Review

Generic aspects of complexity in brain imaging data and other biological systems

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A key challenge for systems neuroscience is the question of how to understand the complex network organization of the brain on the basis of neuroimaging data. Similar challenges exist in other specialist areas of systems biology because complex networks emerging from the interactions between multiple non-trivially interacting agents are found quite ubiquitously in nature, from protein interactomes to ecosystems. We suggest that one way forward for analysis of brain networks will be to quantify aspects of their organization which are likely to be generic properties of a broader class of biological systems. In this introductory review article we will highlight four important aspects of complex systems in general: fractality or scale-invariance; criticality; small-world and related topological attributes; and modularity. For each concept we will provide an accessible introduction, an illustrative data-based example of how it can be used to investigate aspects of brain organization in neuroimaging experiments, and a brief review of how this concept has been applied and developed in other fields of biomedical and physical science. The aim is to provide a didactic, focussed and user-friendly introduction to the concepts of complexity science for neuroscientists and neuroimagers.

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Introduction

The human brain is nothing if not complex, in any sense of that word. It comprises approximately 100 billion neurons, each of which makes about 10,000 synaptic connections. The total size of the human brain’s “connectome” (Sporns et al., 2005), at a cellular level of description, is therefore in the order of $10^{13}$, or one thousand trillion. This enormous number of microscopic connections between individual processing elements provides the fundamental substrate for neuronal ensembles to become transiently synchronized or functionally connected (Buzsáki, 2006; Singer, 1999). The emergence of such dynamically coupled cell assemblies is widely regarded as key to the neurophysiological representation of cognitive or mental states including perception, emotion and action (Fries, 2005). Moreover, observations of human brain structure and function by neuroimaging indicate that complex network configuration and dynamics exist also at a macroscopic scale of description (Bressler, 1995; Friston, 2002). In short, we can say that the organization of the brain is quantitatively complex at many scales of space and time (Bullmore and Sporns, 2009).

However, it is becoming increasingly clear that complexity may be a characteristic of biological systems in general; and that some of the same mathematical tools and concepts can appropriately be used to quantify and compare aspects of complexity in substantively very diverse systems. To take a single, illustrative example in brief: many complex systems have been shown to have a modular or nearly-decomposable organization (Simon, 1962) including systems as different as the human brain transcriptome (comprising multiple, correlated gene expression profiles) (Oldham et al., 2008), the global air transportation network (comprising multiple airports and the scheduled flights between them) (Guimerá et al., 2005), and ecological or economic networks (Saavedra et al., 2008).

The important generalization is that one way forward in dealing with the formidable complexity of the human brain may be to recognize that certain key principles of its organization are shared in common with other complex systems in biology and elsewhere. This idea that both brain and biological systems may have generic properties in common is one implication of the more general universality hypothesis: that certain network organizing principles are highly conserved and more-or-less universally instantiated in real-life networks. Studies addressing network organization have proliferated recently in an interdisciplinary research area, sometimes called complexity science, which is driven largely by technical developments in statistical physics and has begun to demonstrate a startling degree of commonality in the organization of substantively distinct complex systems. The further growth of complexity science seems very likely to be important in understanding the organization of biological systems – at all scales from molecular to ecological – and for developing a network approach to the understanding and treatment of clinical disorders — whether of body, brain or mind (Barabási, 2007).

In the rest of this paper, we provide a non-technical introduction to four somewhat related aspects of complexity that occur frequently in systems neuroscience and systems biology: fractality, criticality, small-worldness and related attributes, and modularity. The overall aim is to show how these concepts and related quantitative tools can provide a mathematical common ground to foster integrated understanding of brain systems in relationship to bodily systems more generally.

Fractality or scale-invariance

The defining characteristic of a fractal is its self-similarity or scale-invariance. In simple terms, a fractal looks at least approximately the same over several scales of magnification.

A prototypical example from biomedicine is the tree-like structure of the pulmonary airways in the lung: the branching structure of the bronchioles is approximately the same as both the larger scale bronchial tree and the smaller scale alveolar tree. Many other biological structures, including cardiovascular systems in animals and water transport systems in plants, also show this characteristically fractal property of scale-invariant organization. Indeed, since the “Fractal Geometry of Nature” was published in 1982 (Mandelbrot, 1982), scale-invariance has turned out to be a very general property of many systems – not just biological – including physical, social and computational systems. A geological example is the coastline of Norway, which has major fjords branching into fjordlets at closer spatial resolution. One consequence of this complexity at all geological scales is that the measured length of the coastline is not fixed but depends on the scale at which it is measured. Finer grained measurements, on smaller scale $r$, lead to greater estimated length $L$, and this relationship is defined more formally as

$$ L \propto r^{1-D} $$

where $D$ is the fractal (Hausdorff) dimension and $D \sim 1.45$ for the Norwegian coast. In other words, this equation shows that the measured length of the coastline increases in inverse proportion to the scale on which the measurements were made. The exponent $D$ controls the form of this power law scaling relationship. Note that this fractal dimension will be in the range $1 < D < 2$ for any process – like a coastline, or an image boundary, or a time series – that has a topological dimension of 1 (it is a Euclidean line) and an embedding dimension of 2 (it is located in a Euclidean plane). The closer the $D$ gets to the embedding dimension, the greater the geometric complexity of the fractal process.

Monofractals and multifractals

There are many different ways to measure the “fractality” of a massively complex system like the brain. The first approach we will consider is to measure the fractal dimensions, $D$, of its constituent processes. For example, we can estimate the fractal dimension of anatomically localized regional fMRI time series. Results show that $D \sim 1.7$ is typical for regional mean fMRI time series recorded under resting-state conditions. This quantifies the visual impression we have on looking at an fMRI time series that it is considerably rougher or more irregular than a Euclidean line but not rough enough to occupy entirely the plane of the page. Variability of the fractal or scaling properties of fMRI time series has been measured under various experimental conditions using a wavelet-based estimator of the Hurst exponent $H$ (which is simply related to the fractal dimension, $D = 2 - H$).

Studies have shown that fractal scaling of resting-state fMRI time series is related to the distribution of grey matter and is a marker of acute pharmacological challenge with scopolamine (a muscarinic acetylcholine receptor antagonist) (Wink et al., 2006). Abnormalities in fractal dimension of fMRI time series have also been reported in early Alzheimer’s disease (Maxim et al., 2005) and attention-deficit hyperactivity disorder (Anderson et al., 2006). Preliminary studies further showed that performance of a cognitively effortful (episodic memory) task was associated with changes in fractal scaling of “resting” state fMRI data recorded about 30 min after task completion (Wink et al., 2008; Suckling et al., 2008). These data collectively provide evidence that changes in the fractal dimensions of neurophysiological signals are influenced not only by neuropathology and pharmacology but also by task-related behaviour. Moreover, there has been some effort to compare fractal scaling parameters to other, equally parsimonious measures of resting fMRI time series activity. For example, the Hurst exponent was compared to the first order autoregression (AR1) coefficient as a measure of endogenous dynamic abnormality in Alzheimer’s disease (AD) (Maxim et al., 2005). In this case, case-control differences in the Hurst exponent were shown to discriminate the elderly control and AD groups more clearly than differences in the AR1 coefficient, indicating that fractal scaling
measure can provide a relatively sensitive diagnostic marker compared to more traditional metrics. However, this is just a first step in an ongoing process of cross-validation that will naturally be entailed in establishing the practical added value of fractal metrics in neuroimaging.

So far, we have considered only the relatively simple case where the same scaling exponent applies to all parts of the process, e.g., $D \sim 1.45$ for both northern and southern halves of the Norwegian coastline, or $D \sim 1.7$ for both the first and last segments of an fMRI time series recorded several minutes. Since one exponent controls all the scaling in such a process, it is called a monofractal. This is arguably a more reasonable assumption for a slowly changing process, that has emerged over many millions of years, like the coastline of Norway, than it is for the more rapidly changing dynamics of human brain function. In the case of physiological processes, whether measured in the heart by electrocardiography (ECG) or in the brain by fMRI, it is probably more reasonable to allow that the scaling exponent $D$ will not be unchanging or stationary in time. We can accommodate this by analysing the process as a multifractal. This means that we will describe the complexity of the process by a spectrum of local scaling exponents – Hölder exponents, $h$ – rather than the single global exponent ($D$ or $H$) used to describe a monofractal. More technically, the local scaling behaviour in the neighbourhood of a singularity $i$, i.e. some point in time where the

Fig. 1. Effects of task performance on monofractal and multifractal scaling of endogenous fMRI dynamics. (a) A region of right inferior frontal gyrus (IFG) was part of a cortical network activated by performance of a facial recognition task. (b, c) Monofractal scaling of endogenous fMRI dynamics, measured by the fractal dimension $D$ or Hurst exponent $H$ about 20–30 min later in the same IFG region, was negatively correlated with latency of successful recognition during task performance. Faster performance was associated with greater fractal complexity (larger $H$ or $D$) of “resting state” fMRI data recorded subsequently. (d) Multifractal analysis of the same IFG time series shows that faster performance is associated with a shift to larger mean and greater spread of the singularity spectrum of Hölder exponents, $h$. Full details are given in Wink et al. (2008); figure reproduced with permission.

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signal is non-differentiable, is controlled by a Hölder exponent $h$ and the singularity spectrum or distribution of $\{h_i\}$ over all singularities summarises the scaling of a multifractal process (Muzy et al., 1993; Turiel et al., 2006). Multifractal dynamics are present in a variety of biophysical signals: human gait recordings (West and Latka, 2005); electroencephalographic and magnetoencephalographic data (Song et al., 2005; Stam, 2005), and ECG signals. In particular ECG signals have shown sensitivity to fractal dynamics with respect to disease (cardiac failure) and ageing (Ivanov et al., 1999; Ivanov et al., 2001; Wang et al., 2007; Pavlov et al., 2005) as well as treatment (Chiu et al., 2007; Amaral et al., 2001).

Although the stationarity or otherwise of the underlying fractal process is the basis upon which a monofractal or multifractal analysis is chosen, a combined approach may prove useful (Wink et al., 2008). A voxelwise univariate test with the monofractal exponent $H$, is an efficient method of locating the spatial location and extent of differences in fractal scaling of endogenous fMRI dynamics arising from manipulation of an experimental parameter. This is illustrated in Fig. 1, where a region of right inferior frontal gyrus is first activated by a facial recognition memory task; some 30 min later, when the subjects were scanned again “at rest”, the fractal dimension of endogenous dynamics in this region was correlated with latency of task performance. This result suggests that performance of a cognitive task may have prolonged effects on fractal properties of endogenous oscillations at the low frequencies (<0.5 Hz) typically measured by fMRI. Through a more detailed multifractal analysis of the time series extracted from this region it is possible to refine our understanding of the time series changes by task performance. Thus decreased latency of task performance was associated with increases in the maxima of the singularity spectra, confirming the result from the monofractal analysis. However, it is also noticeable that faster reaction times are associated with increases in the width of the singularity spectrum towards higher values of $h$. Higher values of $h>0.5$ correspond to those points at which the dominant contribution to the time series is from (slowly decaying) singularities at lower frequencies.

Summary

The basic idea of fractal, self-similar or scale-invariant organization is simple: fractal systems “look the same” on many scales of space and time. It is clear that this property is common to almost all natural systems. In dynamic physiological systems, such as represented by ECG or fMRI time series, a multifractal model, which allows scaling relationships to change over time is arguably more appropriate.

There are excellent general reviews of fractal and related mathematics in Schroeder (1991) and Eke et al. (2002). For more technical introductions to fractal and wavelet analysis of time series in general see Percival and Walden (2000) and Wornell and Oppenheim (1992); and for the case of fMRI time series analysis, Bullmore et al. (2003). In subsequent sections, on criticality, network topology and modularity, we will see that the fundamental principle of scale-invariance recurs also in these aspects of brain and other physiological systems.

Criticality

Perhaps the easiest way in to the concept of criticality is to start with a physical system driven by an external control parameter. For example, as the temperature of liquid water is reduced towards 0 °C and beyond it will undergo – within a narrow temperature range – a phase transition, and become solid water or ice. At around the critical temperature 0 °C, on the cusp of phase transition, water in the form of snowflakes can also have complex, fractal scaling properties. The general hypothesis of criticality is that many systems close to the critical point of a phase transition will demonstrate power law scaling, with complex patterning or fluctuations at all scales of space and/or time.

The idea of self-organized criticality (SOC) (Bak and Paczuski, 1995) is essentially to translate this concept to the case of physical systems where the control parameters may not be known or are not being experimentally controlled (as temperature can be controlled to take water to freezing point). Such systems are supposed to emerge spontaneously from the interactions between multiple agents. Many physical and biological systems have been described as demonstrating self-organized criticality. Often this claim has rested on demonstration of fractal scaling properties for the dynamics of the natural system in question, be it avalanches, forest fires, respiration, intra-cellular signalling, or brain function.

However, it is important to recognize that the emergence of fractal or power law scaling, although necessary, is not sufficient to prove that the system is self-organized critical. To be more assertive about SOC we need to know also how the system has evolved or developed towards its currently critical state, and we need to exclude alternative mechanisms for power law scaling, such as turbulence, which involve major external drivers and therefore are not self-organized.

More formally, the following properties were highlighted as key features of a self-organized system (Jensen, 1998):

- Interaction dominated: the local dynamics is essentially governed by interactions between the constituents of the system.
- Time scale separation: the time scale of any external driving force has to be much slower than the time scale of the response of the system (the internal relaxation process); else the dynamics would be externally dominated.
- Existence of a large number of threshold separated metastable states with a subset of minimally stable states which are the critical states.

Thus one can expect SOC in slowly driven, interaction-dominated systems showing scale-free behaviour. The existence of power laws for the spatial and temporal statistics of critical systems is compatible with the related observations that the dynamics of individual units or components of such systems will show long-range correlations in space and time, and change in state of a single unit can rapidly trigger macroscopic reconfiguration of the system.

Self-organized criticality (SOC) and brain systems

Due to these characteristics, self-organized criticality is intuitively attractive as a model for the dynamics of brain function (Pak and Chialvo, 2001; Chialvo, 2004; Thatcher et al., 2009; Beggs, 2008). Coherent oscillations in transient neuronal ensembles can give rise to emergent phenomena such as perception, memory and action, corresponding to cognitive and behavioural states of the brain (Singer, 1999; Gray et al., 1989; Gray, 1999; Womelsdorf et al., 2007).

Critical dynamics of such neurophysiological systems are consistent with their rapid reconfiguration in response to changing external challenges, requiring the ability to switch quickly between behavioural states in order to adapt (Bassett et al., 2006).

Moreover, critical systems are thought to be optimal in terms of the capacity for information storage and transfer (Beggs, 2008; Bornholdt and Rohl, 2003; Haldeman and Beggs, 2005; Chialvo et al., 2008).

There is already a large body of evidence for critical brain dynamics in neurophysiological processes including spike frequency, endogenous EEG and fMRI oscillations (Maxim et al., 2005; Bullmore et al., 1994; Linkenkaer-Hansen et al., 2001), which all display characteristic power law scaling in anatomically localized recordings. However, in order for criticality to be relevant for the function of the brain, it has to be present in the interaction of anatomically distributed neurophysiological systems as well. Direct evidence that this is indeed the case comes from multielectrode array recordings of cortical slices performed by Beggs, Plenz and colleagues (Haldeman and Beggs, 2005; Beggs and Plenz, 2003), who have demonstrated criticality in the observed neuronal spike activity. Human magnetoencephalography (MEG) can...
be used to study the dynamics of neurophysiological systems at a much larger spatial scale comprising the whole brain. Complex network analysis of MEG data at various frequency scales revealed a small-world topology of human brain functional networks consistent with critical dynamics, and self-similar over a range of scales (Bassett et al., 2006). More direct evidence for critical dynamics of human brain functional networks comes from Kitzbichler et al. (2009), who studied both functional magnetic resonance imaging (fMRI) and MEG data over a large frequency range. They found spatio-temporal power law scaling in measures of synchronization between different brain regions and demonstrated that analogous scaling of these synchronization metrics was also found in computational models of critical dynamics; see Fig. 2.

Self-organized criticality has been studied in computational models and experiments, in a large range of different disciplines from astrophysics to linguistics, from archaeology to economics, and from biology to sociology, demonstrating that the systems which show emerging complexity are extremely diverse.

Examples of computational models displaying self-organization are the sand/rice-pile model, the forest fire model, the Bak–Sneppen model of evolution (Bak and Sneppen, 1993), and the Olami–Feder–Christensen model of tectonic plate movement (Olami et al., 1992). In experimental data, SOC related power laws were claimed to have been found in the systems modelled above, i.e. rice-piles, forest fires, evolution/extinction, earthquakes and landslides, but also in solar flares, climate fluctuation, stock market crashes, traffic jams, and even in the historic changes of pottery styles and the occurrence of wars (see reviews by Turcotte (1999) and Paczuski and Bak (1999)).

Focussing on the topic of this review, criticality is found in, and indeed may be a fundamental property of, most biological systems and at all scales, from the cell to the whole organism, because the ability to quickly adapt and reconfigure in response to the environment is a characterizing common feature of all types of living systems.

For example an intriguing study of gene expression changes in the macrophage, found evidence of critical dynamics in normal intracellular signalling and non-critical dynamics in cells that had been impaired by specific gene knock-outs, implying that criticality in this signalling system conferred an adaptivity advantage (Nykter et al., 2008).

At the next larger scale of cells, Beggs and Plenz found criticality in recordings of spike activity of neuronal networks, already mentioned in the previous section. At the level of individual organs, Kiyono et al. (2004) demonstrated scale-invariance in healthy human heart rate increments, for the quiescent as well as the dynamic state, supporting the view that a healthy human heart rate is controlled to converge continually to a critical state. For the whole organism there is evidence for critical dynamics of anatomically distributed physiological systems, manifesting itself in the intermittency of synchronization between different functional areas in the brain. Lability of endogenous synchronization may also represent spontaneous changes in subjective mental state, or conscious perception of internal objects. A natural extension of this paradigm is the critical dynamics found in the interaction of biological organisms in general and of humans in particular, reaching from fractality found in the constructions of termite colonies (O’Toole et al., 2003) to the metastability in the lifetimes of pottery styles observed in archaeology (Bentley and Maschner, 2001) spanning millennia of human history.

Small-worldness and related topological attributes

One important approach to complex systems has been to analyse the topology of the network of connections between interacting agents. A key tool for this purpose is graph theory, see Fig. 3. In this framework, networks are represented graphically as a collection of nodes connected by edges. In neuroimaging data, the nodes may represent specific regions-of-interest and the edges some statistical measure of association, such as correlations in physiological time series (Bassett et al., 2006; Achard et al., 2006); or inter-regional covariance in anatomical parameters, e.g., cortical thickness, grey matter density, etc. (He et al., 2007; Bassett et al., 2008). If two nodes are connected, e.g., they show correlated activity, or a fiber tract can be traced from one region to another, an edge is drawn on the graph; if no biological interaction is apparent, the nodes remain graphically unconnected.

The connecting edges in a graph can be binary, i.e., nodes are either connected or not, or weighted to reflect the strength of interaction. Edges can also be directed (drawn as arrows rather than lines) if the causal structure of interactions between agents is known. Graphical representation of brain networks enables calculation of numerous measures indexing different aspects of network structure and dynamics; see Table 1. Perhaps more importantly, network interactions in other bodily systems can be represented in a similar manner.

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allowing brain and body to be studied within a common framework. Indeed, the application of these techniques has revealed that various types of biological and non-biological networks show striking convergence in their organizational properties, pointing to universal laws and principles that drive network formation. In the following sections, we briefly consider how graph analysis can enhance understanding of macroscopic brain networks, as measured by neuroimaging, and compare these results with those found in other biological networks at micro and macro scales.

**Small-worldness**

Two important parameters of network organization are the clustering coefficient and characteristic path length. The clustering coefficient measures how cliquish network connectivity is; that is, the likelihood that two nodes connected to a third node are also connected to each other (an analogy in a social network is the likelihood that two of my acquaintances also know each other). Characteristic path length reflects the average number of edges that must be traversed to transfer information between any two nodes. Regular networks (e.g., lattices), where each node is only connected to its immediate neighbours, have high clustering and path length; i.e., each of a node's neighbours are always connected to each other, but many edges must be traversed to get between any two nodes that are not adjacent to each other. In contrast, randomly connected networks have low path length, but also show low clustering. In their seminal study, Watts and Strogatz (1998) showed that adding a few long-range connections to a regular network drastically reduces the mean path length while preserving high clustering, resulting in a so-called 'small-world' topology.

**Cost-efficiency**

The small-world combination of high clustering and low path length has been found in many complex systems, including social networks, ecological food webs and the internet (Albert and Barabási, 2002). For the brain, this architecture provides an optimized trade-off between segregated, local processing (high clustering) and global integration (low path length), and is directly related to the efficiency of information transfer in the system. That is, path length is inversely related to global network efficiency (i.e., a more efficient network will require fewer connections to transfer information between any two nodes), while clustering is proportional to local network efficiency, or fault tolerance (Latora and Marchiori, 2001, 2003; see Table 1). In

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Name</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k )</td>
<td>Degree</td>
<td>Number of connections emanating from or entering into a node</td>
</tr>
<tr>
<td>( C )</td>
<td>Clustering</td>
<td>Probability that two nodes which are connected are also neighbours</td>
</tr>
<tr>
<td>( L )</td>
<td>Path-length</td>
<td>How many nodes must be passed through to get from start to finish</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>Small-worldness</td>
<td>How strongly the graph lies between randomness and order</td>
</tr>
<tr>
<td>( r )</td>
<td>Assortativity</td>
<td>Nodes with similar degree connect preferentially to each other</td>
</tr>
<tr>
<td>( \beta )</td>
<td>Hierarchy</td>
<td>Hubs' connections are sprawling rather than clustered provincially</td>
</tr>
<tr>
<td>( \epsilon_{glob} )</td>
<td>Global efficiency</td>
<td>How simple it is for information to get from one node to any other</td>
</tr>
<tr>
<td>( \epsilon_{local} )</td>
<td>Local efficiency</td>
<td>How efficient a node's local neighbourhood is</td>
</tr>
<tr>
<td>( \zeta )</td>
<td>Synchronizability</td>
<td>How likely it is that all nodes will produce the same wave pattern</td>
</tr>
<tr>
<td>( \xi )</td>
<td>Length scale</td>
<td>Spatial length of connections in Euclidean space</td>
</tr>
</tbody>
</table>

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principle, one could maximize both local and global efficiencies simply by adding more connections, but metabolic constraints limit the number of the connections that can be formed in the brain (Chen et al., 2006). Indeed, available data suggest that brain connectivity is sparse—the neural network of Caenorhabditis elegans, the only such network to be completely mapped at the synaptic level, possesses <3% of the total number of possible synapses (Watts and Strogatz, 1998), while inter-regional connectivity in mammalian cortex is estimated to comprise ~18–38% of all possible connections (Bassett and Bullmore, 2006). Thus, the brain must try to maximize efficiency while minimizing wiring costs. In both the macaque and C. elegans, the small-world topology has been shown to provide an optimum trade-off between these competing interests, conferring high local and global efficiencies for relatively low connection costs (Latora and Marchiori, 2001).

Robustness

Another important property of the brain's small-world architecture is its degree distribution. The nodal degree, \( k \), is simply a measure of how many connections a node in the network has. In most complex networks, the nodal degree distribution can be categorized as either scale-free, broad-scale or single-scale (Amaral et al., 2000). In scale-free networks, the degree distribution follows a power law of the form \( P(k) \sim k^{-\gamma} \), indicating that the network contains a number of nodes, termed “hubs”, each of which has high degree (large \( k \)). Broad-scale networks display a power law regime truncated with an exponential or Gaussian decay, suggesting a lower probability of the existence of hubs possibly due to constraints on network growth in physically embedded systems (Amaral et al., 2000). The degree distribution of single-scale networks shows a fast decaying tail implying an equal distribution of connections across nodes. Three fMRI studies have reported evidence of scale-free architecture in human functional and anatomical networks (Cecchi et al., 2007; Eguílluz et al., 2005; van den Heuvel et al., 2008), although the majority of studies, using fMRI, structural MRI, DTI, DSI and MEG, have found broad-scale connectivity (Bassett et al., 2006; Achard et al., 2006; Gong et al., 2008; He et al., 2007; Bassett et al., 2008). The distinction has implications for the brain's robustness to failures: scale-free networks are very robust to attacks on randomly chosen nodes but susceptible to attacks on hubs (Albert and Barabási, 2002). This is because the vast majority of nodes in a scale-free network have very few connections, so removing them will not have a major impact on the network. However, targeted deletion of hub nodes, which mediate large numbers of connections, will quickly result in network fragmentation. In contrast, broad-scale networks are more robust to targeted attacks and show comparable resilience to random errors because connectivity is more evenly distributed across the nodes. Thus, the broad-scale architecture of the brain likely confers enhanced resilience to damage or disease. Interestingly, one recent study found that alterations in network organization in Alzheimer's disease rendered patients' brains more susceptible to targeted attack (Stam et al., 2008). Integrating such experimental findings with theoretical work predicting the functional consequences of simulated lesions (e.g., Honey and Sporns, 2008) will greatly facilitate a more comprehensive understanding of how disruptions in brain connectivity give rise to, and are affected by, injury and illness.

Effects of age, disease and genes on brain network topology

Increasing evidence indicates that small-world and other topological parameters are affected by ageing and disease, albeit in different ways (Bassett et al., 2008; Achard and Bullmore, 2007; Meunier et al., 2009). For example, one resting-state fMRI study found intact global but reduced local efficiency in patients with schizophrenia (Liu et al., 2008), while a separate study found evidence of increased local efficiency in children with attention-deficit hyperactivity disorder (ADHD) (Wang et al., 2008). Further evidence from a structural MRI study (Bassett et al., 2008) suggests that the dysconnectivity of schizophrenia may be characterized by an inverted hierarchical structure (Ravasz and Barabási, 2003; Sporns, 2006) in heteromodal association cortex in addition to an abnormally large average wiring length. Such findings, combined with evidence that individual differences in these network organization parameters are heritable (Smit et al., 2008; Schmitt et al., 2008), suggest that these measures represent viable phenotypic markers for complex psychiatric and neurological conditions associated with disordered brain connectivity.

Topology of other complex networks

The application of complex network theory to the study of the human brain and many other related systems is proving to be highly informative as well as innovative. Diverse physiological systems are composed of many subcomponents with complicated interrelations between them and are therefore well suited to this whole-systems analysis approach. The study of microvascular (Wang et al., 2008; Wahl et al., 2004), co-expression (Horvath and Dong, 2008; Oldham et al., 2006), protein–protein interaction (Cusick et al., 2005), protein signalling (Pieroni et al., 2008), transcriptional regulatory (Babu et al., 2004), signal transduction (Christensen et al., 2007), and metabolic (Lee et al., 2008) networks can give us insight into far-reaching and diverse phenomena from evolution (Oldham et al., 2006) to disease (Wang et al., 2007) and further lay the foundation for a degree of personalized healthcare previously thought impossible (Barabási, 2007; Weston and Hood, 2004). In fact, complex network theory has enabled us to better understand the structure of disease families (Goh et al., 2007) (e.g., the “diseasome”) as well as the rules governing the spread of infectious diseases (Keeling and Eames, 2005) through complex social networks (Ward, 2007; Newman et al., 2002).

Summary

Thus, graph analysis provides a unifying analytic framework within which to characterize and understand the topological properties of brain and other bodily networks, thereby potentially providing a powerful means for identifying continuities and discontinuities in their organizational properties. We illustrate some of these ideas with specific reference to the modular properties of networks in the following section.

Modularity

Modularity is a word which has resonance in many different areas of neuroscience. For example, it is an important concept in Fodorian accounts of cognitive neuropsychology, developmental psychology, and neurobiology (Fodor, 1983; Zeki and Bartels, 1998; Redies and Puelles, 2001; Callebaut and Rasskin-Gutman, 2005). Recently it has become possible to quantify the modularity of complex networks using the conceptual framework of graph theory (Newman and Girvan, 2004; Newman, 2004; Danon et al., 2005; Newman, 2006). But whereas the topological parameters so far discussed, such as clustering and path length, can be used to describe aspects of the global organization of a network, the investigation of modularity looks at its internal organization or community structure. A module is thus defined as a group of nodes with dense intrinsic or intramodal connectivity and relatively sparse extrinsic or intermodular connectivity (Newman and Girvan, 2004). Once the modules have been identified, this information can be used to refine the definition of the topological role of any particular node (Guimerà et al., 2005) — see Fig. 4. Various mathematical measures of modularity have been introduced, allowing us to quantify the goodness of a community partition...
Modularity of brain and other networks

The community structure of human brain networks has been investigated using MRI to infer anatomical connectivity between major cortical and subcortical regions (Chen et al., 2008). This study confirmed that the human brain anatomical network, derived from analysis of MRI data on a large group of healthy volunteers, had a modular organization which broadly conformed to known functional specializations (Salvador et al., 2005); for example, many occipital regions specialised for visual processing were identified as members of the same anatomical module.

A first attempt to study the modular organization of human brain functional networks was made by Ferrarini et al. (2008). They studied the hierarchy between brain areas in resting-state functional MRI, using a distance parameter called topological overlap, and applying a clustering method. By looking at the resulting dendrogram, showing the hierarchical decomposition, they showed that a modular structure was mainly visible at a small scale of the brain, and became less obvious when considering the interactions at a larger scale. Another study investigated the modular structure of resting-state functional MRI networks in two samples of healthy young and older people (Meunier et al., 2009). The modular decomposition of networks in the young age group showed the emergence of three main modules corresponding respectively to a posterior module, a central module and an anatomically distributed module, involving prefrontal, posterior cingulate, and parietal cortical areas, including several components of the “default-mode network” (Raichle et al., 2001). After assigning roles to individual nodes according to this modular decomposition, the anatomically distributed module was shown to involve more connector nodes than the other modules. This was considered compatible with a key role in the integrated distribution of information between the other modules. In the older population, this fronto-striato-parietal module was reduced in size and contained fewer connector nodes. This observation was regarded as indicative of modular reorganization, or modularization of functional networks, as an aspect of normal adult brain ageing. As noted earlier, modular community structure is widespread in biochemical, social and transportation networks (Guimerà et al., 2005). One of the main advantages of modular organization, explaining why it is found in so many diverse systems, is that it favours evolutionary and developmental optimization of multiple or changing selection criteria (Redies and Puelles, 2001; Slotine and Lohmiller, 2001; Kashtan and Alon, 2005; Pan and Sinha, 2007): in a modular network, each module can grow or develop one at a time, without risking loss of function in other modules.

Concluding remarks

In this article, we have endeavoured to provide a brief introduction to four concepts that are central to the interdisciplinary research field of complexity and that have been identified as generic properties of a wide range of complex systems in neuroscience, biology and other sciences. As a source of additional technical detail, and for examples of applications to neuroimaging and other biomedical data, we have provided an extensive bibliography. Our main objective has been to stimulate the idea that, as we begin to think about how neuroimaging data on the brain can be related to other systems of the body, it may be useful to bear in mind that many complex systems share certain key physical principles in common and can be described by the same powerful but relatively simple mathematical tools. We conclude with some remarks about efforts directly to address brain–body relationships using tools drawn from complexity analysis, and about the potential limitations of these approaches.

Only a few studies to date have used these relatively innovative techniques explicitly to integrate brain and body dynamics but Foss et al. (2006) provide an interesting example of how this can be done. They first examined time series of subjective pain ratings, recorded by patients suffering from chronic back pain or postherpetic neuropathy, and demonstrated that these serial self-rated measurements of a somatic symptom had scale-invariant properties that were most parsimoniously described in terms of fractal dimension. They also examined the fractal scaling properties of simultaneously recorded resting-state fMRI time series in 5 patients and found that the fractal dimensions of endogenous brain dynamics in medial prefrontal cortex and genual cingulate cortex were highly correlated with the fractal dimension of pain severity time series ($r > 0.9$ for both regions). This result indicates that the complex variability of somatic sensations can be strongly linked to the presumably causative variability of brain

![Fig. 4. Schematic illustration of modularity. Starting from a graph (left), the modularity decomposition aims at finding the sub-graphs whose constituent nodes are more densely connected with each other than they are with the rest of the graph (middle). Once a set of optimal modules has been defined, it is then possible to attribute a role to each node (right), according to the number of intramodular connections they have with other nodes in the same module compared to the number of intermodular connections they have with nodes outside their module: so-called “connector” nodes (squares) have some intermodular connections, whereas “provincial” nodes (circles) have almost exclusively intramodular connections.](image-url)
dynamics in relevant cortical regions. Future studies might profitably explore the relationships between fractal and other complex properties of neuroimaging time series and somatic time series, such as the electrocardiogram or skin conductance measurements.

Finally, although we are enthusiastic about the potential value of complexity science for analysis of brain and body systems, we appreciate that these techniques have not yet been widely applied or cross-validated in this application, and their limitations, as well as their benefits, have therefore not yet been fully appreciated. We see two particular limitations in prospect. First, most complexity metrics perform better on the basis of larger quantities of data and the modest number of time points in most fMRI time series, for example, may curtail the extent to which such metrics can be applied to realistically sized datasets. Second, we acknowledge the analysis of complexity is (perhaps inevitably) somewhat more complex or at least unfamiliar than relatively traditional approaches (such as linear modelling of time series). This added degree of complexity creates challenges for the appropriate use and interpretation of these measures. More studies, involving larger numbers of subjects, and more explicit efforts to evaluate the merits of complexity analysis by comparison to more traditional alternatives, will be needed to build confidence in the replicability of results, their neuroscientific significance, and the degree to which they quantify properties of the data more succinctly or relevantly than other metrics. We have rehearsed the theoretical arguments in favour of encompassing complexity, and provided a supportive example of methodological cross-validation (Maxim et al., 2005), but more needs to be done in this respect. We hope that the introduction provided by this article may encourage more investigators to explore the potential value of these approaches in addressing the natural complexity of brain and body systems and the interactions between them.

References


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