Assessment of system dysfunction in the brain through MRI-based connectomics

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Network-based analysis of structural and functional connections has provided a new technique to study the brains of healthy people and patients with neurological and psychiatric disorders. Graph theory provides a powerful method to quantitatively describe the topological organisation of brain connectivity. With such a framework, the brain can be depicted as a set of nodes connected by edges. Distinct modifications of network topological organisation in the brain have been identified during development and normal ageing, whereas disrupted functional and structural connectivities have been associated with several neurological and psychiatric disorders, including dementia, amyotrophic lateral sclerosis, multiple sclerosis, and schizophrenia. These assessments have improved understanding of the clinical manifestations noted in these patients, including disability and cognitive impairment. Future network-based research might enable indentification of different stages of disorders, subtypes for cognitive impairment, and connectivity profiles associated with different clinical outcomes.

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Introduction

Brain function depends on local processing of information and effective global communication and integration of information. Attempts to comprehensively map the neural connections supporting these interactions—the so-called connectome[1,2]—are motivated by the notion that brain function does not depend solely on the properties of individual regions, but rather emerges from interaction patterns across the entire network.

Present estimates suggest that the human brain consists of about 89 billion neurons, with 1000–10 000 times as many synapses.[3] However, similar to the notion that neurons form a network at the microscopic level, at the macroscopic level large-scale bundles of axonal projections interconnect brain areas and form a macroscopic network of white matter pathways that enable functional communication between distinct, anatomically separated regions of the brain. Recent advances in MRI enable imaging of both the structural and functional connections of this large-scale neural system, thus enabling efficient mapping of connectivity across the entire brain.[4] This approach has led to mapping of developmental trajectories of brain networks and of modification of these networks during normal ageing. Because cognitive and behavioural functions rely on large-scale network interactions,[5] mapping of the structural and functional connectome in the brain will probably help to clarify fundamental pathophysiological aspects of neurological and psychiatric disorders. For example, connectomic approaches lend support to longstanding theories that schizophrenia is a disconnection syndrome,[6,7] and have yielded new insights into the progressive changes associated with neurodegeneration.[8–10]

In this Review, we summarise the methodological aspects related to graph theoretical analysis, the key mathematical framework for much of this research, and provide an up-to-date summary of modifications of brain network topological organisation associated with normal development and ageing, and of how these networks are perturbed in the course of brain disorders.

Measurement of brain connectivity

Brain structural network analyses can be constructed from correlations among grey matter volume measurements in structural MRI data and from quantification of white matter connections with diffusion tensor imaging. This latter technique enables the identification of large-scale white matter pathways in vivo, by measurement of the magnitude and direction of the restricted diffusion of water molecules in brain tissue. Within white matter, the diffusion of water molecules is restricted to the axonal bundles, hindering their movement transverse to the axons. By mapping the diffusion profile at each point in the brain, white matter pathways can be reconstructed from the main direction of diffusion between points. Although early studies using diffusion tensor imaging were focused mostly on the mapping of an individual white matter tract, the specialty of magnetic resonance connectomics aims to map all (measurable) pathways of the human brain and analyse the spatial and topological organisation of the resulting macro description of the connectome (figure 1).[4,11] The brain regions interconnected by these pathways can be defined in various ways (eg, based on acquisition protocol, template choice, etc) and at several resolutions.[12,13]

Although the term connectome was initially invoked to describe structural brain connectivity,[1] it has since been adapted to refer to maps of both structural and functional interactions between brain regions.[14] Although these maps are commonly acquired with MRI, other modalitites—eg, electroencephalography (EEG) and magnetoencephalography—can also be used to measure the functional connectivity in the brain with high temporal resolution,[15] albeit at relatively low spatial resolution. For this reason, whole-brain functional interactions have been assessed most commonly with use of blood-oxygenation-level-dependent functional MRI (fMRI). Such analyses fall into two broad classes: functional connectivity and effective connectivity. Functional connectivity refers to a statistical dependence between haemodynamic signals

recorded from spatially distinct regions of the brain, and is most commonly measured with the correlation coefficient.[16] Effective connectivity refers to the causal effect that one neural system has on another, and is modelled at the neuronal rather than the haemodynamic level of neuronal interactions.[17,18] The connectome is an inherently directed network (ie, activity in one region effects changes in another region); therefore, modelling of connectome dynamics is desirable,[19] particularly because some measures of functional connectivity that are based purely on time series derived from fMRI (haemodynamic) data can represent simplified (undirected) approximations that distort the true functional architecture.[18] Techniques such as dynamic causal modelling for fMRI explicitly

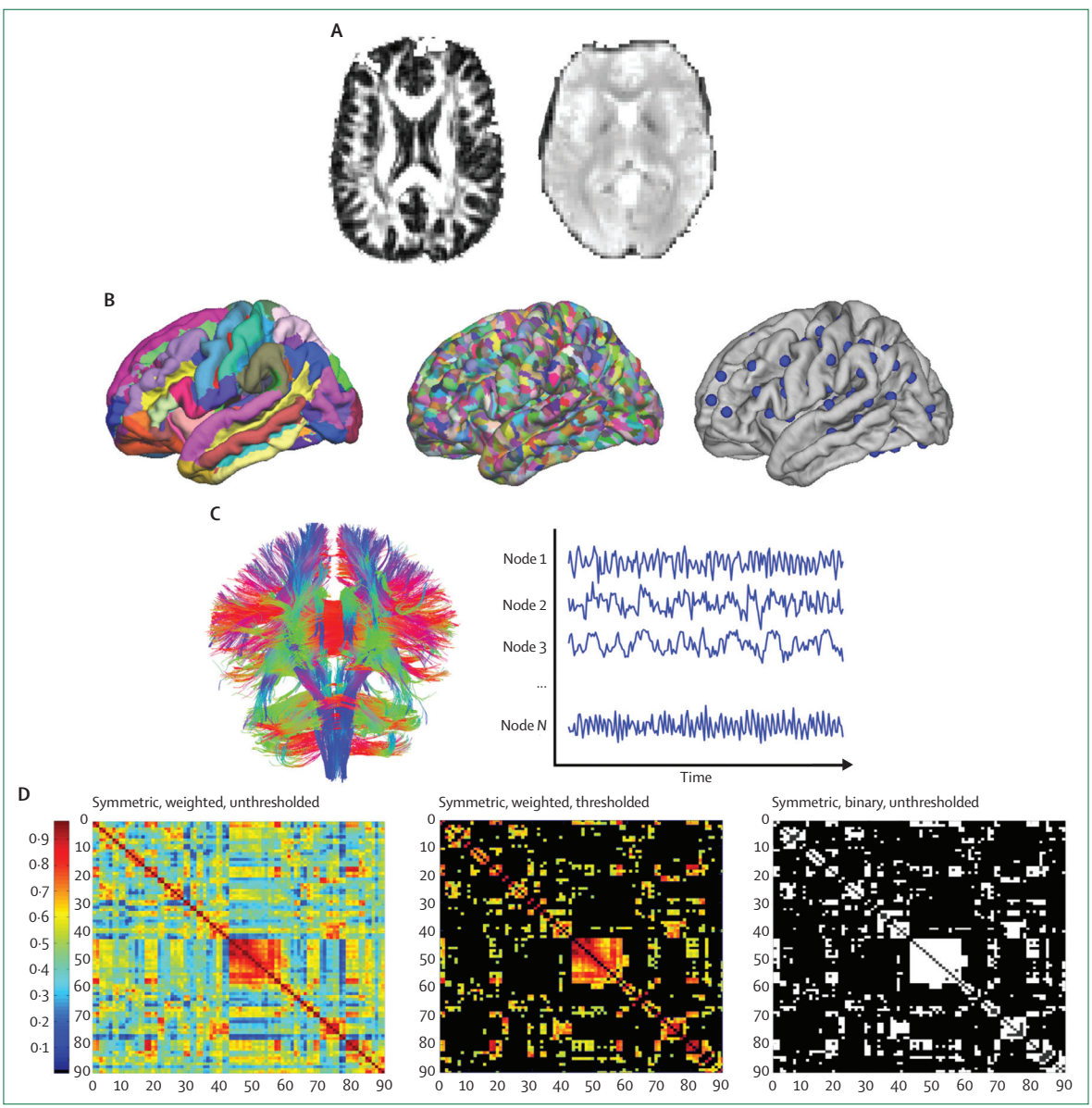

Figure 1: **Illustration of how a connectomic map is generated with MRI**
(A) Maps of anatomical connectivity can be generated with diffusion tensor imaging (left); maps of functional connectivity can be generated with fMRI (right). (B) Network nodes, corresponding to different brain regions, are identified by division of the brain into sections with a range of strategies—eg, a priori anatomical templates (left), random division (middle), and functionally defined regions of interest (right). (C) After definition of brain regions, inter-regional connectivity is typically measured with either whole-brain tractography for diffusion tensor imaging (left) or analysis of statistical dependencies in regional-activity time courses for fMRI (right). (D) After some measure of connectivity has been calculated for every pair of brain regions, connectome architecture can be represented by a connectivity matrix encoding the strength and type of connectivity between each regional pair. In MRI studies, these matrices are typically symmetric (ie, connections are undirected), weighted (ie, variations in the strength of inter-regional connectivity are captured), and unthresholded (ie, the values are continuous, with few zero entries; left). A threshold is usually applied to distinguish real from spurious connections (middle), and to binarise the resulting matrix to encode the presence or absence of a connection (right). fMRI=functional MRI. Figure adapted from Fornito and colleagues,[7] by permission of Elsevier.

model the neuronal changes that cause the haemodynamic signals,[20,21] but are computationally intensive and have traditionally been applied only to small subnetworks of brain regions. Recent advances in dynamic causal modelling, which enable modelling of stochastic neural dynamics,[22] and efficient methods to select the best model from a wide range of candidates[23] hold promise for the application of these techniques to large-scale networks. However, at present diffusion imaging cannot differentiate between afferent and efferent anatomical connectivity. Another important distinction in functional connectomics is made between resting-state and task-related functional connectivity.[19] Resting-state functional connectivity is assessed as participants lie in the scanner without engaging in an explicit task; task-related functional activity refers to task-induced changes in brain network dynamics. Isolation of task-related functional connectivity needs consideration of how task stimuli modulate brain activity.[24]

Analysis of the connectome with graph theory

Once connectivity between brain regions has been determined, a formal description of the network is needed to express its local and global properties (figure 1). A neural network can be described with graph theory as a graph (*G*), consisting of a collection of nodes (*V*), such as brain regions, and connections or edges (*E*), expressing the interactions between the nodes (structural or functional connections, figure 2). On the basis of such a formal description of a neural network, constructs from graph theory can be used to describe several properties of the network's architecture. Commonly examined graph metrics in brain connectomics include degree, clustering, global efficiency, and modularity. The degree of a node (or nodal strength in a weighted graph when information about the strength of the connections is included; figure 2) is defined as the node's number of connections, and provides a metric of the effect that a node has on the overall network infrastructure. Nodes with high degrees and an overall central position in a network's topological organisation are often described as hubs. The level of clustering or local efficiency expresses the level of local connectedness of a network, with high levels of clustering interpreted as high levels of local organisation of the network (figure 2). In addition to clustering, the level of modular organisation expresses a network's community structure, often interpreted as a metric of information segregation in neural networks. Furthermore, the level of global efficiency, calculated as the inverse of the number of steps (ie, shortest path length) needed to travel between each pair of nodes in the network, expresses the efficacy of the network to communicate between its remote parts (ie, the degree to which inter-regional communication is globally integrated; figure 2).

Findings of imaging studies examining the connectivity structure of the human brain have shown several aspects that contribute to efficient communication architecture, including economical (ie, sparse, low-volume, and thus low-cost) wiring, high levels of local clustering and community formation (indicative of local neural segregation), and short path lengths (suggestive of the ability to efficiently integrate information between subparts of the system, together with the formation of a small set of centrally placed communication hubs). This economical yet efficient communication architecture is crucial for healthy brain function,[25] is under genetic control,[26,27] and has an important role in cognitive abilities.[28] Conversely, disruption to the wiring of the connectome probably affects both network topological organisation and function.

The accuracy of any attempt to model the connectome will be affected by the inherent limitations of the imaging techniques used.[29–31] For example, fibre tracking based on diffusion-weighted imaging (in particular, diffusion tensor imaging) is hindered at points where information about white matter directionality is scarce (such as where several tracts cross), resulting in an incomplete reconstruction of tracts and a general under-represention of long-distance connections in the brain. Under-representation of long-range brain tracts, leading to a sparse brain network, probably affects computed graph metrics such as local clustering and the computation of the shortest path length between nodes. High-angular-resolution diffusion-imaging approaches, involving the acquisition of many diffusion directions, might overcome some of these difficulties, but the long acquisition times (>10 min) needed for these types of diffusion scans reduces their usefulness in a clinical setting. Additionally, fMRI studies of connectome dynamics can be affected by head motion,[32,33] physiology,[34] preprocessing choices,[35] the measure used to quantify functional connectivity,[16,36] and differences in mental state.[37] Thus, the available imaging

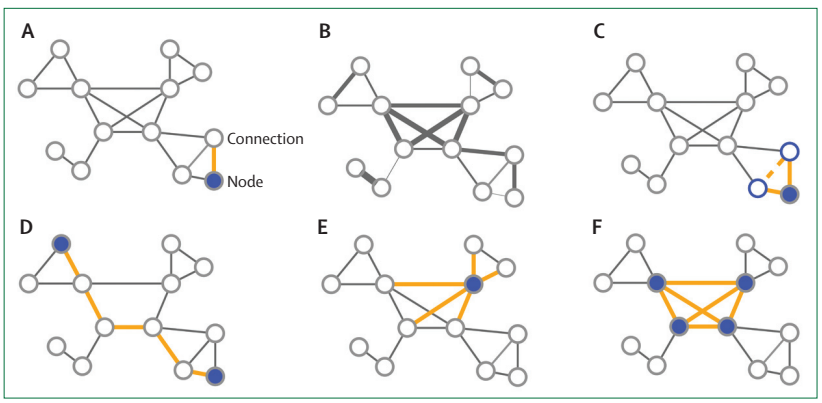

Figure 2: **Summary of the main measures estimated with graph analysis**
(A) A graph is a mathematical description of a network, consisting of a collection of nodes and connections. (B) A weighted graph includes information about the strength of the connections. (C–F) Local and global metrics can provide insight into the topological organisation of a network. (C) The clustering coefficient describes the tendency of nodes to form local triangles, providing insight into the local organisation of the network. (D) The shortest path length describes the minimum number of steps needed to travel between two nodes, and provides insight into the capacity of the network to communicate between remote regions. (E) The degree of a node describes its number of connections. The existence of a small set of high-degree nodes with a central position in the network can suggest the existence of hub nodes. (F) High-level connectivity between hub nodes can suggest the existence of a central so-called rich club within the overall network structure.

techniques for characterisation of connectome structure and brain dynamics remain approximations that should be interpreted with respect to their limitations.[19]

Graph theoretical models of brain connectivity

Normal development

The definition of the trajectories of maturation and ageing for functional and structural topological organisation networks in the brain in healthy individuals is an essential step to understand age-specific expression of neurological and psychiatric disorders.

Graph theoretical methods have been applied to resting-state fMRI data from healthy people aged 7–31 years to investigate the maturation of control networks (which have a role in attentional control) and default mode networks (which contribute to internally directed mental activity).[38,39] In children, the control network was more integrated than was that of adults and was made up of a single system, by contrast with the adult configuration, which was characterised by a dual-network structure consisting of cingulo-opercular and frontoparietal networks. In other words, children have less between-network segregation and more within-network connectivity than adults. The default mode network, which contains a set of regions usually deactivated during goal-oriented tasks, was only sparsely connected in children, whereas adults had a cohesive, integrated network; nearly all developmental changes in correlation strengths among default mode network regions were increased and mainly occurred in an anterior–posterior orientation. By contrast, the developmental pattern of the control network resulted in both increases and decreases in different regions. The same investigators studied the development of whole-brain functional networks in 8–25 year olds.[40] They noted that, although the modular structure was built from 8 years of age, the modules changed substantially from being in anatomical proximity to a distributed architecture, which grouped regions mainly by their functional roles. Additionally, an optimised small-world structure (characterised by high clustering coefficients and short path lengths) was present and conserved through development, suggesting that the functional networks in children were as efficient for both global and local information transfer as were those in adults. These findings have been replicated by another study of resting-state fMRI,[41] which also showed significantly decreased subcortical-cortical connectivity and increased cortico-cortical connectivity in the developing brain. The findings of both these studies showed increased long-range connections and decreased short-range connections, which provides crucial evidence for segregation and integration processes at a system level during brain development. Similar findings were obtained with EEG.[42]

Intriguingly, patterns in resting-state functional connectivity, extracted by multivariate analysis based on support-vector machines (learning modules with associated learning algorithms that analyse data and recognise patterns), can be used to make accurate predictions about individuals' brain maturity across development.[43] With analysis of more than one voxel at once, multivariate pattern analysis can help to differentiate groups (eg, patients from healthy controls) at an individual level, thus complementing the findings of previous studies of group-level statistical analysis. Hwang and colleagues[44] reported that hub locations and architecture were consistent from 10 to 20 years of age, whereas substantial changes occurred to the connectivity linking hub and non-hub regions during this time. The effects of sex differences on whole-brain functional networks have been explored in healthy children aged 6–18 years;[45] boys had higher global efficiency and shorter path lengths than did girls, with regional differences located mainly in the default mode network, language, and visual areas. This finding is consistent with the notion that cognitive and emotional development differs between girls and boys, particularly in visuospatial, language, and emotion processing areas of the brain. Findings from a study of 12-year-old monozygotic and dizygotic twins showed that global network efficiency was under genetic control.[46] Functional brain networks in infancy were also studied.[47] 2-week-old infants have only primitive and incomplete default mode networks, whereas, after a substantial increase in connectivity, the default mode network at 2 years of age is similar to that of adults. Whole-brain functional networks in the infant brain already have functional hubs, located mainly in primary sensory and motor areas, which are distinct from the hub distribution of adults in the heteromodal association cortex (figure 3).[47] Findings from another study of resting-state fMRI showed that functional brain networks had small-world topological organisation immediately after birth, and that network efficiency and resilience substantially improved up to 2 years of age.[48]

The development of structural brain networks has also been investigated. Although the brain structural networks of 2-month-old infants already have economic, small-world topological organisation and non-random modular organisation, network efficiency and modularity significantly increase with development; by 2 years of age, the pattern is similar to that of adults.[49] Raznahan and colleagues[50] proposed a new method to measure the maturation of structural networks by computation of inter-regional correlations of rates of anatomical change, on the basis of structural analysis of longitudinal MRI data from the developing brain. The structural maturational network showed a default mode network and sex differences within a frontopolar-centred prefrontal system (implicated in complex decision making). Girls had increased connectivity between the frontopolar prefrontal system and the dorsolateral and ventrolateral prefrontal cortex compared with boys. With use of diffusion tensor imaging tractography, the white matter structural network showed small-world

architecture and modular structure at birth. During development from 2 months to 2 years of age, the brain network increased in efficiency and evolved progressively from a local connectivity pattern to a distributed and functionally based connectivity pattern, with significantly increased fibre length.[51] A study of developmental changes in children aged 18 months to 18 years investigated the late development of white matter networks.[52] The researchers reported that global network efficiency and nodal strength (ie, the total level of connectivity of a node) significantly increased and clustering decreased with development up to 18 years of age, whereas small-world architecture, major structural modules, and hubs were in place by 2 years of age. Another diffusion tensor imaging study[53] that included 439 individuals aged 12–30 years showed that clustering and modularity decreased, and global efficiency increased, between 12 and 30 years of age, suggesting that networks increasingly integrate during development. Moreover, fibre density decreased disproportionately overall across different brain regions: the frontal cortex had a disproportionate number of decreases whereas the temporal cortex had a disproportionate number of increases.

Normal ageing

Functional and structural MRI studies of the effects of ageing on brain topological organisation have provided consistent and reproducible results. Data from resting-state fMRI has shown that ageing results in changes in the balance of the network's cost of wiring (the number of edges or connections in the network) and communication efficiency (defined as the minimum path length between regions) in older people, with detrimental effects located mainly in the frontal and temporal cortical and subcortical regions.[54] Findings from another study[55] showed that the resting-state functional connectivity of both the default mode network and the dorsal attention network decreased with ageing, and that long-range connections were more susceptible to ageing effects than were short-range connections. Other investigators also showed a decrease in default mode network connectivity (eg, in the precuneus and posterior cingulate regions) with ageing. Findings from a study with support vector machines[56] identified modifications of connectivity in the sensorimotor and cingulo-opercular networks as distinguishing characteristics of age-related reorganisation.

Findings of studies examining ageing effects on the topological properties of structural networks showed that the economical small-world and modular structure was consistent across ages (18–80 years). The local efficiency decreased at first but then increased, whereas global efficiency increased then decreased with ageing.[57] Additionally, elderly people had lower nodal centrality for several brain regions, including the hippocampus, insula, posterior cingulum, and transverse temporal gyrus.[58] The modular structure of structural covariance networks tends to become segregated with ageing.[59]

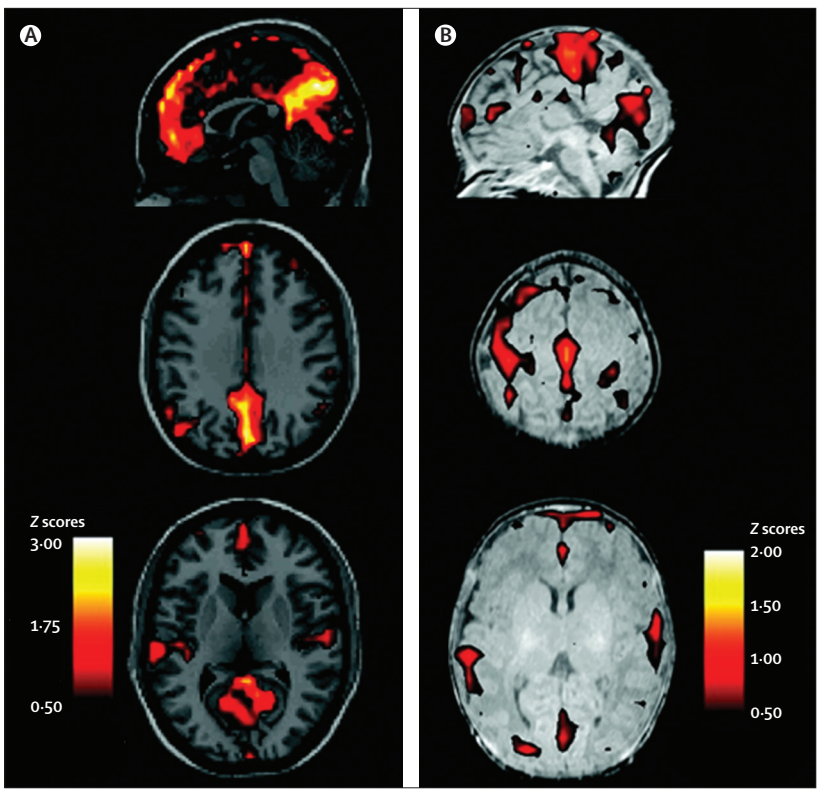

Figure 3: **The pattern of hubs in adults and infants**
The spatial distribution of candidates for cortical hubs in adults (A) and infants (B), based on the degree centrality measure (expressed as *Z* scores). Cortical hubs were mainly located in the heteromodal association cortex in adults—eg, the ventrolateral and posterior medial parietal cortex, medial prefrontal cortex, the insular region, and the temporal cortex. In infants, most cortical hubs were located in the homomodal cortex (particularly in the auditory, visual, and sensorimotor areas), and to a lesser extent in the prefrontal cortex. Figure adapted from Fransson et al,[47] by permission of Oxford University Press.

Findings from a study[60] of diffusion tensor imaging showed that structural covariance networks kept the small-world and hub patterns through the ageing process from 19 to 85 years, whereas local efficiency decreased and the overall connectivity reduced. Sex effects on both global and regional properties were also detected. Age-related decreases in global efficiency correlate with decreases in specific cognitive abilities, including processing speed and visuospatial and executive functions. Decreases in local clustering coefficients (local interconnectivity) in the precuneus, medial orbitofrontal cortex, and lateral parietal cortex are accelerated in carriers of the *APOE*ε4* allele.[61]

Neurodegenerative disorders

Many neurological and psychiatric disorders can be described as disconnectivity syndromes, because their symptoms and clinical manifestations can be related to disrupted integration of spatially distributed regions of the brain that are part of large-scale networks subserving specific functions. Therefore, the use of graph theory might provide new ways to characterise groups of patients and disorders.

Alzheimer's disease and other dementias

Many studies have used graph theoretical analysis in patients with Alzheimer's disease, the most prevalent type of dementia. The site of amyloid β deposition in patients with Alzheimer's disease correlates with the location of major hubs, as defined by graph theoretical analysis of functional connectivity in healthy adults.[62] These regions include the posterior cingulate cortex and precuneus, the inferior parietal lobule, and the medial frontal cortex, suggesting that hubs are preferentially affected in the progression of Alzheimer's disease (figure 4).[62] Furthermore, convergent evidence from methodologically disparate studies using MRI or EEG and magnetoencephalography suggests that Alzheimer's disease is associated with perturbations of the organisation of small-world networks in the brain.[63–67]

Findings from a study of fMRI graph analysis in mild Alzheimer's disease[65] suggest that loss of small-world network properties might provide a clinically useful diagnostic marker; clustering was reduced at a global and local level (in both hippocampi), and global clustering could be used to discriminate between patients with Alzheimer's disease and healthy elderly people, with a relatively high sensitivity (72%) and specificity (78%). The investigators of an fMRI study[64] reported that the characteristic path length in brains of patients with Alzheimer's disease was closer to theoretical values of random networks than to those of controls. Decreased functional connectivity in the parietal and occipital regions and increased connectivity in the frontal cortices and corpus striatum were also reported.[64] Decreased global efficiency and increased local efficiency were reported in patients with moderate Alzheimer's disease, with the altered brain regions located mainly in the default mode network, temporal lobe, and subcortical regions.[68]

Abnormal topological properties have been described in the structural brain networks of patients with Alzheimer's disease with use of structural imaging techniques.[63] Compared with controls, patients with Alzheimer's disease had increased global clustering and path lengths, in addition to decreased centrality (the number of shortest paths between any two nodes that run through a given node) of the classic hubs (ie, the temporal and parietal heteromodal cortices), and increased centrality of the unimodal association cortex (ie, the lingual gyrus, lateral occipitotemporal gyrus, and paralimbic regions). The global clustering coefficient and path lengths of structural networks in individuals with mild cognitive impairment were intermediate between those of patients with Alzheimer's disease and healthy elderly controls.[69] Additionally, compared with controls,

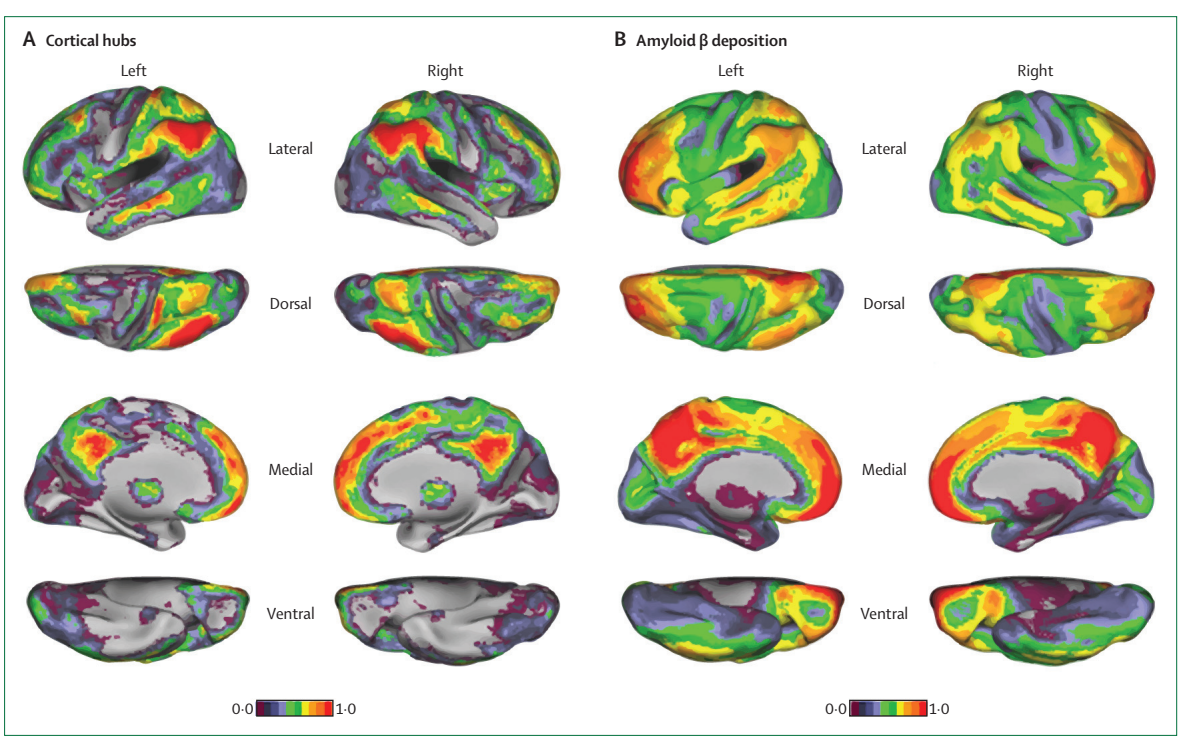

Figure 4: **Cortical hubs shown by functional connectivity, and their relation to Alzheimer's disease**
(A) Spatial location of cortical hubs from 127 healthy individuals, as defined by graph analysis of fMRI data. Prominent hubs are located in the posterior cingulate, lateral temporal, lateral parietal, and medial or lateral prefrontal cortices. The colour bar shows the *Z* score of degree. (B) The pattern of amyloid β deposition in patients with Alzheimer's disease. Amyloid β deposition was measured with use of Pittsburgh-compound-B PET, and is plotted on the cortical surface. The colour bar shows the extent of amyloid β deposition expressed as *Z* scores. Regions showing high functional connectivity mostly overlap with those showing amyloid β deposition in patients with Alzheimer's disease. Figure adapted from Buckner et al,[62] by permission of the Society for Neuroscience.

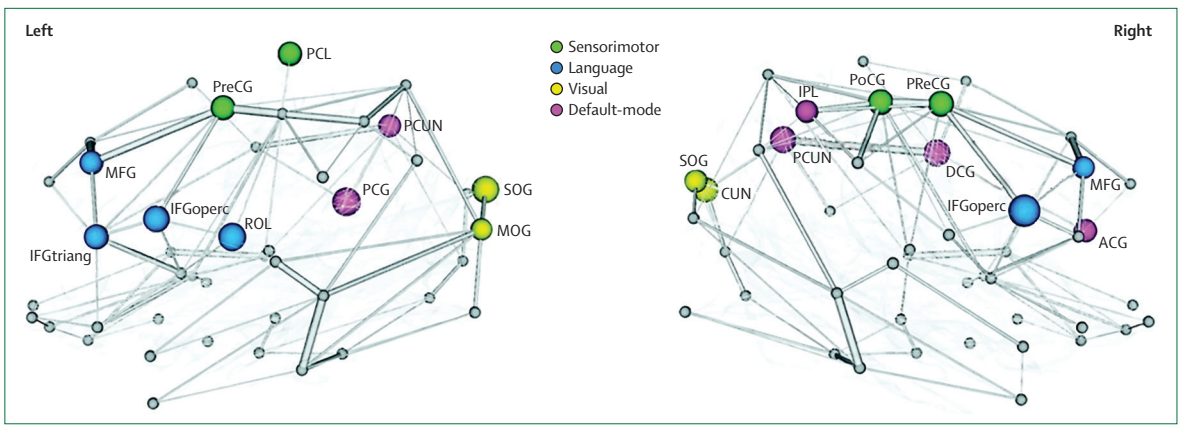

Figure 5: **Brain regions with substantially reduced efficiency in patients with multiple sclerosis**
Regions can be categorised into four functional systems: nodes in green are within the sensorimotor system, including the bilateral PreCG, right PoCG, and left PCL; nodes in yellow are within the visual system, including the bilateral SOG, right CUN, and left MOG; nodes in pink are within the default mode system, including the left PCG, bilateral PCUN, right ACG, right DCG, and right IPL; and nodes in blue are within the language system, including the bilateral IFGoperc, left ROL, left IFGtriang, and bilateral MFG. All brain regions showed reduced regional efficiency at p<0·05 (corrected for false discovery rate). The node sizes show the significance of between-group differences in the regional efficiency. The network shown here was constructed by averaging the anatomical connection matrices of all healthy controls. The nodal regions are located according to their centroid stereotaxic coordinates. The edge widths represent the connection weights between nodes. PreCG=precentral gyrus. PoCG=postcentral gyrus. PCL=paracentral lobule. SOG=superior occipital gyrus. CUN=cuneus. MOG=middle occipital gyrus. PCG=posterior cingulate gyrus. PCUN=precuneus. ACG=anterior cingulate and paracingulate gyri. DCG=median cingulate and paracingulate gyri. IPL=inferior parietal but supramarginal and angular gyri. IFGoperc=inferior frontal gyrus (opercular part). ROL=rolandic operculum. IFGtriang=inferior frontal gyrus (triangular part). MFG=middle frontal gyrus. Figure adapted from Shu et al,[80] by permission of Oxford University Press.

patients with Alzheimer's disease or mild cognitive impairment retained their hub regions in the frontal lobe but not in the temporal lobe.[69] Increased inter-regional correlations within the local brain lobes and disrupted long-distance inter-regional correlations were also detected in these patients.[69] In patients with Alzheimer's disease, abnormal patterns of white matter connectivity have been associated with cognitive deficits.[70]

Graph theoretical analysis has also been used to analyse resting-state fMRI data from patients with the behavioural variant of frontotemporal dementia.[71] Global and local functional networks were altered in these patients, as suggested by reduced mean network degree, reduced clustering coefficient and global efficiency, and increased path length compared with healthy controls. Altered brain regions were located in structures that are closely associated with neuropathological changes in patients with the behavioural variant of frontotemporal dementia, such as the frontotemporal lobes and subcortical regions. Overall, these findings lend support to the theory of the selective susceptibility of large-scale brain networks in neurodegenerative disorders.[8]

Amyotrophic lateral sclerosis

Consistent pathology of motor and extramotor regions of the brain lends support to the notion of amyotrophic lateral sclerosis as a system failure. Overall functional organisation of the motor network (left and right precentral cortex) was unchanged in patients with amyotrophic lateral sclerosis compared with healthy controls, but the level of functional connectedness correlated with the rate of disease progression—ie, patients with a stronger and more interconnected motor network had a more progressive disease course.[72]

The effects of amyotrophic lateral sclerosis on structural brain topological organisation have been assessed with diffusion tensor imaging and graph theoretical analysis.[73,74] Although the organisation of the global brain network was intact in patients with amyotrophic lateral sclerosis, an impaired subnetwork of regions with reduced white matter connectivity was detected;[73] these were centred on primary motor regions but also included secondary motor regions (frontal cortex and pallidum) and high-order hub regions (posterior cingulate cortex and precuneus). More recently, findings from a longitudinal study[74] have shown no progressive impairment of the initially affected (motor) connections, but a propagating subnetwork of affected brain connections over time, with a central role for the primary motor regions.

Multiple sclerosis

Consistent with the known multifocal distribution of structural damage to the CNS, patients with multiple sclerosis have a distributed pattern of abnormalities in resting-state functional connectivity, which are related to the extent of T2 lesions and the severity of clinical disability.[75] Few studies have applied graph analysis methods to analyse structural and functional alterations in these patients.

With use of data from resting-state fMRI and magnetoencephalography, male patients with multiple sclerosis were shown to have reduced network efficiency but normal clustering coefficients, compared with male

controls.[76,77] These abnormalities were not detected in female patients. Decreases in network efficiency in male patients were correlated with reduced visuospatial memory.[76,77] Patients with multiple sclerosis can be discriminated from healthy controls by use of a pattern recognition technique based on resting-state functional connectivity, with a sensitivity of 82% and specificity of 86%.[78] The most discriminative connectivity changes were in the subcortical and temporal regions, and contralateral connections were more discriminative than were ipsilateral connections.

A graph theory study into correlations of measures of cortical thickness from a large cohort of patients with multiple sclerosis showed disrupted efficiency in small-world networks, which was proportional to the extent of white matter T2 lesions.[79] Decreased regional efficiency in the insula, precentral gyrus, and associative prefrontal and temporal cortices was also detected, lending support to the notion of multiple sclerosis as a disconnection syndrome. With use of diffusion tensor tractography, disrupted topological efficiency has been detected in white matter structural networks of patients with multiple sclerosis, with a reduction of the global and local network efficiency.[80] The most pronounced changes in this study were identified in the sensorimotor, visual, default mode network, and language areas (figure 5). Such modifications of structural connectivity have been detected in patients with relapsing-remitting multiple sclerosis within 2 years of clinical presentation.[81] In these patients, loss of network communicability (the total number of all possible paths between two nodes) affected the frontal and hippocampal regions, motor strip, and occipital lobes, and was correlated with deficits in walking. Notably, increased communicability between

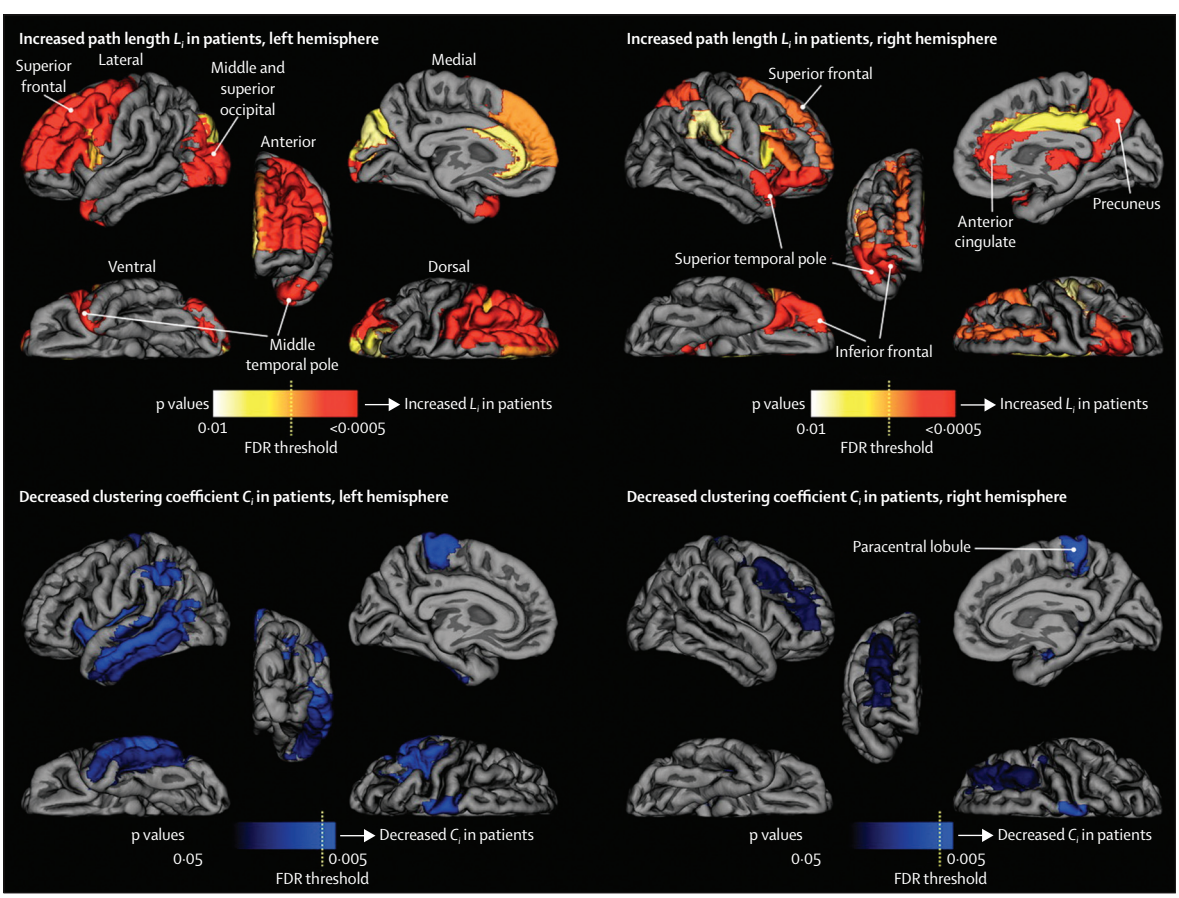

Figure 6: **The structural brain network in schizophrenia**
Group differences in structural brain connectivity between healthy controls and patients with schizophrenia, based on magnetisation transfer ratios and images from diffusion tensor imaging. Upper figures show p values of significant between-group increases in L_i, the average distance from node *i* to every other node in the network (corrected for within-group connectivity strength, S_i), with increased L_i values in olfactory, medial and superior frontal, occipital, and medial temporal pole regions of the brain in patients with schizophrenia compared with brain networks of matched healthy controls. Lower figures suggest significantly decreased values for the node-specific clustering coefficient, C_i, in patients with schizophrenia, with significantly decreased clustering coefficient in the right paracentral lobule and right hippocampus. The L_i effects, together with the low number of C_i effects, suggest that patients with schizophrenia might have less global integration of structural brain network than do controls, with a reduced central role for key frontal hubs resulting in a reduced structural capacity to integrate information across brain regions. Yellow dotted lines express the critical FDR threshold (q=0·05). FDR=false discovery rate. Figure adapted from van den Heuvel et al,[25] courtesy of the Society for Neuroscience.

deep grey matter nuclei and the major interhemispheric and intrahemispheric tracts was also detected, which might result from compensatory changes.

Schizophrenia

Evidence is accumulating that neural network changes underlie structural and functional brain changes in psychiatric disorders, and might provide a more sensitive measure to detect brain abnormalities than those provided by measurements of structural and functional properties of separate brain areas alone.[25,82] The potential application of network approaches to psychiatry are shown by research in schizophrenia, a severe psychiatric disorder that has long been hypothesised to result from a disconnection syndrome. Wernicke[83] first proposed that schizophrenia might involve disruption of the brain's association fibres. However, only with the advent of in-vivo imaging, particularly after early studies using PET, was experimental evidence for this hypothesis identified.[84,85] In parallel with similar trends in other disorders,[86] this work led to the development of formal disconnectivity hypotheses for schizophrenia.[6,87] Subsequent research suggested a potential structural basis for these abnormalities.[88] With use of connectome reconstruction and analysis, findings of several structural and functional studies have shown network disruptions in patients with schizophrenia. Functional studies of both resting-state and task-related functional connectivity,[89,90] in addition to investigations using EEG,[91] have shown clear reductions in the overall level of functional coupling in patients with schizophrenia, a deficit that is particularly severe for assumed hub regions located in the prefrontal cortex.[89] Consistent with these functional findings, investigators of structural connectome studies reported disruptions of the connectome, with longer communication pathways[92,93] and fewer central hubs in the brain networks of patients with schizophrenia than in those of controls (figure 6).[25] Generally, these findings suggest that schizophrenia might involve a reduced global integration of structural brain networks and a reduced role for key frontal and parietal hubs in the overall network architecture, in turn leading towards diminished capacity to integrate information across different regions of the brain.[7,25] In line with such a hypothesis of reduced integration, reduced connectivity has been shown between brain network hubs, together with decreased coupling between structural and functional connectivity, in patients with schizophrenia.[94] Thus, more than a century after Wernicke's original ideas about schizophrenia, the pathophysiology is being substantiated by imaging connectomics.

Conclusions and future directions

Graph theoretical approaches have defined network topological organisation in both healthy and diseased brains to characterise the structural and functional abnormalities associated with different neurological and psychiatric disorders, and to test hypothesised effects of disconnectivity in these diseases. Patients with neurological and psychiatric disorders have disrupted connectivity in functional and structural networks in the brain, which might explain some of the clinical manifestations of these diseases, including global disability and cognitive impairment. However, findings from studies are inconsistent, possibly as a result of the clinical heterogeneity of the patient groups and differences in imaging and analytical methods. Future network-based research might be used to identify different stages of the different diseases, subtypes for cognitive impairments, and connectivity profiles associated with different clinical outcomes.

Challenges for the specialty of MRI-based connectomics include development of improved measures and models of the directed, weighted, and signed structure of brain connectivity, and of accurate techniques to define appropriate parcellations of the brain.[19,95] Imaging techniques to improve the biological validity of measures of structural connectivity,[96] and the temporal precision of fMRI for sampling of functional dynamics,[97] are also needed.

Contributors

MF and GC drafted the introduction and conclusions. MPvdH and AF drafted the methodological section. YH drafted the sections on normal development and ageing. HEHP drafted the section on psychiatric conditions. FA drafted the section on neurodegenerative diseases. MAR drafted the section on multiple sclerosis. All authors revised the Review for important intellectual content and gave approval of the submitted version.

Conflicts of interest

MF serves on scientific advisory boards for Teva Pharmaceutical Industries and Genmab A/S; has received funding for travel from Bayer Schering Pharma, Biogen Idec, Genmab A/S, Merck Serono, and Teva Pharmaceutical Industries; serves as a consultant to Bayer Schering Pharma, Biogen Idec, Genmab A/S, Merck Serono, and Teva Pharmaceutical Industries; serves on speakers' bureaus for Bayer Schering Pharma, Biogen Idec, Genmab A/S, Merck Serono, and Teva Pharmaceutical Industries; and receives research support from Bayer Schering Pharma, Biogen Idec, Genmab A/S, Merck Serono, Teva Pharmaceutical Industries, the Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and Cure PSP. FA has received research support from the Italian Ministry of Health, funding for travel from Teva Pharmaceutical Industries, and speaker honoraria from Bayer Schering Pharma, Biogen Idec, Sanofi Aventis, and Serono Symposia International Foundation. GC has received personal compensation for activities with Teva Neuroscience, Merck Serono, Bayer-Schering, Novartis, Sanofi-Aventis Pharmaceuticals, and Biogen Idec as a consultant, speaker, or scientific advisory board member. MAR has received speakers honoraria from Biogen Idec and Serono Symposia International Foundation, and receives research support from the Italian Ministry of Health. All other authors declare that they have no conflicts of interest.

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