Functional network disruption in the degenerative dementias

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Despite advances towards understanding the molecular pathophysiology of the neurodegenerative dementias, the mechanisms linking molecular changes to neuropathology and neuropathological changes to clinical symptoms remain largely obscure. Connectivity is a distinctive feature of the brain and the integrity of functional network dynamics is crucial for normal functioning. A better understanding of network disruption in the neurodegenerative dementias might help bridge the gap between molecular changes, pathological changes, and symptoms. Recent findings on functional network disruption as assessed with resting-state or intrinsic connectivity functional MRI and electroencephalography and magnetoencephalography have shown distinct patterns of network disruption across the major neurodegenerative diseases. These network abnormalities are somewhat specific to the clinical syndromes and, in Alzheimer's disease and frontotemporal dementia, network disruption tracks the pattern of pathological changes. These findings might have practical implications for diagnostic accuracy, allowing earlier detection of neurodegenerative diseases even at the presymptomatic stage, and tracking of disease progression.

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Introduction

Historically, clinicians have identified patients with neurodegenerative dementias on the basis of their clinical symptoms. In recent years, advances in basic science have allowed researchers to recategorise these diseases on the basis of molecular phenotype—ie, the toxic, misfolded disease protein aggregates that are identified in the brain post mortem, such as amyloid β (Aβ) and hyperphosphorylated tau in Alzheimer's disease; tau, TAR DNA-binding protein of 43 kDa (TDP-43), or fused in sarcoma (FUS) in frontotemporal dementia; and α-synuclein in Parkinson's disease and dementia with Lewy bodies.[1] These pathological changes are thought to be early events in a cascade that begins at the synaptic and neuronal levels and ultimately leads to the clinical syndrome. Within this temporal window, quantifiable biological, imaging, and physiological markers of pathology have been identified that can be thought of as in-vivo intermediate phenotypes. Such surrogate markers of pathology can improve understanding of disease pathophysiology—ie, indicate links between the molecular phenotype and clinical symptoms—and have the potential to allow earlier, more accurate diagnosis and monitoring of disease progression. In Alzheimer's disease, PET amyloid ligands enable in-vivo mapping of cerebral Aβ deposition,[2] whereas structural MRI findings have been shown to relate to hyperphosphorylated-tau-mediated neurodegeneration.[3] These biomarkers have recently been incorporated into the new diagnostic criteria for Alzheimer's disease.[4,5] In disorders such as Parkinson's disease, frontotemporal dementia, and dementia with Lewy bodies, structural biomarkers have been used to elucidate disease pathophysiology by showing patterns of atrophy associated with histopathology on the one hand,[6–8] and clinical symptoms on the other (table 1).[8,9]

Localisation-based approaches (such as in-vivo mapping of molecular changes and neurodegeneration) have helped build much of the present knowledge of disease pathophysiology. However, these approaches are less suited to investigation of neuronal or synaptic dysfunction, which is thought to underlie cognitive and functional deficits. Because brain functions rely on the integrity of dynamic communication between interconnected brain regions and circuits, a network perspective accounting for such interactions has the potential to provide new and meaningful intermediate phenotypes of pathology

	Alzheimer's disease	Frontotemporal degeneration (behavioural variant)	Parkinson's disease	Dementia with Lewy bodies
Molecular phenotype	β-Amyloid—distributed throughout neocortex; hyperphosphorylated tau—medial temporal lobe	Tau, TDP-43, or FUS—frontal cortex, anterior temporal cortex, striatum, amygdala, and thalamus	α-Synuclein—brainstem (dorsal motor nucleus of the vagus nerve, locus coeruleus, and substantia nigra)	α-Synuclein—brainstem (dorsal motor nucleus of the vagus nerve, locus coeruleus, and substantia nigra)
Intermediate phenotypes				
Molecular imaging	Widespread diffuse neocortical amyloid ligand uptake on PET	NA	NA	NA
Connectivity	Default-mode-network disruption on task-free functional MRI/EEG/MEG	Salience network disruption	Basal ganglia–thalamocortical loop abnormalities	NA
Structural imaging	Atrophy in the medial temporal lobe	Atrophy in the anterior cingulate cortex, frontoinsula, frontal pole, temporal pole, striatum, thalamus, and amygdala	Mild atrophy in the frontal and temporal cortices, and basal ganglia	Atrophy in the substantia nigra, midbrain, hypothalamus, basal forebrain, and amygdala
Clinical phenotype	Episodic memory loss	Social–emotional deficits	Motor impairment (tremor, rigidity, bradykinesia, and postural instability)	Hallucinations, parkinsonism, fluctuations in cognition, and motor impairment

TDP-43=TAR DNA-binding protein of 43 kDa. FUS=fused in sarcoma. NA=not available. EEG=electroencephalography. MEG=magnetoencephalography.

Table 1: **Connectivity as an intermediate phenotype in the degenerative dementias**

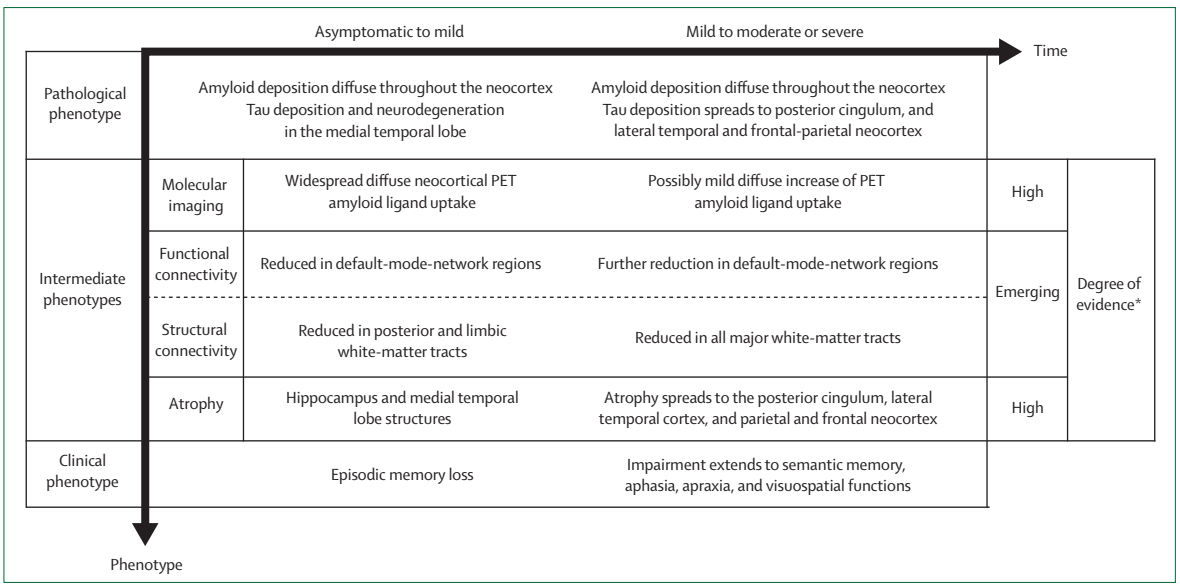

Figure 1: **The pathophysiological framework of Alzheimer's disease: connectivity as an intermediate phenotype between pathology and symptoms**
*Evidence that intermediate phenotypes are associated with pathological or clinical phenotypes.

(table 1). Prevalent views on the relation between symptoms and pathological changes in Alzheimer's disease help illustrate this notion (figure 1). In typical Alzheimer's disease, the progression of symptoms occurs in a stereotyped order that relates to the topographic progression of hyperphosphorylated tau:[10] episodic memory loss takes place first (hippocampus and medial temporal lobe, and posterior cingulate cortex), followed by semantic memory loss (lateral temporal cortex) and aphasic, apraxic, and visuospatial symptoms (frontal, temporal, and parietal neocortex), and finally by motor and visual deficits (sensorimotor and occipital cortex). Although atypical variants exist,[11] this orderly progression might be indicative of an incremental spread throughout interconnected regions within large-scale networks, and, ultimately, a spread into adjacent or upstream regions.

The brain can be thought of as a complex neural network consisting of structurally and functionally interconnected regions at many scales (panel 1).[12] At the macroscopic level, neural networks can be assessed non-invasively in health and disease with functional MRI (fMRI) and neurophysiological techniques (electroencephalography [EEG] and magnetoencephalography [MEG]).[13,14] The aim of our Review is to provide a comprehensive overview of findings on functional network disruption in the most prevalent neurodegenerative dementias. Although several reviews have addressed functional network disruption in Alzheimer's disease and in psychiatric disorders,[15–20] we summarise studies across many neurodegenerative dementias. By including frontotemporal dementia, dementia related to Parkinson's disease, and dementia with Lewy bodies, we highlight functional network similarities and differences in disorders that share common mechanisms (toxic protein aggregation and neuronal loss) but have distinct clinical phenotypes. Towards this aim, we review resting-state task-free functional imaging and neurophysiological studies. Because our primary goal is to review functional methods that are broadly applicable across neurodegenerative diseases, we have omitted task-activation studies, which require the design of disease-specific experiments (see Dickerson, 2007, for a review of task-activation studies in Alzheimer's disease[21]), as well as studies of grey-matter structural covariance.[22,23]

Techniques to assess network integrity

fMRI, EEG, and MEG techniques enable researchers to assess large-scale neural networks at different spatial and temporal resolutions. Functional connectivity between brain regions can be measured at a spatial resolution of 2–3 mm with fMRI and about 5–30 mm with EEG or MEG. fMRI and neurophysiological techniques contrast most sharply in their temporal resolutions, which differ by three orders of magnitude (seconds *vs* milliseconds). Structural connectivity within networks can be measured at a spatial resolution of 3–6 mm with diffusion tensor imaging.

Task-free fMRI

Task-free fMRI allows functional network mapping at high spatial resolution. Resting-state or so-called intrinsic connectivity fMRI is used to measure spontaneous low frequency (<0·08–0·1 Hz) fluctuations in the blood oxygen level dependent (BOLD) signal while participants lie quietly in the scanner and do no specific task.[24] The BOLD signal relates to changes in the ratio between

oxyhaemoglobin and deoxyhaemoglobin after neuronal activity; therefore, resting-state fMRI provides an indirect marker of neuronal function on a timescale of seconds. Functional connectivity is defined by temporal correlations (over minutes of data acquisition) of the BOLD signal between spatially distinct regions.[24]

Resting-state networks can be identified with several analytical methods, including so-called seed or region-of-interest-based methods and independent component analysis.[24] Region-of-interest-based approaches are used to measure the temporal correlation between an a-priori-selected brain region and all other brain voxels. The choice of the seed region is investigator driven and depends on the goals of the analysis. This approach enables identification of a network of brain areas (nodes; panel 1) that are functionally connected with the seed region. Independent component analysis is a data-driven method that does not require a priori hypotheses about the regions of interest. This approach enables identification of several networks consisting of spatially independent and temporally correlated regions.[25] Several networks have been consistently identified with each method (figure 2):[26] the default mode network, which is a posterior cingulate cortex–precuneus/medial temporal/lateral temporoparietal/medial frontal network that is often deactivated during cognitively demanding tasks;[27] bilateral executive control networks made up of lateral frontal-parietal nodes;[28] the salience network, which is an anterior cingulate/frontoinsular system with links to limbic and subcortical autonomic control centres;[28] a dorsal attentional system embedded in high frontoparietal sensorimotor association regions;[29] and networks related to primary visual, auditory, and sensorimotor regions.[26] One active area of work concerns the number of brain networks that can be meaningfully outlined at the group and single-participant levels with these methods.

In the absence of an experimental task, these networks show a tight spatial correspondence with the neuronal circuits activated during cognitive, emotional, and sensorimotor tasks.[30] Moreover, connectivity strength within these networks at rest has been related to cognitive and emotional states,[28,31] further supporting resting-state fMRI as a technique to assess symptoms and deficits in the context of disease. Functional networks can also be assessed within a graph theoretical framework by defining brain regions as the network nodes (eg, through atlas-based or functional brain parcellation) and the temporal correlation strengths between node pairs as the weighted edges.

Task-free EEG and MEG

Task-free EEG and MEG allow functional network mapping at high temporal resolution. These techniques represent a complementary approach to studying resting-state networks and are based on the synchrony of spontaneous electrical and magnetic activity of the brain. Investigators have assumed that oscillating neuronal assemblies relate to cognitive processing.[32] Synchronous neuronal activity generates a fluctuating electromagnetic field that can be detected with scalp electrodes. EEG can be used to detect the electrical component of this field and to provide a direct indication of (large-scale) neuronal activity. Factors that limit the use of EEG are the modest spatial resolution and the difficulty of recording subcortical sources of activity. In this regard, MEG provides an important step forward. MEG enables recording of the very weak magnetic field around the brain (about 100–1000 femtotesla); this requires advanced equipment including superconducting quantum devices and a magnetically shielded room, but offers clear advantages including higher spatial resolution (about 5 mm), less artifact interference, and a shorter set-up time without electrodes.[33] The EEG and MEG signals are usually analysed in separate frequency bands: delta (between 0–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–45 Hz).

Oscillatory synchronisation between different brain regions can be quantified with several procedures. Coherence, one of the most commonly used synchronisation measures, describes the linear similarity between two EEG or MEG time series at a given frequency.[34] Examples of more advanced markers of functional coupling are the synchronisation likelihood, which is sensitive to both linear and non-linear interdependencies between EEG or MEG signals, and

***Panel 1:* Glossary of basic network concepts**

Network
A mathematical representation of a complex system made of a finite number of nodes and links. Many real-world complex systems, such as biological, social, and neuronal systems, can be modelled as networks.

Node
A basic network element.

Link (or edge)
A connection between two nodes.

Neural network
A complex system whose node and links are represented by neurons and their connections. Neural networks can be defined at many scales: microscopic (neurons and synapses), meso-scale (neural assembles and circuitry), and macro-scale (anatomical regions and fibre tracts). Connections can be either structural or functional. Node choice largely depends on the technique used. Common choices for imaging and neurophysiological techniques are grey-matter regions and electrodes.

Functional connectivity
The presence of functional connections between nodes (eg, synchronous neuronal oscillations). Functionally connected nodes might have no direct physical connection.

Structural connectivity
The presence of physical connections between nodes (eg, fibre tracts).

Module
Subset of network nodes with high internal connectivity.

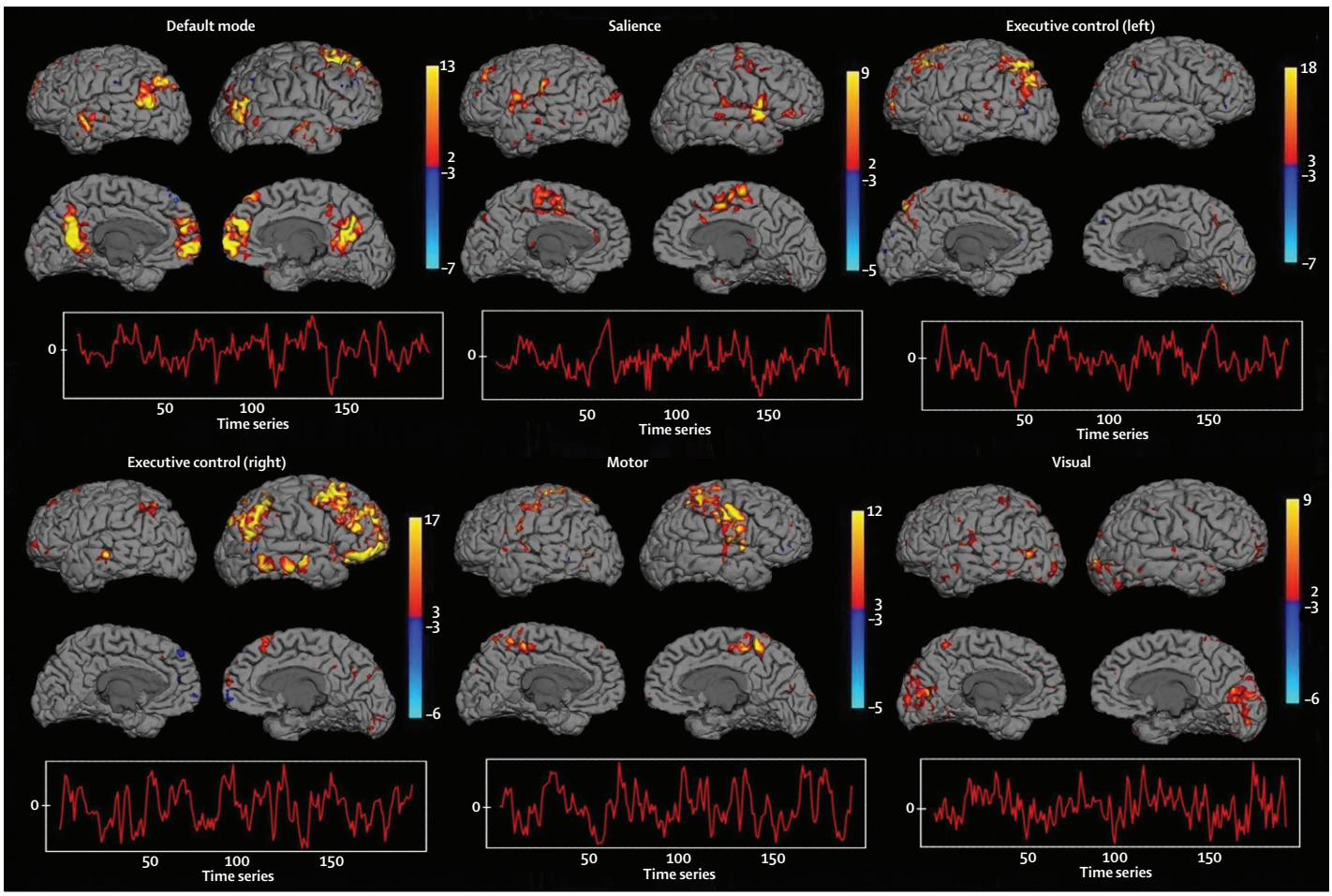

Figure 2: **Functional connectivity on resting-state fMRI in healthy people**
Independent-component-analysis-derived resting-state fMRI networks (default mode, salience, left and right executive control, visual, and motor networks)[26-28] of a healthy man aged 33 years. Red-to-yellow colours show the strength of each voxel's connectivity to overall component time series. fMRI=functional MRI.

the phase-lag index, which overcomes the problem of volume conduction (ie, neighbouring electrodes detecting common sources and spuriously increasing synchronisation).[13] Functional networks can be constructed by taking signals recorded at different regions as network nodes, and their mutual synchronisation as connection strengths (figure 3).[13] Subsequently, these networks can be analysed with graph theoretical algorithms.

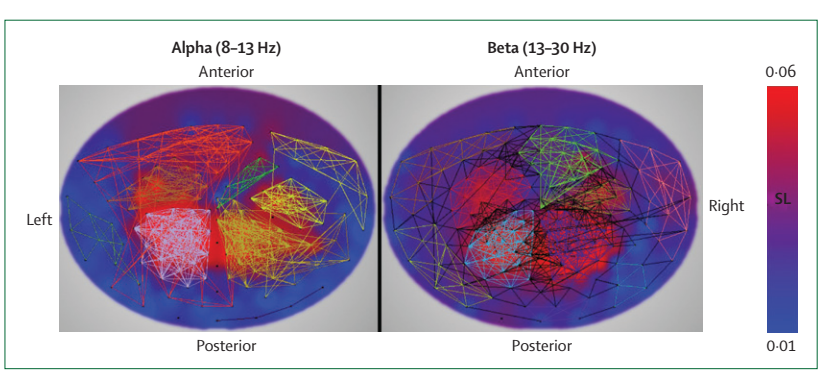

Figure 3: **Functional connectivity on resting-state MEG in healthy people**
Headplot showing functional MEG network of a healthy woman aged 63 years in the alpha (8–13 Hz) and beta (13–30 Hz) frequency ranges.[13] Coloured lines show different functional subnetworks (modules), black lines represent their interconnections (only shown in beta-band example). Background colours show connectivity strength (red are hub—ie, highly connected—regions). MEG=magnetoencephalography. SL=synchronisation likelihood.[13]

Diffusion tensor imaging

Diffusion tensor imaging provides markers of structural connectivity. Brain regions showing synchronous BOLD, electrical, or magnetic fluctuations often (but not always) feature some form of direct physical connection. Diffusion tensor imaging can be used to assess the structural integrity of brain connections (ie, axons and fibre tracts) by providing measures of changes in the diffusion of water molecules through tissues.[35] Two markers of structural integrity are commonly investigated: fractional anisotropy, a marker of white-matter fibre disruption (loss of fibre coherence, demyelination, axonal loss), and mean diffusivity, a marker for cell density.[35] Axial and radial diffusivity might provide more specific markers of axonal damage and demyelination.[35] Common methods to assess structural disruption are voxel-wise,

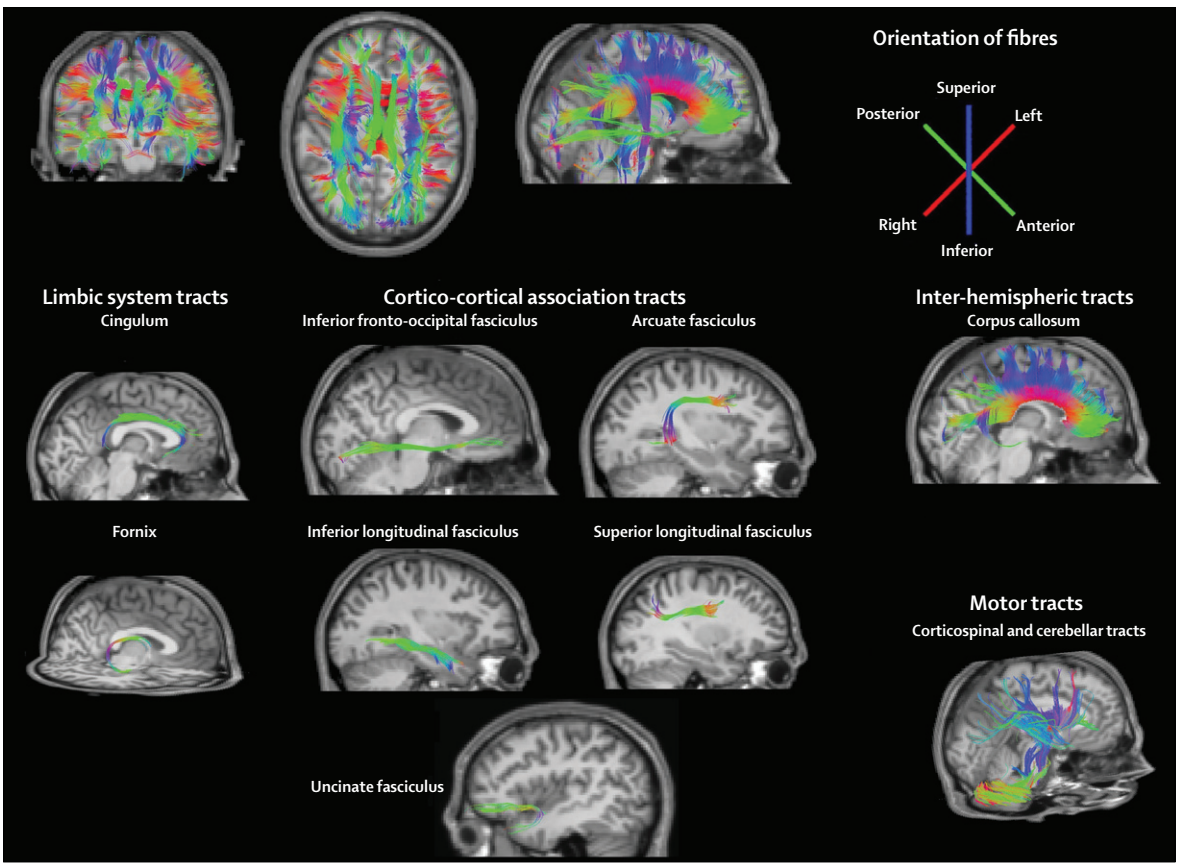

Figure 4: **Structural connectivity assessed with diffusion tensor imaging in a healthy man aged 33 years**
Diffusion tensor imaging tractography shows long (mainly visible in sagittal view as green and blue colour-coded fibres) and short (mainly visible in axial and coronal views as red colour-coded fibres) white-matter connections (top row). Specific tracts can be identified that subserve distinct cognitive and non-cognitive functions. The fornix and cingulum are mainly associated with memory and emotional processing, cortico-cortical association and intra-hemispheric tracts are associated with a broad range of cognitive processes, and the corticospinal and cerebellar tracts are generally involved in motor disorders.[36]

diffusion tensor imaging tractography, and region-of-interest-based techniques.[35] Diffusion tensor imaging tractography might be preferable on an individual participant basis, allowing reconstruction and visualisation of specific white-matter connections between cortical nodes (figure 4).[36] Graph theoretical analysis can be used to build structural networks and study their topology, in a similar way to that used to assess functional networks derived from resting-state fMRI, EEG, and MEG data.

Network organisation

Graph theory provides a framework for exploring brain network organisation in normal and pathological conditions.[13,14,37] Graph theoretical analysis of fMRI, EEG, MEG, and diffusion tensor imaging data can be used to model the whole brain as a single network and assess its properties, such as network structure, modularity, and resistance to damage (panel 2).[14] The healthy human brain is thought to be organised into a so-called small-world topology,[38] a network architecture that combines an efficient balance between local (short range) and global (long range) connectivity. This small-world configuration is thought to be better suited for information transfer and thus presumably for cognitive processing than the topology of random or regular networks.[39] Graph theory can also be used to extract functional subnetworks (modules) and quantify interactions between them with data-driven modularity algorithms.[40] Another aspect of graph theory is devoted to the investigation of highly connected (hub) nodes, since these regions are crucial for network integrity (panel 2).

Increasing evidence suggests that functional and structural network properties are related to development,[41] age, and cognition.[42–44] Older (mean age 67 years) versus young (mean age 24 years) adults show a distinct modular organisation of the brain, the former with greater connectivity between posterior and central regions, and the latter with higher connectivity between fronto-cingulo-parietal modules.[42] Furthermore, intelligence quotient scores have been negatively correlated with global functional connectivity (characteristic path length) in young adults,[43] and the structural efficiency of networks has been negatively associated with age, and positively

Panel 2: **Glossary of graph theory terms**

Graph
A visual representation of a network.

Graph theory
A branch of mathematics investigating network characteristics such as topology (ie, network structure), cost, efficiency, and robustness.

Degree
The total number of connections (edges) of a node. Can be averaged over the whole network to obtain a global measure of connection density or so-called wiring cost.

Hub
A highly connected node (ie, with a high degree). These nodes are relevant for efficient network communication, and damage to these nodes might be especially disruptive for network integrity.

Clustering coefficient
The interconnectedness of a node's immediate neighbours (note that neighbouring nodes need not be anatomically proximal). Clustering coefficient values can be averaged over a region to obtain a measure of local connectivity.

Path length
The travel distance (number of intermediate links) from one node to another. Path lengths between all nodes in a network can be averaged to obtain the characteristic path length, which is a measure of global connectivity.

Small-world network
A network topology characterised by a high clustering coefficient coupled with a low characteristic path length. Investigators presume this network structure is optimum for efficient communication between regions, and it can be found in many real-world systems, including neural networks.

Random network
A network topology characterised by a lower clustering coefficient and a smaller characteristic path length than small-world networks.

Efficiency
The inverse of the characteristic path length, which is thought of as a measure of information processing capability.

Robustness
Resilience of a network against damage to nodes or links. This property is influenced by factors such as the degree, clustering coefficient, and the presence of hubs.

Modularity
Extent to which a network can be described as a set of interconnected subnetworks (modules). Modular networks are often efficient and robust, and many real-world networks (including neural networks) can be thought of as modular.

correlated with processing speed, and visuospatial and executive functions.[44]

Functional networks and clinical impairment

Imaging and lesion studies have provided valuable information on the functional anatomy of the brain, and localisation principles are vital to the clinical neurologist. However, as we outlined in our introduction, localisation-based perspectives often do not explain the complex inter-relation between neurodegenerative pathological changes and clinical symptoms. Even focal lesions such as stroke (eg, strategic infarction), brain tumour, or traumatic brain injury can cause widespread disturbance of functional connectivity and unexpected cognitive symptoms that can be explained by various lesion locations.[45–47] There is also increasing evidence that local damage can change the overall network structure in a way that can lead to pathological hypersynchronisation and epilepsy.[48] In an elegant simulation study,[49] the effect of focal brain lesions on the patterns of functional connectivity was assessed by simulating lesions at different brain locations. The investigators showed that focal lesions located in the precuneus, medial anterior cingulate cortex, temporo-parietal junction, or superior frontal cortex produced widespread and substantial changes in functional connectivity with intrahemispheric and contralateral regions. Conversely, lesions to the visual or motor cortices had restricted effects on global connectivity.[49] Neurodegenerative processes, characterised by gradual and selective spreading of pathological changes across brain regions, might cause a progressive targeted network injury, leading to specific disconnection syndromes and progressive cognitive dysfunction.[50,51] The difference between neurological disorders due to focal lesions and most neurodegenerative diseases is that in the former case networks are affected at random, with no specific topographic and chronological pattern, whereas in the latter case networks are affected with a stereotyped sequence. Network analysis might therefore help to explain the link between local damage, long-range disconnection, and more widespread physiological and clinical dysfunction. Published work in this emerging area of study is still scarce but already points to intriguing new hypotheses.

Alzheimer's disease

Alzheimer's disease results from deposition of Aβ in the neocortex and hyperphosphorylated tau in the entorhinal cortex and hippocampus.[52,53] More recent evidence suggests that even earlier hyperphosphorylated-tau-related neurofibrillary changes might occur in the brainstem dorsal raphe nucleus or the locus coeruleus.[54] In human beings, hyperphosphorylated-tau pathology is associated with memory deficits,[55] whereas Aβ deposition is not directly related to cognition,[55] but shows topographical correspondence with the default mode network.[56] Moreover, the sequence of functional and structural disruption within and between default-mode-network regions is reminiscent of the spread of tau pathology. Buckner and colleagues[56] mapped in-vivo Aβ deposition with Pittsburgh compound B (^{11}PiB) PET in patients with Alzheimer's disease and cortical hubs in healthy controls and showed that regions of high Aβ deposition in patients largely overlap with default-mode-network cortical hubs in the healthy brain, especially the posterior cingulate cortex. Disruption of default-mode-network regions in Alzheimer's disease has been

consistently reported in resting-state fMRI studies that have involved independent component analysis or seed-based methods.[57–61] Similar changes have been reported in people with mild cognitive impairment, a condition that clinicians believe often represents preclinical Alzheimer's disease.[62–64] Early default-mode-network functional disruption in Alzheimer's disease involves the medial temporal lobe and posterior cingulate cortex/precuneus,[57,58,62,63] subsequently worsening and extending to the lateral parietal and medial frontal regions with increasing disease severity.[59] Structural connectivity disruption follows a similar pattern to default-mode-network functional disruption: the posterior white-matter tracts, connecting the hippocampus/medial temporal lobe with the posterior cingulate cortex and the limbic regions, are affected first,[65–67] whereas frontal white-matter tracts (genu of corpus callosum, anterior cingulum) are minimally affected, except for the uncinate and arcuate fasciculi, which connect the temporal to frontal cortex.[66–68] Electrophysiological studies are consistent with fMRI studies in reporting a reduction in cortico-cortical connectivity in Alzheimer's disease. Through EEG and MEG analyses, investigators have shown reduced connectivity between long-distance fronto-parietal and fronto-temporal regions in the alpha and beta frequency bands.[69–71] These frequency bands show good topographic correspondence with the default mode network and the greatest correlation between EEG power and default-mode-network fMRI fluctuations.[72,73]

When tau pathology has extended through the entire network, cognitive deficits generally involve several domains and patients will have developed overt Alzheimer's disease. Therefore, the breakdown of this network resulting from neurodegeneration might track progression to dementia. In people with mild cognitive impairment, preliminary evidence suggests that reduced default-mode-network connectivity is a significant predictor of conversion to Alzheimer's disease independently of global atrophy.[74] The predictive value of default-mode-network connectivity was not significant when memory performance was taken into account,[74] suggesting that functional connectivity changes are related to memory deficits.

In addition to reduced default-mode-network connectivity, increased intrinsic connectivity has been reported in several resting-state fMRI studies between frontal-parietal regions.[59,61,63] The basis for these connectivity increases remains unclear; although some investigators suggest that they represent compensatory mechanisms,[59,61,63] there is as yet no evidence that such changes improve cognition. An alternative explanation is that damage to one network enhances connectivity within regions that normally feature an anticorrelated relation to the damaged network.[58]

Graph theoretical analysis of network organisation in Alzheimer's disease has shown a loss of small-world structure towards a more random network topology,[75–78] indicated by a reduction in the clustering coefficient values[75,76,78] and lower characteristic path length.[75,77,78] The topography of network abnormalities assessed with this technique accords with previous studies showing reduced connectivity in the hippocampus and posterior parietal regions with fMRI,[76,77] and in the alpha (8–10 Hz) and beta (13–30 Hz) frequency bands with MEG.[75,78] Additionally, Stam and colleagues[75] have shown greater hub vulnerability in Alzheimer's disease, as simulated targeted attacks on highly connected nodes better explained the network changes recorded in the alpha frequency band than random removal of nodes. Structural network connectivity was assessed in a single study, in which abnormal network topology in Alzheimer's disease was reported.[79]

Frontotemporal dementia

Frontotemporal dementia refers to a group of clinical syndromes associated with underlying frontotemporal lobar degeneration (FTLD) pathology. Three major clinical syndromes are recognised: a behavioural variant (bvFTD), which presents with social–emotional dysfunction, and two primary progressive aphasia (PPA) subtypes, the semantic and nonfluent/agrammatic variants.[80] A high proportion of people with FTLD present with associated motor neuron disease. A third PPA subtype, the logopenic variant, has been included in the recently revised diagnostic criteria,[81] although many patients with this variant show underlying Alzheimer's disease at autopsy. FTLD pathology, in turn, can be divided into three major molecular classes based on the underlying disease protein: tau (FTLD-tau), TDP-43 (FTLD-TDP), or FUS (FTLD-FUS).[80] For some clinical syndromes, such as semantic variant PPA and frontotemporal dementia with motor neuron disease, the underlying FTLD molecular class can be predicted with good confidence during life.[82,83] For other syndromes, such as bvFTD, existing criteria do not enable reliable prediction of the underlying molecular pathology.[83]

Recent work has shown that bvFTD syndrome, like typical Alzheimer's disease, relates to the progressive degeneration of a specific large-scale network, the so-called salience network.[6,84] This network is involved in processing emotionally significant stimuli and is inversely correlated with the default mode network in task-free settings,[28] leading Seeley and colleagues[85] to predict that bvFTD and Alzheimer's disease would feature divergent network connectivity patterns. This hypothesis was subsequently tested with task-free fMRI and independent component analysis of the default mode and salience networks in patients with bvFTD and Alzheimer's disease.[58] Divergent patterns were identified in the two clinical groups, with reduced salience-network connectivity and increased default-mode-network connectivity in bvFTD and the opposite pattern in Alzheimer's disease. Furthermore, reduced salience-network connectivity in patients with bvFTD was associated with greater disease

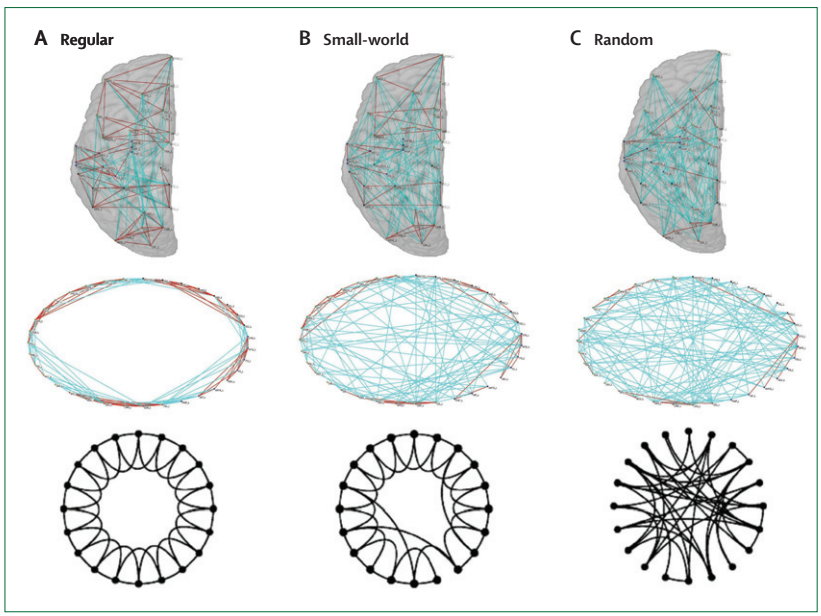

Figure 5: **Schematic representation of a small-world brain functional network and of simulated regular and random networks with 35 nodes and 120 connections**
Regular networks (A) have many connections between neighbouring regions (red lines) and few connections with distant nodes (light blue lines). Small-world networks (B) have fewer local connections and more long-distance connections. Random networks (C) have few local connections and many connections between distant regions. Each network is shown overlaid onto a standard template (top row) and in schematic representation (middle row). Nodes represent 35 cortical points of the left hemisphere drawn from the automated anatomical labelling template, and edges represent functionally connected nodes. The real-world network was extracted from a single person, the corresponding regular (A) and random (C) networks were simulated with the Brain Connectivity Toolbox.[89] The corresponding theoretical Watts–Strogatz network models are also shown (bottom row). Adapted from Watts and Strogatz[38] by permission of Macmillan Publishers Ltd.

severity.[58] A score incorporating default-mode-network and salience-network connectivities better discriminated between the two clinical groups than did either network alone,[58] suggesting that network-based patterns, which are sensitive to decreases and increases, might prove more specific to a given disease. Studies of structural connectivity in bvFTD support the role of disruption of specific frontal-temporal white-matter tracts, such as the bilateral uncinate and anterior cingulate tracts.[66,86] The frontotemporal dementia language syndromes (PPAs) have not yet been directly assessed with resting-state network mapping; however, findings of atrophy-mapping studies suggest that they are similarly associated with degeneration of specific networks.[84] Diffusion tensor imaging studies indeed support the role of disruption of specific white-matter tracts within the PPA-targeted networks.[86,87]

Published work on functional networks in FTLD remains scarce. One resting-state EEG study was done to assess functional connectivity in Alzheimer's disease, FTLD, and people with subjective memory complaints, and did not show group differences.[88] However, a subsequent MEG study of network organisation in patients with frontotemporal dementia showed changes in the opposite direction to those recorded in patients with Alzheimer's disease, towards an overly regular, ordered topology.[78] This intriguing contrast aligns with results of resting-state fMRI studies in Alzheimer's disease and frontotemporal dementia,[58] suggesting that these disorders might exert divergent effects on large-scale networks (figure 5),[89] and that these effects might help distinguish between the disorders during life.

However, it is unknown whether the underlying frontotemporal dementia molecular class can be identified by its effect on network-specific connectivity. Considering the role of anatomy (rather than the specific misfolded protein) in driving the clinical syndrome, there is reason to suspect that anatomically based methods (including resting-state network mapping) might not reliably differentiate patients with bvFTD caused by FTLD-tau from those with bvFTD caused by FTLD-TDP or FTLD-FUS, for example. However, it is possible that bvFTD is an overly inclusive clinical syndrome. If so, further clinical or anatomical differentiation might improve our ability to predict pathology during life.[90,91]

Parkinson's disease and dementia with Lewy bodies

Parkinson's disease and dementia with Lewy bodies are two neurodegenerative syndromes associated with deposition of α-synuclein-containing Lewy bodies and Lewy neurites within brainstem, limbic, and cortical neurons.[92] Despite a common molecular substrate, Parkinson's disease and dementia with Lewy bodies show important differences with regard to the timing and severity of symptoms.[93] A proportion of patients with Parkinson's disease develop dementia in later disease stages (Parkinson disease dementia; PDD), clinically resembling dementia with Lewy bodies.[93]

Available evidence suggests that Parkinson's disease and dementia with Lewy bodies are associated with distinct patterns of functional network dysfunction—namely, enhanced basal ganglia–thalamocortical connectivity in Parkinson's disease and reduced global and local cortico-cortical connectivity in patients with dementia with Lewy bodies. The basal ganglia–thalamocortical loop includes the striatum, globus pallidus, thalamus, subthalamic nucleus, substantia nigra, and cortical motor areas (primary motor cortex, supplementary motor area, premotor cortex).[94] In resting-state fMRI studies of this network, there have been consistent reports of increased connectivity between the basal ganglia and motor regions in patients with Parkinson's disease.[95–98] These network abnormalities were normalised after levodopa administration.[95,98]

Furthermore, reduced connectivity within this network has been reported in resting-state fMRI studies between the putamen and parietal and motor regions.[95,96] In resting-state EEG and MEG studies, there have been reports of increased connectivity in the alpha and beta (8–30 Hz) frequency ranges, between the subthalamic nucleus and the motor cortex,[99] and cortico-cortically.[100] Findings in a resting-state MEG study of patients in early, drug-naive stages showed an increase in alpha-band

(8–10 Hz) cortico-cortical functional connectivity that expanded towards other frequency bands (4–30 Hz) with increasing disease severity.[101] Increased connectivity affected both global and local connections and was associated with motor deficits.[100,101] It is less clear whether levodopa administration and deep brain stimulation normalise these abnormalities, since one study showed a normalisation of connectivity and motor involvement after intervention,[100] and another study reported a further increase in connectivity.[99] In PDD, preliminary studies have shown a different pattern, with decreased functional connectivity reminiscent of the changes in Alzheimer's disease.[102] In dementia with Lewy bodies, the most consistent finding is a reduction of global cortico-cortical coherence in the alpha (8–13 Hz) frequency band.[103–105] A MEG study specifically assessed coherence in long (anterior and posterior) and short (lateral and medial) cortico-cortical connections, and showed more substantial loss of connectivity in long-distance than short-distance connections in this frequency band.[103] Inconsistent changes have been reported in the delta (0·5–4 Hz) frequency range.[104,105]

In Parkinson's disease and dementia with Lewy bodies, it is difficult to identify a clear relation between structural and functional connectivity changes in specific networks, in part because dementia with Lewy bodies has yet to be linked to a particular network detectable with resting-state fMRI.[106] Diffusion tensor imaging shows microstructural abnormalities in the basal ganglia of patients with Parkinson's disease,[107–109] but evidence of structural disconnection within this circuit needs confirmation.[109,110] Reduced connectivity in the frontal and parietal association tracts has been reported, but without detection of a clear pattern of white-matter involvement.[111–113] Patients with Parkinson's disease who develop dementia show specific involvement of the posterior cingulum compared with both Parkinson's disease patients without dementia and controls.[114,115] In dementia with Lewy bodies, the most consistent finding is a reduction of connectivity in the inferior longitudinal fasciculus,[114,116–118] which connects the posterior temporal and occipital visual cortices, a finding that accords with visual hallucinations in these patients.[116] Additionally, patients with dementia with Lewy bodies have reduced connectivity between fronto-temporal and fronto-occipital regions compared with controls.[114,118] This pattern of white-matter disruption is overall similar to that detected in patients with PDD[114] and Alzheimer's disease,[118] but damage in the visual association areas is greater in dementia with Lewy bodies than in other dementias.[114,118] Because these studies were based on patients diagnosed according to clinical features, whereas the pathological changes of dementia with Lewy bodies and Alzheimer's disease often co-occur at autopsy,[119] it is perhaps not surprising that efforts so far show substantial overlap in the patterns of network disruption in dementia with Lewy bodies and Alzheimer's disease.[103,116,118]

Graph theoretical studies of network organisation in Parkinson's disease, PDD, and dementia with Lewy bodies are scarce. One study involved assessment of motor circuit connectivity in Parkinson's disease, in which it was reported that abnormal basal ganglia–thalamocortical connectivity accords with previous fMRI studies,[120] and another study showed reduced global efficiency.[121]

Neurobiological and clinical implications of network disruption

The research findings that we have reviewed suggest that functional neuroimaging can be used to detect distinct patterns of network disruption across the major neurodegenerative diseases (table 2). These networks are specific to the clinical profiles and might represent intermediate phenotypes between pathological changes and clinical syndromes. In Alzheimer's disease, the topography of Aβ deposition overlaps with the default mode network, broadly defined, whereas hyperphosphorylated-tau pathology is most prominent within a default-mode-network subsystem devoted to episodic memory.[122] In frontotemporal dementia, the salience network is highly disrupted in the behavioural variant. In

	Alzheimer's disease	Frontotemporal degeneration (behavioural variant)	Parkinson's disease	Dementia with Lewy bodies
Functional connectivity				
Resting-state functional MRI	Reduced connectivity—default mode network	Reduced connectivity—salience network	Increased connectivity—basal ganglia–thalamocortical loops; normalisation after levodopa administration	Insufficient evidence
Resting-state EEG/MEG	Reduced connectivity—alpha and beta (8–30 Hz) range between long-distance fronto-parietal and fronto-temporal regions	Insufficient evidence	Increased connectivity—alpha and beta (8–30 Hz) range locally and globally	Reduced connectivity—alpha (8–13 Hz) range locally and globally
Structural connectivity (diffusion tensor imaging)	Reduced connectivity—posterior and limbic white-matter tracts	Reduced connectivity—anterior white-matter tracts	No change in the major white-matter tracts	Reduced connectivity—visual pathway
Network organisation	Change towards a different topology—small-world to random; hub vulnerability	Change towards a different topology—small-world to regular	Insufficient evidence	No evidence

EEG=electroencephalography. MEG=magnetoencephalography.

Table 2: **Connectivity disruption in the degenerative dementias**

Parkinson's disease, α-synuclein pathology affects the cortico-striatal motor loops. In dementia with Lewy bodies, forebrain α-synuclein deposition has not been matched to a specific network with resting-state techniques, but neuropathological evidence supports an ascent through the brainstem to the limbic and cortical regions associated with clinical symptoms.[92] Disruption of ascending brainstem projection systems might soon prove detectable with network-based methods.[123]

Important network differences have emerged from comparisons between Parkinson's disease, PDD, and dementia with Lewy bodies, with an opposite EEG pattern of connectivity associated with dementia onset (increased *vs* decreased connectivity). Changes in PDD and dementia with Lewy bodies were less severe although similar to those of Alzheimer's disease with respect to the involvement of long-distance connections, although molecular in-vivo and post-mortem studies do not support a diagnosis of comorbid Alzheimer's disease.[119,124] With regard to long-distance connections, hub regions might have a key role.[125] Posterior parietal regions are among the brain regions with the highest connectivity, consistent with their role as multimodal association areas.[126] Damage to heteromodal association hub regions, as identified prominently in Alzheimer's disease,[56,75] might prove particularly disruptive by causing disintegration of unimodal and polymodal representations that normally converge at hubs after being processed in secondary and association cortices.[126] In Parkinson's disease, cognitive symptoms are generally milder than in Alzheimer's disease, and pathology targets the motor circuits, damage to which might have more restricted effects on whole brain connectivity.[49] Future studies will probably enable elucidation of whether the relatively preserved cognition in Parkinson's disease is explained by the sparing of cortical hub regions until late disease stages.[115]

From a clinical perspective, further pursuit of network-based strategies might lead to the development of sensitive and specific biomarkers for diagnostic, prognostic, and disease-monitoring purposes. Although the studies we reviewed were done at the group level, preliminary data on the sensitivity and specificity of network-derived markers seem promising. In Alzheimer's disease, two studies have been done to explore the accuracy of resting fMRI derived-markers to discriminate between patients with Alzheimer's disease and healthy elderly people, reporting a sensitivity of 85% and a specificity of 77% with default-mode-network connectivity,[57] and a sensitivity of 72% and a specificity of 78% with the clustering coefficient.[76] In the study by Zhou and colleagues,[58] the combination of default-mode-network and salience-network activity allowed 100% separation of Alzheimer's disease and frontotemporal dementia, although the reliability and accuracy of these measures remains to be tested in independent samples of patients. Task-free fMRI, EEG, and MEG techniques also offer practical advantages over existing biomarkers such as PET and CSF sampling. In general, these techniques are non-invasive and safe. Task-free fMRI data can be obtained in 8 min and added to the structural MRI most patients receive as part of a routine dementia assessment, creating minimum new costs for data acquisition. Moreover, fMRI, EEG, and MEG can be repeated as often as needed (within clinical trials, for example), without radioactivity exposure concerns. However, some factors might impede the clinical implementation of these techniques in the short term. The expertise needed to analyse these data is at present confined to few centres and the analysis itself is time-consuming.

Conclusions and future directions

Brain connectivity studies allow questions to be addressed that have so far escaped a convincing answer. For example, what is the mechanism whereby, in Alzheimer's disease, the deposition of Aβ and hyperphosphorylated tau takes place in largely distinct but highly interconnected hub regions? Why does damage spread to the whole network? Similar questions apply to α-synuclein in dementia with Lewy bodies and tau, TDP-43, and FUS in frontotemporal dementia. Several working models for network-based molecular pathogenesis have begun to emerge. One conservative account contends that misfolded disease proteins first spread intraneuronally, like prions, by inducing misfolding of adjacent normally folded (or unfolded) proteins.[127–130] This process might then move from pre-synaptic to post-synaptic cells via one of several transmission modes.[127] Evidence supporting a prion-like mechanism has come from cellular and rodent models of tau, α-synuclein, and Aβ disorders,[127–129] as well as from patients with Parkinson's disease who received transplanted dopaminergic neurons from fetal donors only to develop Lewy bodies within those neurons a few years after transplantation.[130] Other models emphasise the roles of network-based dysregulation of the excitation–inhibition balance (especially at the local microcircuit level),[131] disruption of activity-based or connectivity-based interneuronal trophic factor support,[132] and the long-term metabolic demands of high synaptic plasticity and turnover.[133,134] These accounts need not be thought of as mutually exclusive and each presents a potential therapeutic target for exploration.

Although the mechanisms we note are built around the idea that networks constrain and determine the anatomical disease pattern, apparent network-based spread could emerge, in a network-independent manner, if individual nodes within each target network possessed differential vulnerability to the disease process, leading those nodes to succumb sequentially according to their vulnerability. These mechanistic considerations raise the question of whether neurodegenerative diseases should be deemed primary diseases of networks. Alternatively, networks might be damaged and disrupted in these illnesses without representing the most relevant primary target.

One unifying framework might suggest that these diseases begin by targeting selectively vulnerable, region-specific neuron classes, such that early-stage disease is best thought of as a primary neuronopathy. Next, the disease might spread within local microcircuitry, producing accentuated damage within the site of initial injury. Long-range disease spread, during a subsequent phase, might be uniquely constrained by the long-range connectivity profile of the early-affected neurons and microcircuits, such that later-stage disease is most accurately regarded as a network-opathy and will need or benefit from treatments that target mechanisms of network-based disease propagation.

The analysis of functional networks is a multistep procedure, in which methodological choices and assumptions must be made. The choice of the postprocessing techniques such as artifact reduction, filtering, normalisation, and nuisance variable regression can influence the results. Both independent component analysis and seed-based analysis of fMRI data have technical and practical limitations that remain to be addressed and have been outlined in a recent review.[135] Similarly, graph theoretical network investigation requires methodological decisions that can bias outcomes and conclusions. For example, appropriate statistical thresholding for network definition and extraction is a crucial issue for this approach.[14] Furthermore, it is important to recognise that the spatial resolution of present EEG and MEG recording techniques poses limitations on the measurement of deep brain neuronal activity and therefore on the interpretation of the results.[33] Finally, data on the sensitivity, specificity, and reliability of task-free fMRI, EEG, and MEG data are still restricted.[136] However, despite these important limitations, recent brain connectivity studies with different recording techniques and analytical approaches show converging results,[137] suggesting that a more cohesive view of brain (dys)function in dementia might arise from the study of networks.

In broad terms, the study of functional network disruption in the degenerative dementias is in its infancy. Some disorders, such as Alzheimer's disease, have been widely studied with the described approaches. Other diseases, such as PDD and dementia with Lewy bodies, as well as frontotemporal dementia language variants, largely remain to be explored. In Parkinson's disease and dementia with Lewy bodies, a disease-specific independent-component-analysis network has not yet been identified with task-free fMRI, but recent work suggests a link to a basal ganglia network, anticorrelated with the default mode network, which might be affected in these disorders.[123] Similarly, graph theoretical approaches might be used to assess functional changes in the Parkinson's disease spectrum. Additionally, new and more advanced approaches such as Bayesian network modelling might provide additional markers of connectivity through the assessment of causal relations between nodes. Preliminary findings from the analysis of the default mode network with this method in Alzheimer's disease look promising.[138]

In the coming years, technical improvements will help refine the topography of network degeneration. Furthermore, a complete understanding of network organisation will depend on knowledge of how brain structure influences brain function, and vice versa. Strictly speaking, functional connectivity is unrelated to anatomy—ie, functionally connected regions might show no direct structural connection, although the presence of structural connectivity generally implies functional connectivity.[139,140] For some brain regions, a functional connection might be established by intermediate regions or through a common source that drives activity in both regions. Efforts are under way to integrate structural and functional connectivity into a common framework. Important advances are expected from a recently funded US$40 million National Institutes of Health project that aims to identify the brain network architecture with advanced diffusion imaging, fMRI, and EEG and MEG recordings.

For the **NIH Human Connectome Project** see http://www.humanconnectomeproject.org/

How might increasing focus on functional brain networks lead to more effective dementia therapies? The first hope relates to patient categorisation, and Alzheimer's disease provides an illustrative example. In healthy older people without cognitive impairment, high levels of brain Aβ are suspected to represent preclinical Alzheimer's disease.[141] Pinpointing presymptomatic, Aβ-associated network disruption, as reported in several recent studies,[142,143] might enable identification of a subgroup most likely to benefit from a disease-modifying drug treatment. Similarly, network analysis might provide sensitive markers of preclinical frontotemporal dementia (eg, in gene mutation carriers) and help to distinguish patients on the spectrum from Parkinson's disease to dementia with Lewy bodies. Other approaches might aim to recalibrate networks directly. Phase 1 trials of deep brain and transcranial magnetic stimulation targeting cognitive circuits have shown improvement of network-wide metabolic function or cognitive function in patients with Alzheimer's disease.[144,145] Finally, task-free

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "network", "network dysfunction", "connectivity", "resting state functional MRI", "electroencephalography", "magnetoencephalography", "diffusion tensor imaging", "tractography", "dementia", "neurodegenerative disorders", "frontotemporal dementia", "Alzheimer", "mild cognitive impairment", "Parkinson", "Lewy bodies dementia", "stroke", and "tumour" from 1986 until June, 2011. Furthermore, we identified articles through searches of the references of retrieved articles. We only reviewed papers published in English. The final list of publications was selected by the authors on the basis of relevance to the topic.

fMRI and neurophysiological methods provide attractive candidates for longitudinal, disease-monitoring biomarkers owing to the safe and repeatable nature of these techniques. Whether these methods will prove successful in detecting and monitoring clinical change is a question that awaits future studies. In view of cross-sectional correlations between network connectivity strength and clinical severity,[58,59] cautious optimism seems justified.

Contributors

GBF wrote the conceptual framework and manuscript architecture, and supervised manuscript preparation. MP wrote the initial draft. MP, WdH, TW, and WWS searched published works and contributed to subsequent versions of the draft. MP and WdH prepared the illustrations. All authors contributed to critical review of the manuscript. All the authors have seen and approved the final version.

Conflicts of interest

GBF has served on advisory boards for Lilly, BMS, Bayer, Lundbeck, Elan, AstraZeneca, Pfizer, Baxter, Taurx, and Wyeth, and has received research support from Wyeth, Lilly, and Lundbeck Italia. The other authors declare no conflicts of interest.

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