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Introduction

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Complex network theory and the brain

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1. Brain networks: from anatomy to topology

The first clear, recognizably scientific representations of the human brain were the drawings and engravings of the Renaissance anatomists. These prototype anatomical maps of brain organization demonstrated a physical structure somewhat walnut-like in appearance: an approximately symmetrical pair of deeply wrinkled lobes connected to each other by a central bridge of tissue. More extensive and detailed dissection of the human brain revealed that its convoluted surface is thinly covered (less than 3 mm) by a layer of so-called grey matter—the cortex; and that anatomically separated regions of cortical grey matter are extensively interconnected to each other (and to subcortical grey matter nuclei) by axonal projections that are bundled together to form macroscopically visible white matter tracts, including the major white matter tract linking the two cerebral hemispheres.

Even these few fundamental observations on the anatomical organization of the brain indicate that it must be considered as a large-scale (more than 1 mm) network of grey matter regions connected by white matter tracts. It has also been increasingly well understood, since the first microscopic neuro-anatomists of the nineteenth century, that there is an intricate pattern of synaptic connections between locally neighbouring neurons in the same cortical column or area. So there has long been strong evidence that the brain has a qualitatively complex network organization at micro (less than 1 mm) as well as macro scales.

At a microscopic scale, we know that drawing a complete network diagram of the human brain would be a task of currently unmanageable scale and technical difficulty. The brain comprises an estimated 10^{11} neurons (10^5 mm^{-3}) and axonal projections or 'wires' connecting neurons have an estimated total length of 10^5 km (5 km mm^{-3}). These large numbers are naturally magnified by focusing on the connections between neurons: the association matrix of pair-wise synaptic weights between neurons will be of the order of 10^{100} . To these challenges of scale must be added the technical difficulties of accurately measuring all the synaptic connections between densely packed neurons (glia and other cells) in even a small block of cortical tissue post-mortem. For the foreseeable future, it seems likely that our best data on complete micro networks will continue to come from smaller nervous systems such as *Caenorhabditis elegans*.

However, there is a more tractable opportunity to map the large-scale network organization of the human brain at the macroscopic scale provided by neuroimaging techniques such as magnetic resonance imaging (MRI). MRI has sufficient spatial resolution (approx. 1 mm) to measure structural properties (such as cortical thickness) and functional properties (such as low-frequency endogenous oscillations) in hundreds of cortical areas and major subcortical nuclei. Diffusion-weighted MRI (DW-MRI) can also be used to measure white matter tracts between grey matter regions. From these data, we can estimate measures of anatomical or functional *connectivity* between regions. For example, the probability of a white matter connection between two regions can be inferred by various methods for DW-MRI tractography; and functional connectivity between a pair of regions can be simply estimated as the correlation between the two functional MRI (fMRI) time series measured simultaneously, while the subject lies quietly 'at

rest' or is scanned during the performance of a cognitive task. A complete, large-scale (MRI) association matrix comprises of the order of 10^4 pair-wise anatomical or functional connectivity weights. Thus, the challenges of scale and measurement are more manageable for human brain network mapping at the macro scale; but MRI brings its own challenges—especially biological interpretability of the various statistical estimators of connectivity.

Here we are focused on how a more formal, quantitative analysis of complex network organization could help us to understand the brain at micro and macro scales. Specifically, we are interested in the potential value added to neuroscience by the application of contemporary complex network theory [1–3]: a statistical physics understanding of graph theory, itself a much older branch of pure mathematics. The statistical physics approach aims at explaining observable macroscopic behaviour of a given system as emerging in a non-trivial way from the interactions of a vast number of microscopic units or agents. Complex network theory can be thought of as a subfield of statistical physics for structurally disordered, dynamically heterogeneous systems with non-trivial topology; and as an extension of graph theory to systems with high structural heterogeneity and inherently dynamical properties, two key properties of the vast majority of real-life systems, including brains.

Graphs are simple models of complex systems, defined as a set of nodes or vertices V connected by a subset of edges E . Mathematically, this can be represented as a graph, $G = (V, E)$, where E is a subset of non-zero elements in the $V \times V$ adjacency matrix. The simplest graphical model assumes that all nodes are identical except in terms of their connectivity; and that all the non-zero connections have identical weight (1) and are symmetrical (undirected). None of these assumptions is entirely realistic for brains but nonetheless binary graphs have been constructed for a wide range of species. In non-human mammals, histological tract-tracing—by localized cortical injection of a fluorescent or radioactive tracer that then propagates by mono-synaptic axonal projections to or from other cortical areas—has been used to construct large-scale (inter-areal) anatomical brain graphs in the cat, the macaque monkey and the mouse. In humans, anatomical brain graphs have been inferred from tractography of DW-MRI data; or from estimates of the covariance in local volume or cortical thickness between pairs of grey matter regions in structural MRI data. In humans and less frequently in non-human species, functional brain graphs have been constructed from association matrices of pair-wise measures of functional connectivity (e.g. correlation or coherence) estimated from fMRI or electrophysiological recordings [4,5].

The main immediate impact of these and other early graph theoretical studies has been to promote a change of perspective in how we look at the brain. Graph theory is primarily concerned with the *topology* of the system, not with its anatomy, which has provided the dominant perspective on brain organization for hundreds of years. A topology is a general set of elements endowed with some relationship among them. Importantly, in the most general case, V is not a set of points in the ordinary Euclidean space, but an arbitrary set of points, with no physical structure. In particular, edges have no distance in millimetres or other physical units, so that a graph representation typically involves non-metric abstract relationships, where the path length between vertices is defined as the minimal number of edges in a path

connecting them, but the connection distance (in millimetres; often used as a proxy for 'wiring cost') is irrelevant.

The abstraction of graphs from the details of the underlying data means that the same mathematical language can be used to quantify topological properties at micro and macro scales, to link the organization of anatomical and functional networks, to compare the topology of brain networks across species, and to consider the topology of brain networks in general compared with other complex systems, including non-biological networks. This in turn has encouraged a shift in perspective towards fractal, scale-invariant or indeed universal properties of brain networks that complement the traditional focus on the unique and species-specific anatomical details of their organization.

2. Graphical models of the connectome

It has now been demonstrated across multiple studies that brain anatomical networks—or *connectomes*—have a remarkably consistent repertoire of topological properties. Like random graphs, where each pair of nodes has a uniform probability of an edge between them, brain graphs have a short characteristic *path length*, i.e. the average of the path length between each pair of brain regions is close to its minimum in a comparable random graph. This is equivalent to saying that brain graphs have high *global efficiency* compared with the maximum efficiency of a random graph. Both path length and global efficiency are often interpreted as measures of the integrative or information-sharing capacity of a network.

However, brain graphs also have topological features that are not so typical of random graphs. For example, the number of edges connecting each brain region to the rest of the network, i.e. the *degree* or degree centrality of each node, is more variable than the probability distribution of degree in a random graph. Brain graphs generally have a fat-tailed degree distribution that is best fit by (exponentially truncated) power laws, whereas random graphs have Poisson degree distributions. The scale-free or heterogeneous degree distributions of brain graphs are compatible with the existence of *hub* nodes with much higher degree than most non-hub nodes—and identification of brain network hubs by various metrics of topological centrality, including but not limited to degree, has been quite ubiquitously reported [6,7].

Brain graphs also have higher *clustering* than random graphs. For any graph, clustering can be quantified by counting the proportion of triangular *motifs* that completely connect a subset of three nodes. Motifs are prototypical topological patterns of connection between a subset (typically 2, 3 or 4) of the nodes in a brain network or other complex system [8,9]. In other words, in a network with high clustering, two of the nearest neighbours of an arbitrary index node are more likely to be nearest neighbours of each other, or directly connected by a single edge, than would be expected in a random graph. The combination of high clustering and short path length (or high global efficiency) is often described as 'small world', reflecting the prior observation of a similar combination of global topological properties in social and many other complex networks [10].

There is also convergent evidence that brain networks typically have a *community structure*, or non-random topological properties at an intermediate or mesoscopic level between the global level of efficiency or small-worldness and the

nodal level of degree or other measures of centrality. Community structure can be described by a modular decomposition of the network as a number of *modules* that each comprises a group of nodes densely connected to each other but sparsely connected to nodes in other modules. The relatively few nodes that mediate inter-modular connections are quantified by a high participation coefficient and have been designated as *connector hubs*. Hierarchical modularity refers to a multi-scale community structure comprising nested sub-modules within modules. All of these aspects of modular organization have been widely reported in brain graphs [11–13]. Modularity, like clustering, is often interpreted as a measure of segregated network architecture or the tendency for information exchange to be restricted to subsets of nodes.

An alternative approach to analysis of community structure has been to partition the network into a small ‘core’ or *rich club* of high degree nodes that are highly interconnected to each other and a larger periphery of nodes that are not so well connected. Rich clubs have been shown to have an important role in mediating most of the minimum path length motifs connecting pairs of peripheral nodes and, as such, are often interpreted as an integrative aspect of brain network topology [14].

Finally, graphical models of the connectome lend themselves to computational modelling of network generation and network degeneration. For example, the *robustness* of a network to attack can be simulated by deleting nodes or edges at random and monitoring the rate at which global efficiency is degraded as a function of increasing percentage of randomly attacked nodes; alternatively, computational attack can be targeted on the higher degree nodes [15]. As might be expected from their fat-tailed degree distributions, brain graphs are notably less resilient to targeted attack than random graphs.

These and other discoveries about the complex topology of brain networks have been widely replicated in species ranging from *C. elegans* to *Homo sapiens*, at micro and macro scales, and on the basis of a wide variety of experimental data. It seems likely that they amount to robust new knowledge about brain network organization; certainly, there has been an impressive growth in the number of neuroscientific studies using graph theoretical techniques in the past 10 or so years; and, naturally, a number of important questions and issues have been raised by this ‘first wave’ of topological studies of the connectome.

How does the topology of a brain network relate to its anatomical organization? In particular, how can the complex topology of nervous systems be reconciled to the obvious fact that they are embedded in physical space and there is abundant prior evidence to suggest that the wiring and metabolic costs of brain networks are controlled if not strictly minimized [16–18]? Minimization of wiring cost is compatible with the spatial co-location of nodes in the same module and with the observation that topologically clustered nodes are often also close neighbours anatomically. But more integrative aspects of brain network topology such as the existence of connector hubs mediating long-distance inter-modular connections, or a rich club of densely interconnected but anatomically separated hub nodes, are less readily explained by minimization of wiring cost and associated metabolic costs. It seems likely, although not yet fully elucidated, that anatomical design of brain networks represents the outcome of adaptive trade-offs between multiple competitive selection

pressures on cost, efficiency, resilience and other topological factors [19].

How does the topology of a brain anatomical network relate to its functional and dynamical properties? The human brain performs of the order of 10^{15} synaptic operations/second, with a computational efficiency of the order of 10^{14} operations/joule, and has an estimated storage capacity of 10^{12} bytes [20]. It is known that many of the impressive computational and information-processing functions of the brain are delivered by dynamically coupled or synchronized neuronal populations. The spontaneous or task-related waxing and waning of synchronization between different neuronal populations induces observable transient functional networks. Indeed, synchronization has been identified as a fundamental dynamical feature modulating cortical interactions by increasing the effectiveness of interactions between brain regions [21], and there is now large consensus on its role in many aspects of the brain’s cognitive function. But it remains a largely open question how the topology of functional networks is related both to their information-processing capacity and to the topology of the anatomical network, which is the structural substrate for their emergence.

Insofar as anatomy and dynamics can be endowed with potentially isomorphic network representations, network theory can help in understanding the relationship between the topology of anatomical networks and the dynamical processes taking place on them, and ultimately the way that cognitive function can be represented in terms of these two aspects of network organization. In this context, it is arguably important to distinguish the terms functional and dynamical networks. Although functional network is often used to describe a brain graph constructed by analysis of correlations or coherences between nodal time-series activity (as we have used the term above), such graphs should perhaps be more accurately described as dynamical networks. Functional network should then be a designation reserved for networks defined by mapping the observed ability to carry out a given task or neurophysiological function onto observed topological properties of anatomical or dynamical networks. In other words, genuine functional networks can be thought of as *macrostates* of either anatomical or dynamical ones. On the other hand, once nodes are endowed with their own dynamics, it is possible to distinguish between dynamics *in* the network, i.e. node dynamics, and topological dynamics *on* a network. The interdependence of these two dynamics is a defining feature of *adaptive networks* such as the brain [22].

The phenomenology of possible interactions between the various levels is extremely rich, particularly as one considers the relative time scales over which anatomical, resting state and task-activated dynamical and functional networks can evolve. The relationship between resting state and task-activated dynamical networks can be seen as the consequence of the fluctuation–dissipation theorem [23], a fundamental result of basic physics which establishes a general relationship between the response of the system to small external perturbations, and the internal autocorrelation of fluctuations of the system in the absence of perturbation [24]. On the other hand, the relationship between dynamical networks, both at rest and during the execution of cognitive tasks, and anatomical networks seems of an altogether different nature. The extent to which a given process depends on the structure of the network on which it unfolds is a matter of relative time scales of the topology and of the relevant dynamics. For

instance, in a sense, anatomical networks can be seen as homeomorphic to resting dynamical networks in the limit of an infinitely slow time scale [25], whereas anatomical structure, which evolves or develops on much longer time scales, should only act as a boundary condition for very fast dynamical processes. The anatomy–dynamics–function interplay and the role played by topology and dynamics and time-scale separation remains a vast and open field of investigation.

How should we best use graph theory to quantify and more completely understand brain network organization? Neuroimaging techniques such as fMRI effectively coarse-grain brain anatomy and neural activity, so that what is observed is in fact the result of spatially and temporally coherent structure. However, as soon as one leaves the spatial observation scale of single neurons, identifying nodes and links of the system becomes a non-trivial task [26–28]. Identifying nodes supposes that the system can be decomposed into different parts, and that each of these parts can be reduced to structureless points. How to best segment or parcellate the anatomical space and how to accurately sample the underlying dynamical system are two of the main issues encountered. Functional connectivity is generally defined using statistical relationships between activity recorded at different brain sites or sensors, but there is as yet no universally accepted criterion for choosing the most appropriate metric of brain activity out of the set of available ones, and the question of how different connectivity metrics affect the topological properties of the resulting networks is still poorly understood [28,29].

3. Overview of this issue

In this *Theme Issue*, we hope to orientate readers to the current state of this rapidly moving field and to address these and other key questions concerning the future applicability and utility of graph theoretical methods for understanding brain network organization.

De Vico Fallani *et al.* [30] introduce the basic concepts of brain graphs from network reconstruction to the interpretation of results, with special attention paid to the definition of nodes and edges in functional networks. Appropriate methods for graph construction or filtering are proposed, and statistical analyses as well as technical and methodological limitations are discussed.

While the standard graphical analysis of brain networks typically identifies neuronal populations with nodes and axonal connections with edges, important information may be obtained by taking an opposite perspective. de Reus *et al.* [31] investigate how complex network theory can be applied to the analysis of anatomical networks from a link-based perspective, instead of the traditional view of node-based analysis. The authors analyse how links between brain regions are organized in communities and evaluate their robustness introducing a new class of edge removal metrics. Central hubs acting as hot spots in the interplay between the communities of links are detected. Considering that functional networks are shaped by the underlying structural connections, these link communities can be interpreted as subsystems of the connectome with different roles and could be associated with localized processes of functional specialization.

Another important problem arising at the early stage of complex network analysis is that of directionality. In their

review paper, Keller *et al.* [32] propose the use of cortico-cortical evoked potentials (CCEPs) as a tool for measuring effective connectivity and thus directed networks that capture the causal interactions between brain regions. The measurement of CCEPs induced by electrical stimulation allows the direction of flow of electrical activity to be assessed by stimulating one site and measuring the cortical response at another site. The N1 event-related component of the CCEP is found to partially reflect the structural connectivity strength between regions, whereas the N2 may be influenced by factors such as brain state and cognitive demands. Furthermore, CCEP-based network analysis allows estimation of the reciprocity of connections between regions: approximately 30% for short-distance connections and approximately 10% for long-distance connections, with the proportion of reciprocal connections in the brain decreasing as a function of connection distance. The use of CCEPs also supports comparison of the network topology at rest, during sensory stimuli, and during electrical stimulation of specific subnetworks. Comparing the large-scale network structure of the brain during these conditions can yield important information regarding local and global network reorganization following the activation and disruption of specific cortical regions.

Hütt *et al.* [33] examine the extent to which anatomical structure constrains dynamical processes in the brain by drawing on the theory of spatio-temporal pattern formation. A novel perspective is proposed to evaluate how the brain's self-organized dynamics are constrained by its network architecture to a small set of permissible collective states. The role of topological features of brain connectivity such as hubs, modules and hierarchy in shaping activity patterns is explored. Computational simulations are used to illustrate the notion of network-guided pattern formation, demonstrating how it can facilitate the understanding of neural dynamics.

Network theory also allows investigation of the interplay between structure and dynamics at spatial scales below that of whole brain macroscopic behaviour. Gollo & Breakspear [34] analyse how basic network properties can determine two complementary influences on zero-lag synchronization and ultimately functional activity patterns. The mesoscopic dynamics arising from dynamical features of network motifs of coupled neural masses are examined. It is shown that reciprocally coupled pairs of neural masses synchronize in a stable way and at zero-lag, but only when certain motif configurations are adopted. The effects of this local synchronization can then propagate along connected chains. On the other hand, closed loops between coupled neural masses disrupt stability and synchrony, enabling multiple stable configurations to coexist, thus introducing meta-stability and variability. Similar results are obtained when the same kind of motifs are translated into ensembles of modular networks. These results illustrate the effect that resonance pairs have on promoting synchronization and, conversely, how frustration destabilizes the stable state in weakly coupled small motifs, enriching and diversifying the dynamical landscape of synchronized cortical states. Thus, these two principles give rise to multi-stable dynamics in systems of different scale, from motifs to cortical networks, and may represent the substrate for flexible neuronal integration, bridging across cognitive tasks.

Another fundamental problem arising from the interplay between structure and dynamics is how the different spatial scales are related to the dynamical scales. Neuronal activity evolves at temporal scales ranging from a few milliseconds

to tens of seconds and emerges from neuronal assemblies that extend from micrometres to several centimetres. At the microscopic scale, individual neurons exhibit action potentials that last about 1 ms, while the coordinated multiunit activity or local field potentials generated by the synchronization of multiple neurons operates on time scales up to tens of seconds. To study the interactions between these scales, Barardi *et al.* [35] introduce a hybrid computational model in which two mesoscopic neural masses are coupled to each other through a microscopic neuronal network. The two neural mass oscillators are taken to operate in a low-frequency regime with different peak frequencies and distinct dynamical behaviour. The microscopic neuronal population is described by a network of several thousands of excitatory and inhibitory neurons operating in a synchronous irregular regime, in which the individual neurons fire sparsely but collectively give rise to a well-defined rhythm in the gamma range. This neuronal network, which operates at fast temporal scales, is sufficient to mediate the coupling between the two mesoscopic oscillators, which evolves dynamically at a slower scale. These results reveal how synchronization observable at coarser scales may depend on the topological properties of more fine-grained neuronal networks, their size and oscillation frequency.

Kim & Kaiser [36] examine how different spatial scales are inter-related and how metabolic, functional and developmental constraints shape the topology of anatomical networks. The neural network of *C. elegans* and the human connectome are investigated, with special attention paid to the detection of communities within the network and the hierarchical relationships between them. Several properties are found to be network-specific and not to be fully explained by the modular organization alone. For both *C. elegans* and humans, the density of local connections and the probability of finding long-range connections are high compared with alternative networks with similar modularity. Furthermore, the total wiring length is smaller than for alternative network configurations with similar modularity. Both brain networks show lower algorithmic entropy compared with computational models, indicating that fewer rules are needed to encode the organization of nervous systems. While the first two findings indicate that brain network topologies are efficient from an information-processing viewpoint, the latter result suggests that they are also efficient from a developmental point of view. Taken together, these results show that brain networks are selected for emergence of additional features beyond those specified by their modularity alone.

At evolutionary or developmental time scales, observed brain properties can be thought of as the result of an optimization process. Complex network theory can potentially help to understand the generative rules underpinning the observed formation of brain networks. One possible strategy consists of reverse engineering observed brain networks, i.e. building generative models that more or less accurately reproduce or simulate their topological and spatial properties. Insofar as complex network theory is a statistical mechanical approach to graphs, observed networks can be thought of as realizations of a given probability density function. Generative models are thus essentially explanations of the emergence of distributions, under constraints. Vertés *et al.* [37] use this strategy to investigate the formation of the rich club of interconnected hubs in brain networks. Because rich club nodes are spatially distributed within the whole

brain network their functioning is associated with relatively high wiring and metabolic costs, raising questions about the selection pressures favouring their formation. A number of generative models were used to simulate the emergence of the rich club organization in large-scale brain functional networks. An economical clustering model, which instantiates a trade-off between favouring the formation of new connections between nodes that already share the same nearest neighbours (clustering) versus penalizing the formation of edges with long connection distance, was found to simulate rich club emergence at a macro scale. And in computational models, an explicitly Hebbian learning rule led to clustering and the emergence of rich clubs.

Observed networks together with their topological properties can be understood as exemplars of an ensemble of networks, subject to some constraint. In turn, one may consider them as the result of a particular evolutionary path, the idea being that in order for configurations to become observable, they must be 'accessed' through an evolutionary path. An effective way to account for both viewpoints is a representation wherein all possible network configurations together with a set of possible variation operators are provided. A *morphospace*, i.e. a phenotype space with a set of quantitative traits as its axes, allows representation of all possible configurations accessible given the constraints under which the system operates. If the axes represent true constraints, the topological relations (in a loose way, distances) within the morphospace may be thought to somehow reflect the variational operators corresponding to the selection pressures operating on the system during the course of evolution. In this framework, Avena-Koenigsberger *et al.* [38] analyse the capacity of anatomical brain networks to evolve towards topologies exhibiting optimal information-processing features, while preserving the network cost. The authors explore the position of the network topology in a three-dimensional morphospace, the axes of which are represented by efficiency, diffusion efficiency and neural complexity. This approach allows investigation of how selection pressures may have shaped the network architecture of the human brain. It is found that while a randomization of the network topology leads to less efficiency in routing communication, real networks are close to their optimal topologies if information transfer is considered as a diffusion process, but may be further optimized if communication is defined as a routing process along shortest paths between node pairs.

The way that brain networks reorganize and adapt to varying conditions and evolve through learning [39] is still poorly understood. Krienen *et al.* [40] explore how cognitive tasks shape functional networks, highlighting both stable and reconfigurable features of functional organization. Their goals are both conceptual and practical since they sought to understand how network configurations change across a broad range of task states to better characterize what is stable and what is reconfigurable in terms of network organization. With this aim, they used fMRI to measure the brain activity of a group of 48 individuals performing 14 different tasks with different levels of difficulty, ranging from passive activities to stimulus-driven classification. Task-related reconfigurations of functional connectivity were shown to deviate around a central tendency of coupling patterns similar across all tasks. Certain broad properties appear most stable, suggesting that they are anatomically constrained. However, details differ from task to task and it is unclear whether any particular state provides

a privileged view of cortical organization: functional networks share common properties but, at the same time, cortical regions or neuronal subpopulations reconfigure their coupling in response to task demands. These results may indicate that studying coupling patterns associated with the execution of a single task or during passive rest is insufficient to distinguish the stable network properties from task-varying contributions. These results may also be taken as a sign that each cognitive task explores a minor part of the vast repertoire of resting brain activity, which in turn may not be sufficiently explored under standard experiments.

Almost 10 years since its early application, what contributions has complex network theory made to our current understanding of the brain? What pitfalls should it seek to avoid, and what new frontiers can graph theory help to achieve, in the future? Papo *et al.* [41] critically review the major contributions as well as the limitations of this new approach. It is argued that the complex networks approach to functional neuroimaging represents a conceptual revolution, not just an incremental refinement of existing techniques, as it offers a qualitatively different view of brain activity and brain-behaviour mapping, shifting from a computer-like to a complex system vision of the brain, where networks are endowed with properties which stem in a non-trivial way from those of their constituent nodes, and function is an emergent property of interactions. This in turn complexifies the notion of locality of function. However, there is a fundamental contradiction between the basic tenet of the classical statistical physics approach, whereby nodes are thought of as identical and playing equivalent roles, and the locally specialized character of brain anatomy and function. This raises the following question: at what level does complex network theory describe brain structure and dynamics? In other words, at what observation scale can brain anatomy and dynamics be considered more than a collection of well-defined nodes?

Possible ways of taking full advantage of graph theory include resorting to cutting edge theoretical concepts, e.g. analysis from a multiplex or multi-scale viewpoint. They could also involve incorporating the temporal dimension of brain activity, considering the time-varying aspects of dynamical networks that change their topological configuration over time [42]. Alternatively, existing graph theoretical tools could be used to describe other aspects of brain activity. For instance,

a network representation need not be isomorphic to brain anatomy, as it could for example be used to characterize the phase space associated with brain dynamics. If the network representation is not merely a convenient descriptive tool, but reflects intrinsic properties of brain structure and dynamics, then it could be used in a number of ways that far exceed the current predominantly descriptive use of complex network theory. A criterion to assess the relevance of complex network representation can be provided, for example, by the extent to which a given network representation helps to categorize experimental conditions or subject populations, or to predict or control brain activity and guide it therapeutically towards desired regimes [29].

Major developments in future will probably require conceptual efforts, particularly in the characterization of functional brain activity. For instance, it will be important to go beyond information encoded *in* a network and capture that encoded *by* the network, and even further, to understand the meaningfulness of this information [43]. One of the major challenges will consist of better representing the functional space and improving the specificity of observed anatomical and dynamical networks associated with functional activity, and understanding which observed differences in network representations are neutral with respect to function. This in turn implies defining the boundaries of the space of possible phenotypes of task-related or condition-specific structure and dynamics as well as their topology; and understanding how discontinuities in the functional space, associated with pathological conditions or the switching between different cognitive tasks, are a consequence of mappings between brain network and behavioural phenotypes.

Further major breakthroughs in complex network theory applications to neuroscience will probably demand that, instead of borrowing already available graph theoretical metrics designed to describe complex systems differing in fundamental ways from the brain, neuroscientists should inspire fresh network theory where the specific properties of the brain are taken into account. This will involve accounting for the brain's complex adaptive nature and redefining concepts at all levels, from distances to community structures to robustness in more directly biological terms [44,45]. Ultimately, perhaps, neuroscience-based constructs may represent the next major revolution in complex network theory.

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