Modern network science of neurological disorders

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Abstract | Modern network science has revealed fundamental aspects of normal brain-network organization, such as small-world and scale-free patterns, hierarchical modularity, hubs and rich clubs. The next challenge is to use this knowledge to gain a better understanding of brain disease. Recent developments in the application of network science to conditions such as Alzheimer's disease, multiple sclerosis, traumatic brain injury and epilepsy have challenged the classical concept of neurological disorders being either 'local' or 'global', and have pointed to the overload and failure of hubs as a possible final common pathway in neurological disorders.

Small-world networks
Networks characterized by a combination of high clustering (which represents local connectedness) and short path lengths (that is, short distances between any two nodes).

Scale-free networks
Networks in which the probability that a randomly chosen node has degree (number of connections) k is inversely proportional to k.

Hierarchical modularity
A type of network organization where each component (for instance, a module or cluster) is composed of smaller components but at the same time is part of a larger component.

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Modern network science (BOXES 1, 2) has introduced exciting new opportunities for understanding the brain as a complex system of interacting units. The discovery of small-world networks and scale-free networks has given rise to a rapidly growing interdisciplinary science of complex networks, which spans the range from genetic and metabolic networks all the way up to social and economic systems[1,2]. One of greatest challenges for network science is the brain. In the past decade, structural and functional brain networks have been studied in species from *Caenorhabditis elegans* to humans[3–5]. There is now a growing consensus that normal brain networks are cost-efficient small-world networks, which combine strong local connectivity with efficient long-distance connections[6]. Brain networks are also approximately scale-free, with a preponderance of highly connected hub areas that together constitute a 'rich club' (REF. 7). In addition, brain networks display hierarchical modularity, in which the modules correspond to major functional systems, such as motor, sensory and association networks[8] (FIG. 1). These patterns of brain-network organization arise during development, are strongly regulated by genes and are important for cognitive function[9].

The improved understanding of normal brain-network organization has made it possible to address network changes in neurological and psychiatric diseases, especially in dementia, epilepsy and schizophrenia, but also in traumatic brain injury (TBI), multiple sclerosis (MS), cerebrovascular disease, coma and many other conditions[4,10–13]. These studies are challenging the idea that brain disease involves either 'local' or 'global' pathology. In particular, in several typically global brain disorders, such as Alzheimer's disease (AD), network studies have shown that the pathology is in fact not equally distributed over the brain, but preferentially affects the hub areas[14,15]. Conversely, network studies have revealed that local brain pathologies, such as brain tumours or vascular lesions, have a far more global impact than has been recognized before, and this can explain some of the executive cognitive deficits in these disorders[16–18]. These findings can now be reproduced in increasingly realistic models of large-scale structural and functional brain networks[19–21] (FIG. 2). In combination with current initiatives to delineate the full connectome of the brain, this modelling creates opportunities to develop exact mathematical models of normal and disturbed brain networks[22]. The new field of 'computational neurology' has the potential to provide a rational approach towards the development of new diagnostic and therapeutic strategies for brain diseases.

In this Review, I first briefly describe the organization of normal structural and functional brain networks. I then discuss network studies of neurological disorders, with a particular focus on AD, MS, TBI and epilepsy, aiming to identify possible general patterns in these studies and to assess whether network science is changing the concept of brain disease. I propose that a scenario of hub overload and failure, resulting in a disruption of the normal hierarchical architecture of brain networks, is a potential final common pathway of several neurological diseases. The key challenge for the future, in the face of the oncoming 'tsunami' of neuroimaging data on brain networks, will be to develop exact and mathematical models of brain networks that will enable a rational approach to diagnosis and treatment.

Box 1 | **Modern network science**

Modern network science is a mixture of graph theory, dynamical systems theory and ideas from statistical mechanics[4]. Graph theory is a relatively old branch of mathematics that started with the solution by Leonhard Euler in 1736 of the problem of the 'Seven Bridges of Königsberg'. The central idea in graph theory is to represent a complex set of relationships (in other words, a network) with a set of nodes and their connections. The strength of this idea, as always in mathematics, is its generality: nodes and connections can represent any sort of entity and relationship, respectively. Originally, graph theory studied small, deterministic (that is, ordered, regular) graphs. The scope was widened considerably by the introduction of models for large, random graphs[144,145]. The real breakthrough occurred at the end of the twentieth century with the introduction of two elegant models for networks that display a mixture of order and randomness. Watts and Strogatz introduced the small-world network, which combines the high clustering (a measure of local connectedness) of a regular network with the short path length (the distance between any two nodes) of a random network[2]. Subsequently, a model of a growing network was introduced, wherein new nodes attach preferentially to existing nodes that have many connections[1]. The degree distribution of the resulting scale-free networks can be described by a power law. Scale-free networks, in contrast to their small-world counterparts, are characterized by the presence of highly connected hub nodes.

The introduction of small-world and scale-free models has given rise to the rapidly growing interdisciplinary field of network science[146,147]. A major factor in the success of network science is the fact that the models are powerful enough to explain a wide range of empirical phenomena that are observed in all sorts of real complex networks, while at the same time they are simple enough to enable a deep mathematical understanding. In this sense, network science is reminiscent of the marriage between dynamics and calculus. Currently, network science is developing along a number of lines. First, the sophistication of network measures and models has increased rapidly. This has led to the introduction of new concepts, such as cost-efficiency, hierarchical modularity, vulnerability to random or targeted attack, and the notion of rich clubs. In addition, graph theory has been combined with dynamical systems theory to study flow processes on complex networks[148]. This has shown that certain types of network architecture (known as 'topology') may facilitate the emergence of synchronized dynamical states. Finally, the tools of network science are now applied, with increasing success, to understand the structural and functional properties of complex networks, from gene, protein and metabolic networks, all the way up to language and social networks[148].

The organization of healthy brain networks

Watts and Strogatz were the first to apply graph theoretical analysis to a nervous system[2]. They showed that the *C. elegans* nervous system, which consists of 302 neurons and 6,393 connections, has the typical properties of a small-world network (see below). In the past 10 years, graph theoretical analysis has been applied extensively to the nervous systems of animals and of humans, from the cellular level up to macroscopic levels (BOX 3). Some of the findings from such analyses have now been fairly well established and have been summarized in several reviews and textbooks[3,6,23,24]. I briefly review and interpret some of the key results, as they provide a background against which the results of clinical studies can be evaluated.

There is strong agreement that nervous systems in animals and humans, from the neuronal level up to macroscopic levels, are characterized by a combination of high clustering (a measure of local connectedness) and short path length (indicative of global integration) — typical of small-world networks[3]. This combination provides a balance between the segregation and integration of information and has been interpreted to be an optimal kind of architecture. Specifically, networks with a small-world organization may constitute an optimal solution to the conflicting constraints of reducing wiring costs and facilitating information flow[6]. However, brain networks not only display small-world features, but also have broad degree distributions that often follow a power law over at least some orders of magnitude. This broad degree distribution implies that different nodes of brain networks differ widely from one another in terms of their centrality and connectedness. A subset of highly connected hub nodes constitutes a 'connectivity backbone' that is sometimes referred to as a rich club[25,26] (BOX 2). It is important to note that hubs in general — and rich-club components in particular — handle most of the information traffic in brain networks[15]. Healthy brain networks also display a hierarchical modular structure, with subnetworks within networks[8]. Large-scale modules correspond to well-known functional systems in the brain — for example, motor, somatosensory, auditory, visual and association networks. Like small-world features, hierarchical modularity may reflect the outcome of multiconstraint optimization[4,27].

There are indications that the characteristic optimal organization of healthy brain networks emerges during development, but the exact nature of this process is still unclear[9]. There is little doubt, however, that genetic factors have a crucial role[28–30]. Ageing is also associated with brain-network changes[31,32]. Somewhat surprisingly, brain-network topology in males has been shown to be different from that of females, possibly owing to an as yet unknown influence of sex hormones[33–38]. Furthermore, brain-network organization is closely related to function. For example, a relatively simple network feature such as path length is strongly correlated with intelligence[39,40]. Several other studies support the relationship between network organization and cognitive function[38,41,42]. The modular organization of networks is also highly relevant in this respect[43]. In summary, healthy brain networks have a characteristic organization that enables optimal cognitive function at a low wiring cost. Against this background, it is possible to consider what happens to these networks in neurological diseases.

Brain network organization in disease

Dementia. Dementia, which is most frequently due to AD, is one of the major health problems in the ageing population, and this demands a multidisciplinary approach[44]. Currently, the exact cause of AD is unknown, and no effective treatment exists. The development of such treatments would require a better knowledge of the aetiology and pathophysiology, as well as effective diagnostic tools and biomarkers to identify the disease at an early phase, when treatment is most likely to be effective.

Graph theoretical analysis of structural and functional brain networks in AD has been pursued mainly to gain a better understanding of the pathophysiological processes, and to develop biomarkers for early diagnosis and for monitoring the effects of treatment. More recently, network analysis has also been applied, with similar objectives, to related neurodegenerative disorders, such as frontotemporal dementia (FTD) and Parkinson's disease (PD)[45–48]. Many reviews of network studies of these neurodegenerative disorders are available[4,10,11,13,14,49–53].

Connectedness
A measure of the existence of connections (structural or functional) between network elements.

Degree distributions
The probability distribution ($P(k)$) of degrees over a network. $P(k)$ is the probability P that a randomly chosen node has degree k.

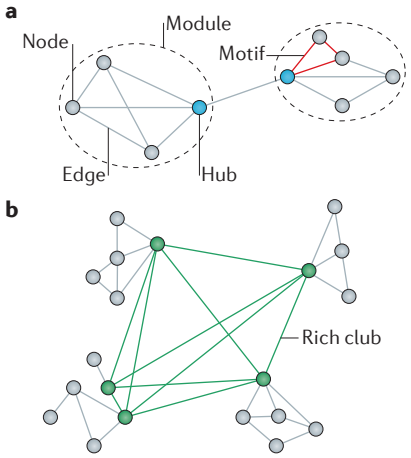
Centrality
A measure of the relative importance of a node in a network. Various centrality measures exist (including degree, betweenness and eigenvector).

Multiconstraint optimization
Optimal network organization that takes into account multiple, often conflicting, constraints (for instance, wiring cost and path length).

Box 2 | **Concepts in graph theory**

Graph theory is the mathematics of networks. Networks are represented as sets of nodes (technically called vertices) and links (known as edges) (see the figure, part **a**). Graphs can be unweighted — when edges are simply either present or absent — or weighted, when a weight is assigned to each link. Graphs are undirected when links indicate symmetric relationships, and directed when links correspond to directed relationships. The number of links connected to a node is called its degree. The degree distribution $P(k)$ describes the probability that a randomly chosen node will have degree k. If the probability distribution $P(k)$ is proportional to $k^{-\gamma}$, where γ is a scaling exponent, the distribution and the corresponding network are described as being scale-free.

Complex networks can display structure at multiple scales. All nodes that are connected to a node by a direct link are called the neighbours of this node. The probability that any two neighbours of a node are also connected is the clustering coefficient of this node. The clustering coefficient can also be defined in terms of the fraction of triangles (triples of nodes connected by edges) in the graph. A triangle is one of the simplest types of small subnetwork. Small subnetworks are referred to as motifs. The prevalence of different types of motifs — known as the motif count — gives information about the composition of a network. Larger subnetworks are referred to as modules. Different definitions of modules exist, but typically the nodes of a module are more connected to each other than to nodes outside their module. Modularity can also be hierarchical, with modules consisting of submodules, sometimes over several scales. Centrality refers to the importance of a node relative to other nodes in the network. Different measures of centrality exist, including degree, closeness centrality, eigenvector centrality and betweenness centrality. Nodes that have high centrality are called hubs. A set of highly interconnected hubs is referred to as a rich club (see the figure, part **b**). The tendency of hub nodes to connect to each other is called assortativity.



However, there is still considerable controversy in the literature on the exact nature of network changes in dementia, which can be explained to some extent by differences in methodological aspects[14,54]. Here, I review the most salient studies in an attempt to address the following three questions. First, what network changes occur in AD and AD-related disorders? Second, can these network changes be explained in terms of underlying mechanisms? And third, what could be the clinical usefulness of a network perspective in dementia?

AD is often considered to be a 'disconnection syndrome' (REF. 55). This view suggests that a loss of neurons and their connections will interfere with the structural and functional connections between neurons and macroscopic brain regions, and that this will give rise to clinical symptoms — in particular, cognitive and behavioural deficits. However, results from network studies suggest that this view may be too simplistic, as a network is more than the sum of its connections[4]. Although a loss of structural and functional connections has been reported in several studies[56–58], there are also indications of increased connectivity in AD[59,60] (FIG. 3). One might expect that this mixture of increased and decreased connectivity would give rise to changes in network organization.

The local connectivity of brain networks is probably best captured by the clustering coefficient or the related measure of local efficiency (BOX 2). Many studies have reported a lower clustering coefficient or reduced local efficiency in AD[45–47,56,61–69]. This result has been obtained with various imaging techniques, including MRI tractography, MRI grey-matter network assessment, electroencephalography (EEG), magnetoencephalography (MEG) and positron emission tomography (PET). However, as mentioned above, an increase in local connectivity has also been reported[58,59,70–72]. Interestingly, studies that report increased local connectivity in AD often used different types of imaging techniques, such as group-level cortical thickness correlations and functional MRI (fMRI)[58,59,70,72,73]. This suggests that differences in the imaging technology used may greatly influence the assessment of local connectivity. Furthermore, methodological aspects of graph theoretical analysis — such as the use of weighted or unweighted networks, or the thresholding and normalization of graph measures — may have a role (BOX 3). It is important to note that studies that used normalized measures more often reported a decrease of clustering and local efficiency in AD[14,64,65].

The clustering coefficient and the local efficiency mainly capture local connectivity, whereas measures of the global efficiency and the average shortest path length reflect long-distance connections, which are probably supported by large commissural and association fibres. These long-distance connections are of special interest in view of the level of integration in large-scale networks. A loss of long-distance structural and functional connections — as reflected by an increased average path length or decreased global efficiency — has been reported in AD and in FTD in several studies, using a variety of imaging techniques[46,59,62,70,74]. However, a shorter path length has also been reported in AD and in PD[14,45,47,60,64–66,69,72]. Here, an important point to keep in mind is that one should distinguish between absolute and normalized path length. A decrease in normalized path length only implies that the network topology is closer to that of a random network; it does not imply that the absolute path length is shorter. This interpretation is supported by the observation that in EEG and MEG studies of AD and PD the use of normalized path length often resulted in lower values (indicating more 'random' networks) for the patient group[45,64–66]. The imaging technique itself may also be relevant. Increased path length in certain disorders has been reported in studies using group-level cortical thickness correlations, MRI tractography and fMRI[46,59,62,70,73]. However, even using a single imaging technology, such as fMRI, opposite changes in path length have been reported[46,60,72,73]. This state of affairs is frustrating, particularly in view of the fact that path length has been shown to correlate very well with cognitive function, both in healthy subjects and in patients with dementia[39–41,61,63]. This stresses the need to develop new tools that can characterize brain-network topology in an unbiased way, such that a meaningful comparison between groups may become possible. Use of the minimum spanning tree, which fixes the number of

Minimum spanning tree
An acyclic connected subnetwork that minimizes the cost function that is associated with edges.

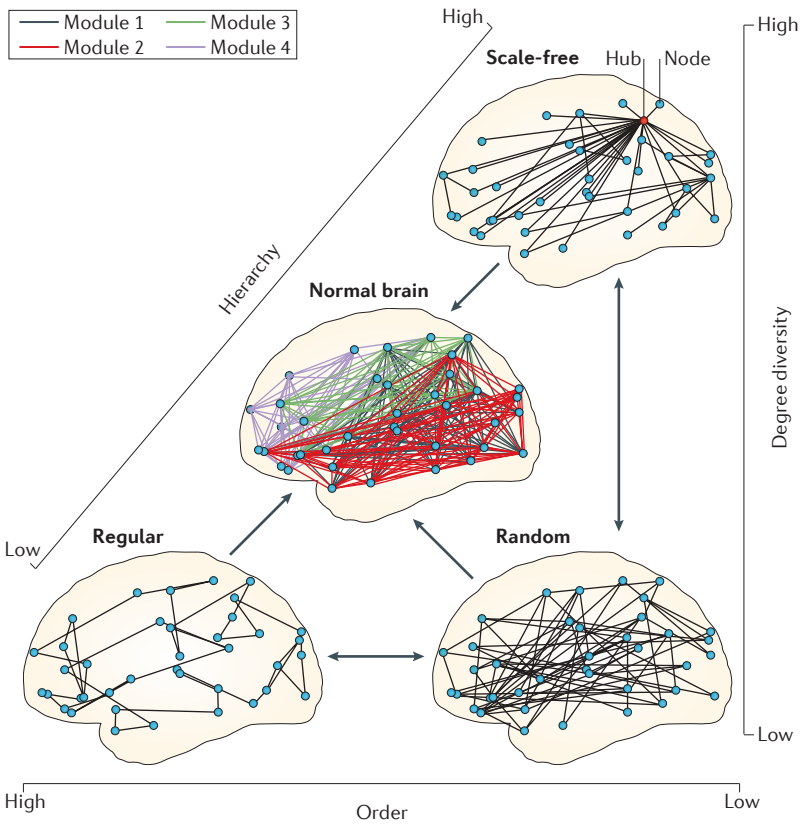


Figure 1 | **Organization of normal brain networks.** The organization of normal brain networks, interpreted as an intermediate structure between three extremes: a locally connected, highly ordered ('regular') network; a random network; and a scale-free network. The order component is reflected in the high clustering of regular brain networks. Randomness, or low order, is reflected in short path lengths. The scale-free component (high degree diversity and high hierarchy) is indicated by the presence of highly connected hubs. A normal brain network is a composite that contains these three elements. This results in a hierarchical, modular network (normal brain).

connections in the networks to be compared and enables the reconstruction of a unique minimal subnetwork on the basis of a connectivity matrix, could be a step in this direction[54].

Although the results from studies that have measured clustering and path length do not show a consistent pattern of network changes in AD, other topological features seem to be more promising. Complex brain networks consist of subnetworks (or modules), which are associated with specific cognitive functions[43]. There is some evidence that the normal modular structure of the brain is disrupted in AD[68,75,76]. In particular, the parietal module seems to be affected, and an MEG study showed that both the connections within this module and the connections between this module and other modules are decreased[75]. A pattern of module disconnection has also been observed in studies that used MRI[68,76,77]. Two other interesting, but less investigated, network features are synchronizability and assortativity. Synchronizability is a measure of the stability of synchronized oscillations in a network, and can be studied using a mathematical technique called graph spectral analysis. Two EEG studies showed a decrease in synchronizability in AD, which suggests that this may be an interesting property for further study[57,78]. Assortativity refers to the tendency of high-degree nodes (that is, nodes with a high number of connections to other nodes) to connect to other high-degree nodes. Interestingly, assortativity is decreased in AD, but increased in FTD[46,64]. However, although the observations of changes in modularity, synchronizability and assortativity are promising — for instance, for the differential diagnosis of AD and FTD — they are based on only a few studies and are in need of confirmation.

One of the important messages of network theory is that nodes within a network vary widely in their relative importance, and this has consequences for their normal function, as well as for their vulnerability to pathogenic influences. Many studies have investigated measures of node centrality — such as maximum degree, eigenvector centrality or betweenness centrality — in structural and functional networks in dementia. Almost all studies report a decrease in node centrality in AD, particularly in brain regions that can be considered higher-order association areas, such as the temporal lobe, medial parietal, posterior and anterior cingulate, and medial frontal areas[45,46,57,62,68–70,79]. Few studies report an increase of centrality in AD, and only in combination with a decrease of centrality in other regions. The selective damage to highly central hub nodes thus seems to be one of the most consistent features of brain-network changes in AD, as well as in FTD and PD. In the case of AD, there is a close spatial association between areas with large amounts of amyloid deposition and areas with high-degree hubs[80], suggesting a possible link between amyloid pathology and hub vulnerability. Two studies that performed simulations to investigate the spatial distribution of network changes in AD[59,65] concluded that highly connected hub nodes must be specifically vulnerable in AD. An extensive simulation study showed that many findings in AD may be explained by a process known as activity-dependent degeneration[19]. Specifically, this study showed that synaptic damage that is due to excessive neural firing starts a process that, after an early phase of oscillatory slowing and increased connectivity, results in an end stage characterized by decreased connectivity, more-random networks and selectively damaged hub nodes. This kind of hub overload and failure scenario as a putative general scenario for brain-network disturbance is discussed in more detail below.

In summary, the following picture of network changes in AD and related disorders emerges. Currently, the findings regarding some basic network features, such as clustering and path length, are not very consistent. This is likely to be due to the methodological aspects of imaging technology and network analysis. More promising results have been obtained with respect to decreased modularity, decreased synchronizability and changes in assortativity, which is decreased in AD but increased in FTD. The most consistent finding is the disruption of hub nodes, especially the highly connected brain regions in the temporal, parietal and frontal higher-order association areas. This suggests that the pathophysiological processes in AD specifically affect hub regions (FIG. 3).

Synchronizability
A property of a network that indicates whether a dynamical process on this network will reach a stable synchronized state.

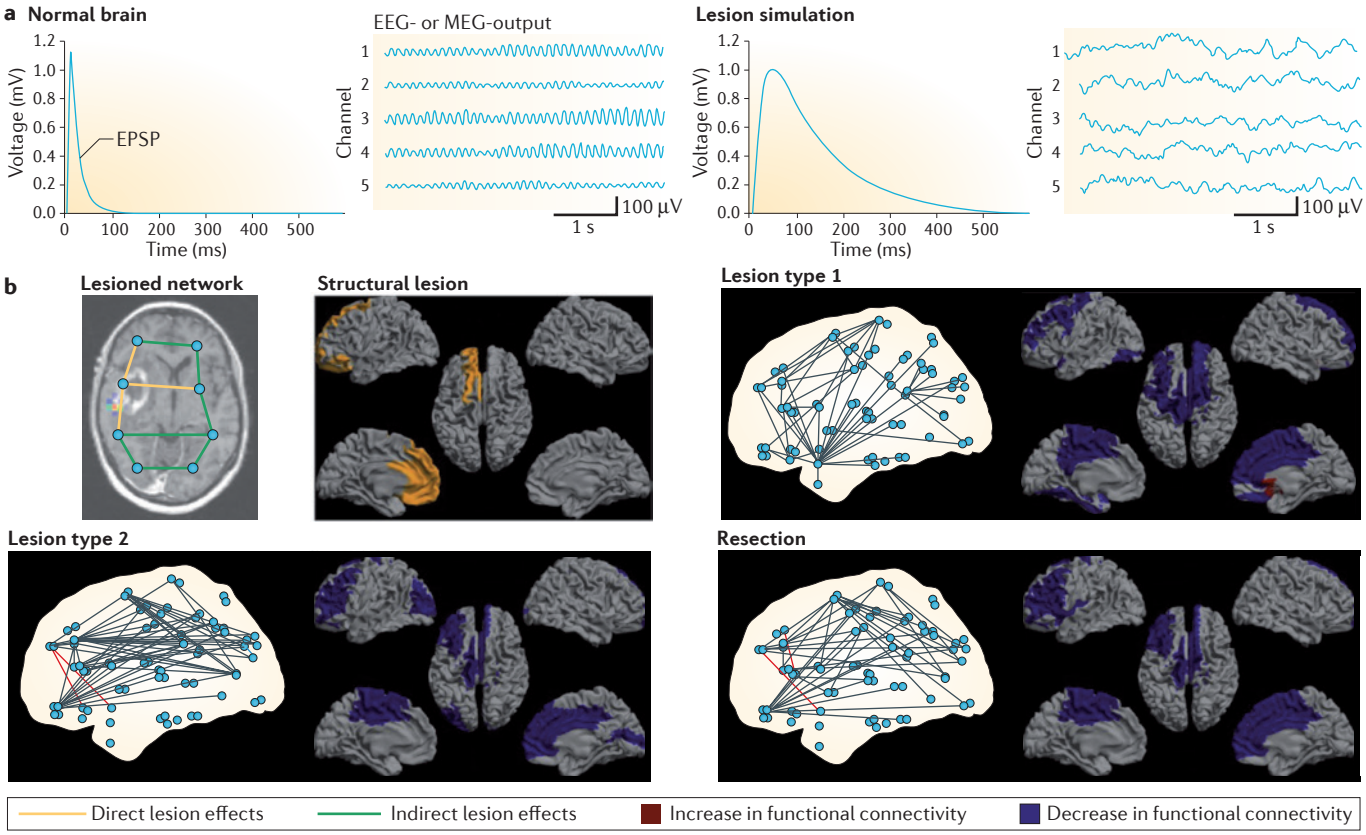


Figure 2 | **Simulation of widespread effects of local lesions.** Simulation of widespread effects of local lesions on functional networks, using electroencephalography (EEG)-like or magnetoencephalography (MEG)-like signals that were generated by neuronal masses and placed on nodes ($N = 78$; each node representing a brain area) of a structural brain network (constructed on the basis of human tractography data). **a** | By changing the shape of the excitatory postsynaptic potential (EPSP), the normal EEG- or MEG-output can be converted to abnormal, slow delta waves, which are typical of a severe local brain lesion. In addition, the thalamic input to the neural masses is changed (not shown). **b** | By changing a subset (yellow lines, representing the brain 'lesion') of the 78 nodes of the network, the influence of a local lesion on the rest of the network (green lines) can be studied ('lesioned network'). The next panel to the right ('structural lesion') shows in which brain regions a lesion (orange) was simulated in this way. The network diagrams in each of the other three panels show, on the left, the edges (in red and grey, indicating increases and decreases in connection strength, respectively) that were significantly changed as a result of different types of lesion and, on the right, the changes in functional networks that occurred as a consequence of each local lesion (dark blue, decrease in functional connectivity; dark red, increase in functional connectivity). The impact of the local lesion clearly extends beyond the lesion site itself. Reprinted from *Neuroimage*, **83**, van Dellen, E., Hillebrand, A., Douw, L., Heimans, J. J., Reijneveld, J. C & Stam, C. J., Local polymorphic delta activity in cortical lesions causes global decreases in functional connectivity, 524–532, Copyright (2013), with permission from Elsevier[21].

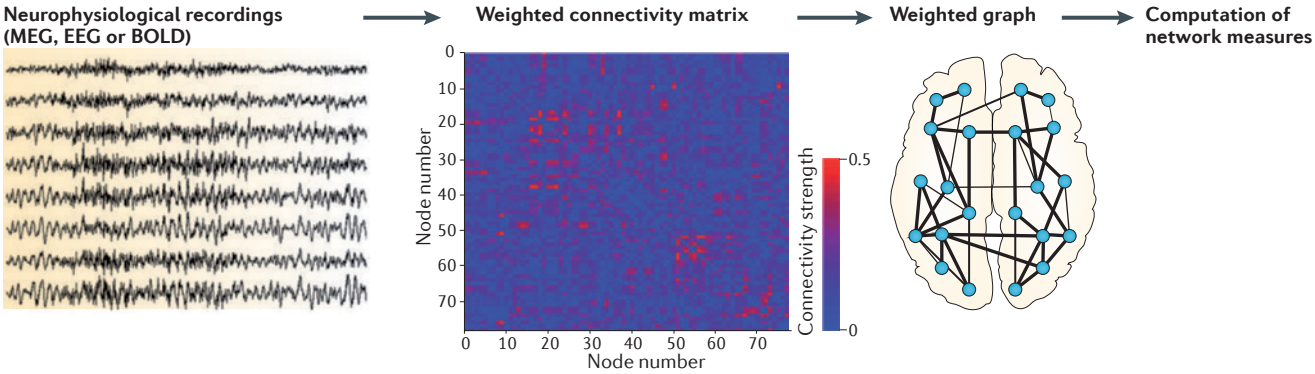
It is of clinical interest that many of these network changes are associated with cognitive deficits and behavioural changes[57,61–63,68,75,81,82]. In particular, as in healthy individuals, changes in path length are associated with changes in cognitive function[61,63]. So far, most studies of network changes in dementia have been conducted in individuals with AD, and only a few studies have been performed in patients with FTD or PD[45–48]. However, when more studies in different types of dementia become available, the usefulness of network analysis in differential diagnosis could be assessed. Furthermore, network analysis might be useful in therapeutic trials in AD. A good example is a study that has shown that the progressive decrease in clustering and path length in a group of patients with untreated AD could be prevented by a food supplement[66].

Multiple sclerosis. MS is classic disorder of CNS white matter, although grey-matter and thalamic involvement are increasingly recognized. One might expect that damage to the heavily myelinated, long-distance white-matter tracts, and its effect on neurological — and in particular, cognitive — function could be detected in network studies. One clinical aim here is to contribute to solving the clinical radiological paradox — namely, the observation that the lesion 'load' on MRI scans does not always correlate very well with clinical symptoms.

Measurement of cortical thickness in individuals with MS has demonstrated a disruption of normal small-world topology in MS, and the strength of this disruption was found to correlate with the extent of white-matter damage[83]. A tractography study confirmed

Box 3 | **Methodology of network studies**

Network analysis requires that the original empirical data are represented in the form of a graph (see the figure). This graph can be weighted or unweighted, and it can be directed or undirected. The first step is to decide what can be considered as a node, and what can be considered as a link. For instance, in the case of functional MRI (fMRI) data, a node can be a voxel or a group of voxels that perhaps correspond to an anatomical region; in the case of electroencephalography (EEG) or magnetoencephalography (MEG) data, a node can be a channel or a sensor, but also a source. Links can also be defined in various ways: as white-matter tracts, as correlations in the cortical thickness of structures between brain areas, or as a measure of synchronization between two fMRI blood oxygen level-dependent (BOLD) signals, two EEG signals or two MEG signals. The empirical data can be represented as an *N*-by-*N* connectivity matrix (see the figure), with *N* being the number of nodes and with each matrix cell providing information about the presence and strength of any relation. Such a matrix can be analysed as a weighted graph, but more commonly a threshold is applied such that all the cells in the matrix that have a value above the threshold become links in the graph. The fraction of edges (of the total number of possible edges) in the graph is called the density or cost. Often, the values of the computed measures of a graph (such as clustering or path length) are compared with average values of random versions of the same graph, in which all of the edges are shuffled. A problem is that methodological decisions — such as what is considered to be a node and what is considered to be a link, whether to use weighted or unweighted graphs and what threshold to use — are somewhat arbitrary, but can have a large impact on the outcome of graph measures. This problem cannot be solved by comparisons with random networks. It is possible that some of these problems can be addressed by the use of exponential random-graph modelling, motif counts or minimum spanning tree analysis.



the decrease in the global and local efficiency of structural networks (as described above)[84], including the default-mode network and several local networks in primary motor and sensory areas. Even in patients with the related, but much more localized, condition neuromyelitis optica, widespread changes to structural networks could be detected, although small-worldness, normalized clustering and path length were increased[85]. Furthermore, the tractography study[84] showed both decreases (in the default-mode network as well as in sensorimotor and visual systems) and increases in node centrality in different brain regions (in orbital parts of the superior-, middle-frontal and fusiform gyri), which is compatible with a reorganization of brain networks.

An MEG study showed increased functional connectivity in the theta, lower alpha and beta bands, and decreased functional connectivity in the upper alpha band in individuals with MS compared with healthy controls[37]. In addition, functional networks in the lower alpha band had a more regular topology, and changes in normalized clustering were associated with impaired cognition. Remarkably, these effects were greater in male patients than in female patients[37]. A second MEG study investigated networks in source space by using a connectivity measure that was unbiased by volume conduction, and by using either resting-state network analysis or a minimum spanning tree analysis[86,87]. Compared with healthy controls, individuals with MS had functional networks that were more integrated (that is, more tightly functionally connected) in the theta band and less integrated in the alpha and beta bands. A disruption of hierarchical network organization in the upper alpha band was associated with impaired cognition, whereas disturbed beta band connectivity of the default-mode network was associated with both impaired cognition and motor deficits[86]. The importance of using a proper measure to assess EEG functional connectivity was revealed in a study of 308 individuals with MS who were divided into cognitively impaired and cognitively unimpaired subgroups[88]. This study provided evidence for a shift from global to local connectivity in cognitively impaired patients, but not in cognitively unimpaired patients; however, these results were dependent on the specific synchronization measure that was used. Finally, a resting-state fMRI study found decreases in functional connectivity, which correlated with cognitive impairment, in male patients with MS but not in female patients[36].

In summary, graph theoretical studies of individuals with MS suggest that there are widespread changes in structural and functional brain networks, with global integration — which is often dependent on the default-mode network and hub structures — being especially affected. Such network changes are related to white-matter pathology[84], as well as to clinical and cognitive deficits[84,87,88]. Thus, these changes may contribute to understanding the relationship between the lesion load that is visible in MRI scans and the clinical symptoms of this disorder.

Neuromyelitis optica
A demyelinating disorder that affects optic nerves.

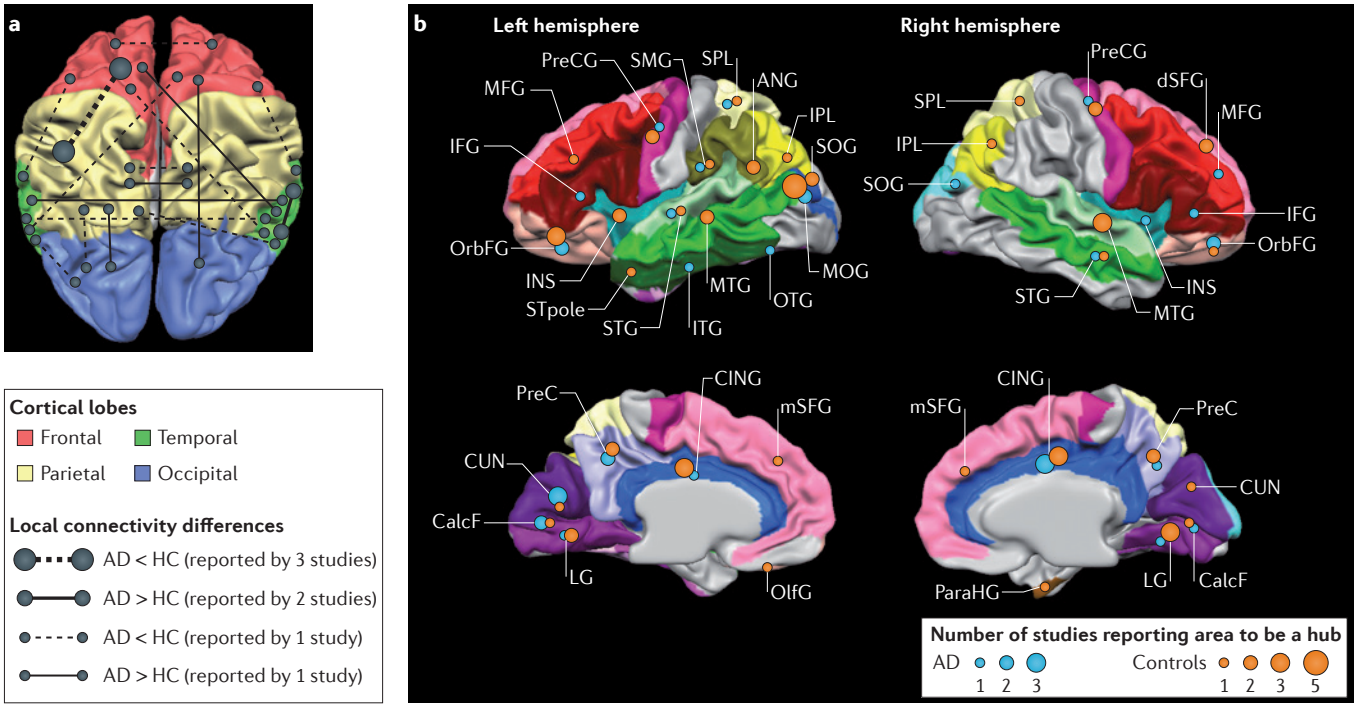


Figure 3 | **Network changes in Alzheimer's disease. a** | The top left panel summarizes changes in local connectivity in individuals with Alzheimer's disease (AD) as reported in four studies (dorsal view). Continuous lines indicate higher connectivity in AD compared to controls; dashed lines indicate lower connectivity in AD compared to controls. Circle diameter corresponds to the number of studies that have reported local connectivity differences between AD and controls. **b** | An overview of the anatomical regions that have a hub role in healthy controls (orange) or in AD (blue). Circle diameter corresponds to the number of studies that have reported the hub status of a region. Hubs that were reported in control networks, but not in AD networks, correspond to the regions that typically show AD pathology. These associative regions — in the temporal, parietal and frontal cortices — link to other cortical areas through long-range corticocortical connections. ANG, angular gyrus; CalcF, calcarine fissure; CING, cingulum; CUN, cuneus; dSFG, dorsal superior frontal gyrus; IFG, inferior frontal gyrus; INS, insula; IPL, inferior parietal lobe; ITG, inferior temporal gyrus; LG, lingual gyrus; MFG, medial frontal gyrus; MOG, medial occipital gyrus; mSFG, medial superior frontal gyrus; MTG, medial temporal gyrus; OlfG, olfactory gyrus; OrbFG, orbitofrontal gyrus; OTG, occipitotemporal gyrus; ParaHG, parahippocampal gyrus; PreC, precingulum; PreCG, precingulate gyrus; SMG, supramarginal gyrus; SOG, superior occipital gyrus; SPL, superior parietal lobe; STG, superior temporal gyrus; STpole, superior temporal pole. Reprinted from *Neurobiol. Aging*, **34**, Tijms, B. M., Wink, A. M., de Haan, W., van der Flier, W. M., Stam, C. J., Scheltens, P. & Barkhof, F., Alzheimer's disease: connecting findings from graph theoretical studies of brain networks, 2023–2036, Copyright (2013), with permission from Elsevier[14].

Traumatic brain injury. TBI can give rise to diffuse axonal injury, which can interfere with normal communication between brain areas. In view of this, the study of structural and functional brain networks has become an important approach for understanding cognitive dysfunction and late encephalopathy in TBI[13].

An MRI tractography study of 17 individuals with TBI and 12 control participants reported a widespread loss of structural connections in the patients with TBI[89]. This was associated with lower local efficiency, increased path length and increased betweenness centrality. Studies of functional networks in TBI have also demonstrated an extensive disruption of connections and network reorganization. For example, in patients who are in a minimally conscious state following TBI, the loss of connectivity (as assessed by EEG) occurs in all frequency bands[90]. At the other extreme, patients with very mild TBI only show disturbances in EEG-network topology in the theta and alpha bands during performance of an episodic-memory task[91].

Most studies of functional network organization in TBI have used resting-state fMRI. Often, fMRI studies report a loss of connectivity, in particular with respect to long-distance connections[92–94]. This loss is typically associated with a disturbance of the normal small-world topology — reflected in particular by an increase in path length — which may recover to some extent[95,96]. One fMRI study reported an increase in connectivity during a motor-switching task in patients with TBI[97]. The same researchers also reported a lack of correspondence between the structural and functional changes to the brain networks[98]. TBI can also be associated with changes in the modular structure of functional brain networks[92,95]. In a study of individuals who sustained TBIs that were due to shock blast, the main network abnormality concerned the connectivity between modules, as reflected by a decrease in the so-called 'participation coefficient' (REF. 95). Interestingly, a similar pattern of disturbed intermodular communication has also been observed

in AD[75]. Another feature of TBI is the selective damage of hub-like structures in the association cortices and the default-mode network[94,96]. An important study that compared individuals with severely impaired consciousness (following a range of acute medical events) with healthy subjects showed that although the groups had similar overall network characteristics[96], the spatial distribution of the hub nodes over the network was clearly different in the individuals with impaired consciousness. Such hub redistribution — from areas such as the precuneus and fusiform gyrus in controls, to areas such as the angular gyrus in patients with TBI — could be a late signature of post-trauma network reorganization.

These studies suggest that TBI can result in a loss of (especially long-distance) structural and functional connectivity, probably via the mechanism of diffuse axonal injury. This loss of connectivity is accompanied by network reorganization that is characterized by increased path length, abnormal modularity and a redistribution of hubs.

Epilepsy. Epilepsy, which is defined as a tendency towards recurrent unprovoked seizures, is one of the most prevalent neurological conditions worldwide. It presents one of the most interesting applications of modern network analysis, as here, more than in other disorders, network analysis is very close to the stage at which new treatment approaches, particularly surgery, can be realized[99–103]. Indeed, the classic concept of an 'epileptic focus' is being replaced by that of an 'epileptic network', and graph theory has had a major role in pointing out the key properties of the most important elements of this network.

In patients with temporal lobe epilepsy (TLE), structural networks based on cortical thickness correlations have increased clustering, a longer path length, an altered hub distribution and a higher sensitivity to attacks that are targeted specifically at hubs[104]. Importantly, these network abnormalities increased over time, and more severe abnormalities were associated with a worse outcome of epilepsy surgery[104]. MRI tractography studies have confirmed the presence of widespread abnormalities in structural networks[105–109], not only in focal epilepsy, but also in generalized types of epilepsy[109]. A general pattern that is observed in these studies includes changes in local connectivity in combination with disruptions to long-distance connections that often involve important hub regions in the default-mode network[107,108]. Furthermore, the extent of network changes often correlates with the severity of cognitive disturbances, the outcome of epilepsy surgery and the disease duration[106,108,109].

Not surprisingly, the focus of network studies of epilepsy has been on functional networks, particularly those derived from EEG and MEG recordings. Studies that have assessed network changes that occur during the ictal state have produced the most consistent results. One early study assessed functional networks that were derived from depth-electrode recordings that were taken before, during and after temporal lobe seizures, and reported a more regular topology, with high clustering and long path length during the ictal state[110]. Studies that used intracranial recordings also reported a shift towards a more regular network topology[111–113]. Such ictal network regularization was confirmed in scalp EEG and MEG recordings during absence seizures with generalized 3 Hz spike–wave discharges[114,115]. Although there is support for the concept of pathological ictal network regularization, it is not clear whether interictal and preictal networks also have an abnormal topology. I therefore discuss studies on interictal network topology in the context of two questions. First, are interictal networks abnormally regular, like ictal networks are? And second, what is the role of hub nodes in the spread of seizure activity?

Regarding the first question, some studies show that EEG- or MEG-based functional brain networks of individuals with epilepsy in an interictal state are abnormally regular compared with those of healthy subjects[116,117]. Such interictal network regularization has also been observed using depth-electrode recordings in individuals with TLE[118]. One study suggested that in the interictal state, regularization might occur in the theta band, whereas alpha band networks are abnormally random[119]. However, in another study, interictal network randomness increased with disease duration in individuals with TLE[120]. Other studies have also shown an association between excessive synchronization in the theta band and epilepsy[121–123]. In general, the interictal network topology in individuals with epilepsy seems to have shifted from the small-world organization that is seen in healthy subjects towards the excessive regularity that is observed during seizures. Unfortunately, this does not yet imply that interictal network topology can be used to predict when a seizure will occur[124].

The second question regarding interictal network topology is whether hubs are important for the propensity of seizures to spread through the brain[125]. Functional brain networks can be derived in an unbiased way using a minimum spanning tree approach[126]. One study that used a minimum spanning tree analysis of acute corticography recordings from individuals with TLE to identify hub nodes (on the basis of several criteria) suggested a possible association between node centrality and surgical outcome[127]. In a prospective study in individuals with both brain tumours and epilepsy, the networks of individuals who became seizure-free after surgery were more integrated and showed higher centrality at follow-up than the networks of patients who were not seizure-free after surgery[128]. In another study, surgical removal of the tissue that corresponded to network nodes with high betweenness centrality was associated with a more favourable outcome[129]. Additional studies also suggest the importance of hub-like structures, particularly in high-frequency ranges, for the spreading of seizure activity[130–132]. Indeed, hub-like features identified in EEG recordings can be valuable for predicting whether children will develop epilepsy after an initial seizure-like event[133]. Two studies compared the phase synchronization and node centrality of functional networks exhibiting high-frequency oscillations (HFOs), which are an important feature of epileptogenic tissue[134,135]. Somewhat surprisingly, the number of HFOs

Ictal state
Brain state during an epileptic seizure.

was inversely correlated with node centrality in the theta band[135]. This finding suggests that areas with HFOs and areas with high-degree nodes may not be the same, and could represent two different and perhaps even spatially separated components of the epileptogenic zone.

The pattern of increased local connectivity and decreased global connectivity (features that are typical of more regular networks) that is observed in structural MRI studies of individuals with TLE has been confirmed in resting-state fMRI studies[136,137]. The connectivity of the default-mode network is diminished both in individuals with TLE and in individuals with generalized epilepsy. Changes in fMRI-based functional networks are also associated with impaired cognition in such patients. For example, a study in individuals with cryptogenic localization-related epilepsy showed an association between lower clustering coefficients and increased cognitive impairment[138], and stronger modularity was associated with more-impaired cognition in children with frontal lobe epilepsy[139]. These observations are in line with a previous report of abnormal modularity in individuals with absence epilepsy[116].

Some recent studies have combined the use of fMRI with structural MRI in the same subjects[140–142]. One such study found reduced coupling between structural, tractography-based and functional networks in individuals with idiopathic generalized epilepsy, with the strength of hub nodes and the default-mode network connectivity being diminished in particular[142]. In contrast with this finding, a study that related fMRI-based networks with cortical thickness-based networks showed increased coupling between functional and structural networks[140]. In a study in children with frontal lobe epilepsy, fMRI-derived functional networks showed the well-known pattern of increased clustering, longer path length and higher modularity, but structural networks were not different between patients and healthy controls[141]. Moreover, the increased modularity of structural networks in these individuals was associated with more-severe cognitive impairment.

Several patterns emerge from network studies in epilepsy. In both focal and generalized epilepsy, there is a widespread involvement of structural and functional brain networks. MRI studies show that epilepsy is characterized by a tendency towards increased local connectivity and decreased global, long-distance connectivity that affect, in particular, the default-mode network and hubs in association areas. These changes are associated with cognitive disturbances, longer disease duration and poor surgical outcome. During seizures, functional brain networks display a pathological regularization. Similar changes can be observed, to a lesser extent, in the interictal state. Furthermore, the strength of hub nodes in functional networks is associated with the outcome of epilepsy surgery and has diagnostic value.

Is it possible to sketch the outlines of a 'network theory of epilepsy' on the basis of these findings? Here we should distinguish between the local and the global levels. At the local level, epilepsy is characterized by a small brain area with abnormally increased excitability (the epileptogenic zone and the origin of HFOs), increased structural connectivity (possibly the result of damage and rewiring) and one or more highly connected hubs. The local components may be responsible for the increased activity, synchronization and network regularity in the interictal state. Only if the activation exceeds a critical threshold will activity spread — through general hub-like structures such as the default-mode network — to the rest of the network, and this then results in a generalized seizure and a transiently hyper-regular functional network. If this process occurs repeatedly, long-distance connections and general hubs will become damaged, resulting in a loss of long-distance connectivity and, eventually, in cognitive dysfunction. Understanding the network aspects of epilepsy may lead to new approaches to epilepsy treatment, for instance in the context of epilepsy surgery. A hypothetical scenario for such an application is depicted in FIG. 4.

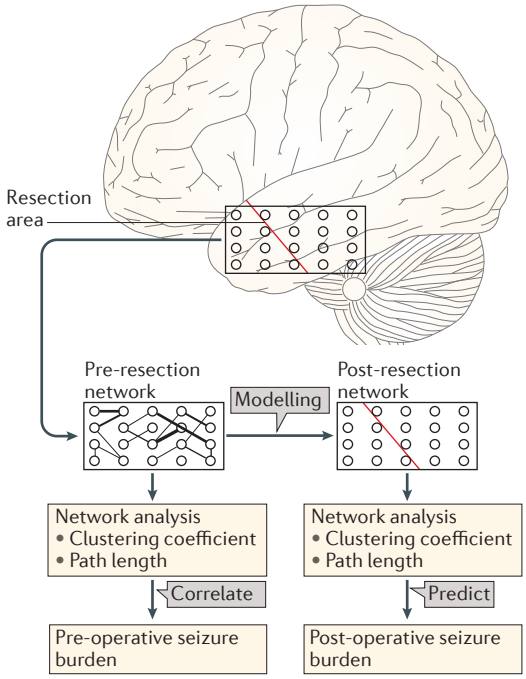


Figure 4 | **Future clinical use of network modelling in epilepsy surgery.** This hypothetical scenario sketches one possible way in which network analysis could be put to clinical use in epilepsy surgery. A recording of brain activity, for instance an electroencephalography recording from a grid during surgery, can be analysed using graph theory, and the network properties can be related to pre-surgical clinical features — for instance, characteristics of epilepsy. Subsequently, the effects on the network of a planned resection (shown here as a resection of the anterior part of the temporal lobe; red line) can be simulated, and the properties of the resulting network can be used to predict the post-resection clinical epilepsy symptoms. In this way, various 'virtual resections' could be investigated before the real resection is performed. The algorithms that are used to relate network features to epilepsy characteristics can then be improved by relating the actual outcome to the model prediction, adjusting the model where necessary.

Cryptogenic localization-related epilepsy
Focal epilepsy that is putatively due to a local structural abnormality which cannot yet be demonstrated.

Absence epilepsy
A form of generalized epilepsy that is characterized by 3 Hz spike–wave discharges in the electroencephalogram.

Complex networks: a new view on brain disease

As the sections above show, clinical studies have revealed a bewildering variety of structural and functional network changes in different neurological disorders. The challenge is to identify, if possible, some common patterns among these changes. Below I provide a few general conclusions that can be drawn from the findings reviewed above. I discuss in more detail how hubs may be affected in neurological disorders, and then propose a possible mechanism that may explain network changes in neurological disease.

The first general conclusion is that network organization in neurological disease almost always reflects a deviation from the optimal pattern, which is characterized by high clustering, short path length, hierarchical modularity, scale-free degree distribution and hub nodes that are interconnected in a rich club. However, even between studies of a single disorder or between studies that use a single neuroimaging modality, there is little agreement on the nature of this deviation, at least with respect to such measures as clustering and path length[14,103]. Second, these changes tend to become stronger in progressive disorders such as AD or PD, but may improve over the recovery phase of stroke or TBI or as a result of treatment. Furthermore, the extent of network changes is often correlated with the extent of the underlying structural pathology (such as white-matter damage, microbleeds or amyloid deposition), with the severity of the clinical symptoms (notably, cognitive dysfunction) and with disease duration. Finally, network studies show that local brain lesions (for example, brain tumours or in TLE) are almost invariably associated with widespread network changes, whereas diffuse brain disorders (for example, AD, PD and TBI) tend to affect some critical brain regions more severely than others. In other words, from the perspective of network science, all brain diseases are system disorders, where 'system' refers to the complex structural and functional interactions, all the way from neuronal to macroscopic levels.

Hubs. A remarkable pattern is the consistent involvement of hub nodes in a wide variety of neurological diseases[46,59,61,65,87,107]. In most complex networks, including the brain, nodes vary widely in their relative importance. This importance can be quantified by measures of centrality, such as degree, eigenvector centrality or betweenness centrality. A key feature of healthy brain networks is the presence of a rich club of interconnected hubs — that is, nodes with a high centrality. Hubs are crucial for optimal information flow in brain networks and this is reflected by the correlation between the level of hub centrality and general intelligence[39–41]. The downside of this crucial importance of hubs is that hubs are at the same time a typical vulnerable spot in brain networks. This might explain why damage to hub nodes — especially those that are part of the default-mode network, but also hub nodes in other association areas — is one of the most consistent findings in all network studies of brain disease, seemingly irrespective of the specific underlying pathology. Indeed, damage to hubs, and a redistribution of hub nodes, has been reported in AD, PD, MS, TBI and epilepsy. This raises the question of why hub failure is such a universal feature of brain disease. In other words, what physiological or other network-related properties of hubs make them prone to damage?

Hub overload and failure as a final common pathway. The fact that hub nodes are vulnerable to damage in very different neurological diseases suggests that a general mechanism may underlie this vulnerability. Here I propose one putative scenario (FIG. 5). Under normal conditions, a brain network constitutes a multilayered hierarchical structure. This is an efficient organization in which information flow is handled locally if possible, and globally if needed. This organization corresponds to an optimal balance between the segregation and integration of information, although the fact that the structure is hierarchical suggests that the transition between these extremes is gradual, and more than two levels may exist.

In brain disease, the capacity of one or more nodes (that are either distributed or clustered in one large lesion) to handle incoming information is diminished. This problem may be overcome by two types of network reorganization. In the acute phase, nodes that project to the affected nodes redirect their input to other nodes higher up in the hierarchy (FIG. 5b). As a result, the traffic load higher up in the hierarchy will increase, particularly in the hubs with the highest centrality. But this is an expensive solution, as hubs will be overloaded with traffic that is normally handled locally. If this abnormal rerouting is severe and sustained, the hub nodes themselves may become affected, resulting in a diminished capacity to handle traffic — in other words, 'hub overload' (FIG. 5c). In the chronic phase, hub overload is avoided by rerouting traffic through lower (rather than higher) levels in the hierarchy. As a consequence, the traffic load and centrality of the original hubs decreases, whereas the traffic load and centrality of other nodes increases. This local rerouting can be thought of as a local outgrowth of new connections and could be referred to as 'hub failure' (FIG. 5d). Thus, in the acute phase there is a shift from local to global processing, whereas the opposite happens in the chronic phase. Interestingly, acute and chronic rerouting will also affect the hierarchical modular organization of the network. The central idea of this proposed mechanism is that any type of brain disease, be it local or global, can give rise to a scenario of rerouting and rewiring that is characterized by hub overload followed by hub failure.

Challenges and future directions

The application of network science to the study of brain disorders is a new but rapidly developing field. However, a number of challenges will have to be met to enable further progress. Three topics deserve particular attention: methodology, modelling and clinical application. First, with the rapid growth of the number of network studies, it is becoming increasingly clear that the lack of a generally accepted method to reconstruct graphs from empirically observed structural and functional data is a major problem in comparing results from different studies and from different technologies. The outcome of a network analysis can be influenced by the choice of what defines

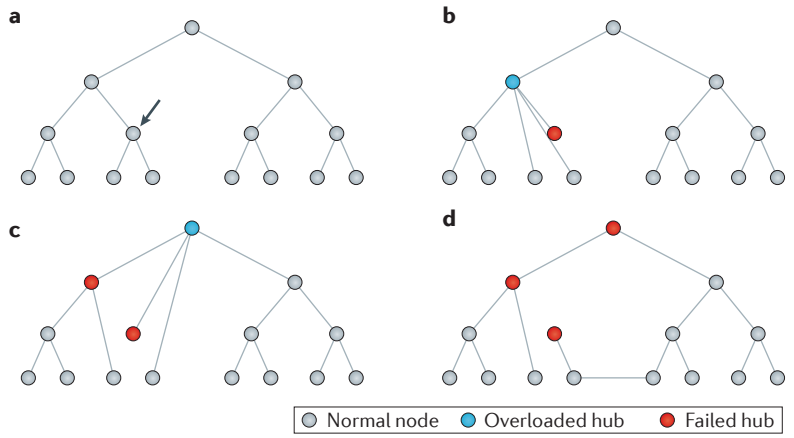


Figure 5 | **Hub overload and failure as final common pathway of brain disease.** **a** | Schematic representation of a normal brain network as a hierarchical tree. Nodes at the lowest level can be thought of as representing primary sensory and motor regions. Nodes, or hubs, at subsequent higher levels may represent unimodal, multimodal or supramodal association areas. Node centrality increases from the bottom to the top. The arrow points to a node where failure may start. **b** | Failure of node: acute phase. Traffic that would normally be directed to the failing node, now shown in red, is rerouted to nodes higher up in the hierarchy, in this case to the blue node. **c** | When the blue node in part **b** starts to fail as well (now shown in red), part of its incoming traffic — including traffic from the initial damaged node — is rerouted to nodes even higher up in the hierarchy, to the highest node (blue). The centrality and traffic load of this highest node will increase, leading to 'hub overload'. **d** | Chronic phase. When the highest node becomes damaged, owing to excess traffic load, the traffic from nodes at the lower levels can only be rerouted locally. Note that, as a consequence, the traffic load and centrality of the highest node in the hierarchy will be disturbed, whereas the traffic load and centrality of some of the other nodes will increase. This is the phase of 'hub failure'.

a 'node' or a 'link', the use of weighted versus unweighted graphs, the choice of threshold (or range of thresholds), the normalization of cost and comparisons with (different types of) random networks[143]. An important challenge is to find simple yet meaningful ways to characterize brain networks while avoiding arbitrary choices. Future research will have to demonstrate whether the use of the minimum spanning tree, or related concepts, can solve this problem[54].

Second, in view of some large-scale initiatives that aim to decipher the full human connectome, it is likely that a wealth of high-quality, high-resolution data on structural and functional brain networks in health and in pathological conditions will become available in the near future. The challenge will be to identify effective ways to detect meaningful patterns in this multitude of data. In a sense, the connectome revolution may well expose the Achilles heel of neuroscience: the current lack of a powerful, general theory of brain function. This challenge is starting to be met by the introduction of increasingly sophisticated simulation studies of realistic structural and functional normal brain networks. A similar approach — dubbed computational neurology — is providing new insights into the mechanisms of brain disease. However, the ability to make detailed computational simulations of the brain does not yet constitute a theory of brain function. The real challenge is to come up with general models that explain the data and that can be analysed mathematically.

Finally, an important challenge is to find useful clinical applications of brain network science. At the present stage, network science is mostly challenging some current concepts of brain disease. For instance, the failure of hub areas in many different types of brain disease seems to be associated with cognitive deficits — mainly, impairments in attention, executive function and working memory. A better awareness of these symptoms, even in disorders in which they may not be directly obvious (such as low-grade glioma, MS or local vascular lesions) could have implications for the treatment approach for patients. An additional challenge is to extract new diagnostic measures or biomarkers from network data. The use of network features in the diagnosis of epilepsy is an example of this approach[103]. The last challenge will be to devise new treatments on the basis of a proper understanding of the underlying network mechanisms of disease. Perhaps in the future a rerouting of information traffic in diseased brains could be induced by the rational application of medication, brain stimulation or surgery.

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Competing interests statement
The author declares competing interests: see Web version for details.