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The economy of brain network organization

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Abstract | The brain is expensive, incurring high material and metabolic costs for its size — relative to the size of the body — and many aspects of brain network organization can be mostly explained by a parsimonious drive to minimize these costs. However, brain networks or connectomes also have high topological efficiency, robustness, modularity and a 'rich club' of connector hubs. Many of these and other advantageous topological properties will probably entail a wiring-cost premium. We propose that brain organization is shaped by an economic trade-off between minimizing costs and allowing the emergence of adaptively valuable topological patterns of anatomical or functional connectivity between multiple neuronal populations. This process of negotiating, and re-negotiating, trade-offs between wiring cost and topological value continues over long (decades) and short (millisecond) timescales as brain networks evolve, grow and adapt to changing cognitive demands. An economical analysis of neuropsychiatric disorders highlights the vulnerability of the more costly elements of brain networks to pathological attack or abnormal development.

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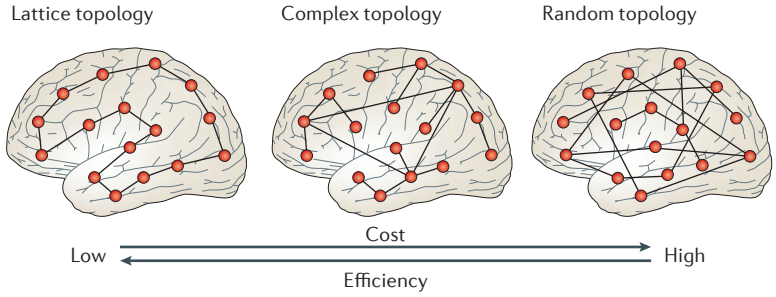
Social and natural systems are generally organized as complex networks of interconnected elements[1] that, when represented as graphs, have topological properties that are neither purely random nor regular[2]. It has been shown extensively that topological complexity is very common in real-world systems, from scientific collaboration networks to infrastructure and transportation networks, and to the brain networks of worms, monkeys and humans[3].

The topological organization of networks is important for their overall function, performance and behaviour[4–6]. For example, on a cellular level, the topology of network interactions between proteins is critically related to the performance of metabolic and gene regulatory functions[7,8]. On a social level, the topology of network interactions between people is related to the cultural spread of ideas and innovations as well as the population vulnerability to epidemic diseases[9,10]. Changes in the topology of a complex network during evolution or development can often be related to characteristic aspects of the network's robustness or functional performance[11,12].

Some complex networks can be regarded as virtual: they do not occupy physical space. The network of interactions between stock prices that emerges from trading activity on a stock exchange is an example of a virtual system with a complex topology that is not greatly affected by the geographical locations of the traders or the traded companies[13,14]. By contrast, many social and natural systems are clearly defined spatially as well as topologically[15,16]. Airline networks are representative of such spatially embedded networks: the topology of connecting flights between airports is strongly influenced by the distance between airports, resulting in a 'hub and spoke' topology. Another example is that the World Wide Web network of hyperlinks between content-related websites is more virtual than the infrastructure of the Internet, which is spatially embedded in the form of routers and cables[17]. Like an airline network, the topological formation of the Internet is strongly constrained by its physical properties, including the greater wiring cost of longer-distance links (cables) between nodes.

Brains are obviously not virtual: they are embedded in a three-dimensional anatomical space (BOX 1). They are physically expensive systems to build and to run, and many aspects of brain anatomy seem to have been organized to control these wiring costs[5,18,19]. However, some of the adaptive behaviours of a brain network — such as its capacity for information processing and its robustness to adverse perturbation — are probably related to topological properties that would not have emerged if cost minimization was the only factor to drive brain organization. For example, if a parsimonious principle of cost control was the only criterion for brain network selection, we

Box 1 | **Network topology and spatial embedding**



Brain networks that are wired to minimize cost would have a lattice-like topology. For example (see the figure, left panel), each node could have two nearest neighbours topologically that were also its closest neighbours spatially. However, this topology does not favour global integration of information processing; there are not enough topologically direct connections between regions that are physically far apart. Brain network efficiency for integrative processing would be maximized by a random topology in which each node is expected on average to connect to any two other nodes (see the figure, right panel). However, this topology comes at a high wiring cost owing to the large number of long-distance connections. Human brain networks seem to sit between these two extreme cases (see the figure, middle panel): there are clusters of lattice-like short-distance connections between spatially neighbouring nodes, often aggregated topologically and anatomically as modules, and these features will tend to minimize wiring cost. But brain networks also include high-cost components, such as long-distance short-cuts between connector hubs in different modules and different anatomical regions. Topologically direct interconnections between spatially remote brain regions will increase the efficiency of information processing, which is expected to yield benefits in terms of adaptive behaviour. Brain networks can therefore be said to negotiate an economical trade-off between minimizing physical connection cost and maximizing topological value.

would not expect to see high global efficiency of information transfer between processing nodes (neurons or brain regions) located far apart from each other in anatomical space[20]. These considerations suggest that brain networks may be selected to negotiate a trade-off between competitive criteria of minimizing wiring cost and maximizing adaptive value[19,21], a trade-off that underpins the economy of brain network organization.

In economic theory, producers in a market economy seek to be profitable by adding value to raw materials so that their product can be priced higher than the cost of its production. Successful producers will typically look to maximize their profit in the long term by both controlling their cost base and finding new ways to add value for their customers in a competitive and changing market. The key economic question is therefore not simply how to cut costs but how to optimize a trade-off between the costs of production and the market value of the products; that is, how to maximize the margin of profit. Similarly, we could say that the brain is a successful producer if its adaptive value to the organism exceeds its biological costs. Furthermore, we propose that evolutionary or developmental selection criteria have acted as 'customers' in the market for adaptive behaviour that brains are supplying and, as a result, brain networks are selected — like profitable businesses — to optimize a trade-off between the costs of production and the value of production.

In this Review, we explore this economic model of brain organization in detail. We focus on how we can use recent results from the rapidly growing field of brain network science rigorously to address and test key questions that arise from this hypothetical base. Which quantifiable aspects of brain organization are important for cost control? Which are valuable for adaptive behaviour? Can we provide empirical evidence (not just an eclectic metaphor) that brain network organization optimizes an economic trade-off between the cost and the behavioural value of network function? And what does an economical analysis add to our understanding of clinical disorders of brain network organization?

Brain networks are expensive

It has been recognized since the late nineteenth century that many aspects of brain organization can be accounted for by a parsimonious principle aimed at minimizing the wiring cost involved in anatomically connecting neurons to constitute circuits or networks. This fundamental insight was clearly articulated by Ramón y Cajal in 1899 on the basis of his microscopic studies of Golgi-stained neurons[22,23]:

> *"All of the various conformations of the neuron and its various components are simply morphological adaptations governed by laws of conservation for time, space and material."*[22]

These 'Cajal conservation principles' of brain organization have endured and have been experimentally supported in many ways over the past 100 years[21,24,25]. They have been restated in more contemporary terms as conservation of wiring cost (space), conduction speed (time) and cytoplasmic volume (material)[26].

Network wiring costs. The wiring cost of the brain fundamentally derives from the fact that brain networks are spatially embedded. Neural elements and their connections are contained in a limited space — brain volume — and the three-dimensional space that they occupy must not exceed the narrow bounds imposed on it by the body[27]. This places severe constraints on the number and density of neurons, and on the distance and cross-sectional diameter of axonal projections. As the dimensions of axons play a major part in determining conduction velocities, volume constraints on wiring cost have functional implications for the speed of signal transmission between remote regions of the brain.

In general, the cost of building and maintaining axonal connections, as well as the speed of signal transmission, can be assumed to increase with wiring volume, which itself is proportional to the length or distance of inter-neuronal connections[28] and the cross-sectional diameter of axonal projections[29].

The fundamental cost constraints of brain and body size on brain organization are revealed by well-established allometric scaling laws[30] (FIG. 1). Across a range of species, larger animals tend to have larger brains[31], and this relationship is defined by a simple power law. In addition, variation in brain size predicts the variation in size of many other parameters of brain organization: an increase in the number of neural elements generally

Graphs
Simple models of a system that are based on a set of nodes and the edges between them. The nodes represent agents or elements, and the edges represent interactions or connections between nodes.

Topology
Applied to a network, the layout pattern of interconnections, defined in terms of the relations of nodes and edges.

Robustness
The degree to which the topological properties of a network are resilient to 'lesions' such as the removal of nodes or edges.

Hub
A topologically important or central node, as defined by one of several possible measures of centrality, including degree centrality (number of edges) or betweenness centrality.

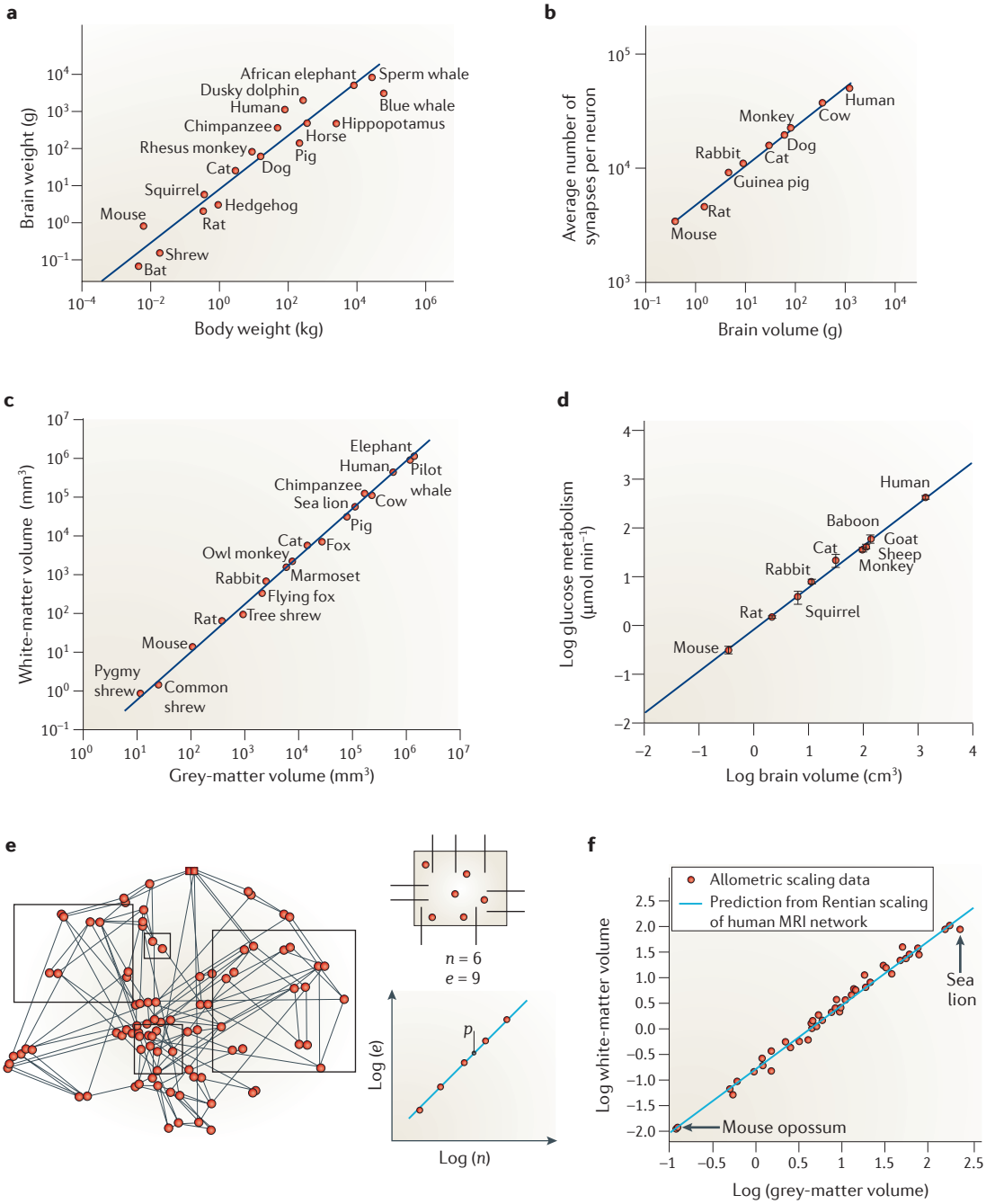


Figure 1 | **Allometric and fractal scaling of brains and human brain networks. a** | Larger organisms have larger brains[158]. **b** | Larger brains have more synapses per neuron[159]. **c** | Larger brains have disproportionately more white matter than grey matter[34]. **d** | Larger brains are metabolically more expensive. These allometric scaling relationships show how important parameters of mammalian brain network organization are constrained by physical size. **e** | Within the brain network of a single species (human), there is fractal scaling of the number of connections to or from a region of the brain (left panel): regions of grey matter that contain more nodes (higher *n* value) have more connections (higher *e* value) in accordance with a power law; the top right panel shows an example region with 6 nodes and 9 connections. This is called fractal or Rentian scaling (bottom right panel), with scaling exponent *p*, and it is recognized as a hallmark of cost-efficient spatial embedding of complex network topology in the design of high-performance computing chips[109]. **f** | The Rentian scaling exponent of the human brain network can be used to accurately predict the allometric scaling relationship between grey-matter volume and white-matter volume over a range of mammalian species (data from REF. 160). These data provide evidence that cost constraints, including the limited physical volume of the head and the wiring cost of connections between brain regions, have a strong influence on the network topology. Part **a** is modified, with permission, from REF. 158 © (2005) Elsevier. Part **b** is reproduced, with permission, from REF. 159 © (2006) Academic Press, Oxford. Part **c** is modified, with permission, from REF. 34 © (2000) National Academy of Sciences. Part **d** is reproduced from REF. 51. Parts **e** and **f** are modified from REF. 109.

Wiring cost
The fixed cost of making anatomical connections between neurons, often approximated by the wiring volume of anatomical connections.

Efficiency
A topological measure of the reciprocal or inverse of the path length between nodes. In brain networks, global efficiency is often used as a measure of the overall capacity for parallel information transfer and integrated processing.

Economy
Applied to brain network organization, economy refers to the careful management of resources in the service of delivering robust and efficient performance.

Allometric scaling
Allometric scaling concerns the relationships between body size (scale) and other anatomical, functional or metabolic properties of organisms. These scaling relationships are often described by power laws.

Box 2 | **Cortical folding and connectivity**

The surface of the cerebral cortex of higher mammals is folded into many convolutions, resulting in a complex anatomical configuration that has long been thought to increase cortical surface area while conserving axonal volume. The developmental origin of cortical convolutions can be traced to a combination of genetic factors and 'developmental mechanics', such as the physical forces arising from tissue growth and expansion. Early studies suggested that cortical folding is driven by limitations in cranial volume[144] or by specific growth processes that anchor sulci in place and move gyral walls and crowns outward[145]. More recent proposals emphasize that cortical folding is influenced by genetic factors that control regional specialization. For example, differences in the cellular structure and connectivity of cortical regions may cause mechanical variations across the developing cortical sheet and thereby bias cortical convolutions.

Thus, cortical folding may be an example of how the spatial embedding of cortical regions and their connection topology interact during development. An influential proposal focused on the effects of tensile forces that arise from the pattern of long-range inter-regional axonal connections[47]. Tension-based folding would lead to a shortening of dense pathways between highly interconnected regions, thus naturally promoting a reduction in wiring length and shorter conduction delays. Several testable predictions arose from this proposal. First, pathways should mainly connect brain regions within cortical gyri rather than across sulci. Data from cat and macaque cortex seem to support this idea[146], although questions remain about correlations between cytoarchitectonic boundaries and macroanatomical landmarks such as gyri and sulci[147]. Second, denser pathways should exhibit white-matter trajectories that are straighter than those of less-dense pathways. Morphological observations of the density and curvature of projections in macaque cortex indeed suggest that straight projections have greater density than those following intermediate or curved trajectories[148]. Finally, variations in connectivity, including variations due to developmental anomalies, should become expressed in variations of gyrification or of the placement of gyri and sulci across the cortical surface. Supporting this idea, data on localized and hemispherically symmetric folding abnormalities in Williams syndrome, a neurodevelopmental disorder, may reflect disturbances in the size, spatial layout or connectivity of a set of brain regions[149].

requires an increase in the number of connections, hence imposing additional wiring costs[30,32,33]. This is reflected in a robust allometric scaling relationship between grey- and white-matter volume across mammalian species[34]. White-matter volume grows faster than grey-matter volume as a function of increasing brain and body size, and this seems to be driven by increases in axonal diameter and in the number of synapses per neuron[35]. The different rates of increase in grey- and white-matter volume with increasing cerebral cortex size observed in primates implies that the fraction of grey-matter neurons that send myelinated axons into the white matter slowly reduces with brain size, thus resulting in increasingly sparse long-range connections among grey-matter neurons in larger brains[36,37].

There is also support for the principle of wiring-cost minimization in more detailed studies of brain network organization in a single species. At a microscopic or cellular scale, the anatomical layout of the nervous system of the nematode worm *Caenorhabditis elegans* quite closely resembles the pattern of neuronal component placements defined by a computational search for a layout that minimizes wiring costs for the given topology of the *C. elegans* connectome[28,38,39]. In mammalian neocortex, connection probabilities among cortical neurons generally show distance dependence, with greater probability of synaptic connections between cells that are spatially close[40,41]. Similarly, at a macroscopic scale, a shorter distance between two brain regions is a strong predictor of the presence[42] and the density of connecting axonal projections between these two regions[43], indicating that the probability distribution of connection distances is skewed towards short distances that will be relatively parsimonious in terms of wiring cost[44]. This is supported by observations from functional MRI (fMRI) studies that the strength of functional connectivity between brain regions decays as an inverse square or gravity-law function of physical distance[45], and that most edges in a sparsely thresholded functional network have relatively short distances[46]. Moreover, certain aspects of global brain organization, such as the sulco-gyral folding of the cerebral surface, could help to minimize axonal projection distance[21,47] (BOX 2).

Thus, there is no shortage of evidence in support of the idea that wiring costs of brain networks are nearly minimal, for a given network topology. However, it is also clear that brain networks are not absolutely minimized for wiring cost[48]. Various countervailing factors prevent strict cost minimization of brain networks. At least in cellular systems, volume exclusion is a factor that exacts a cost premium: as neuronal elements are packed into a finite volume, some axonal projections must be perturbed from the minimal-cost straight line and some cell bodies must be displaced from their optimal spatial locations[38]. Furthermore, computational modelling studies of neuronal placement in a module of the brain of the fruitfly (*Drosophila melanogaster*) have shown that neuronal placement predictions based on models representing a competition between wiring minimization and volume exclusion are more realistic than predictions based on models that include either factor alone[27].

Another plausible factor that might compete with wiring-cost minimization is the functional or behavioural properties of the network, which are assumed to be related to its connectivity or topology. For example, two neurons that are topologically nearest neighbours are directly connected by a single synapse, and the time it takes to transmit a signal between them is considerably shorter than that for the polysynaptic connection between a pair of neurons that are separated by the same physical distance but a greater topological distance. Thus, there is a functional advantage to direct, monosynaptic connection between nodes even if they are located far apart in space, and the wiring cost of a direct connection will be correspondingly high. In another example, the strength of synchronized oscillations in neuronal networks is enhanced when the wiring cost of the networks is increased above minimum by the inclusion of long-distance axonal projections, which mediate topological short-cuts between spatially remote oscillators[37]. Graph theoretical models of neuronal morphology that incorporated a competition (or a trade-off) between wiring cost minimization and path length minimization generated remarkably realistic simulations of diverse neuronal types and their laminar packing patterns in cortex[26]. We will return to this theme of a trade-off between wiring cost and network topology as we articulate an economic model of brain network organization.

Connection distances
Spatial measures that describe the physical distance between nodes that are connected by an edge in the network; often approximated as the Euclidean distance between nodes.

Functional connectivity
Statistical association — for example, significant correlations — between neurophysiological measurements recorded from anatomically distinct neurons or regions at several time points.

Edges
In a brain graph, an edge between nodes (regions or neurons) indicates that the nodes are anatomically or functionally connected.

Path length
A measure of network topology. In a binary graph, the path length between two nodes is the minimum number of edges that must be traversed to get from one node to another.

Network running costs. In addition to the costs of building an anatomical brain network, we need to consider the costs of running it. Although conservation of energy was not prominent among Cajal's original principles, it has become increasingly clear that the metabolic costs (also known as energetic costs or running costs) of the brain are large in relation to the body, but are also quite rigorously controlled to be as low as possible for any given function[29,49,50].

The metabolic (or energetic) cost of the brain follows an allometric scaling relationship with brain volume: anatomically bigger brains are metabolically more expensive. Moreover, the rate of increase in oxygen and glucose consumption as a function of brain size (that is, the allometric scaling exponent for brain metabolism on brain volume) is somewhat greater than the rate of increase in overall body oxygen and glucose consumption as a function of body size[51] (FIG. 1). Thus, volume expansion of the brain has a disproportionate impact on the body's total metabolic budget.

Much of the brain's massive metabolic cost is attributable to the active maintenance of electrochemical gradients across neuronal membranes, which is required to support signalling and coordination of neuronal activity at anatomically separated sites[29,49]. The metabolic costs of the brain increase in proportion to the total surface area of the neuronal membrane that must be biochemically maintained in readiness for transmission of electrical signals; these costs are pushed down by myelination (which restricts the amount of membrane depolarized by transmission of an action potential) but pushed up as a function of axonal length and diameter, with longer-distance connections being metabolically more expensive to maintain[51]. Controlling the wiring cost — by minimizing the length of anatomical connections in the network — will therefore also conserve potential running costs. However, there is strong evidence that metabolic costs are controlled dynamically within the upper limit imposed by the anatomical architecture of the network. That is, brain networks are often functionally activated or configured less expensively than they could be within the anatomical constraints, so that metabolic resource is used frugally. Some well-known examples of such control of running costs are: sparse coding strategies, by which great diversity of information representation can be achieved for low metabolic cost[52]; the repetition suppression of neuronal response to repeated presentation of visual stimuli[53]; and the habituation of limbic cortical activation to repeated emotionally valent stimulation[54]. Interestingly, these observations on reduced neuronal activation in response to repeated — and therefore predictable or unsurprising — stimuli suggest a possible connection between minimization of the metabolic costs of a network and minimization of prediction error in its computational performance[55–57].

Measures of functional connectivity and connection distance in human neuroimaging studies are often interpreted as resulting from underlying anatomical connections. This assumption is important for attaching cost implications to the distance between functionally connected regions[28,38]. The validity of this assumption depends on the metric of functional connectivity and the timescale over which it is estimated[58,59]. Computational studies suggest that functional connections correspond more closely to underlying anatomical connections when they are measured over longer time periods[58]. Empirical studies suggest that robust patterns of functional connectivity are induced by a combination of direct and indirect anatomical links[58,60], which have wiring costs that tend to increase with connection density and distance. Further studies are needed to better understand how the wiring (or anatomical) costs of a connection between regions can be inferred from statistical association of patterns of activity over time simultaneously recorded from those regions, for example, using fMRI or magnetoencephalography (MEG). Here, we will proceed on the simple assumption that wiring costs and running costs generally grow with increased distance between functionally connected regions.

Brain networks are topologically complex

The increasing availability of empirical data on brain networks, from tract-tracing studies of mammalian brains[61,62] to studies involving non-invasive neuroimaging[63,64], has triggered concerted efforts to create comprehensive connectivity maps (connectomes) for various organisms, including humans[65]. Connectome maps, or brain graphs[66], are beginning to reveal topological principles of brain network organization.

Brains have a small-world architecture. In their seminal 'small world' paper, Watts and Strogatz[2] analysed the nervous system of *C. elegans* as a binary graph, in which synaptic connections were rendered as edges between neuronal nodes. This worm brain graph was found to be neither random nor regular in pattern, having both high clustering like a regular lattice and short path-length like a random graph. The short characteristic path-length of connections between neuronal nodes was shown to be equivalent to the high efficiency of information transfer between any pair of neurons[67]. It was recognized immediately that these complex topological properties of the *C. elegans* nervous system are also evident, at different spatial scales of resolution, in many other biological systems, including nervous systems in other species, as well as in non-biological systems such as transport or infrastructural networks.

More recently, graph theoretical tools have been applied widely to networks constructed from different types of human neuroimaging data (structural MRI and fMRI, electroencephalography (EEG) and MEG). There is now strong evidence that human brain networks generally have small-world properties of high clustering and high global efficiency[20], a modular community structure[68–72] and heavy-tailed degree distributions[63,72] that indicate a number of highly connected nodes or hubs[73] (FIG. 2). Many other topological properties have been measured in human brain networks, and numerous studies are devoted to addressing methodological issues in the construction of brain graphs from neuroimaging data[74]. There has also been parallel growth in topological analysis of other, non-human nervous systems[75–77] and

Sparse coding
A type of neural coding that represents information by the activation of a small subset of the available neurons and/or by activation of neurons over a brief instant of time.

Connection density
A topological measure that describes the number of edges in a network as a proportion of the maximum possible number of edges, namely $(N^2 - N)/2$ for an undirected network of N nodes.

Small world
A term used to describe complex networks that have a combination of both random and regular topological properties; that is, high efficiency (short path-length) and high clustering, respectively.

Clustering
A measure of that captures the 'cliquishness' of a local neighbourhood, based on the number of triangular connections between groups of three nodes.

Community structure
The sub-global organization of a complex network. Modularity is an example of community structure, but not all network communities are simply modular.

Heavy-tailed degree distributions
A term that is generally used to mean that the proportion of high-degree nodes (nodes with a large number of edges connecting them to other nodes (hubs)) is greater than that in random graphs.

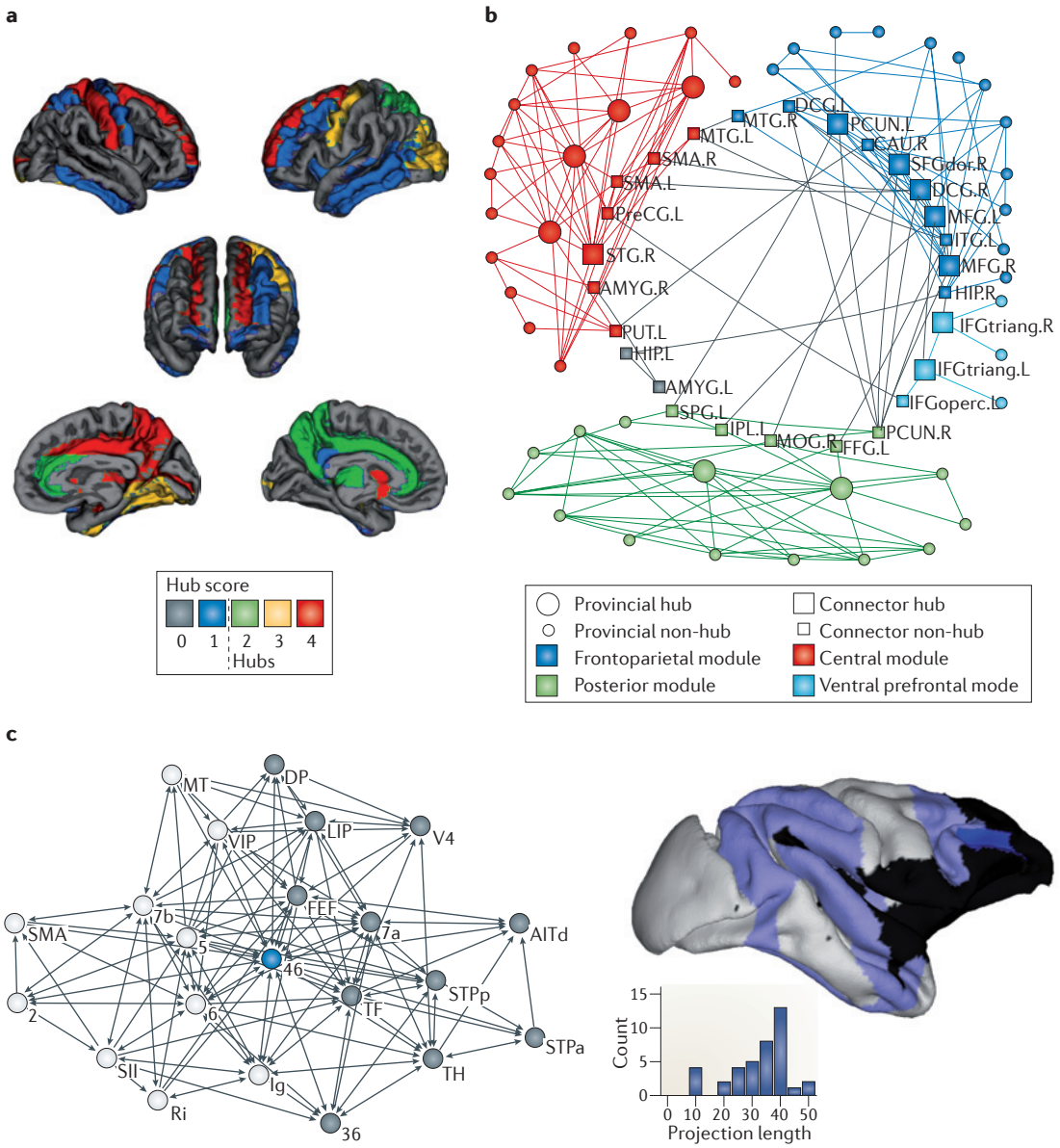
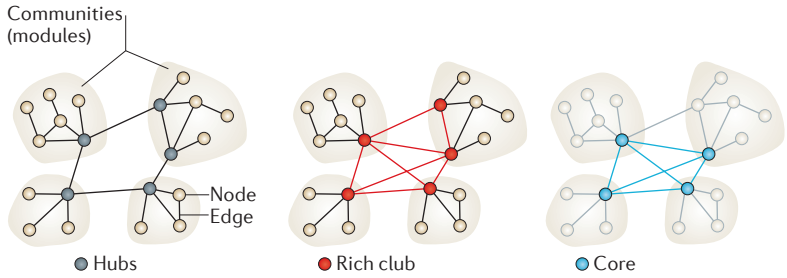


Figure 2 | **Hubs and modules in the brain. a** | In human brain networks, some regions have more connections to the rest of the network, greater clustering, shorter path-lengths and greater betweenness centrality (that is, they mediate a greater proportion of the shortest path connections between other regions). Such regions are called 'hubs' and include parts of medial parietal cortex, cingulate cortex and superior frontal cortex, indicated here by their 'hub score' (regions with a hub score of 2 or higher are defined as hubs). The lab score is based on the ranking of the brain region relative to other regions in terms of numbers of connections, centrality, clustering and path length[139]. **b** | Human brain networks are also modular. Brain regions are colour-coded according to their membership in major modules comprising frontal (dark blue), central (red) and posterior (green) brain regions as well as a smaller module of inferior frontal regions (light blue). The connector hubs, which mediate most of the longer-distance inter-modular connections, are shown as a ring of square markers[107]. **c** | Connector hubs are often regions of multimodal association cortex. For example, Brodmann area 46 (blue circle in left panel; dark blue area in right panel) in the dorsolateral prefrontal cortex of the macaque brain has a large number of long-distance connections (inset) to remote brain areas[73]. The figure shows area 46 as a hub connecting two modules (indicated in white and grey). Part **a** is reproduced, with permission, from REF. 139 © (2010) Society for Neuroscience. Part **b** is reproduced, with permission, from REF. 107 © (2010) Frontiers Media. Part **c** is reproduced from REF. 73. AITd, anterior inferotemporal (dorsal); AMYG, amygdala; CAU, caudate; DCG, middle cingulate and paracingulate gyri; DP, dorsal parietal; FEF, frontal eye fields; FFG, fusiform gyrus; HIP, hippocampus; IFGoperc, inferior frontal gyrus, opercular part; IFGtriang, inferior frontal gyrus, triangular part; Ig, insular cortex (granular); IPL, inferior parietal lobule; ITG, inferior temporal gyrus; LIP, lateral inferior parietal; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; PCUN, precuneus; PreCG, precentral gyrus; PUT, putamen; Ri, retroinsular cortex; SFCdor, superior frontal cortex, dorsal part; SII, secondary somatosensory area; SMA, supplementary motor area; SPG, superior parietal gyrus; STG, superior temporal gyrus; STPa, superior temporal polysensory (anterior); STPp, superior temporal polysensory (posterior); VIP, ventral inferior parietal; .L, left; .R, right.

Box 3 | **Communities, cores and rich clubs**



Network communities consist of groups of densely interconnected nodes, and the existence of several communities is characteristic of modular networks (see the figure). Such modular organization is ubiquitous in biological systems. It is encountered in genetic regulatory and protein-interaction networks, in developmental routines and in the structure of ecosystems. Modularity enables the formation of functional communities and specialization, and is thought to be an important ingredient of evolvability — the capacity of biological systems to generate heritable phenotypic variation[150]. Topologically, modularity refers to the existence of multiple communities of neurons or brain regions as defined by patterns of connectivity: the density of connections is generally greater within a module than between modules. Network modularity can be objectively measured with various graph-based clustering methods[151].

Modules consisting of highly interconnected brain regions often reflect their spatial arrangement[69], such that within-module connections tend to be shorter than between-module connections. This way, spatial modules help to conserve cost related to wiring and communication and improve the local efficiency of specialized neural computations. Computational studies suggest additional advantages of modular organization: modular networks deal more effectively with the increased processing demands imposed by variable environments[152,153], and modularity confers a degree of resilience against dynamic perturbations and small variations in structural connectivity[154]. Hierarchical arrangement of modules further extends these benefits over multiple spatial scales[107].

Although intra-modular edges conserve wiring cost, functional integration between modules requires the addition of high-cost or long-distance axonal projections to interconnect spatially remote brain regions. This gives rise to connector hubs, which receive a disproportionate number of long-distance, inter-modular connections, have a high participation index[155] and occupy a topologically more central or 'potential bottleneck' role in the network, expressed by the extent to which they contribute to short paths across the network[73]. Further analysis of hub regions in cat, monkey and human brains generally reveals an integrated core[64] — or a 'rich club' (see the figure) — of densely inter-connected hubs[130,156,157] that has a central role in generating globally efficient information flow. Several of the concepts introduced in this box are shown (see the figure): network modules linked by sparsely interconnected hubs, which, with the addition of high-cost inter-module connections, form a dense rich club and structural core. In the example shown in the figure, the rich club consists of five nodes with a degree of four or higher, whereas core decomposition (that is, the iterative removal of low-degree nodes, shown here in grey) results in a core network comprising four nodes with a minimal degree of three.

many other, diverse, real-world systems. One idea that has emerged from a high-level synthesis of this spectrum of 'network science' is that the important topological properties shared by many different systems may reflect their formation in response to shared selection pressures[78,79].

Segregation and integration. The combination of high clustering and high efficiency in a modular small-world architecture has seemed attractive as a principle of brain network organization because such a complex network could deliver both segregated and integrated information processing[11,80–84]. In this view, segregated (or specialized) processes, such as aspects of visual-input analysis, would benefit from highly clustered connections between topological neighbours, whereas integrated (or distributed processes), such as executive functions, would benefit from high global efficiency of information transfer across the network as a whole.

Consistent with this idea, it has been found that functionally specialized brain regions typically show high clustering owing to an abundance of connections to other areas with the same functional specialization (for example, visual processing) and in the same anatomical neighbourhood (for example, the occipital cortex). The community structure of brain networks has been described as a set or hierarchy of modules, with each module consisting of a number of densely intra-connected regional nodes, and each node often sharing functional specializations and/or anatomical locations with the other nodes in the same module[69–71,85]. Thus, clustering and modularity are related topological properties that favour specialized or segregated information processing in brain networks (BOX 3; FIG. 2).

By contrast, more integrated processes reflect the global efficiency (or path length) of brain networks. For example, the IQ scores of healthy volunteers were negatively correlated with the characteristic path-lengths of structural and functional networks among regions of the cerebral cortex[86,87]: higher IQs were associated with shorter path-lengths (that is, greater global efficiency). Network efficiency was also predictive of a measure of non-verbal IQ, and there was a significant association between IQ and centrality of nodes in the parietal cortex, consistent with frontoparietal theories of intelligence[88].

These observations are generally consistent with workspace theory[89], which predicts that attending to more-salient stimuli or performing more consciously effortful cognitive tasks depends on the emergence of synchronized oscillations in large ensembles of anatomically distributed 'workspace neurons'[90]. Such an integrated workspace is capable of rapid information exchange between many elements of a globally distributed network. The formation and disintegration of workspaces is thought to be a dynamic process; 'ignition' of an integrated workspace can be triggered by demanding stimuli or tasks, and will disrupt or 'break' modularity and other topological properties that favour more automatic or segregated processing[91,92].

In addition to these analyses of how the topology of brain networks might be related to their cognitive functions, there have been efforts to relate topology to network dynamics[93]. Topological modularity (or near-decomposability) has long been proposed to confer advantages of adaptability or evolvability on diverse information processing systems[94]. For example, recent computational modelling studies have shown that hierarchical or fractal modularity of network topology confers robustness to dynamics when the connections between nodes are reconfigured[95], and that small-world and other biologically realistic topological properties encourage the emergence of complexity[11] and critical dynamics[96]. The idea is that the topology of brain networks enables rapid and robust large-scale

Centrality
A topological measure of the importance or influence of a node or edge for network organization.

Critical dynamics
If a system is dynamically on the cusp of a phase transition between random and regular dynamics, it is said to be in a critical state or demonstrating critical dynamics.

reconfiguration of functional networks in response to exogenous stimuli, and that brain network dynamics are endogenously in a critical state close to a phase transition between regular and random dynamics[97,98]. Such self-organized criticality of brain dynamics is compatible with the power law (or fractal) scaling of 'avalanches' of dynamic synchronization between multiple nodes observed in brain functional networks at cellular and whole-brain scales of physical space[99–101].

Brain networks make cost–value trade-offs

So far, we have provided brief accounts of the evidence that brain networks are both parsimoniously wired and topologically complex. Here, we consider how these two principles can be related to each other. In general, this is a question of understanding how the physical embedding of a network in a three-dimensional space constrains, or is constrained by, its topological properties.

Parsimonious and permissive cost-drives to achieve segregated and integrated topology. The brain is a part of the body, and many features of the spatial arrangement of neurons and brain regions — for example, those involved in sensory and motor processing — reflect the body plan of the organism[102]. Genetically regulated and epigenetic developmental processes, such as cell proliferation, migration and differentiation, not only give rise to body morphology but also to the shape and connectivity of the nervous system[103]. Molecular gradients of attractive and repulsive guidance cues determine the trajectories of growing nerve fibres, confining them to local regions of space or enabling them to link neurons over long distances. The expression levels of genes that are involved in neural development are correlated with synaptic connectivity across individual neurons in *C. elegans,* supporting a mechanistic link between molecular-signalling gradients and network formation[104]. Similarly, in the rodent, brain regions with similar gene expression profiles tend to have similar connection patterns with other regions, and similarity in gene expression partially predicts mutual synaptic connectivity. These relationships are strongest for a set of genes that is involved in neuronal development and axonal guidance[105].

The spatial distribution of molecules that are involved in neural development and the simple physical constraints on axonal outgrowth tend to limit the spatial range of many connections, and this could bias the topology towards high clustering within spatially confined neighbourhoods. In large-scale brain networks, regions in the same topologically defined cluster or module are often also anatomical neighbours. Thus, the topological properties (such as clustering and modularity) that favour segregated processing and rapid reconfiguration dynamics are also parsimonious in the physical sense of low wiring cost[106].

However, the topological property of global efficiency, which favours integrated processing, demands some connections between modules, and such intermodular connections are typically longer than the intra-modular connections between regions within the same module[107]. Long-distance connections in the brain preferentially link to hub regions, and this is often seen in other spatial networks as well[46,66,73]. Although such long-distance connections are costly in terms of energy and volume, they greatly reduce the path-length for information transfer between regions in different modules (compared to the longer path-length of a series of short-distance connections) and hence could provide faster, more direct and less noisy information transfer[37] (BOX 3).

These basic considerations support the idea that brain networks negotiate an economical trade-off between minimizing connection cost and maximizing the value that topological efficiency adds to the integrative processing capacity of the brain. We next discuss empirical evidence that brain networks are indeed organized to satisfy such competitive criteria.

Nervous systems have high network efficiency for low cost. Early studies of the *C. elegans* connectome indicated that it is parsimoniously connected — only comprising approximately 5% of all possible synaptic connections between its 302 neurons — but highly efficient, with ~46% of the maximum possible efficiency of an equivalent random graph[67]. Recently, it was shown that the wiring cost of the *C. elegans* nervous system is not strictly minimized; it could be reduced further *in silico* by a rewiring algorithm that more rigorously minimizes wiring cost by simulated annealing[19,108]. However, the total path-length of these minimally rewired *in silico* networks is greater than that of the actual *C. elegans* network, consistent with the concept of a trade-off in nature between wiring cost and efficiency[19] (FIG. 3).

The *C. elegans* nervous system has been compared to wiring diagrams of very large-scale integrated (VLSI) circuits[109]. The logic of information flow and processing in a VLSI circuit is related to the topological complexity of the wiring between processing elements: a higher topological complexity is associated with more advanced processing capacity, but it also incurs a greater-than-minimum wiring cost[109]. Therefore, a key challenge in circuit design is to find the embedding solution that minimizes, as far as possible, the physical cost of wiring a complex network in a fairly low-dimensional (that is, three-dimensional) space. The study showed that the *C. elegans* connectome shares aspects of topological complexity and spatial embedding with a reference VLSI circuit[109]. Both worm and chip circuits had high-dimensional fractal scaling of connection density that was too complex to be minimally wired, but both circuits were near-minimally wired, given their degree of topological complexity. Other studies have shown that the fractal or Rentian scaling of the connection density in the anatomical human brain network accurately predicts the allometric scaling of grey- and white-matter volume measurements across a wide range of mammalian species[34,109] (FIG. 1). These results suggest that physical information processing systems generally satisfy natural and technological selection criteria for cost-constrained spatial embedding of topologically complex networks.

Simulated annealing
A computer algorithm used to find a good approximation to the global optimum of a function over a large search space.

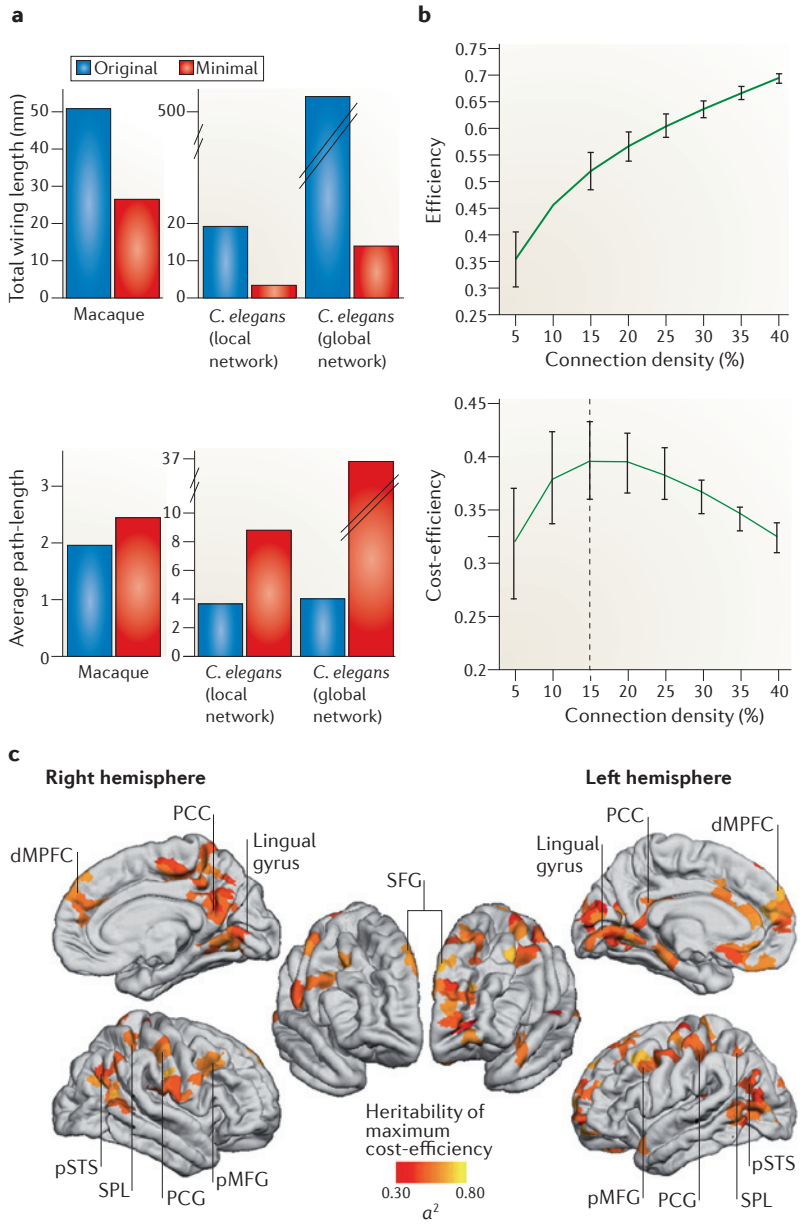


Figure 3 | **Economical trade-offs between wiring cost and topological efficiency of brain networks. a** | The large-scale anatomical network of the macaque monkey can be computationally re-wired to minimize wiring cost (top panel; left side) but only at the expense of increasing path-length (bottom panel; left side). Similarly, the connectome of *C. elegans* can be rewired to minimize connection distance (top panel; right side), but path-length in both local and global networks is increased as a result (bottom panel; right side)[19]. **b** | The global efficiency of functional networks derived from human functional MRI data increases monotonically with increasing connection density (top panel). The difference between efficiency and connection distance (each expressed as a proportion of its maximum value so as to lie in the same numerical range, 0–1) — so-called cost-efficiency — increases as a function of connection density to a maximum (when the networks are about 20% connected) and declines thereafter (bottom panel). **c** | In a twin study, the maximum cost-efficiency was found to be heritable at global and nodal levels: a bilaterally symmetric set of cortical nodes, many of them connector hubs (for example, in medial posterior parietal and dorsal medial prefrontal cortex), had the highest heritability of nodal cost-efficiency[111]. dMPFC, dorsal medial prefrontal cortex; PCC, posterior cingulate cortex; PCG, precentral gyrus; pMFG, posterior middle frontal gyrus; pSTS, posterior superior temporal sulcus; SFG, superior frontal gyrus; SPL, superior parietal lobule. Part **a** is modified from REF. 19. Part **b** is modified and part **c** reproduced, with permission, from REF. 111 © (2011) Society for Neuroscience.

Functional human brain networks, which are derived from fMRI or MEG data, have also shown trade-offs between cost (approximated by connection density or connection distance) and topological efficiency[20,110]. The trade-off between topology and connection cost in functional networks in humans has inevitably been investigated with less precision than is possible for cellular or computational circuits of which the physical wiring is known. Nevertheless, it has been shown that the efficiency of fMRI and MEG networks monotonically increases with increasing connection density (a topological measure of connection cost) and with increasing total connection distance (a spatial measure of connection cost), as is expected for all spatial networks. Fairly sparse fMRI networks — comprising ~20% of all possible connections — typically maximize the efficiency of the network topology in proportion to its connection cost[20] (FIG. 3).

Interestingly, an analysis of the trade-off between connection distance and topological efficiency of fMRI networks measured in a sample of monozygotic and dizygotic twins found that ~60–80% of the variation in the cost–efficiency trade-off was heritable (that is, attributable to additive genetic effects)[111]. This must be regarded as a provisional estimate of the heritability of human connectome phenotypes, given the modest size of the twin samples studied ($N = 16$ monozygotic pairs and $N = 13$ dizygotic pairs). Nevertheless, the results are compatible with the idea that brain networks have been naturally selected to negotiate a trade-off between connection distance (interpreted as a measure of wiring cost) and topological efficiency (FIG. 3).

Economical reconfiguration of functional networks. Most network studies of functional neuroimaging data acquired under resting-state conditions have only considered network topology, connection distance or the relationship between topology and connection cost, as any of these states exists on average over a single extended period of time. In other words, functional network analysis has generally presented a stationary picture of systems that are naturally expected to continuously and sometimes rapidly change configuration over time.

Recently, however, brain functional connectivity and network parameters have also been measured more dynamically: both spontaneously[112] and in response to changing experimental task demands[113], deviant sensory stimuli[114] or progressive learning of a task[115]. For example, during performance of an effortful version of a working memory task, MEG networks emerge with high efficiency and a high proportion of long-distance, inter-modular edges[116]. When cognitive demands were reduced, the networks immediately reconfigured (in the order of tens of milliseconds) with higher clustering, higher modularity and a smaller proportion of long-distance connections. Thus, it seems that the trade-off between efficiency and connection distance can be rapidly renegotiated by functional systems. When there is greater demand for cognitive processing, networks adopt a more efficient but more costly workspace configuration, and when cognitive demand is lower, brain networks 'relax' into a more clustered and less costly lattice-like configuration[116].

Connector hubs
Hubs that mediate a high proportion of inter-modular (often long-distance) connections.

Changes in anatomical and functional brain networks have also been measured over the much longer time period of postnatal development. For example, in a diffusion tensor imaging (DTI) study, adolescence was associated with increasing global network efficiency and reduced clustering of anatomical networks[117], and in an fMRI study in healthy children and adolescents, increasing age was associated with an increasing proportion of long-distance connections in functional networks[118,119]. There is also evidence of changes in the modular community structure of fMRI networks in healthy elderly volunteers compared with younger adults[68]. It is too early to claim that these first few empirical studies of human brain network development support any particular model of what factors drive network formation, or that they define how network development might be related to changes in cognitive function over the lifespan. Further studies are needed to address these issues and to ensure that the potentially confounding effects of age-related differences in head movements are adequately controlled in resting-state fMRI studies of developmental change in functional connectivity and networks[120]. However, one testable hypothesis is that attainment of adult cognitive capacities depends on consolidation of the high-cost, long-distance connections that are necessary to break modularity and that support the emergence of highly efficient networks. In other words, brain networks may continually renegotiate an economical trade-off between cost and efficiency over the course of the lifespan.

Disorders of brain network economy

We know that the cognitive, emotional, perceptual and motor symptoms of chronic brain disorders represent a disruption of normal cognitive or behavioural functions of the brain; that these 'higher-order' functions are normally associated with synchronized oscillations or co-activations of several distributed brain regions (measured by electrophysiological or neuroimaging data); and that there is strong evidence from neuroimaging studies for abnormal connectivity and network phenotypes in many neurological and psychiatric disorders[121,122]. Thus, it appears that many disorders are associated with abnormalities of brain network organization. Next, we discuss what an economical analysis might add to our understanding of these abnormalities in organization.

Cost-related brain network disorders. Because the brain is so expensive to build and run, it is highly vulnerable to any condition that threatens its energy supply. The brain obtains most of its metabolic energy by means of oxidative metabolism of glucose. Thus, if a brain network is subjected to oxidative stress — that is, if it is pathologically prevented from paying the metabolic costs of its activity — we might expect the most metabolically expensive nodes and edges to be particularly sensitive to functional disruption. There is evidence that the metabolic costs of a node are proportional to its degree (the number of edges connecting it to other nodes) and/or its centrality, and that the metabolic costs of an edge are proportional to the physical distance it spans between nodes (FIG. 4). We can therefore predict that brain disorders that are associated with metabolic distress will selectively manifest network abnormalities in high-cost components such as hubs and long-distance connections.

So far, this model of a cost-driven network disorder has been developed most completely for Alzheimer's disease, which is a chronic, progressive neurodegenerative disorder that causes dementia. Alzheimer's disease has been associated with a reduced proportion of long-distance connections[123], greater path-length (that is, reduced network efficiency) and greater clustering[124–126]. This pattern of global network reconfiguration could be described as a shift in the cost–efficiency trade-off in the direction of lowering metabolic connection costs at the expense of losing integrative capacity. It is notable that this disease process has a somewhat selective impact on network hubs. Brain regions that are consistently identified as high-degree hubs in structural and fMRI networks, such as the medial posterior parietal cortex, are also among the first brain regions to show deposition of amyloid-β protein, which is a molecular marker of cellular damage in Alzheimer's disease[127] (FIG. 4). Selective damage to network connector hubs would be expected to have a disproportionate impact on the capacity of the network as a whole for efficient workspace processing, and this could explain the early emergence of cognitive and behavioural symptoms in the course of Alzheimer's disease[124].

In a similar way to which Alzheimer's disease provides a putative example of a pathological process that selectively attacks the most expensive (hub) nodes of a brain network, multiple sclerosis provides an example of a disease process that selectively attacks the most expensive (longest) connections in the network. Multiple sclerosis is a disorder that causes sporadic autoimmune attacks and demyelination of axonal tracts in the brain. The probability that a specific tract will be affected by a focal lesion is proportional to its volume, rendering longer tracts more vulnerable. Accordingly, greater degrees of lesion load are associated with greater loss of topological efficiency owing to greater damage to long-distance axonal projections[128].

These observations suggest that the high-cost elements of brain network organization — the long-distance, inter-modular connections between a 'rich club' of connector hubs[129,130] — are important for adding cognitive value in health but are also points of vulnerability to pathological damage (BOX 3). In other words, the value drivers of economical brain organization are also some of its greatest risks, because they are the most expensive and therefore the most vulnerable to; for example, pathological restriction of metabolic resources. This point is reinforced by computational modelling of neural dynamics in the primate cerebral cortex, which has shown that simulated pathological attacks on high-centrality nodes, which are important for global integration and inter-modular communication, have greater effects on information flow and functional connectivity than attacks on less-central nodes[131,132].

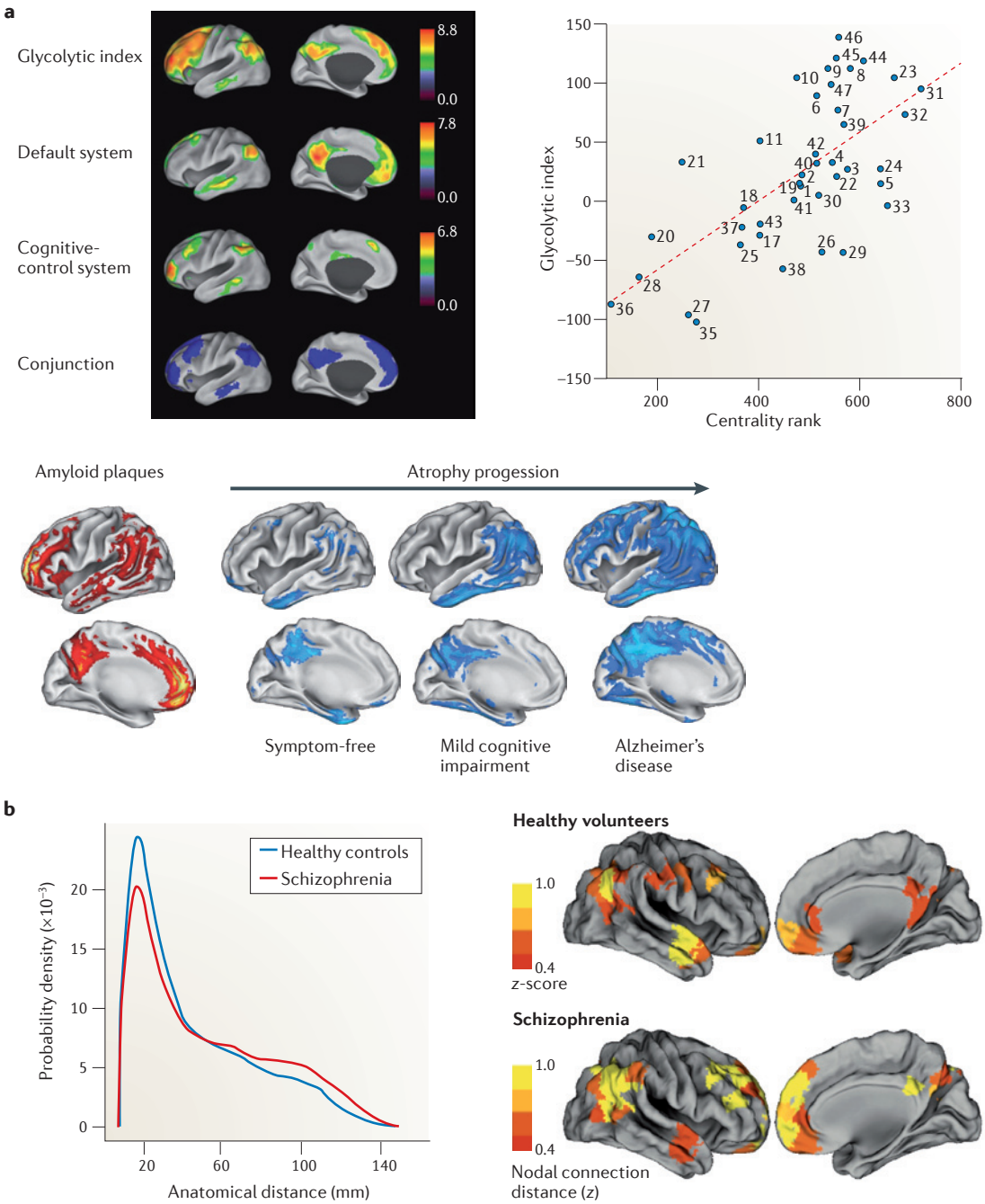


Figure 4 | **Brain disorders affect high-cost components of networks. a** | Brain networks and brain metabolism. The top left panel shows the regional distribution of aerobic glycolysis (as measured using the glycolytic index), the default mode system and the cognitive control system (as mapped by resting-state functional MRI (fMRI)) and the conjunction of these two systems with the glycolytic index, illustrating their overlap[161]. The top right panel shows a scatter plot of the centrality rank (which is estimated from the betweenness centrality of the connectomes of five participants[64]) and the glycolytic index[161] for 41 Brodmann areas of the cerebral cortex. The correlation is highly significant, with $r = 0.66$ ($P < 0.00005$), indicating that areas with high centrality — that is, the structural hubs — have a high glycolytic index[64,161]. Several of these hub nodes are members of the default and cognitive control systems. The bottom panel shows that high-cost hub nodes (including regions comprising the default mode system and the cognitive control system; see top left panel) are typically first affected by amyloid deposition and grey-matter atrophy in Alzheimer's disease, leading to disruption of memory functions that are dependent on large-scale network integrity[162,163]. **b** | fMRI networks in patients with schizophrenia contain proportionally more long-distance connections than fMRI networks in healthy controls (left panel), perhaps owing to excessive developmental pruning of shorter-distance connections. Accordingly, inter-modular connector hubs that have a large number of long-distance connections (indicated by areas with high connection distance in the right panel) are more extensive in functional brain networks of people with schizophrenia than in healthy volunteers[46]. Part **a** is reproduced, with permission, from REF. 161 © (2010) National Academy of Sciences, and from REF. 163 © (2008) New York Academy of Sciences. Part **b** is reproduced, with permission, from REF. 46 © (2012) Oxford Journals.

Developmental brain network disorders. Alzheimer's disease, multiple sclerosis and many other inflammatory, degenerative and vascular disorders typically afflict an adult brain that has developed and functioned normally up to the moment of disease onset. However, there are many other clinical disorders (such as schizophrenia, autism and obsessive–compulsive disorder) that are better understood as the consequence of abnormal brain development, rather than as an adventitious insult or lesion to a normally formed network. The definitive network analysis of such disorders will therefore involve a description of the diagnostic abnormalities at the level of the connectome and an understanding of how these abnormalities could have been generated as an aberrant expression of the normal processes of brain network development. This is a challenging two-part objective, particularly as our current understanding of the generative processes of normal brain network formation is far from complete. However, progress in this strategic direction can be summarized in relation to recent work on schizophrenia.

Schizophrenia is a heritable disorder of brain development that can lead to chronic psychosis and cognitive impairment. Several fMRI studies have reported reduced clustering[133], reduced modularity[134] and preserved or marginally increased global network efficiency[135] in patients with schizophrenia. This profile of results has been described as a 'subtle randomization' of global network topology[136]. At the more fine-grained level of individual network nodes, there is some evidence that high-degree hubs have abnormal topological properties in patients with an established diagnosis of schizophrenia[46] and in 'at risk' individuals with less severe psychotic symptoms[137]. However, it is important to acknowledge that the topological results are not entirely consistent within or between neuroimaging modalities[122,138]; for example, recent DTI data have shown that path length may be increased (that is, the network efficiency is reduced) in schizophrenia[139,140].

There have also been reports of increased connection distance of structural MRI and fMRI networks in schizophrenia[46,141]. These are based on measurements of Euclidean distance between nodes that have correlated grey-matter regional volumes (structural MRI) or correlated time series oscillations (fMRI) and therefore provide no more than an indirect measure of wiring cost. In an MEG study of working memory that measured the ratio between connection distance and topological efficiency as a proxy measure of the network cost–efficiency trade-off, working memory performance was correlated with maximum cost-efficiency (FIG. 3), and people with schizophrenia had both impaired task performance and abnormal network cost-efficiency[110].

One idea that has arisen from these results is that functional networks in schizophrenia are characterized by an abnormal shift in their topological properties and wiring costs. In other words, the schizophrenia connectome can be described as abnormal in terms of how it has negotiated an economical trade-off between topological and physical network properties. As mentioned earlier, in the course of normal adolescent and young adult brain development, there is some evidence for changes in both connection distance and network topology[117,118], implying that a trade-off between these and other network parameters may be renegotiated in the process of normal brain maturation. Thus, it is tenable that abnormal connectomics in patients with schizophrenia emerge developmentally from a biased trade-off between topology and wiring cost over the course of adult network formation. For example, it has been proposed that genetic risks for schizophrenia may bias network formation in the direction of greater robustness (which is a potentially adaptive property) at the expense of greater-than-normal connection cost[135].

Continued efforts to build quantitative models of network formation that can mechanistically link adult connectomics to developmental factors and constraints will be important[18,44,142] in testing such ideas more rigorously. For example, the probability of a functional connection between regions of an fMRI network has been modelled as the outcome of an economical trade-off between a factor that penalizes long-distance connections and a factor that promotes the formation of additional (clustered) connections between nodes that already have one or more nearest neighbours in common[143]. The parameters of this generative model were abnormal when estimated from fMRI data from a group of patients with schizophrenia, indicating the potential to link system phenotypes of neurodevelopmental disorders to a trade-off between spatial and topological parameters of normal network development[143].

Conclusions and future directions

The central idea of this Review is that the brain's connectome is not optimized either to minimize connection costs or to maximize advantageous topological properties (such as efficiency or robustness). Instead, we argue that brain network organization is the result of an economical trade-off between the physical cost of the network and the adaptive value of its topology. Studies of the brain as a topologically complex and spatially embedded network have shown that, like profitable businesses, brains are usually organized to produce high value for low cost. Impairment or loss of cognitive functions with disease can be accounted for by abnormal trade-offs that have an impact on often preferentially the most costly components of the networks that are also the most important for integrative processing and adaptive behaviour.

To be rigorously evaluated, these ideas will demand further experimental and computational testing. It will be important to achieve a greater understanding of the relationships between anatomical and functional networks; in particular, we need to know more precisely how the fundamental concept of wiring cost can be best inferred from human neuroimaging data. It will also be important to investigate further the putative links between topological properties, such as efficiency or robustness, and behavioural advantages, such as cognitive performance, or resilience to ageing or disease. Better knowledge of the cost and value measures of the connectome can then inform more quantitative and formal models of the economical trade-offs that we propose may be conceptually central principles of brain network organization.

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Competing interests statement
The authors declare competing financial interests; see Web version for details.

FURTHER INFORMATION
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