The brain is a complex system whose function relies on a diverse set of connections or interactions between brain regions. Using the mathematical framework of complex networks, these interaction patterns can be parsimoniously represented as brain graphs: each brain area is represented as a network node and each connection is represented as a network edge. These methods have been used to demonstrate that human brain networks display properties such as a small-world architecture that may directly facilitate cognitive processes. Moreover, mounting evidence suggests that these properties are altered in disease states, potentially providing important biomarkers for psychiatric and neurological disorders and informing our understanding of the mechanisms of altered cognitive function. Here, the basic concepts in network science are reviewed, and the properties of healthy and diseased brain networks discussed. Relationships between network diagnostics and alterations in behavioural or cognitive variables associated with Alzheimer’s disease, schizophrenia and epilepsy are highlighted.

Introduction

The human brain consists of 80 to 100 billion nerve cells and an estimated 100 trillion connections between them, making it arguably one of the most complex interconnected systems known. However, how this network is organised to support human thought remains elusive.

Historically, one prominent theory of brain function originating in the late nineteenth century focused on assigning single brain regions, often consisting of millions of neurons, to single, specific functions. In more recent years, it has come to be increasingly appreciated that these specialised brain areas do not work in isolation, but instead interact with each other to enable more complex mental functions. This intriguing conceptualisation of the brain as a system of interconnected, interacting and intercommunicating parts has found its way into modern day science, calling for a balanced examination of both functional segregation (localised processing of information) and integration (combining information from different brain areas).

In the past decade, the accelerated development of innovative and noninvasive neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and diffusion spectrum imaging (DSI), has facilitated the study of human brain interconnection patterns in vivo. These advances have produced multiple lines of evidence in support of viewing the human brain as a network, composed of many interacting parts. At this exciting juncture, several questions remain. How exactly do single brain areas dynamically interact to form large-scale brain networks or systems? And how do these networks ultimately enable human behaviour and cognition? Answers to these questions require the development of methods to extract meaningful organisational principles from complex interacting systems.

Progress in this area has accelerated in recent years, as neuroscientists have begun to apply tools from network science to the study of the human brain, leading to considerable insights into neurophysiological function. Given here is a short introduction to this rapidly evolving field, along with a description of how tools from network science can be used to characterise complex brain networks in ways that are biologically meaningful and directly related to normal and disordered function.

Theoretical Background

The branch of mathematics that historically dealt with the description and analysis of (complex) networks is known as graph theory. The extensions of graph theory to real-world
systems exploded in the 1950s in the context of questions in the social sciences. Only in recent years have neuroscientists begun to grasp the potential of these tools to address brain organisation and function from a holistic, mathematically rigorous and statistically principled perspective.

Networks (or graphs) are defined as a set of nodes $V$ (also called vertices) that are connected through links $E$ (also called edges). A network is most commonly represented using an adjacency matrix $A$ in which the $ij$th entry gives the strength of the edge between node $i$ and node $j$. Edges can either be directed ($A_{ij} \neq A_{ji}$) or undirected ($A_{ij} = A_{ji}$). Edges can also be weighted or unweighted. In unweighted (or binary) networks, edges carry the weight 1 if they are present and the weight 0 if they are absent. In weighted networks, edges carry any numerical weight as an indicator of the strength of the linkage between the two nodes that they connect. While additional types of networks exist (e.g. those that contain more than one type of edge or vertex), the features described above form the most common elements of networks commonly used in neuroscience.

Static networks

There exist several diagnostics (These diagnostics are often referred to as metrics or measures. Here, the term diagnostics is preferred as these variables are not metrics or measures in the formal mathematical senses of those terms.) for quantitatively characterising the structure of a network. Some of these diagnostics provide information about individual elements of the network (e.g. nodes or edges) and are referred to as local diagnostics; others provide information about the global structure of the network and are referred to as global diagnostics.

In the neuroscientific literature, there are several diagnostics that are utilised commonly: the degree, clustering coefficient, path length and efficiency. Provided here is a short conceptual introduction to these concepts to assist the reader’s appreciation of the following literature review which discusses how these diagnostics are utilised to understand healthy cognitive function and its alteration in disease states. For mathematical definitions of these diagnostics, see Rubinov and Sporns (2010).

- **Degree:** The degree of a node is the number of its connection to all other nodes in the network. A node displaying a high degree is often thought of as being important in a network, as it can influence many other nodes via its direct connections. Nodes displaying a particularly high degree are called hubs, emphasising their potentially influential role.

- **Degree Distribution:** The degree distribution is the probability distribution of node degrees. The probability, $P(k)$, of a node with a particular degree, $k$, indicates the chance that a randomly chosen node from that network has degree $k$. Different types of networks can display characteristic degree distributions that quantify the balance of hubs and nonhubs in the system. Scale-free and small-world networks display a heavy-tailed degree distribution: many nodes have low degree and only a few nodes have high degree. The node degrees in finite random networks follow a binomial distribution: most nodes have a similar degree.

- **Clustering Coefficient:** The clustering coefficient of a node is a measure of local connectedness or cliquishness. It can be defined as the proportion of triangles (neighbours of a node are also connected to each other) to connected triples (neighbours of a node are not connected to each other). In binary networks, the clustering coefficient ranges from 0, indicating that no neighbours have connections to each other, to 1, indicating that all nodes in the network connect to one another. The clustering coefficient is sometimes interpreted as a marker of local information processing or integration.

- **Path Length:** In a binary network, the shortest path between a pair of nodes is given by the number of edges that must be traversed to go from one node to the other. The path length of a node is given by the average shortest path to all other nodes in the network. The average path length of the network is simply the mean path length of all nodes in the network. A low value of the path length is sometimes interpreted as an estimate of network efficiency: information exchange might occur quickly if little distance separates all nodes in the network and might occur more slowly if long distances separate nodes in the network.

- **Efficiency:** Global efficiency is the inverse of the harmonic mean of the path length. The local efficiency of a particular node is given by the average efficiency of the local subgraphs surrounding that node. In practice, the global efficiency is often inversely correlated with the path length across subjects in a clinical group, and the local efficiency is positively correlated with the clustering coefficient; path length and clustering coefficient are often inversely correlated with one another.

These diagnostics provide the quantitative descriptors of local and global network structure. In addition to reporting these diagnostics, many neuroscientific studies seek to delineate the meso-scale structure in brain networks. For example, does the network contain groups of brain areas that are densely interconnected with one another? How are these groups connected to one another? Are some groups more densely interconnected than other groups? To answer these questions, one can study several meso-scale features including modularity, small-worldness, and core-periphery structure. Provided here is a short introduction to these concepts; for mathematical details, see the further reading section.

- **Modularity:** A module is a subset of vertices in a graph that have more connections to each other than to the rest of the network. A modular architecture has the advantage of creating a high degree of flexibility and adaptability of the system while constraining change to existing advantageous properties. For example, damage to one module only impairs the function of one subsystem embedded in this module, while the other functional modules remain intact. Furthermore, new functions can be added to a system by simply adding a distinct functional module without changing the entire wiring of the whole network. These are features likely to be important to biological networks under evolutionary pressure from natural selection.
• **Small-Worldness**: A phenomenon that has received considerable attention in the past two decades is the concept of small-worldliness. Many small-world networks have highly interconnected clusters of nodes and only a few long-range connections; an organisation that might minimise network wiring costs while maximising the effectiveness of global information exchange. One way to identify a small-world network is to calculate its average shortest path length and average clustering coefficient. In one popular modelling framework, small-world networks display a path length that is similar to that observed in a random network (i.e. very short), and a clustering coefficient similar to that observed in a regular lattice network (i.e. very large) (Watts and Strogatz, 1998). Humphries and colleagues propose a scalar measure of small-worldness $\sigma$ as the ratio of the normalised clustering coefficient (the clustering coefficient of the real network divided by the clustering coefficient of a random network) to the normalised pathlength (the path length of the real network divided by the path length of a random network) (Humphries et al., 2006). Humphries et al. suggest that if $\sigma$ is larger than one, the network can be said to display small-world properties (Humphries et al., 2006).

• **Core-Periphery**: A core-periphery structure can be thought of intuitively as a hub-and-spoke structure: a core of densely interconnected nodes is combined with a sparse periphery of nodes that tend to connect to members of the core but not to other members of the periphery. This structure can separate different types of information processing, and channel information swiftly through the core (hub) to the outer periphery (spoke). The presence of this organisation can be quantified using a core-score. A complementary notion to that of core-periphery structure is that of a so-called ‘rich club’, which is a set of highly connected nodes (hubs) that tend to preferentially connect to one another. The presence of this feature can be quantified using the **rich club coefficient**.

### Dynamic networks

The intuitive concepts described have traditionally been examined in the context of static networks – that is, networks that do not change in topology over time. However, functional brain networks are not static but rather dynamic, changing their configuration on time scales from milliseconds to years. To capture these network dynamics, scientists from several fields including mathematics, physics and engineering are beginning to extend the common network properties to so-called **multilayer networks**. In a temporal multilayer network, adjacency matrices representing the state of the network at a particular point in time are linked together by connecting each node in one network to itself in the adjacent time windows, forming an adjacency tensor. Many classical network diagnostics such as the path length and clustering coefficient have been defined for multilayer networks, and these have begun to be applied across many disciplinary domains.

The concept of viewing the brain as a dynamic network is one that is gaining increasing traction. In a recent review, Hutchison and colleagues distill the evidence from recent studies that the brain’s endogenous activity, captured by spontaneous blood-oxygen-level-dependent signal (BOLD) in fMRI at rest, displays time-dependent patterns of functional connectivity. The authors argue that these changing patterns of functional connectivity might enable dynamic integration, coordination and response to internal and external stimuli across multiple time scales. The same concept of dynamic reconfiguration in brain networks is being pursued in studies of task-based processing. In the first application of multilayer network techniques to neuroimaging data, it was shown that brain networks reconfigure during learning, enabling a flexibility of functional connectivity patterns that predicts individual differences in learning (Bassett et al., 2011a). Fedorenko and Thompson-Schill argue that these types of dynamic network techniques are fundamentally necessary to understand cognitive functions more broadly (Fedorenko and Thompson-Schill, 2014).

### Human Brain Networks in Health

Network-based techniques can be applied to neuroscientific questions across a range of spatial scales to understand the interaction patterns among genes, proteins, neurons, cortical columns and large-scale brain areas. In this review, the focus is on macroscopic brain networks that measure the connectivity between human brain regions using noninvasive neuroimaging techniques, including functional and structural MRI, electroencephalography (EEG), and magnetoencephalography (MEG).

### Structural brain networks

To construct a structural network from neuroimaging data, one must first define the regions of interest (network nodes) and measure of interaction (network edges); see **Figure 1**. The definition of nodes and edges depends highly on the imaging modality used. In constructing structural brain networks from diffusion MRI data, network nodes are often defined by a standard brain atlas; common choices include the AAL, Harvard-Oxford, Lausanne, Brodmann and LPBA40. Network edges are defined on the basis of a measure of white matter microstructure, such as the number of streamlines or average fractional anisotropy along a tract connecting node $i$ to node $j$. (Morphometric networks differ from structural networks in that their edges are defined on the basis of cross-subject correlations between regional morphometric variables including grey matter volume, cortical thickness or surface area.)

According to the most recent diffusion imaging MRI protocols, healthy structural brain networks tend to be sparse, with as little as 3% of the possible edges present (Hagmann et al., 2008). These networks exhibit small-world properties: dense local connectivity and sparse long-range connectivity. The average distance of anatomical connections is small in comparison to that expected in randomly wired physical networks, suggesting a near minimisation of wiring costs (Kaiser and Varier, 2011). These and similar observations have led to the emerging theory that the brain’s architecture can be understood as the evolutionary outcome of the need to minimise wiring cost, conduction speed and...
cytoplasmic volume while maximising network function (Bullmore and Sporns, 2012).

The architecture of these sparsely connected networks is strikingly organised, being composed of modules of highly interconnected nodes that are hierarchically organised, or nested within one another (Bassett et al., 2011b). This architecture arguably provides the structural features necessary for swift adaptation – across multiple functional scales – in response to a changing environment, forming a critical backbone for cognitive function. Within these modules, a small subset of brain regions are hubs, displaying a particularly high degree. These hub nodes tend to be tightly connected to one another, forming the structural core or ‘rich-club’ of the network through which the majority of shortest paths pass. It has been argued that the rich-club of hub regions may play a role as the communication backbone of the brain (van den Heuvel et al., 2012).

**Functional networks**

In functional MRI studies, the activity of a brain region is measured indirectly by its change in oxygenation using the BOLD, a proxy for neuronal activity. fMRI data can be collected either while subjects perform a cognitive task or while subjects lie quietly in the scanner without performing a task – a condition called the ‘resting state’. In networks derived from fMRI, the nodes of the network commonly correspond to large-scale regions defined by the atlases mentioned in the previous section or by functional atlases; see Figure 2. While fMRI provides exquisite spatial resolution of BOLD activity on the order of 1–2 mm, EEG and MEG provide exquisite temporal resolution of electromagnetic activity at a sampling frequency of up to 2000 Hz. Nodes in EEG or MEG data have traditionally been defined by sensors placed on the scalp, although recent efforts have also utilised source localisation techniques to define nodes within the cortical volume.
Figure 2  Networks and Network Diagnostics: An adjacency matrix (a) and its associated toy binary network (b). Nodes are represented as enumerated circles; edges are depicted as lines. Node number 17 has a degree of 3, as it is connected to 3 other nodes in the network (green lines). The blue lines indicate the shortest path connecting node 7 to node 10, which traverses 5 edges leading to a path length of 5. In red is shown the edges that form triangles. The clustering coefficient is an indicator of how many of a node's nearest neighbours are connected to each other, therefore forming triangles. Here, for example node 11 has a clustering coefficient of 0.33, indicating that 2 of its neighbours have a connection (1 out of 3 possible connections). The yellow area marks a module: nodes 1, 2, 4 and 5 are densely interconnected, but have few connections to other nodes. Reproduced with permission from Danielle S Bassett and Edward T Bullmore (2009) © Wolter Kluwer Health.

(Maldjian et al., 2014). To measure the strength of edges connecting these nodes in fMRI, EEG and MEG networks, the similarity between time-courses of regional activation is calculated, using for example a Pearson correlation coefficient or synchronisation.

A large and growing body of literature reports converging evidence of a few key topological features in functional brain networks. These include a small-world architecture (Bassett and Bullmore, 2006), which may enable (i) rapid synchronisation and information transfer while minimising wiring costs, and (ii) a balance between local processing and global integration (Sporns, 2013). Similar to structural networks, functional brain networks also display hierarchically modular organisation particularly in the resting state (Achard et al., 2006). The large-scale modules are composed of densely functionally connected groups of brain regions that map to known subnetworks responsible for specific cognitive functions (Power et al., 2011) and present across many task domains (Cole et al., 2014).

The full cognitive utility of functional network architecture remains unknown. Preliminary work indicates that network architecture at rest is related to several cognitive variables, including intelligence (van den Heuvel et al., 2009) and verbal memory scores (Lynall et al., 2010) among others. A fuller appreciation of the role of network architecture in cognitive function may require more concerted effort to study network organisation in task-based studies (for examples, see Bassett et al., 2006; Vourkas et al., 2014 and for direct comparisons between rest and task-based networks see Cole et al., 2014; Hermundstad et al., 2014).

Human Brain Networks in Disease

Human brain networks have been constructed and examined in a plethora of altered states in psychiatric disease, neurological disorders and following injury. Connectomics, or the study of these networks, provides a new paradigm for understanding these altered states (Fornito and Bullmore, 2014). Briefly surveyed here is the large literature examining brain network organisation in schizophrenia, Alzheimer’s disease (AD) and epilepsy with the goal of illustrating the new insights provided by network methods.

Schizophrenia

Schizophrenia is a severe psychiatric disorder that is characterised by disturbances in cognition and affect, as well as the so-called positive symptoms such as delusions, hallucinations and thought disorder. Very early hypotheses regarding the origins of schizophrenia have established the idea that its symptoms arise from aberrantly connected networks or brain regions (Stephan et al., 2009), making it an especially appropriate context for the application of network-based analysis tools. For a recent review in this area, the reader is pointed to Fornito et al. (2012).

In people with schizophrenia, the structural connectome displays an overall reduction in global connectivity and in the strength of hubs, especially in frontal and parietal regions (Filipp et al., 2013). A specific reduction in the connectivity of rich-club regions is also apparent (van den Heuvel et al., 2013),
suggesting a reduction in the communication capacity of core brain areas potentially leading to a decrease in global information processing.

The functional connectome of people with schizophrenia displays many alterations, but results are inhomogeneous across imaging modalities, methodological approaches and patient populations. Core pathologies consistently observed across studies include (i) reductions in putative measures of local processing including the clustering coefficient and local efficiency (Lynall et al., 2010), and (ii) increases in putative measures of global integration including the global efficiency and path length (Lynall et al., 2010; Fornito et al., 2012). Weakly connected nonhubs (Bassett et al., 2012) and strongly connected hubs (Rubinov and Bullmore, 2013) also appear to be affected, although this latter alteration is not specific to schizophrenia (Buckner et al., 2009; Achard et al., 2012). Together, these findings have collectively been referred to as supporting a theory of ‘subtle randomisation’ (Rubinov and Bullmore, 2013), which states that schizophrenic brains are shifted towards more random networks (Bullmore and Sporns, 2012) with higher global integration and reduced local processing.

In conclusion, there is accumulating evidence that schizophrenia is associated with a disruption of large-scale network organisation, both structurally and functionally. Alterations in functional networks might be the consequence of deficits in the temporal coordination of neural activity, which in turn could be based on disruptions of structural connections (Uhlhaas and Singer, 2010). However, further research is needed to understand how functional and structural networks interact and how the functional alterations observed in schizophrenia relate to clinical parameters or to known cognitive deficits associated with the disease state.

Alzheimer’s disease

AD is the most common form of dementia, a neurodegenerative disease characterised by a failing short- and long-term memory as well as general cognitive decline and mood disturbances. Neurophysiologically, the disease is associated with a progressive loss of nerve cells, beginning in the hippocampal areas and slowly spreading over the remainder of the brain. These neurophysiological changes lead to pervasive alterations in structural and functional brain networks, as recently reviewed by Tijms et al. (2013).

Structural studies in patients with AD have shown (i) a reduction in putative markers of global integration (Reid and Evans, 2013), as evidenced by a longer average path length and reduced global efficiency, and (ii) an increase in putative markers of local processing such as local efficiency and clustering coefficient (He et al., 2008). Some authors interpret these observations as evidence of an alteration in the balance of information segregation and integration derived from a more regular-like network organisation, and demonstrate correlations between these topological measures and changes in cognitive variables and memory performance (Lo et al., 2010). In very recent work, Raj and colleagues provide initial evidence that the organisation of the structural connectome can explain the progression of disease in dementia states including AD (Raj et al., 2012), further highlighting the cognitive relevance of structural brain network architecture.

Hub regions appear to play a key role in the formation of the disease. In an early study, Bruckner et al. (2009) observed a spatial similarity between the locations of functional network hubs and the locations of greatest A-beta amyloid deposition, a protein strongly implicated in AD’s pathology. They argue that hubs are preferentially targeted by the disease, causing mental deficits. Following this observation, several studies have reported reduced connectivity of hubs in AD, specifically in regions of the frontal and temporal lobes (Filippi et al., 2013). These changes in hub structure may partially explain the longer path length and decreased global efficiency observed in AD (Sanz-Arigita et al., 2010), as well as the reductions in global clustering that distinguish patients from controls (Supekar et al., 2008). Together, these observations are consistent with a reduced small-world architecture and a loss of long-range connections (He et al., 2008; Sanz-Arigita et al., 2010; Supekar et al., 2008).

Epilepsy

Epilepsy is a common neurological disorder that affects approximately 1% of the world’s population and is characterised by recurrent seizures. Despite epilepsy’s prevalence in society, much remains unknown about the mechanisms that give rise to seizures. However, recent studies suggest that epileptic brain dynamics can be described as originating from an underlying complex epileptic network that links multiple brain regions across many spatial and temporal scales (Stead et al., 2010; Kramer and Cash, 2012).

When studying epilepsy from a network perspective, much work has focused on meso-scale interactions, generally characterised by functional relationships between intracranial EEG (also called electrocorticoigraphy or ECoG) sensors, which are placed on the surface of the brain to record local brain activity. Functional networks are then derived from the sensor signals to study the evolution of network structure as the brain transitions between normal and epileptic activity (see Figure 3). Network analysis has shown that seizures are not disorganised or chaotic events, but in fact display an organised temporal and spatial structure. By calculating the path length and clustering coefficient of networks sampled at different time windows during seizures, it has been shown that seizures evolve from a more random to regular (Schindler et al., 2008) and then back to random network structure before termination (Schindler et al., 2008; Kramer et al., 2010). In addition, Kramer and Cash (2012) show that at seizure onset, the network contains one large connected component which then becomes fractured as the seizure progresses and reforms near the end of the seizure, which is in line with the observation that network assortativity (the tendency of nodes to be linked to nodes with a similar degree) is increased during the middle of the seizure (Bialonski and Lehnertz, 2013). Other studies have focused on the relationship between node centrality and the spatial proximity to the seizure onset zone (Varotto et al., 2012). The ability to identify the seizure onset zone through the computation of network diagnostics has important clinical implications, as it could better localise areas of the brain that are candidates for surgical resection in patients with drug-resistant epilepsy.
While much work has examined networks derived from ECoG data owing to its high temporal resolution and widespread clinical use to monitor seizures, some recent studies have used other modalities such as fMRI or MEG to extract structural and functional epileptic brain networks. These other modalities offer the advantage of using a noninvasive approach to study epileptic networks and could prove to be an alternative to the highly invasive surgery required for the implantation of ECoG sensors. Using combined fMRI and diffusion MRI scans, it has been shown that epileptic patients have a decreased coupling between functional and structural networks (Zhang et al., 2011), and analysis of functional fMRI networks has revealed an increased asymmetry between brain hemispheres (Zhang et al., 2012). Recent work using functional MEG networks revealed a decreased number of hub nodes in patients with successful respective surgery (removal of brain tissue suspected to be crucial in the formation and propagation of epileptic activity) (van Dellen et al., 2014), and MEG networks have also been found to have an increased local clustering and decreased path length at the seizure onset (Gupta et al., 2011), similar to that observed in ECoG networks.

Although the work discussed focuses on meso-scale networks where nodes represent sensors or brain regions, network research in epilepsy is now at an exciting new phase as patients are increasingly being implanted with new electrodes that allow for the identification of activity patterns of individual neurons during epileptic activity (Alvarado-Rojas et al., 2013). This new wave of data will allow exploration of the microcircuitry of the human epileptic network, where nodes are represented by neurons and edges represent correlations in the firing patterns of single cells. Integrating analysis across these two spatial scales will be essential in understanding how individual networks of neurons give rise to the larger scale EEG signals and how network reorganization at different scales relates to pathological brain activity.

Conclusion

Briefly reviewed in this short article (and far from exhaustively) are three main bodies of literature related to (i) basic concepts in network science, (ii) observed properties of healthy brain network structure and function and (iii) alterations to this structure in AD, schizophrenia, and epilepsy. This has been done in the hope that this work provides a natural and easily accessible introduction to the use of network science to study large-scale human brain networks in health and disease.

References


Further Reading


that contains sections specifically devoted to synchronization and applications to brain networks.)


Sporns O (2011) *Networks of the Brain*. Cambridge, MA: MIT press. (This book by Olaf Sporns provides an extended introduction to and summary of the field of network neuroscience. Of immediate use to practicing neuroscientists, it is also highly accessible to undergraduate readers.)