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Functional Network Disruption in the Degenerative Dementias

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Abstract

Despite considerable advances toward understanding the molecular pathophysiology of the neurodegenerative dementias, the mechanisms linking molecular changes to neuropathology and the latter to clinical symptoms remain largely obscure. Connectivity is a distinctive feature of the brain and the integrity of functional network dynamics is critical for normal functioning. A better understanding of network disruption in the neurodegenerative dementias may help bridge the gap between molecular changes, pathology and symptoms. Recent findings on functional network disruption as assessed with “resting-state” or intrinsic connectivity fMRI and EEG/MEG have shown distinct patterns of network disruption across the major neurodegenerative diseases. These network abnormalities are relatively specific to the clinical syndromes, and in Alzheimer's disease and frontotemporal dementia network disruption tracks the pattern of pathological changes. These findings may have a practical impact on diagnostic accuracy, allowing earlier detection of neurodegenerative diseases even at the pre-symptomatic stage, and tracking of disease progression.

1. Introduction

Historically, clinicians have recognized patients with neurodegenerative dementias based on their clinical symptoms. In recent years, basic science advances have allowed researchers to re-categorize these diseases based on molecular phenotype, i.e. which toxic, misfolded disease protein aggregates are observed in the brain post-mortem, such as beta amyloid (Aβ)

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and hyperphosphorylated tau (HP-tau) in Alzheimer's Disease (AD); tau, TAR DNA-binding protein of 43 kDa (TDP-43), or fused in sarcoma (FUS) in frontotemporal dementia (FTD), and alpha-synuclein in Parkinson's Disease (PD) and Dementia with Lewy Bodies (DLB).[1] These pathological changes are considered 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 considered *in vivo* intermediate phenotypes. Such surrogate markers of pathology can clarify disease pathophysiology, i.e. link the molecular phenotype to clinical symptoms and have the potential to facilitate earlier, more accurate diagnosis and monitoring of disease progression. In AD, PET amyloid ligands enable *in vivo* mapping of cerebral Aβ deposition,[2] whereas structural MRI has been shown to reflect HP-tau-related neurodegeneration.[3] These biomarkers have recently been incorporated into the new AD diagnostic criteria.[4,5] In disorders such as PD, FTD and DLB, structural biomarkers have clarified 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]

Localization-based approaches (such as *in vivo* mapping of molecular changes and neurodegeneration) have helped build much of the current knowledge regarding disease pathophysiology. These approaches, however, are less suited to investigate neuronal/ 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 novel and meaningful intermediate phenotypes of pathology (Table 1). Prevalent views on the relationship between symptoms and pathology in AD help illustrate this notion (Figure 1). In typical AD, the progression of symptoms follows a relatively stereotyped order which mirrors the topographic progression of HP-tau:[10] episodic memory loss occurs first (hippocampus and medial temporal lobe, posterior cingulate cortex), followed by semantic memory loss (lateral temporal cortex), aphasic, apraxic, and visuospatial symptoms (frontal, temporal, and parietal neocortex), and finally motor and visual deficits (sensorimotor and occipital cortex). Although atypical variants exist,[11] this orderly progression may reflect incremental spread throughout interconnected regions within large-scale networks, and ultimate spread into adjacent or upstream regions.

The brain can be viewed as a complex neural network consisting of structurally and functionally interconnected regions at multiple scales (Panel 1).[12] At the macroscopic level, neural networks can be investigated non-invasively in health and disease with functional MRI and neurophysiological techniques (electro- and magneto-encephalography, EEG and MEG).[13,14] The aim of this review is to provide a comprehensive overview of findings on functional network disruption in the most prevalent neurodegenerative dementias. Although several excellent reviews have addressed functional networks disruption in AD and in psychiatric conditions,[15-20] here we summarize studies across multiple neurodegenerative dementias. By including FTD, PD dementia and DLB, we highlight functional network similarities and differences among conditions that share common mechanisms (toxic protein aggregation and neuronal loss) but have distinct clinical phenotypes. Toward this aim, resting-state “task-free” functional imaging and neurophysiological studies will be reviewed. 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 (for a review of its applications in AD, see Dickerson 2007),[21] as well as studies of gray matter structural covariance.[22,23]

2. Techniques to investigate networks integrity

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

2.1 Functional network mapping at high spatial resolution: task-free fMRI

Resting-state or "intrinsic connectivity" fMRI measures spontaneous low frequency (<0·08-0·1 Hz) fluctuations in the blood oxygen level dependent (BOLD) signal while subjects lie quietly in the scanner and perform no specific task.[24] The BOLD signal reflects changes in the ratio between oxy- and deoxy-haemoglobin following neuronal activity, therefore resting fMRI provides an *indirect* marker of neuronal function on a time scale 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 "seed" or region-of-interest based methods and independent component analysis (ICA).[24] Region-of-interest based approaches 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 identifies a network of brain areas ("nodes"; Panel 1) functionally connected with the seed region. ICA is a data-driven method that does not require *a priori* hypotheses about the regions of interest. This approach enables identification of multiple networks consisting of spatially independent and temporally correlated regions.[25] Several networks have been consistently identified with either method (Figure 2):[26] the default mode network (DMN), a posterior cingulate cortex-precuneus/medial temporal/lateral temporoparietal/medial frontal network that often deactivates during cognitively demanding tasks;[27] bilateral executive-control networks made up of lateral frontal-parietal nodes;[28] the salience network, an anterior cingulate/frontoinsular system with links to limbic and subcortical autonomic control centers,[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 area of active work concerns how many brain networks can be meaningfully outlined at the group and single-subject 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 state,[28,31] further supporting resting-state fMRI as a tool to investigate symptoms and deficits in the context of disease. Functional networks can also be investigated within a graph theoretical framework (see section 2.4) by defining brain regions as the network nodes (e.g., through atlas-based or functional brain parcellation) and the temporal correlation strengths between node pairs as the weighted edges.

2.2 Functional network mapping at high temporal resolution: task-free EEG and MEG

A complementary approach to study resting-state networks is based on the synchrony of spontaneous electrical and magnetic activity of the brain. Oscillating neuronal assemblies are assumed to reflect cognitive processing,[32] and generate a fluctuating electromagnetic field that can be detected with scalp electrodes. EEG detects the electrical component of this

field with a high temporal resolution (millisecond range) and provides a *direct* reflection of (large-scale) neuronal activity. Factors that limit the use of EEG are the relatively modest spatial resolution and the difficulty recording subcortical sources of activity. In this regard, MEG provides an important step forward. MEG records the very weak magnetic field around the brain (±100-1000 femtoTesla), which requires advanced equipment including superconducting quantum devices and a magnetically shielded room, but offers clear advantages including higher spatial resolution (±5 millimeters), less artifact interference, and a shorter set-up time without electrodes.[33] The EEG and MEG signals are usually analyzed 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 synchronization between different brain regions can be quantified with several procedures. Coherence, one of the most popular synchronization measures, describes the linear similarity between two EEG/MEG time-series at a given frequency.[34] Examples of more advanced markers of functional coupling are the Synchronization Likelihood, which is sensitive to both linear and non-linear interdependencies between EEG/MEG signals, and the Phase Lag Index, which overcomes the problem of volume conduction, whereby neighboring electrodes detect common sources, spuriously increasing synchronization.[13] Functional networks can be constructed by taking signals recorded at different regions as network nodes, and their mutual synchronization as connection strengths (Figure 3).[13] Subsequently, these networks can be analyzed using graph theoretical algorithms, as outlined in the section 2.4.

2.3 Markers of structural connectivity: DTI

Regions with synchronous BOLD signal, electrical or magnetic fluctuations often (but not always) feature some form of direct physical connection. DTI assesses the structural integrity of brain connections (i.e. axons and fiber tracts) by measuring 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 (WM) fiber disruption (loss of fiber coherence, demyelination, axonal loss), and mean diffusivity, a marker for cell density.[35] Axial and radial diffusivity may provide more specific markers of axonal damage and demyelination.[35] Common methods to investigate structural disruption are voxel-wise, DTI tractography and ROI-based techniques.[35] DTI tractography may be preferable on an individual subject basis, allowing one to reconstruct and visualize specific WM connections between cortical nodes (Figure 4).[36] Graph theoretical analysis can be used to build structural networks and study their topology, in a way similar to that used to investigate resting-state fMRI and EEG/MEG-derived functional networks.

2.4 Network organization

Graph theory provides a framework for exploring brain network organization in normal and pathological conditions.[13,14,37] Graph theoretical analysis to fMRI, EEG/MEG and DTI data can model the whole brain as a single network and investigate its properties such as network structure, modularity, and robustness to damage (Panel 2).[14] The healthy human brain is thought to be organized into a ‘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 considered better suited for information transfer and thus presumably for cognitive processing than the topology of ‘random’ or ‘regular’ networks.[39] Graph theory can also extract functional subnetworks (‘modules’) and quantify interactions between them by using data-driven modularity algorithms.[40] Another area of graph theory is devoted to the investigation of highly connected (‘hub’) nodes, since these regions are critical 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 of 67) vs. Young (mean age of 24) adults show a distinct modular organization of the brain, the former with greater connectivity between posterior and central regions, and the latter showing higher connectivity between fronto-cingulo-parietal modules.[42] In addition, IQ score has 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 correlated with processing speed, visuospatial and executive functions.[44]

3. Disruption of functional networks is associated with clinical impairment

Imaging and lesion studies have led to valuable insights into the functional anatomy of the brain, and localization principles are vital to the clinical neurologist. As outlined in the introduction, however, localization-based perspectives often fail to explain the complex interrelationship between neurodegenerative pathology and clinical symptoms. Even ‘focal’ lesions like stroke (e.g. ‘strategic’ infarction), brain tumour or traumatic brain injury can cause widespread disturbance of functional connectivity and unexpected cognitive symptoms that can be explained by a variety of 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 hypersynchronization and epilepsy.[48] In an elegant simulation study,[49] the effect of focal brain lesions on the patterns of functional connectivity was investigated by simulating lesions at different brain locations. The study showed that focal lesions located in the precuneus, medial anterior cingulate cortex, temporo-parietal junction, or superior frontal cortex produced widespread and pronounced changes in functional connectivity with intra-hemispheric and contralateral regions. Conversely, lesions to the visual or motor cortex had limited effects on global connectivity.[49] Neurodegenerative processes, characterised by gradual and selective spreading of pathology 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 relatively stereotyped sequence. Network analysis may therefore help to explain the link between local damage, long-range disconnection, and more widespread physiological and clinical dysfunction. Literature in this emerging field is still scarce but already points to intriguing new hypotheses, as described in this section.

3.1 Alzheimer's Disease

AD results from deposition of Aβ in the neocortex and HP-tau in the entorhinal cortex and hippocampus.[52,53] More recent evidence suggests that even earlier HP-tau-related neurofibrillary changes may occur in the brainstem dorsal raphe nucleus or the locus ceruleus.[54] In humans HP-tau pathology is associated with memory deficits,[55] whereas Aβ deposition is not directly related to cognition,[55] but shows topographical correspondence with the DMN.[56] Moreover, the sequence of functional and structural disruption within and between DMN regions is reminiscent of the spread of tau pathology. Buckner et al. mapped *in vivo* PIB-PET Aβ deposition in patients with AD and cortical hubs in healthy controls and showed that regions of high Aβ deposition in patients largely overlap with DMN cortical hubs in the healthy brain, especially the posterior cingulate cortex.[56] Disruption of DMN regions in AD has been consistently reported by resting-state fMRI studies using ICA or seed-based methods.[57-61] Similar changes have been reported in subjects with mild cognitive impairment, a condition which is believed to often represent pre-clinical AD.[62-64] Early DMN functional disruption in AD 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: the posterior WM tracts, connecting the hippocampus/medial temporal lobe with the posterior cingulate cortex and the limbic regions, are affected first,[65-67] whereas frontal WM tracts (genu of corpus callosum, anterior cingulum) are minimally affected, except for the uncinate and arcuate fasciculi, which connect temporal to frontal cortex.[66-68] Electrophysiological studies are consistent with fMRI studies in reporting a reduction of cortico-cortical connectivity in AD. EEG and MEG analyses 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 DMN and the greatest correlation between EEG power and DMN fMRI fluctuations.[72,73]

When tau pathology has extended through the entire network, cognitive deficits generally involve multiple domains and patients will have developed overt AD. Therefore the breakdown of this network due to neurodegeneration may track progression to dementia. In subjects with mild cognitive impairment, preliminary evidence indicates that reduced DMN connectivity is a significant predictor of conversion to AD independently of global atrophy.[74] Interestingly, the predictive value of DMN connectivity was no longer significant when memory performance was taken into account,[74] suggesting that functional connectivity changes are related to memory deficits.

In addition to reduced DMN connectivity, increased intrinsic connectivity has been reported by several resting-state fMRI studies between frontal-parietal regions.[59,61,63] The basis for these connectivity increases remains unclear; although some authors 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 anti-correlated relationship with the damaged network.[58]

Graph theoretical analysis of network organization in AD has shown a loss of small-world structure toward 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 is in line with previous studies, showing reduced connectivity in the hippocampus and posterior parietal regions with fMRI,[76,77] and in the alpha (8-10Hz) and beta (13-30Hz) frequency bands with MEG.[75,78] In addition, Stam et al. have shown greater ‘hub’ vulnerability in AD, as simulated targeted attacks to highly connected nodes better explained the network changes observed in the alpha frequency band than ‘random’ removal of nodes.[75] A single study has assessed structural network connectivity, reporting abnormal network topology in AD.[79]

3.2 Frontotemporal dementia

FTD refers to a group of clinical syndromes associated with underlying frontotemporal lobar degeneration (FTLD) pathology. Three major clinical syndromes are recognized: 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 FTLD cases present 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 AD 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 FTD 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 reliably predict the underlying molecular pathology.[83]

Recent work has revealed that bvFTD syndrome, like typical AD, reflect the progressive degeneration of a specific large-scale network, the "salience network".[6,84] This network is involved in processing emotionally significant stimuli and is inversely correlated with the DMN in task-free settings,[28] leading Seeley and colleagues to predict that bvFTD and AD would feature divergent network connectivity patterns.[85] This hypothesis was subsequently tested using task-free fMRI and ICA analysis of the DMN and salience networks in patients with bvFTD and AD.[58] The study identified divergent patterns in the two clinical groups, with reduced salience network connectivity and increased DMN connectivity in bvFTD and the opposite pattern in AD. In addition, reduced salience network connectivity in bvFTD patients was associated with greater disease severity.[58] A score incorporating DMN 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 may prove more specific to a given disease. Studies of structural connectivity in bvFTD support the disruption of specific frontal-temporal WM tracts, such as the bilateral uncinate and anterior cingulate tracts.[66,86] The FTD language syndromes (PPAs) have not yet been directly investigated with resting-state network mapping, however atrophy-mapping studies suggest that they are likewise associated with degeneration of specific networks.[84] DTI studies indeed support the disruption of specific WM tracts within the PPA-targeted networks.[86,87]

Neurophysiological literature on functional networks in FTLD is almost non-existent. One resting-state EEG study assessed functional connectivity in AD, FTLD, and persons with subjective memory complaints, and failed to find group differences.[88] A subsequent MEG study of network organization in FTD patients however showed changes in the opposite direction to that observed in AD patients, toward an overly regular, ordered topology.[78] This intriguing contrast aligns with resting-state fMRI results in AD and FTD[58] to suggest that these disorders may exert divergent effects on large-scale networks (Figure 5),[89] and that these effects may help distinguish these disorders during life.

Whether the underlying FTD molecular class can be identified by its impact on network-specific connectivity, however, remains unknown. 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) may struggle to reliably differentiate patients with bvFTD due to FTLD-tau vs. FTLD-TDP vs. FTLD-FUS, for example. On the other hand, it remains possible that to date bvFTD remains an overly inclusive clinical syndrome. If so, further clinical or anatomical differentiation may improve our ability to predict pathology during life.[90,91]

3.3 Parkinson's Disease and Dementia with Lewy bodies

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

Available evidence suggests that PD and DLB are associated with distinct patterns of functional network dysfunction, namely increased basal ganglia-thalamocortical connectivity in PD and reduced global and local cortico-cortical connectivity in patients with dementia. The basal ganglia-thalamocortical loop includes the striatum, globus

pallidus, thalamus, subthalamic nucleus, and substantia nigra; and cortical motor areas (primary motor cortex, supplementary motor area, premotor cortex).[94] Resting-state fMRI studies of this network have consistently reported increased connectivity between the basal ganglia and motor regions in PD patients.[95-98] These network abnormalities were normalised after levodopa administration.[95,98] In addition, *reduced* connectivity within this network has been reported by resting-state fMRI studies between the putamen and parietal and motor areas.[95,96] Resting-state EEG/MEG studies reported 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] 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 toward other frequency bands (4-30 Hz range) with increasing disease severity.[101] Increased connectivity affected both global and local connections and was associated with motor deficits.[100,101] Less clear is whether levodopa administration and deep brain stimulation normalise these abnormalities, as one study showed a normalization of connectivity after intervention in association with motor improvement,[100] and another showed a further increase in connectivity.[99] In PDD, preliminary studies indicate a different pattern, with decreased functional connectivity reminiscent of the changes in AD.[102] In DLB, the most consistent finding is a reduction of global cortico-cortical coherence in the alpha (8-13Hz) frequency band.[103-105] A MEG study specifically assessed coherence in long (anterior and posterior) and short (lateral and medial) cortico-cortical connections, reporting more pronounced loss of connectivity in long- than short-distance connections in this frequency band.[103] Inconsistent changes have been reported in the delta (0·5-4Hz) frequency range.[104,105]

In PD and DLB, a clear correspondence between structural and functional connectivity changes in specific networks is difficult to draw, in part because DLB has yet to be linked to a particular network detectable with resting-state fMRI.[106] DTI demonstrates microstructural abnormalities in the basal ganglia of PD patients,[107-109] but evidence of structural disconnection within this circuit is limited.[109,110] Reduced connectivity in the frontal and parietal association tracts has been reported but without detecting a clear pattern of WM involvement.[111-113] PD patients who develop dementia show a specific involvement of the posterior cingulum compared with both PD and controls.[114,115] In DLB, 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 in line with the occurrence of visual hallucinations in these patients.[116] In addition, DLB patients show reduced connectivity between fronto-temporal and fronto-occipital regions compared to controls.[114,118] This pattern of WM disruption is overall similar to that detected in patients with PDD,[114] and AD,[118] but damage in the visual association areas is more pronounced in DLB than in other dementias.[114,118] Because these studies were based on patients diagnosed on clinical grounds, whereas DLB and AD pathologies often co-occur at autopsy,[119] it is perhaps not surprising that efforts to date show significant overlap in the patterns of network disruption in DLB and AD.[103,116,118]

Graph theory studies of network organization in PD, PDD and DLB are scarce. One study investigated motor circuits connectivity in PD, reporting abnormal basal ganglia-thalamocortical connectivity in line with previous fMRI studies,[120] and another study showed reduced global efficiency.[121]

3.4 Neurobiological and clinical implications of network disruption

Research findings reviewed here demonstrate that functional neuroimaging is able to detect distinct patterns of network disruption across the major neurodegenerative diseases (Table 2). These networks are relatively specific to the clinical profiles and may represent intermediate phenotypes between pathology and clinical syndromes. In AD, the topography

of Aβ deposition overlaps with the DMN, broadly defined, whereas HP-tau pathology is most prominent within a DMN subnetwork devoted to episodic memory.[122] In FTD, the salience network is profoundly disrupted in the behavioural variant. In PD, alpha-synuclein pathology affects the cortico-striatal motor loops. In DLB, forebrain alpha-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 may soon prove detectable with network-based methods.[123]

Important network differences have emerged from comparisons between PD, PDD and DLB, with an opposite EEG-pattern of connectivity associated with dementia onset (increased *versus* decreased connectivity). Interestingly, PDD and DLB changes were less severe though similar to those of AD with respect to the involvement of long-distance connections, although molecular *in vivo* and post-mortem studies do not support an Alzheimer's etiology.[119,124] With regard to longdistance connections, hub regions may play 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 seen prominently in AD,[56,75] may prove particularly disruptive by dis-integrating unimodal and polymodal representations that normally converge at hubs after being processed in secondary and association cortices.[126] In PD cognitive symptoms are generally milder than in AD, and pathology targets the motor circuits, whose damage may have more restricted effects on whole brain connectivity.[49] Future studies will likely elucidate whether the relatively preserved cognition in PD is explained by the relative sparing of cortical hub regions until late disease stages.[115]

From a clinical perspective, further pursuit of network-based strategies may lead to the development of sensitive and specific biomarkers for diagnostic, prognostic, and disease-monitoring purposes. Although the reviewed studies were conducted at the group level, preliminary data about the sensitivity/specificity of network-derived markers seem promising. In AD, two studies have explored the accuracy of resting fMRI derived-markers to discriminate between AD patients and healthy elderly, reporting a sensitivity of 85% and a specificity of 77% using DMN connectivity,[57] and a sensitivity of 72% and a specificity of 78% using the clustering coefficient.[76] In the study by Zhou and colleagues,[58] the combination of DMN and salience network activity allowed 100% separation of AD and FTD, although the performance of these measures remains to be tested in independent patient samples. Task-free fMRI and EEG/MEG techniques also offer practical advantages over existing biomarkers, such as PET and cerebrospinal fluid sampling. In general, these techniques are non-invasive and safe. Task-free fMRI data can be obtained in eight minutes and added to the structural MRI most patients receive as part of a routine dementia evaluation, creating minimal new costs for data acquisition. Moreover, fMRI and EEG/MEG can be repeated as often as necessary (within clinical trials, for example), without radioactivity exposure concerns. On the other hand, some factors might hurdle the clinical implementation of these techniques in the short term. The expertise to analyse these data is yet confined to few centres and the analysis itself is time-consuming.

4. Conclusions

4.1 Connectivity studies in the larger context

Brain connectivity studies allow to address questions that have so far escaped a convincing answer. For example, what is the mechanism whereby in AD the deposition of Aβ and HP-tau takes place in largely distinct but highly interconnected hub regions? Why damage ensues to the whole network? Similar questions apply to alpha-synuclein in DLB and tau, TDP-43, and FUS in FTD. Several working models for network-based molecular

pathogenesis have begun to emerge. One parsimonious 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 may then move from pre- 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, alpha-synuclein, and Aβ disorders,[127-129] as well as from patients with PD who received transplanted dopaminergic neurons from fetal donors only to develop Lewy bodies within those neurons a few years after transplantation.[130] Other models emphasize the role of network-based dysregulation of excitation-inhibition balance (especially at the local microcircuit level),[131] disruption of activity- or connectivity-based inter-neuronal trophic factor support,[132] and the long-term metabolic demands of high synaptic plasticity and turnover.[133,134] These accounts need not be considered mutually exclusive and each presents a potential therapeutic target for exploration.

Finally, although the mechanisms noted above 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 considered primary diseases of networks. Alternatively, networks might be damaged and disrupted in these illnesses without representing the most relevant primary target. One ecumenical framework might suggest that these diseases begin by targeting selectively vulnerable, region-specific neuron classes, such that early-stage disease is best considered a primary “neuron-opathy”. Next, the disease may spread within local microcircuitry, producing accentuated damage within the site of initial injury. Long-range disease spread, during a next 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 require or benefit from treatments that target mechanisms of network-based disease propagation.

4.2 Technical issues and limitations

The analysis of functional networks is a multi-step procedure, in which methodological choices and assumptions must be made. The choice of the post-processing techniques such as artifact reduction, filtering, normalization, and nuisance variable regression can influence the results. Both ICA 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 remains a critical issue for this approach.[14] In addition, it is important to recognize that the spatial resolution of present EEG/MEG recording techniques poses limitations on the measurement of deep brain neuronal activity and therefore on the interpretation of the results.[33] Finally, data about the sensitivity, specificity and reliability of task-free fMRI and EEG/MEG data are still limited.[136] However, despite these important limitations, recent brain connectivity studies using different recording techniques and analytical approaches show converging results,[137] suggesting that a more cohesive view of brain (dys)function in dementia may arise from the study of networks.

4.3 Future directions

In broad terms, the study of functional network disruption in the degenerative dementias is in its infancy. Some conditions, such as AD, have been widely investigated with the described approaches. Other illnesses, such as PDD and DLB, as well as FTD language

variants, largely remain to be explored. In PD and DLB, a disease-specific ICA networks has not yet been identified with task-free fMRI, but recent work suggests a link to a basal ganglia network, anti-correlated with the DMN, which might be affected in these disorders.[123] Similarly, graph theoretical approaches may be used to assess functional changes in the PD spectrum. In addition, novel and more sophisticated approaches such as Bayesian network modelling may provide additional markers of connectivity by assessing causal relationships between nodes. Preliminary findings from the analysis of DMN with this method in AD look promising.[138]

In the coming years, technical improvements will help refine the topography of network degeneration. In addition, a complete understanding of network organization will require knowledge of how brain structure influences brain function, and *vice versa*. Strictly speaking, functional connectivity is unrelated to anatomy, i.e. functionally connected regions may 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 $40M NIH project, which aims to identify the brain network architecture by using advanced diffusion imaging with fMRI and EEG/MEG recordings (The Human Connectome Project; http://www.humanconnectomeproject.org/).

How might increasing focus on functional brain networks lead to more effective dementia therapies? The first hope relates to patient categorization, and AD provides an illustrative example. Among healthy older persons without cognitive impairment, high levels of brain Aβ are suspected to represent preclinical AD.[141] Pinpointing presymptomatic, Aβ-associated network disruption, as reported in several recent studies,[142,143] might identify a subgroup most likely to benefit from a disease-modifying pharmacological treatment. Similarly, network analysis may provide sensitive markers of preclinical FTD (e.g., in gene mutation carriers) and help to distinguish patients on the PD-DLB spectrum. Other approaches may seek to recalibrate networks directly. Phase I 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 AD.[144,145] Finally, task-free fMRI and neurophysiological methods provide attractive candidates for longitudinal, disease-monitoring biomarkers due 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 light of cross-sectional correlations between network connectivity strength and clinical severity,[58,59] cautious optimism seems justified.

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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”, “tumour” from 1986 until June, 2011. In addition, articles were identified through searches of the references of articles. Only papers published in English were reviewed. The final list of publications was selected by the authors on the basis of relevance to the topic.

Panel 1Glossary of basic network concepts

Network	A mathematical representation of a complex system made of a finite number of nodes and links (see below). 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 connections between them. Neural networks can be defined at multiple scales: microscopic (neurons and synapses), meso-scale (neural assembles and circuitry), macro-scale (anatomical regions and fiber tracts). Connections can be either structural or functional (see below). 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 (e.g., synchronous neuronal oscillations). Functionally connected nodes may show no direct physical connection.
Structural connectivity	The presence of physical connections between nodes (e.g., fiber tracts).
Module	Subset of network nodes with high internal connectivity.

Panel 2Glossary of graph theory terms

Graph	A visual representation of a network
Graph theory	A branch of mathematics investigating network characteristics such as topology (i.e., network structure), cost, efficiency and robustness (see below).
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 ‘wiring cost’.
Hub	A highly connected node (i.e., with a high degree). These nodes are relevant for efficient network communication, and damage to these nodes may 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. This network structure is presumed to be optimal 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 lower clustering coefficient and characteristic path length than small-world networks.
Efficiency	The inverse of the ‘characteristic’ path length, is considered 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 sub-networks (‘modules’). Modular networks are often relatively efficient and robust, and many real-world networks (including neural networks) can be considered modular.

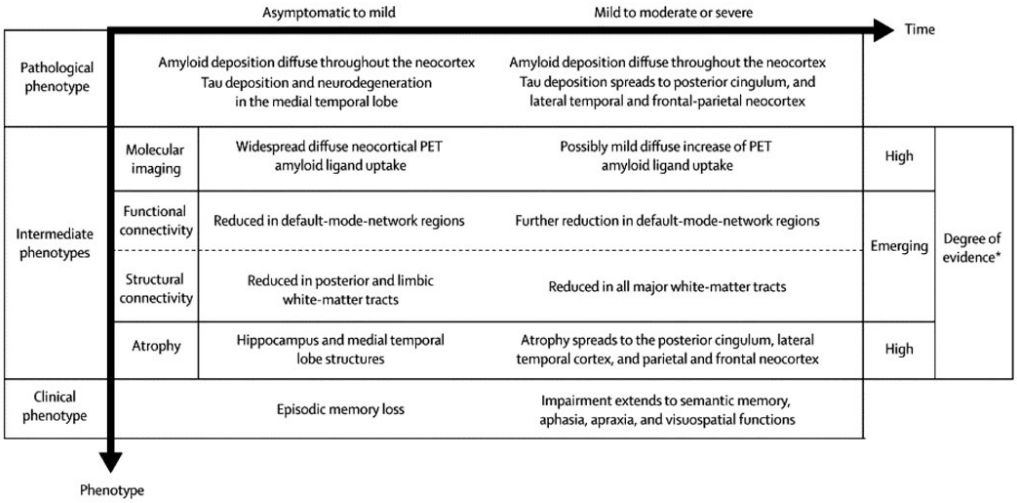

Figure 1.
The pathophysiological framework of neurodegenerative diseases: connectivity as an intermediate phenotype between pathology and symptoms. The case of AD.

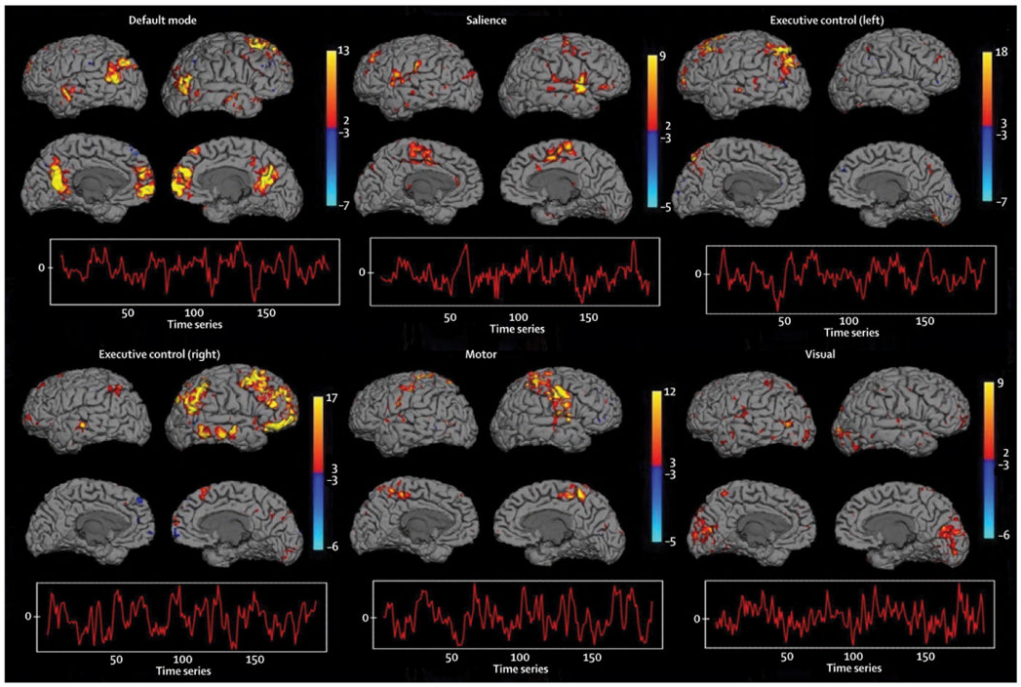

Figure 2.

Functional connectivity on resting-state fMRI in healthy subjects. ICA-derived resting-state fMRI networks (DMN, salience, left and right executive-control, visual and motor networks)[26-28] of a healthy 33-year old male. Red-to-yellow colours indicate the strength of each voxel's connectivity to overall component time series (shown beneath each map).

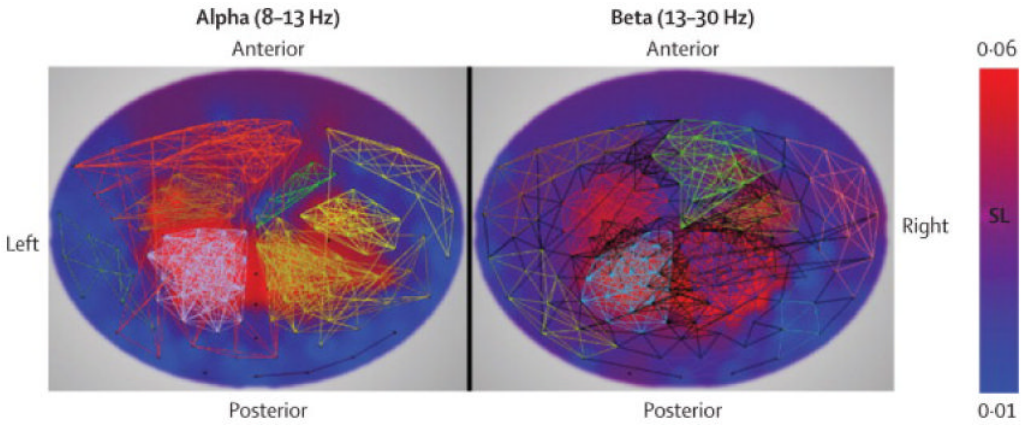

Figure 3.

Functional connectivity of resting-state EEG/MEG in healthy subjects. Headplot showing functional MEG network of a healthy 63-year old female in the alpha (8-13 Hz; *left*) and beta (13-30 Hz; *right*) frequency ranges.[13] Coloured lines indicate different functional sub-networks (modules), black lines represent their interconnections (only visualized in beta band example). Background colours indicate connectivity strength (red indicates hub – i.e. highly connected -regions). SL=synchronization likelihood.[13] A=Anterior; P=Posterior; L=Left; R=Right.

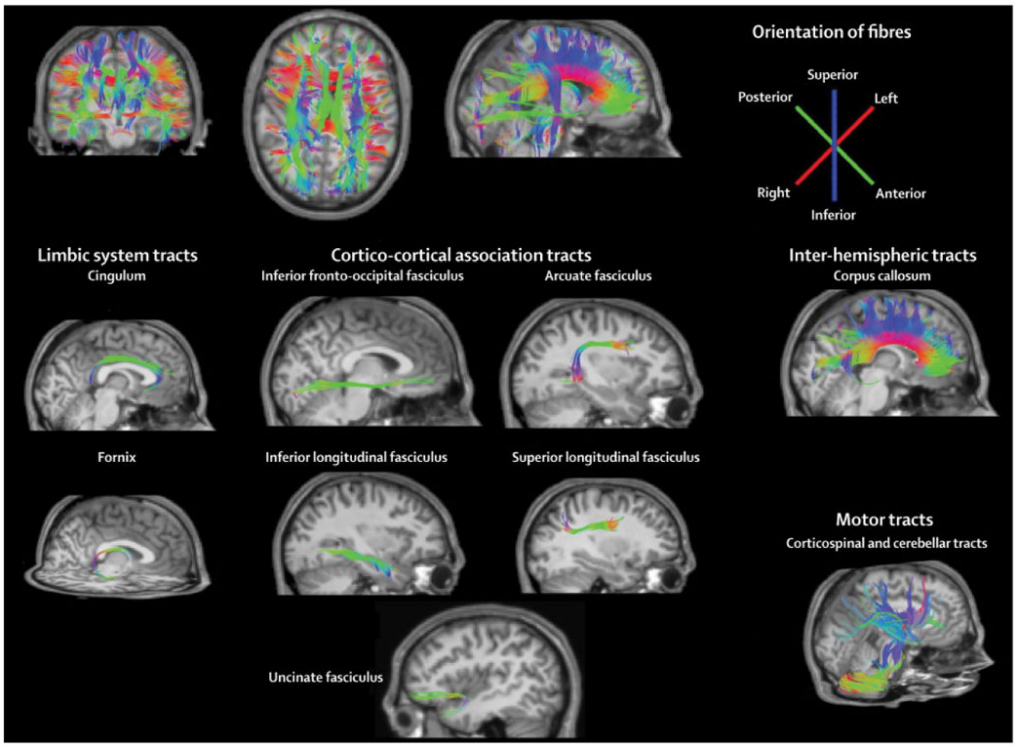

Figure 4.

Structural connectivity assessed with DTI in a healthy (33-year old male) subject. DTI-tractography identifies long (mainly visible in sagittal view as green and blue colour-coded fibers) and short (mainly visible in axial and coronal views as red colour-coded fibers) WM connections. Specific tracts can be identified which 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, the corticospinal/cerebellar tracts are generally involved in motor disorders.[36]

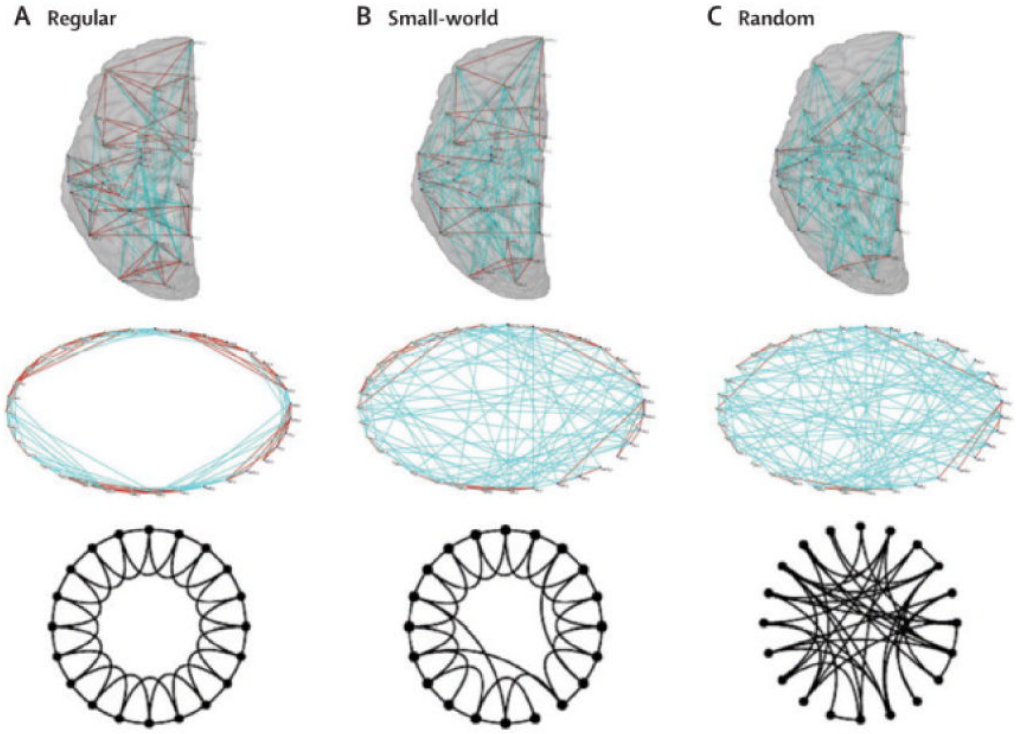

Figure 5.

Schematic representation of (B) 'small-world' brain functional network and of (A) simulated 'regular' and (C) 'random' networks with the same number of nodes (n=35) and connections (n=120). (A) Regular networks have many connections among neighbouring regions (red lines) and few connections with distant nodes (light blue lines). (B) Small-world networks have less local connections and more long distance connections. (C) Random networks have few local connections and many connections among distant regions. Each network is shown overlaid onto a standard template (*upper row*) and in schematic representation (*middle row*). Nodes represent 35 cortical points of the left hemisphere drawn from the Automated Anatomical Labeling template, and edges represent functionally connected nodes. The real-world network was extracted from a single subject, the corresponding regular (A) and random (C) networks were simulated using the Brain Connectivity Toolbox.[89] The corresponding theoretical Watts-Strogatz network models are also shown (*lower row;* adapted from ref [38]). Reproduced from Nature Publishing Group (permission requested).

Table 1

Connectivity as an intermediate phenotype in the degenerative dementias. Details on connectivity are exploded in Table 2.

		Alzheimer's Disease	Frontotemporal degeneration (b.v.)	Parkinson's disease	Dementia with Lewy Bodies
Molecular phenotype		*β-amyloid* Distributed throughout neocortex *Hyper-phosphorylated τ* Medial temporal lobe	*τ, TDP-43 or FUS* Frontal cortex Anterior temporal cortex Striatum Amygdala Thalamus	*α-synuclein* Brainstem (dorsal motor nucleus of c.n., locus coeruleus substantia nigra)	*α-synuclein* Brainstem (dorsal motor nucleus of X c.n., locus coeruleus substantia nigra)
Intermediate phenotype	**Molecular imaging**	Widespread diffuse neocortical amyloid ligand uptake on PET	N.A.	N.A.	N.A.
	Connectivity	Default mode network disruption on “task-free” functional MRI/ EEG/MEG	Salience network disruption	Basal ganglia-thalamocortical loop abnormalities	N.A.
	Structural imaging	Atrophy in the medial temporal lobe	Atrophy in the anterior cingulate cortex, frontoinsula, frontal pole, temporal pole, striatum, thalamus amygdala.	Mild atrophy in the frontal, temporal, and basal ganglia	Atrophy in the substantia nigra, midbrain, hypothalamus, basal forebrain, amygdala
Clinical phenotype		Episodic memory loss	Social-emotional deficits	Motor impairment (tremor, rigidity, bradykinesia, and postural instability)	Hallucinations, parkinsonism, fluctuations in cognition, motor impairment

b.v.: behavioural variant; c.n.: cranial nerve; EEG: Electroencephalography; FUS: FUsed in Sarcoma; MEG: Magnetoencephalography; MRI: Magnetic Resonance Imaging; N.A.: Not Available; PET: Positron Emission Tomography; TDP-43: TAR DNA-binding protein of 43 kDa.

Table 2

Connectivity disruption in the degenerative dementias.

		Alzheimer's Disease	Frontotemporal degeneration (b.v.)	Parkinson's Disease	Dementia with Lewy Bodies
Functional	**Resting-state fMRI**	↓ DMN	↓ salience network	↑ basal ganglia-thalamocortical loops Normalization following levodopa administration	Insufficient evidence
	Resting-state EEG/MEG	↓ alpha and beta (8-30Hz) between long distance fronto-parietal and fronto-temporal regions	Insufficient evidence	↑ alpha and beta (8-30 Hz) locally and globally	↓ alpha (8-13 Hz) locally and globally
Structural connectivity (DTI)		↓ posterior and limbic WM tracts	↓ anterior WM tracts	No change in the major WM tracts	↓ visual pathway
Network organization		small-world → random hub vulnerability	small-world → regular	Insufficient evidence	No evidence

b.v.: behavioural variant; DMN: Default Mode Network; DTI: Diffusion Tensor Imaging; EEG: Electroencephalography; fMRI: Functional Magnetic Resonance Imaging; MEG: Magnetoencephalography; WM: White Matter.

↓reduced connectivity;

↑increased connectivity;

→change toward a different topology