is also of interest to consider the potential constraints of energy and metabolism [47]. Intuitively, long wires may require more energy to develop, maintain, and use. Indeed, extensive prior work supports the notions that energy limitation is a selective pressure on the evolution of sensory systems [50], a constraint on coding and processing of sensory information [51], and a constraint on signaling in gray matter more generally [52]. It is interesting to speculate that such constraints – and the trade-offs between these constraints and information pressures on neural coding [53] – might be arbitrated by genetic material [54,55].

Complementing structural constraints on the spatial embedding of brain networks are considerations of the functions and dynamics that such networks – based on their topology and geometry – can support. Intuitively, a neural system characterized by a preponderance of short distance connections can simply and effectively segregate functions from one another, and localize information processing. Yet, there may also be contrary pressures during development and evolution to maximize the speed of a response (which may require long-distance connections) and to enhance computational complexity (which may require an intricate balance of both short- and long-distance connections) [47]. As a simple example in the structural connectome of the human, the network's mesoscale architecture has been shown not only to contain assortative modules, but also to contain core-periphery and bipartite subgraphs that can potentially support a greater diversity of functional roles including integration and transient control [54]. Indeed, individual differences in the degree of diversity in these meso-scale structures was found to be correlated with individual differences in cognitive control [54]. Consistent with these

competing needs for topological diversity and wiring minimization, structural brain networks show topological properties that allow for fewer processing steps between distant regions than their minimally wired counterparts (Fig. 3). These and related studies support the notion that the observed spatial embedding of brain networks might reflect competing pressures for segregation versus integration, for local processing versus transient top-down control, and for speed of response versus computational complexity [47,56,57].

5. Spatial statistics, generative models, and null models

Because the spatial embedding of an abstract network topology into a physical area or volume can reflect key structural constraints and functional drivers that the system may experience, it is important to develop and apply network analysis tools, models, and theories that account for space. In general, efforts in brain network analysis have incorporated space in three general categories of approaches: descriptive statistics measuring the architecture of the network, generative network models that incorporate spatial considerations directly into the wiring rules, and null models for hypothesis testing that account for varying levels of spatial organization. While these efforts are not comprehensive of the approaches that might yet be useful to develop in the analysis of brain networks, they do represent important first steps in acknowledging that the spatial organization of network topology and geometry may be critical for an understanding of brain development and function.

5.1. Spatial statistics

In brain network analysis, the most common approach used to assess spatial embedding is to calculate spatially-informed statistics. At the smallest scale of individual edges, one might compute the mean, variance, skew, kurtosis or other features of the distribution of edge lengths. At the large-scale of statistics that account for the nature of paths throughout the entire network, one might consider spatially-informed measures of global efficiency. One example is the geometric global efficiency, which is defined as the reciprocal of the harmonic mean of the shortest physical path lengths between nodes [58], and intuitively reflects the routing capabilities of a network [46]. As another interesting alternative, one can consider statistics that explicitly measure the form of the map between abstract topology and physical geometry, such as that found in Rent's rule [7].

To make this exposition more concrete, here we follow [59], and recount several summary spatial statistics that have been previously defined for use in understanding mesoscale organization in brain network architecture. Specifically, we consider community structure given by a partition $\mathcal{C} = \{C_1, \cdots, C_K\}$, where $C_i \subset V$ consists of the nodes in the ith community and K is the number of communities in G. For non-overlapping community structure, note that $C_i \cap C_j = \emptyset$ if $i \neq j$. When this structure is embedded into physical space, it is of interest to quantify the physical, spatial organization of communities within the network. At this meso-scale, we consider the following statistics: the average pairwise spatial distance, spatial diameter, spatial extent, radius, and laterality of communities [59].

Community average pairwise spatial distance: Perhaps the simplest statistic one can compute for a spatially embedded modular network is the community average pairwise spatial distance, l_{C_k}, which has been defined as the average Euclidean distance between all pairs of nodes within a community [61]:

$$l_{C_k} = \frac{2}{N_{C_k}(N_{C_k} - 1)} \sum_{i,j \in C_k} \|\mathbf{r}_i - \mathbf{r}_j\| \tag{5}$$

where $\mathbf{r}_i$ is the position vector of node i and N_{C_k} is the number of nodes in community C_k. Intuitively, the average pairwise spatial distance of the entire network is defined similarly except that the calculation includes all nodes within the network.

Community spatial diameter: Next, we can calculate the maximum Euclidean distance between all pairs of nodes within a community, and we refer to this statistic as the community spatial diameter, d_{C_k} [61]:

$$d_{C_k} = \max_{i,j \in C_k} \left(\|\mathbf{r}_i - \mathbf{r}_j\| \right) \tag{6}$$

Community spatial extent. We can also quantify the spatial extent of a community by estimating the area or volume of the community, normalized by the number of nodes within the community [61]:

$$s_{C_k} = \frac{1}{N_{C_k}} V_h \left(\mathbf{r}_i \right)_{i \in C_k} \tag{7}$$

In 3 dimensions, V_h is the volume of the region bounded by the points of the convex hull of nodes within the community; in 2 dimensions, V_h is the area of the region bounded by the points of the convex hull of nodes within the community. The convex hull can be operationalized as the polygon constructed by connecting all points that constitute the perimeter of the community.

Community radius: The community radius ρ_{C_k} can be estimated by calculating the length of the vector of standard deviations of all nodes in the community [62]:

$$\rho_{C_k} = \left(\frac{1}{N_{C_k}} \sum_{i \in C_k} \|\mathbf{r}_i\|^2 - \frac{1}{N_{C_k}^2} \| \sum_{i \in C_k} \mathbf{r}_i \|^2 \right)^{\frac{1}{2}} \tag{8}$$

Community laterality. The human brain has a marked symmetry: the architecture, function, and dynamics of the left hemisphere is strikingly similar to the architecture, function, and dynamics of the right hemisphere. While we do not yet have a complete understanding of the utility of this symmetry for human cognition and behavior, its existence motivates the question of whether and when mesoscale network structure is the same or different in the two hemispheres. We can operationalize this question as one of estimating community laterality. Consider first that each node can be assigned to one of two categories, $J1$ and $J2$, and we wish to determine the extent to which a community localizes to one category or the other. For an individual community C_k, we can define the laterality Λ_{C_k} as [60]:

$$\Lambda_{C_k} = \frac{\left| N_{J1} - N_{J2} \right|}{N_{C_k}} \tag{9}$$

where N_{J1} is the number of nodes located in category $J1$, and where N_{J2} is the number of nodes located in category $J2$. Intuitively, when Λ_{C_k} is small, the number of nodes in the community are evenly distributed between the two categories, while when Λ_{C_k} is large, all nodes in the community are located in a single category.

5.2. Generative models

Beyond using spatially-informed statistics to describe the architecture of a physically embedded brain network, one might also wish to develop a generative model from which one can construct a network that has statistical similarities to those observed in real neural systems [63]. Formally, a generative network model is comprised of a wiring (or rewiring) rule that, when instantiated, produces a network. The common goal of generative network models is to intuit simple and parsimonious wiring rules that can produce networks similar to those that one hopes to model. Such generative models have been developed for *C. elegans* [64], the cat [65], the macaque [66], and the human [34,63,67]. In several of these models, the wiring rule contains a parameter that tunes a constraint on wiring length, and others even consider changes in the topological wiring constraints throughout the timescales of growth and development [34,64].

Importantly, models that account for spatial constraints tend to produce topologies that are similar to those observed in empirical brain networks (Fig. 4). For example, a common form of these models is the following:

$$P(u, v) = E(u, v)^{\eta} \times K(u, v)^{\gamma} \tag{10}$$

where $P(u, v)$ gives the probability of forming an edge between brain region u and brain region v, $E(u, v)$ denotes the Euclidean distance between region u and region v, η controls the characteristic connection length, $K(u, v)$ represents an arbitrary non-geometric relationship between region u and region v, and γ scales the relative role of $K(u, v)$ in the probability [63]. One particularly useful choice for K is some measure of the local clustering in the network, for example the number of nearest neighbors in common between node u and node v. A generative model instantiating this choice was recently used to suggest that brain networks of patients with schizophrenia are well-fit by models with greater preference for local clustering and decreased penalties on long-distance connections [67]. Collectively, this and other related efforts have demonstrated that across a wide range of species, generative models that incorporate a penalty on long-distance connections produce networks that are more similar to those observed in real neural systems than models that do not incorporate such a penalty.

5.3. Null models

As one develops a generative model to produce an artificial topology reminiscent of the empirically observed topology, one might also wish to produce a family of models that can hold certain spatial constraints constant, thereby allowing formal statistical testing of topological signatures that *are not* explained by those constraints. This general effort falls within the scope of developing appropriate spatially-informed null models. Perhaps the simplest such null model is one in which the locations of edges are permuted uniformly at random while preserving the connection length distribution [68]. This null model allows one to determine whether the network topology one observes in the real system can be explained simply by the connection length distribution. Alternatively, one could also consider a connection length optimized null model, or one in which wiring is formally minimized while maintaining the same number of nodes and edges [7,68]. This null model allows one to determine whether the network topology one observes in the real system can be explained simply by a wiring minimization principle. Other even more complex null models can be constructed [69], and can be directly incorporated into community detection algorithms to identify communities that are not explained by the spatial constraints instantiated in the null [43,70,71].
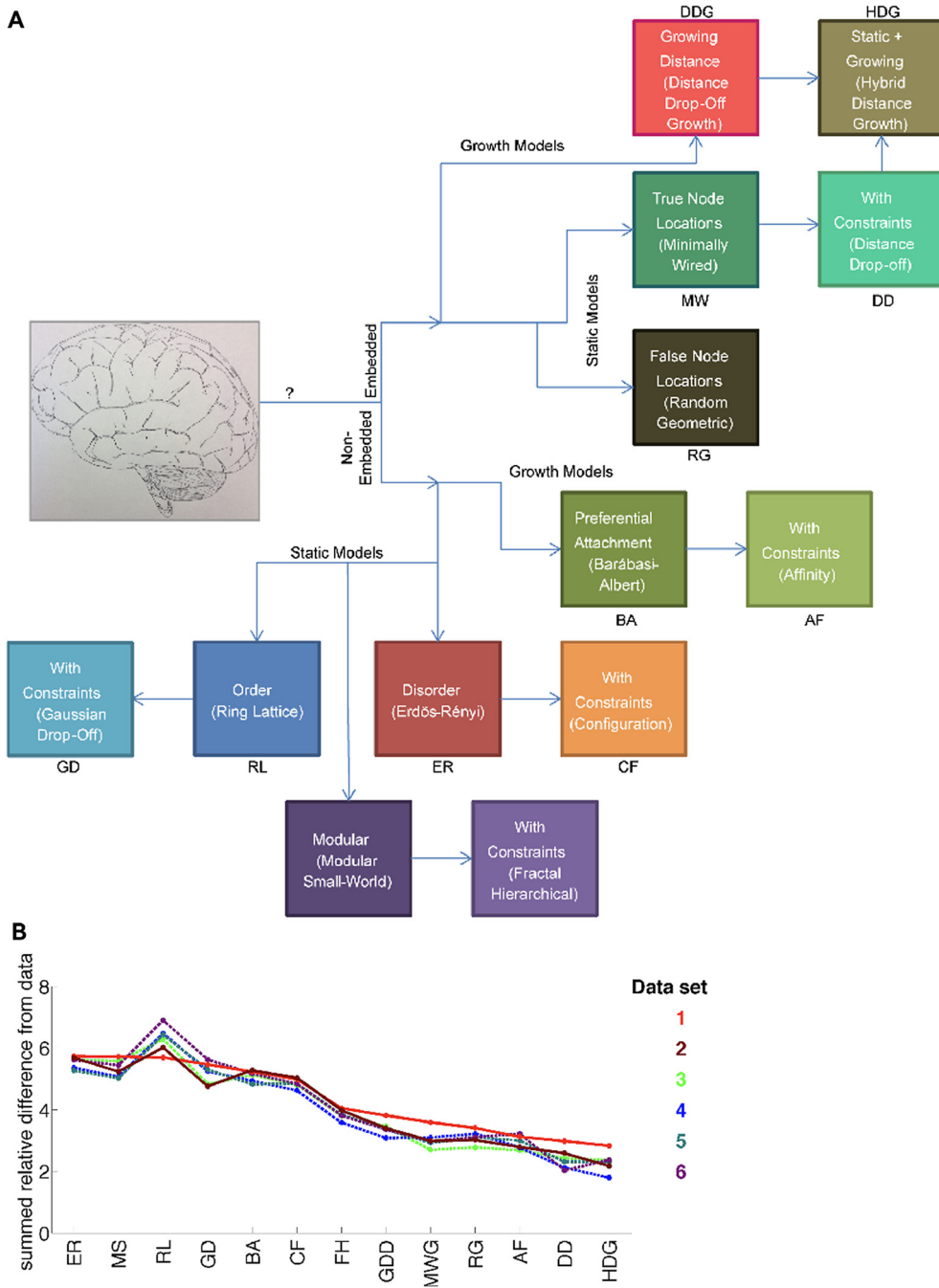
Fig. 4. Comparison of the similarity of models to brain networks. (**A**) A diagram of the 13 models tested. Models include both spatially embedded and non-embedded models, as well as both generative models and static models. Note: The upper right corner shows embedded generative models. (**B**) Sum of the magnitude of the differences in a battery of network statistics between empirical networks and models networks (indicated by abbreviations along the *x*-axis). Colors indicate different human subjects. Network measures included assortativity, hierarchy, clustering, Rentian scaling, fractal dimension, diameter, mean path length, modularity, and number of communities. Note: the hybrid distance-growth model, which is a spatially embedded generative model, displays the smallest difference from the empirically observed network statistics. Figure adapted with permission from [34].

6. Implications for cognition and disease

Given the marked spatial constraints observed in the topology of brain networks across a variety of species, it is natural to ask whether and how such constraints impinge upon cognition, or explain the alterations in cognition that are observed in neurological disease or psychiatric disorders. Answers to these questions remain largely elusive, but preliminary studies
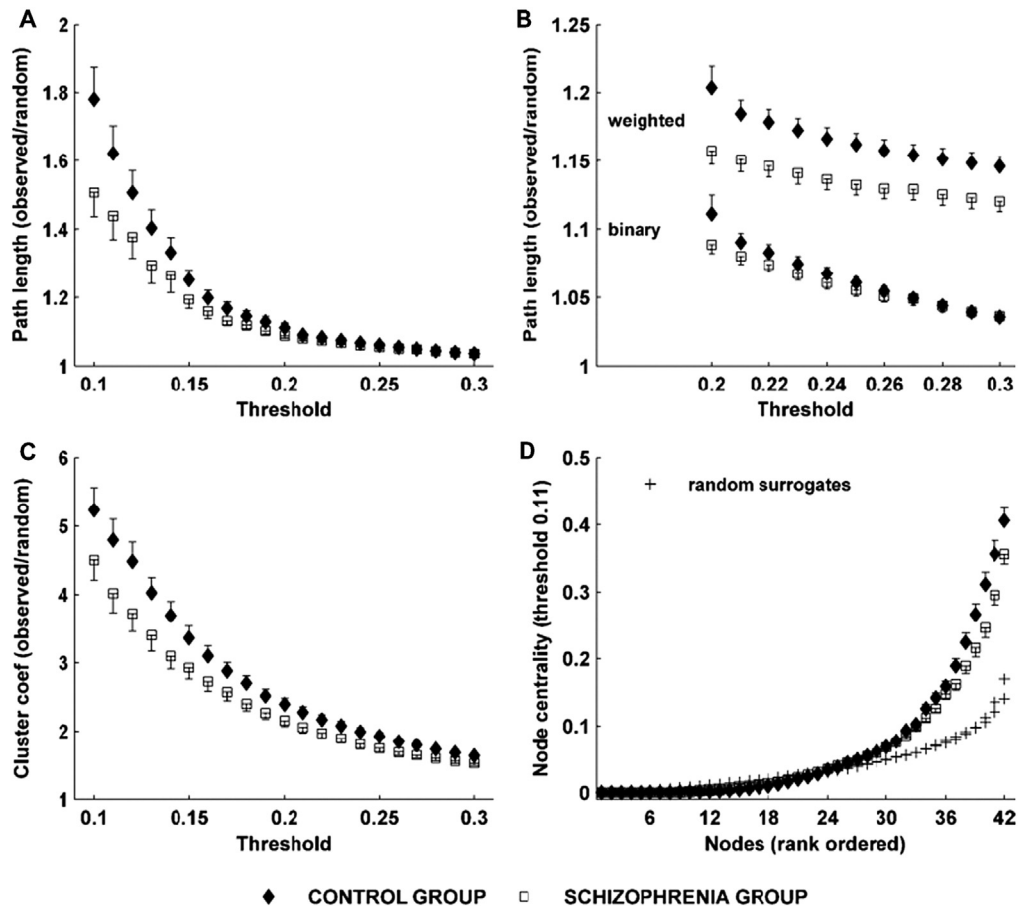
Fig. 5. Observed differences in the statistics of brain networks in patients with schizophrenia compared to healthy controls. (**A**) Difference in path length between patients with schizophrenia and healthy controls across a range of thresholds. Here, the threshold determines the density of the binary network, with a threshold of 0.1 only preserving the 10% strongest edges in the weighted network. (**B**) The same comparison, but for both weighted and binary graphs. (**C**) The same comparison but for the clustering coefficient. (**D**) The same comparison but for the betweenness centrality. All of these findings are consistent with a randomization and decentralization of functional networks in schizophrenia. Figure reproduced with permission from [77].

are beginning to provide a few simple intuitions. We will separate our comments in this section into the implications of spatially embedded brain networks for cognition, and the implications of such networks for disease.

Because information is transmitted throughout neural systems in a physically instantiated manner, the length of physical connections can have direct implications for the lag between information dispersal and information receipt. Such lags are commonly modeled as being proportional to the physical length of tracts (or to the Euclidean distance between the center of mass of regions of interest) [72]. Functionally, lags play an important role in directly modulating the coordination of oscillatory activity [73] and impacting the nature and verity of neural code [74]. It is interesting to consider the potential lags – induced by the physical distances between processing units – that are implicit in the layout of areas and ganglia. Recent work has described a dominant gradient in cortical features from sensorimotor to transmodal areas [75], offering an intrinsic coordinate system that informs our understanding of how increasingly complex cortical functions could emerge from structural constraints [76].

Alterations in the spatial organization of brain networks, and the dynamics that occur atop them, are frequently observed in neurological disease and psychiatric disorders, and may in part explain the observed alterations in cognitive function. Some of the earliest reports of such alterations in brain network organization highlighted a marked functional and structural network randomization in schizophrenia [77,78] both in familial and sporadic subtypes [79], which – at least on the surface – is considered to be related to the thought disturbances present in the disease (Fig. 5). Interestingly, this network randomization also theoretically confers some degree of resilience to injury, offering a candidate explanation for the persistence of the disease in the human population [80]. While schizophrenia displays marked alterations in network structure impacting dynamics, epilepsy displays marked network dynamics suggestive of alterations in underlying structure. Recent evidence suggests that the propagation of epileptic activity throughout cortical and subcortical tissue may manifest as recurrent spiral waves [81], which in their spatially-dependent character are reminiscent of anterior–posterior traveling θ waves observed in the human hippocampus [82]. Indeed, the presence of spatially instantiated wave-like dynamics opens up

important areas for future work in modeling [83] and control [84] for the purposes of benefiting patients with neurological disease.

7. Conclusion & future directions

In summary, in this article we have reviewed recent literature supporting the notion that the spatial embedding of network topology in the brain provides important insights into its development, architecture, and function. We began with a simple summary of the types of brain networks currently being investigated across measurement modalities, spatial scales, temporal scales, and species. We then described three properties of brain networks from which one can intuit the presence of heavy constraints on the manner in which topologies supporting information transmission and computation are instantiated in the physical volume of neural tissue: wiring minimization, spatially localized modules, and physical Rentian scaling. Next, we considered a few candidate mechanisms that could drive the observed rules of spatial embedding, including those that are structural or (bio)physical, and those that are functional or relevant to dynamics and behavior. We described a few initial efforts to incorporate space into brain network analysis: descriptive statistics measuring the architecture of the network, generative network models that incorporate spatial considerations directly into the wiring rules, and null models for hypothesis testing that account for varying levels of spatial organization. We concluded with a discussion of the relevance of these notions for understanding cognition and disease.

Despite the important work to date addressing the architectural, functional, and developmental significance of spatial embedding in brain networks, much remains to be done. We envision that future work will further elucidate the implications of spatial constraints on brain network growth and development for the network's topology, and for the network's symmetry. While both topology and symmetry are known to impact dynamics and control from a theoretical perspective [85], little is known about how that symmetry is instantiated in the brain, or how different sorts of symmetry (radial in the jellyfish, bilateral in the human) might constrain the function of neural systems. We further envision that additional spatially-informed statistics will be constructed, particularly to accurately and parsimoniously characterize the organization of brain networks across diverse spatial scales of measurement. Such efforts could naturally capitalize on recent work developing multilayer and multiplex representations of neural systems. We look forward to these and related advances, which will ensure a better understanding of the spatial constraints on brain networks and their relevance for human cognition and disease.

Acknowledgements

References

[1] E.H. Shen, C.C. Overly, A.R. Jones, Trends Neurosci. 35 (2012) 711.
[2] L. Madisen, T.A. Zwingman, S.M. Sunkin, S. Wook Oh, H.A. Zariwala, H. Gu, L.L. Ng, R.D. Palmiter, M.J. Hawrylycz, A.R. Jones, E.S. Lein, H. Zeng, Nat. Neurosci. 13 (2010), https://doi.org/10.1038/nn.2467.
[3] M. Shariatgorji, A. Nilsson, R. Goodwin, P. Kllback, N. Schintu, X. Zhang, A. Crossman, E. Bezard, P. Svenningsson, P. Andren, Neuron 84 (2014) 697.
[4] E. Bullmore, O. Sporns, Nat. Rev. Neurosci. 10 (2009) 186.
[5] J.C. Reijneveld, S.C. Ponten, H.W. Berendse, C.J. Stam, Clin. Neurophysiol. 118 (2007) 2317.
[6] M. Kaiser, NeuroImage 57 (2011) 892.
[7] D.S. Bassett, D.L. Greenfield, A. Meyer-Lindenberg, D.R. Weinberger, S.W. Moore, E.T. Bullmore, PLoS Comput. Biol. 6 (2010) e1000748.
[8] D.S. Bassett, P. Zurn, J.I. Gold, Nat. Rev. Neurosci. 19 (2010) 30002509.
[9] D.S. Bassett, O. Sporns, Nat. Neurosci. 20 (2017) 353, arXiv:cond-mat/0106096v1.
[10] M. Ekman, J. Derrfuss, M. Tittgemeyer, C.J. Fiebach, Proc. Natl. Acad. Sci. 109 (2012) 16714.
[11] B.A. Zielinski, E.D. Gennatas, J. Zhou, W.W. Seeley, Proc. Natl. Acad. Sci. USA 107 (2010) 18191.
[12] D.S. Bassett, E.T. Bullmore, Curr. Opin. Neurol. 22 (2009) 340.
[13] C.J. Stam, Nat. Rev. Neurosci. 15 (2014) 683.
[14] A. Fornito, E.T. Bullmore, A. Zalesky, Biol. Psychiatry Cogn. Neurosci. Neuroimaging 2 (2017) 9.
[15] M. Barthélemy, Phys. Rep. 499 (2011) 1.
[16] B.T. Yeo, F.M. Krienen, J. Sepulcre, M.R. Sabuncu, D. Lashkari, M. Hollinshead, J.L. Roffman, J.W. Smoller, L. Zollei, J.R. Polimeni, B. Fischl, H. Liu, R.L. Buckner, J. Neurophysiol. 106 (2011) 1125.
[17] B.L. Chen, D.H. Hall, D.B. Chklovskii, Proc. Natl. Acad. Sci. USA 103 (2006) 4723.
[18] S.W. Oh, J.A. Harris, L. Ng, B. Winslow, N. Cain, S. Mihalas, Q. Wang, C. Lau, L. Kuan, A.M. Henry, et al., Nature 508 (2014) 207.
[19] C.-T. Shih, O. Sporns, A.-S. Chiang, BMC Neurosci. 14 (2013) P63.
[20] M. Bota, H.W. Dong, L.W. Swanson, Front. Neuroinform. 6 (2012).
[21] J.W. Scannell, C. Blakemore, M.P. Young, J. Neurosci. 15 (1995) 1463.
[22] R. Bakker, T. Wachtler, M. Diesmann, Front. Neuroinform. 6 (2012) 30.

[23] P. Hagmann, L. Cammoun, X. Gigandet, R. Meuli, C.J. Honey, V.J. Wedeen, O. Sporns, PLoS Biol. 6 (2008) e159.
[24] D.S. Bassett, J.A. Brown, V. Deshpande, J.M. Carlson, S.T. Grafton, NeuroImage 54 (2011) 1262.
[25] A.M. Hermundstad, D.S. Bassett, K.S. Brown, E.M. Aminoff, D. Clewett, S. Freeman, A. Frithsen, A. Johnson, C.M. Tipper, M.B. Miller, et al., Proc. Natl. Acad. Sci. USA 110 (2013) 6169.
[26] A.M. Hermundstad, K.S. Brown, D.S. Bassett, E.M. Aminoff, A. Frithsen, A. Johnson, C.M. Tipper, M.B. Miller, S.T. Grafton, J.M. Carlson, PLoS Comput. Biol. 10 (2014) e1003591.
[27] H.S. Seung, Nature 471 (2011) 170.
[28] S. Teller, C. Granell, M. De Domenico, J. Soriano, S. Gomez, A. Arenas, PLoS Comput. Biol. 10 (2014) e1003796.
[29] D.S. Bassett, M. Yang, N.F. Wymbs, S.T. Grafton, Nat. Neurosci. 18 (2015) 744.
[30] X.N. Zuo, Y. He, R.F. Betzel, S. Colcombe, O. Sporns, M.P. Milham, Trends Cogn. Sci. 21 (2017) 32.
[31] M.P. van den Heuvel, E.T. Bullmore, O. Sporns, Trends Cogn. Sci. 20 (2016) 345.
[32] S.B. Laughlin, T.J. Sejnowski, Science 108 (2002) 22.
[33] J.K. Kim, J.M. Soffer, A.E. Kahn, J.M. Vettel, F. Pasqualetti, D.S. Bassett, Nat. Phys. 14 (2018) 91.
[34] F. Klimm, D.S. Bassett, J.M. Carlson, P.J. Mucha, PLoS Comput. Biol. 10 (2014) e1003491.
[35] C. Cherniak, J. Neurosci. 14 (1994) 2418.
[36] M. Kaiser, C.C. Hilgetag, PLoS Comput. Biol. 2 (2006) e95.
[37] C. Cherniak, Trends Neurosci. 18 (1995) 522.
[38] R.F. Betzel, D.S. Bassett, Proc. Natl. Acad. Sci. USA 115 (2018) E4880.
[39] M.E. Newman, M. Girvan, Phys. Rev. E 69 (2004) 026113.
[40] A. Lancichinetti, S. Fortunato, Phys. Rev. E 80 (2009) 056117.
[41] M. Rosvall, C.T. Bergstrom, Proc. Natl. Acad. Sci. USA 105 (2008) 1118.
[42] D.S. Bassett, M.A. Porter, N.F. Wymbs, S.T. Grafton, J.M. Carlson, P.J. Mucha, Chaos 23 (2013) 013142.
[43] R.F. Betzel, J.D. Medaglia, L. Papadopoulos, G. Baum, R. Gur, R. Gur, D. Roalf, T.D. Satterthwaite, D.S. Bassett, Netw. Neurosci. 1 (2017) 42.
[44] J.D. Power, A.L. Cohen, S.M. Nelson, G.S. Wig, K.A. Barnes, J.A. Church, A.C. Vogel, T.O. Laumann, F.M. Miezin, B.L. Schlaggar, S.E. Petersen, Neuron 72 (2011) 665.
[45] M. Sperry, Q. Telesford, F. Klimm, D.S. Bassett, J. Complex Netw. 5 (2017) 199.
[46] L. Papadopoulos, P. Blinder, H. Ronellenfitsch, F. Klimm, E. Katifori, D. Kleinfeld, D.S. Bassett, PLoS Comput. Biol. 14 (9) (2018) e1006428.
[47] E. Bullmore, O. Sporns, Nat. Rev. Neurosci. 13 (2012) 336.
[48] E. Bruner, Child's Nerv. Syst. 23 (2007) 1357.
[49] A.J. Sherbondy, R.F. Dougherty, R. Ananthanarayanan, D.S. Modha, B.A. Wandell, Med. Image Comput. Comput. Assist. Interv. 12 (2009) 861.
[50] J.E. Niven, S.B. Laughlin, J. Exp. Biol. 211 (2008) 1792.
[51] S.B. Laughlin, Curr. Opin. Neurobiol. 11 (2001) 475.
[52] D. Attwell, S.B. Laughlin, J. Cereb. Blood Flow Metab. 21 (2001) 1133.
[53] J.E. Niven, J.C. Anderson, S.B. Laughlin, PLoS Biol. 5 (2007) e116.
[54] R.F. Betzel, J.D. Medaglia, D.S. Bassett, Nat. Commun. 9 (2018) 346.
[55] B.D. Fulcher, A. Fornito, Proc. Natl. Acad. Sci. USA 113 (2016) 1435.
[56] L.H. Somerville, B.J. Casey, Curr. Opin. Neurobiol. 20 (2010) 236.
[57] M. Kaiser, Trends Cogn. Sci. 21 (2017) 703.
[58] V. Latora, M. Marchiori, Phys. Rev. Lett. 87 (2001) 198701.
[59] J.O. Garcia, A. Ashourvan, S.F. Muldoon, J.M. Vettel, D.S. Bassett, Proc. IEEE 106 (2018) 17718785.
[60] K.W. Doron, D.S. Bassett, M.S. Gazzaniga, Proc. Natl. Acad. Sci. USA 109 (2012) 18661.
[61] S. Feldt Muldoon, I. Soltesz, R. Cossart, Proc. Natl. Acad. Sci. USA 110 (2013) 23401510.
[62] C. Lohse, D.S. Bassett, K.O. Lim, J.M. Carlson, PLoS Comput. Biol. 10 (2014) 25275860.
[63] R.F. Betzel, A. Avena-Koenigsberger, J. Goñi, Y. He, M.A. de Reus, A. Griffa, P.E. Vértes, B. Mišic, J.-P. Thiran, P. Hagmann, et al., NeuroImage 124 (2016) 1054.
[64] V. Nicosia, P.E. Vértes, W.R. Schafer, V. Latora, E.T. Bullmore, Proc. Natl. Acad. Sci. USA 110 (2013) 7880.
[65] S.F. Beul, S. Grant, C.C. Hilgetag, Brain Struct. Funct. 220 (2015) 3167.
[66] S.F. Beul, H. Barbas, C.C. Hilgetag, Sci. Rep. 7 (2017) 43176.
[67] P.E. Vertes, A.F. Alexander-Bloch, N. Gogtay, J.N. Giedd, J.L. Rapoport, E.T. Bullmore, Proc. Natl. Acad. Sci. USA 109 (2012) 5868.
[68] D. Samu, A.K. Seth, T. Nowotny, PLoS Comput. Biol. 10 (2014) e1003557.
[69] J.A. Roberts, A. Perry, A.R. Lord, G. Roberts, P.B. Mitchell, R.E. Smith, F. Calamante, M. Breakspear, NeuroImage 124 (2016) 379.
[70] P. Expert, T.S. Evans, V.D. Blondel, R. Lambiotte, Proc. Natl. Acad. Sci. USA 108 (2011) 7663.
[71] M. Sarzynska, E.A. Leicht, G. Chowell, M.A. Porter, J. Complex Netw. 4 (2017) 363.
[72] P. Ritter, M. Schirner, A.R. McIntosh, V.K. Jirsa, Brain Connect. 3 (2013) 121.
[73] D. Roy, R. Sigala, M. Breakspear, A.R. McIntosh, V.K. Jirsa, G. Deco, P. Ritter, Brain Connect. 4 (2014) 791.
[74] C.A. Runyan, E. Piasini, S. Panzeri, C.D. Harvey, Nature 548 (2017) 92.
[75] D.S. Margulies, S.S. Ghosh, A. Goulas, M. Falkiewicz, J.M. Huntenburg, G. Langs, G. Bezgin, S.B. Eickhoff, F.X. Castellanos, M. Petrides, E. Jefferies, J. Smallwood, Proc. Natl. Acad. Sci. USA 113 (2016) 12574, arXiv:1408.1149.
[76] J.M. Huntenburg, P.L. Bazin, D.S. Margulies, Trends Cogn. Sci. 22 (2018) 21.
[77] M. Rubinov, S.A. Knock, C.J. Stam, S. Micheloyannis, A.W. Harris, L.M. Williams, M. Breakspear 30 (2009) 403.
[78] M. Rubinov, D.S. Bassett, J. Neurosci. 31 (2011) 6263.
[79] J. Zhu, C. Zhuo, F. Liu, W. Qin, L. Xu, C. Yu, Sci. Rep. 6 (2016) 23577.
[80] C.Y. Lo, T.W. Su, C.C. Huang, C.C. Hung, W.L. Chen, T.H. Lan, C.P. Lin, E.T. Bullmore, Proc. Natl. Acad. Sci. USA 112 (2015) 9123.
[81] J. Viventi, D.H. Kim, L. Vigeland, E.S. Frechette, J.A. Blanco, Y.S. Kim, A.E. Avrin, V.R. Tiruvadi, S.W. Hwang, A.C. Vanleer, D.F. Wulsin, K. Davis, C.E. Gelber, L. Palmer, J. Van der Spiegel, J. Wu, J. Xiao, Y. Huang, D. Contreras, J.A. Rogers, B. Litt, Nat. Neurosci. 14 (2011) 1599.
[82] H. Zhang, J. Jacobs, J. Neurosci. 35 (2015) 12477.
[83] G.B. Ermentrout, D. Kleinfeld, Neuron 29 (2001) 33.
[84] S. Ching, E.N. Brown, M.A. Kramer, Phys. Rev. E, Stat. Nonlinear Soft Matter Phys. 86 (2012) 021920.
[85] A.J. Whalen, S.N. Brennan, T.D. Sauer, S.J. Schiff, Phys. Rev. X 5 (2015) 011005.