CNS Neuroscience & Therapeutics

REVIEW

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Propagation of Pathology through Brain Networks in Neurodegenerative Diseases: From Molecules to Clinical Phenotypes

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SUMMARY

The cellular mechanisms underlying the stereotypical progression of pathology in neurodegenerative diseases are incompletely understood, but increasing evidence indicates that misfolded protein aggregates can spread by a self-perpetuating neuron-to-neuron transmission. Novel neuroimaging techniques can help elucidating how these disorders spread across brain networks. Recent knowledge from structural and functional connectivity studies suggests that the relation between neurodegenerative diseases and distinct brain networks is likely to be a strict consequence of diffuse network dynamics. Diffusion tensor magnetic resonance imaging also showed that measurement of white matter tract involvement can be a valid surrogate to assess the *in vivo* spreading of pathological proteins in these conditions. This review will introduce briefly the main molecular and pathological substrates of the most frequent neurodegenerative diseases and provide a comprehensive overview of neuroimaging findings that support the "network-based neurodegeneration" hypothesis in these disorders. Characterizing network breakdown in neurodegenerative diseases will help anticipate and perhaps prevent the devastating impact of these conditions.

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Introduction

Neurodegenerative diseases have an enormous diversity in clinical phenotypes, affecting distinct cerebral functions. In recent years, however, intense research has been made in the field, arising the knowledge that they also share some common features. One of these commonalities is the accumulation of disease-specific proteins into insoluble aggregates [1,2], such as amyloid β (Aβ) in plaques in Alzheimer disease (AD), tau in neurofibrillary tangles (NFTs) in AD and many cases of frontotemporal lobar degeneration (FTLD), TAR DNA-binding protein 43 (TDP-43) aggregates in amyotrophic lateral sclerosis (ALS) and cases of FTLD, and α-synuclein (α-syn) in Lewy bodies (LB) in Parkinson disease (PD) and Dementia with Lewy bodies (Figure 1). This evidence has allowed the diseases to be recategorized in proteinopathies based on their molecular traits. Second, pathological changes in various neurodegenerative diseases progress with time in a stepwise characteristic anatomical pattern. Neuropathological studies have shown that NFTs in AD [3], LB in PD [4], and, more recently, TDP-43 aggregates in ALS [5] and the behavioral variant of frontotemporal dementia (bvFTD) [6] initiate very early in the disease in a circumscribed area of the brain and then progress in a topographically predicted manner through anatomical connections (Figure 1). Until recently, the causative mechanisms for this networked spread were thought to be passive, including secondary Wallerian degeneration, disconnection, loss of signaling, axonal reaction, and postsynaptic dendrite retraction [1,2]. The latest evidence, however, favors the hypothesis that the stereotypical and topographical patterns of pathological progression in the central nervous system (CNS) of patients with neurodegenerative diseases may be explained by a "prion-like" transsynaptic or transneuronal spreading of misfolded proteins between different brain regions over years [1,2]. Understanding how and where pathological protein propagation is initiated and the characterization of the major factors playing a role in the modulation of intracerebral spreading will lead to the identification of new

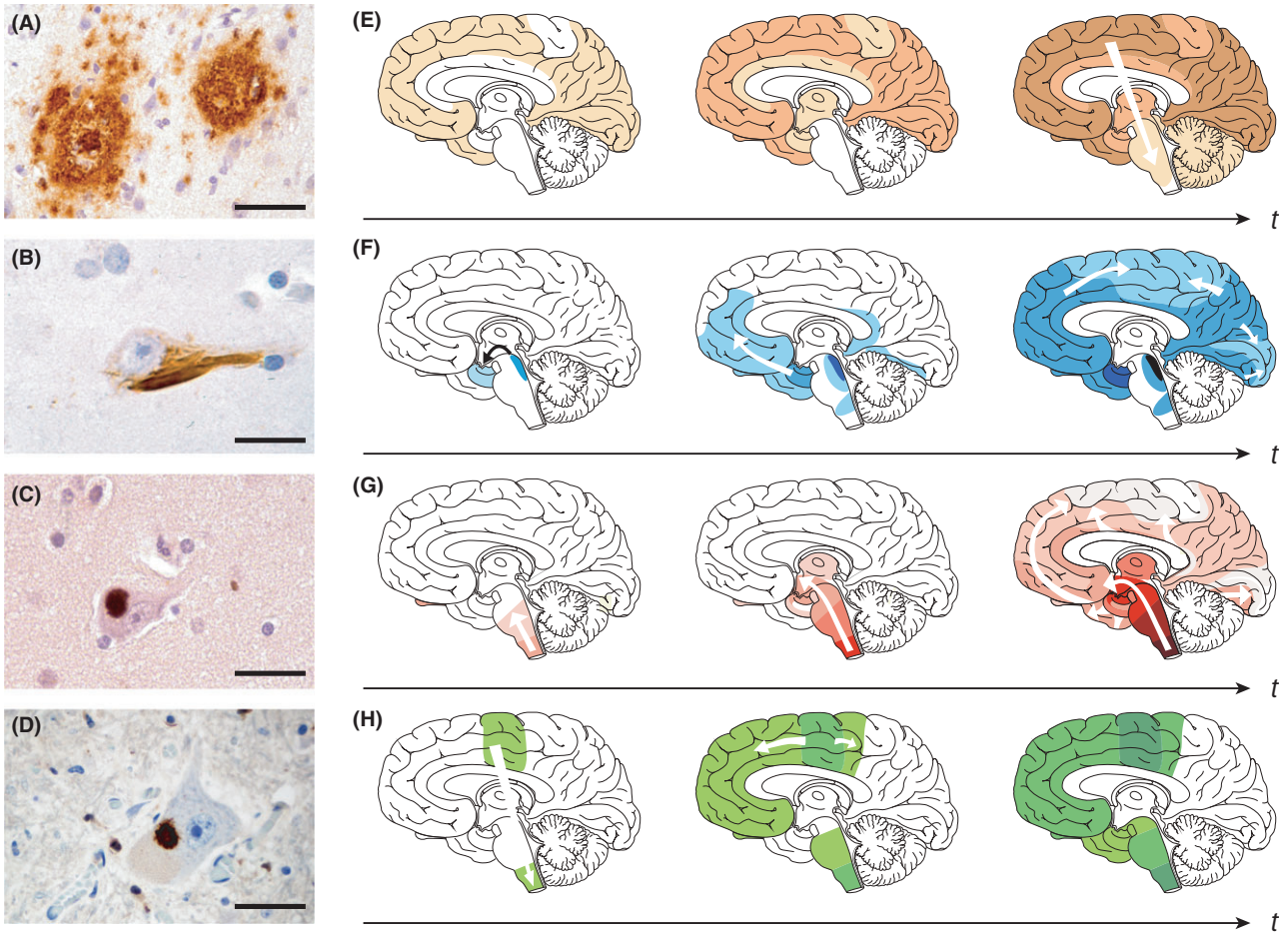

Figure 1 Protein aggregates show "prion-like" self-propagation and spreading in experimental settings, consistent with the progressive appearance of the lesions in the brain of patients with neurodegenerative diseases. (**A**) Aβ deposits in the neocortex of a patient with Alzheimer disease (AD). (**B**) Tau inclusion as a neurofibrillary tangle in a neocortical neuron of a patient with AD. (**C**) α-Synuclein inclusion (Lewy body) in a neocortical neuron from a patient with Parkinson disease (PD)/Lewy body dementia. (**D**) TDP-43 inclusion in a motor neuron of the spinal cord from a patient with amyotrophic lateral sclerosis (ALS). Scale bars are 50 μm in a and 20 μm in **B**–**D**. (**E**–**H**) Characteristic progression of specific proteinaceous lesions in neurodegenerative diseases over time (t, black arrows), inferred from postmortem analyses of brains. Aβ deposits and tau inclusions in brains of patients with AD (**E** and **F**), α-synuclein inclusions in brains of patients with PD (**G**), and TDP-43 inclusions in brains of patients with ALS (**H**). Three stages are shown for each disease, with white arrows indicating the putative spread of the lesions. Reproduced with permission from [2].

therapeutic targets aiming at slowing or stopping the disease progression.

In parallel to the molecular and pathological advances, the idea that the pathological substrates of neurodegenerative diseases spread along discrete brain networks has also been increasingly strengthened by neuroimaging studies [7]. It has been observed, indeed, that neurodegenerative diseases spatially affect patterns that reflect the healthy brain's network architecture [8]. In this review, we will introduce briefly the main molecular and pathological substrates of the most frequent neurodegenerative diseases. Then, we will provide a comprehensive overview of neuroimaging findings that support the "network-based neurodegeneration" hypothesis in patients with AD, bvFTD, ALS, and PD, bringing studies that range from the large-scale brain networks alterations to the microscopic abnormalities of structural pathways.

Clinical Phenotypes, Molecules, and Pathology of Neurodegenerative Diseases

Alzheimer Disease

Alzheimer disease is the most common form of dementia. Typically, AD is characterized by an insidious onset of cognitive decline, starting with deficits in episodic memory. As the disease progresses, other deficits such as aphasia, apraxia, agnosia, visuospatial difficulties, and executive dysfunction arise gradually [9]. The patient becomes increasingly dependent on others. Psychiatric and behavioral problems such as mood disorders, psychosis, agitation, and sleep disorders occur more frequently in the advanced phase of the disease. The term mild cognitive impairment (MCI) identifies those individuals who have subjective

memory and/or cognitive symptoms accompanied by objective evidence of isolated memory and/or other cognitive impairment and whose activities of daily living are considered to be generally normal [10]. Progression to clinically diagnosable dementia occurs at a higher rate from MCI than from normal (typically 10–15% per year—compared to rates of ~1% with normal aging), but is clearly not the invariable clinical outcome at follow-up [10].

Besides the typical neuropsychological profile of AD presenting with early memory deficits, there is evidence from clinicopathological studies that patients with AD may present with different cognitive profiles. Atypical presentations are more often seen in patients with early-onset AD (EOAD) (arbitrarily defined as before the age of 65). EOAD is often characterized by atypical manifestations with greater impairment in attention, executive, language, and visuospatial functions at the time of presentation. Furthermore, AD can present as relatively focal clinical syndromes, more frequently associated with early age-of-onset, that is, as posterior cortical atrophy (PCA) and logopenic variant (lv) of primary progressive aphasia (PPA) [11]. PCA presents with visual and visuospatial impairment with less prominent memory loss [12,13]. Over time, patients with PCA can develop visual agnosia, topographical difficulty, optic ataxia, simultanagnosia, ocular apraxia (Balint syndrome), alexia, acalculia, right–left confusion, and agraphia (Gerstmann syndrome), and later a more generalized dementia. Patients with lvPPA present with language deficits, characterized by slow rate of speech, with long word-finding pauses [14]. Grammar and articulation are usually preserved in lvPPA, although phonological paraphasias could be present. Repetition and comprehension are impaired for sentences but preserved for single words, and naming is moderately affected [14].

Two abnormal protein aggregates characterize AD pathology: neuritic plaques and NFTs [15]. Neuritic plaques are extracellular deposits and consist of a dense central core of Aβ fibrils with inflammatory cells and dystrophic neurites in its periphery. Aβ peptide is a normal proteolytic product of the Aβ precursor protein (APP) [16]. Due to the ability of the protease γ-secretase to cleave APP at multiple sites, Aβ peptides are 39–43 amino acid residues in length, but Aβ_{40} and Aβ_{42} are the predominant species *in vivo*. In contrast, plaques in AD are composed primarily of Aβ_{42} and Aβ_{43}, which are more hydrophobic and aggregation-prone than the slightly shorter and more polar (but very abundant) Aβ_{40}. The second major proteinopathy in AD is aggregated tau, which consists of intraneuronal polymers primarily composed of hyperphosphorylated tau in the form of NFTs [15]. Tau is a natively unfolded cytoplasmic protein that normally helps microtubule stabilization [17]. If hyperphosphorylated, tau becomes prone to aggregation. In AD, the pattern of tau pathology is highly regular, whereas Aβ plaque pathology is much more varied. NFTs follow a stereotypic topographical progression scheme as described by Braak and Braak [3], first appearing in the entorhinal cortex and closely related areas, then progressing to the hippocampus, to paralimbic and adjacent medial-basal temporal cortex, to association cortex, and last to primary sensorimotor and visual cortical areas.

The initiating event in the molecular cascade that eventually leads to clinical and pathological AD has been controversial for decades. The amyloid cascade hypothesis, which posits that Aβ production and aggregation in the brain are the prime pathogenic drivers, leading to tau hyperphosphorylation and other histological and clinical features of AD, has dominated research for the past 20 years [18]. The amyloid cascade hypothesis was reinforced by the identification of gene defects in *APP*, *PSEN1*, and *PSEN2* in patients with an early-onset, inherited form of the disease [19]. The APP gene on chromosome 21 encodes the APP, from which Aβ is liberated after stepwise, amyloidogenic, proteolytic processing. The genes *PSEN1* and *PSEN2* encode presenilin 1 and presenilin 2, which are part of the γ-secretase complex, the enzyme that carries out the second cleavage in APP processing. An alternative position is that tau hyperphosphorylation and Aβ accumulation are independent interacting pathophysiological processes [20–22]. According to this second hypothesis, it is tau-related neurodegeneration that is ultimately responsible for clinical symptoms [23].

Frontotemporal Lobar Degeneration

Frontotemporal lobar degeneration is the umbrella term encompassing a group of progressive proteinopathies, which are heterogeneous with regard to etiology and neuropathology, but share atrophy of the frontal and/or temporal cortex as a morphological feature and the deposition of abnormal, ubiquitinated protein inclusions in the cytoplasm and nucleus of neuronal and glial cells as major pathological constituent [24]. FTLD includes three clinical syndromes and three major underlying neuropathological subtypes. The clinical syndromes, which are distinguished by the early and predominant symptoms, are as follows: a bvFTD; a language disorder (nonfluent and semantic PPA variants); and a motor disorder such as ALS, corticobasal syndrome, and progressive supranuclear palsy (PSP) syndrome [25]. This review focused on evidence for the "network-based neurodegeneration" hypothesis in bvFTD and ALS. bvFTD is characterized by a prominent change in personality and social behavior, with apathy and/or disinhibition, emotional blunting, stereotyped or ritualized behaviors, loss of empathy, alterations in appetite and food preference with limited or no insight [26]. ALS, the most common form of motor neuron disease, is a relatively rare progressive degenerative condition affecting the lower motor neurons within the spinal cord and the brainstem, accompanied by degeneration of the upper motor neurons in the motor cortex [27]. Up to 50% of patients with ALS have also cognitive and/or behavioral changes, ranging from an overt FTD to mild executive and/or nonexecutive cognitive impairment and behavioral deficits [28]. The neuropathological subtypes are characterized by an abnormal accumulation of proteins [29]: microtubule-associated protein tau (MAPT), TDP-43, and fused in sarcoma protein (FUS). FTLD-tau, FTLD-TDP, and FTLD-FUS represent 45%, 50%, and 5% of all FTLD cases, respectively, at postmortem examination.

Frontotemporal lobar degeneration-tau cases include those with the neuropathology of Pick disease, PSP, corticobasal degeneration (CBD), and cases of familial FTLD caused by mutations in the MAPT gene. FTLD-tau subtypes are characterized by specific inclusions: Pick bodies in Pick disease, tufted astrocytes and numerous NFTs in subcortical nuclei in PSP, and astrocytic plaques and abundant thread pathology in CBD [29]. In addition, the biochemical form of tau that accumulates in the inclusions varies among the different subtypes, with Pick bodies composed primarily of tau isoforms with three microtubule-binding domains

(3-repeat), while the inclusions of PSP and CBD contain 4-repeat tau [29].

In 2006, the majority of cases with tau-negative inclusions that stained positive for ubiquitin in FTLD were found to contain TDP-43 protein, as did the majority of sporadic and familial ALS cases [30]. TDP-43 is a highly conserved and widely expressed RNA-binding protein that is a member of the heterogeneous nuclear ribonucleoprotein family of proteins [31]. It is predominantly found in the nucleus, but shuttles between there and the cytoplasm, where it is present only at low levels. Pathological modifications of TDP-43 in the disease state include a redistribution from the nucleus to the cytoplasm in cells with inclusions, hyperphosphorylation, ubiquitination, and N-terminal truncation [31]. Dominantly inherited genetic mutations within the gene that encodes TDP-43 (TAR DNA-binding protein, *TARDBP*) are linked with ALS and FTLD-TDP phenotypes [24]. Different patterns of FTLD-TDP are now recognized, based on the cortical distribution and relative abundance of cytoplasmic inclusions compared to neurites, with each having fairly specific clinical and genetic correlations [29].

Most of the remaining tau-/TDP-negative FTLD subtypes are characterized by cytoplasmic inclusions that are immunoreactive for FUS [32]. FUS is a 526 amino acid protein identified as a fusion oncogene causing human myxoid liposarcomas. When in the nucleus, FUS is thought to be involved in regulation of transcription and pre-mRNA splicing. Cytoplasmic FUS in neurons appears to have a role in mRNA transport, where it can potentially facilitate local protein synthesis at synapse.

Recent pathological studies based upon the distribution patterns of phosphorylated TDP-43 indicate that the disease progression in ALS and bvFTD cases with FTLD-TDP pathology progresses in a sequential regional pattern possibly through axonal pathways [5,6]. ALS and FTLD-TDP bvFTD are characterized by four neuropathological stages. In ALS [5], initial lesions (stage 1) develop in the frontal and sensorimotor cortex, brainstem motor nuclei, and in spinal cord α-motor neurons, with beginning involvement of the prefrontal cortex, brainstem reticular formation, precerebellar nuclei, and red nucleus in stage 2; in stage 3, pathology progresses in the prefrontal and postcentral cortices, and striatum, followed by changes in anteromedial portions of the temporal lobe, including the hippocampal formation, during stage 4. FTLD-TDP bvFTD cases with the lowest burden of pathology (pattern 1) are characterized by widespread phosphorylated TDP-43 lesions in the orbitofrontal cortex and amygdala [6]. With increasing burden of pathology (bvFTD pattern 2), TDP-43 lesions emerged in the middle frontal and anterior cingulate gyrus as well as in anteromedial temporal lobe areas, the superior and medial temporal gyri, striatum, red nucleus, thalamus, and precerebellar nuclei. More advanced bvFTD cases show a third pattern (3) with involvement of the motor cortex, bulbar somatomotor neurons, and the spinal cord anterior horn, whereas cases with the highest burden of pathology (pattern 4) are characterized by TDP-43 lesions in the visual cortex.

Parkinson Disease

Parkinson disease, the most common neurodegenerative movement disorder, is characterized clinically by four cardinal motor symptoms: rigidity, tremor, bradykinesia, and postural instability [33]. Symptoms develop slowly and gradually progress over years. Superimposed on the classic motor symptoms, autonomic and sensory dysfunction, sleep disturbances, cognitive impairments and dementia are also common features in PD [34,35].

The pathological hallmark of PD is the presence of intraneuronal proteinaceous intracytoplasmic inclusions called LB. One of the main protein components of the LB is α-syn [36]. α-syn is a 14-kDa natively unfolded protein, consisting of 140 amino acids, that binds lipids through its amino-terminal repeat region. It is localized in the presynaptic terminals, nucleus, cytosol, and in some cellular membranes, such as the mitochondria-associated membrane in the endoplasmic reticulum. Although the exact function of α-syn remains unknown, substantial evidence suggests that α-syn function is related to its capacity to interact directly with membrane phospholipids, particularly highly curved membranes such as vesicles [37]. In particular, α-syn seems to play a role in the vesicle trafficking during the neurotransmission release. In PD, this protein leaves its binding sites within synaptic boutons and, together with other components such as phosphorylated neurofilaments and ubiquitin, gradually adopts insoluble oligomeric and/or fibrillary conformations [38]. α-syn pathological species are toxic *in vivo* by several mechanisms including the disruption of normal α-syn function in neurotransmission release and vesicular transport, and impairing mitochondrial structure and the efficiency of some protein-degradation mechanism [39].

In 2003, Braak et al. [4] performed several longitudinal analyses to evaluate the neuroanatomical changes in the brain of patients with PD and proposed a model in which the disease stages are correlated with the regional distribution of LB in the CNS. According to the Braak's model, LB formation starts early in the disease (even before the motor symptoms emerge) and LB originate in the olfactory bulb and in the brainstem, specifically at the dorsal motor nucleus of the vagus nerve. In parallel to disease progression, LB are detected in other brain regions and appear to propagate through brain structures, in a stereotypic pattern, to reach the other regions including the midbrain and, at later stages, the cerebral cortex.

The "Prion-Like" Transmission of Pathogenic Proteins in Neurodegenerative Diseases

Prion diseases are a unique group of neurodegenerative disorders in which the conformationally altered prion protein PrP^{Sc} constitutes the infectious agent that corrupts normal cellular PrP through "seeded" fibrillization [40]. Although not being infectious, that is, transmissible between people, a rapidly growing body of literature has provided compelling evidence that a "prion-like" self-propagating mechanism may be applicable to a wide range of disease-associated proteins, including Aβ, tau, TDP-43, and α-syn [1,2]. The self-propagation of aggregates of Aβ was predicted decades ago [1,2]. More recently, the ability of tau to propagate transsynaptically through well-established brain anatomical pathways has been reported, including AD and FTLD cases with argyrophilic grain pathology [17]. Experimental support for the existence of a cell-to-cell transfer of α-syn inclusions has come from the seminal research showing that misfolded intraneuronal α-syn can transfer to neighboring cells both in culture and in the

brains of patients with PD who had received fetal mesencephalic nerve cell transplants 11–16 years earlier revealing the presence of LB in the grafts [41,42]. Then, several *in vitro* and *in vivo* studies suggested that α-syn can undergo a toxic template conformational change, spread from cell to cell and from region to region, and initiate the formation of LB-like aggregates, contributing to the PD pathogenesis [41,42]. Whereas a cell-to-cell transmission of TDP-43 has not been demonstrated conclusively, a recently discovered C-terminal prion-like domain has been implicated in the aggregation of TDP-43 in cultured cells from diseased brains [31,43]. In addition, a notable feature shared by nearly all neurons involved in ALS is that they receive strong afferents from neocortical pyramidal cells, supporting a neuron-to-neuron propagation through corticofugal connections [5].

It seems likely that prion-like aggregates are able to travel within the neuron to reach potential site for interneuronal transfer, to be released from the originating cell and taken up by neighboring cells, where they penetrate the cytoplasm and nucleate further aggregation [1,2]. Both tau and α-syn aggregates can move anterogradely as well as retrogradely within a neuron, possibly by axonal transport. Among the potential mechanisms of the cell-to-cell spreading of proteins, endocytosis or receptor-mediated endocytosis, transfer through exosomes or even by nanotubes that directly connect the cytoplasm of two cells, has been reported [1,2]. Regardless of the mechanism of transmission between cells and the consequent ability of self-amplification, what triggers the initial conversion of normally produced proteins into abnormal aggregates remains unknown.

Functional and Structural Connectivity-Based Findings in Neurodegenerative Diseases

Functional and Structural Connectivity-Based Imaging Techniques

Resting-state fMRI constitutes an advanced technique that measures the spontaneous low-frequency (<0.001–0.001 Hz) fluctuations of the blood oxygen level-dependent signal while the individual rests in the scanner without performing any task. Resting-state fMRI allows to examine brain connectivity between functionally linked brain regions with no bias toward specific motor, visual and cognitive functions [44]. Spatially distributed maps of temporal synchronization can be detected that characterize resting-state networks [45]. Resting-state fMRI assessment has been focused primarily on a characteristic set of brain regions, including the posterior cingulate and precuneus, inferolateral parietal cortex, medial temporal lobe, and medial prefrontal cortex, which is deactivated during a broad range of cognitive tasks and is believed to support a default mode activity of the human brain (i.e., default mode network [DMN]) [46]. Analysis of resting-state fMRI data has more recently suggested the existence of other networks which are thought to subserve cognition, such as the salience, executive, frontoparietal, and associative visual networks [45].

Information on the microstructural integrity of the white matter (WM) pathways connecting the different structures of the human brain can be obtained *in vivo* using diffusion tensor (DT) MRI [47]. DT MRI characterizes the three-dimensional diffusion of water as a function of spatial location [47]. The two most common DT MRI measures are mean diffusivity (MD) and fractional anisotropy (FA). MD is a measure of the magnitude of diffusion and is rotationally invariant. FA describes the degree of anisotropy of the diffusion tensor. The diffusion of water within the tissues will be altered by changes in the tissue microstructure and organization due to many pathologic processes of the CNS, including demyelination, axonal damage, edema, and ischemia [48].

Alzheimer Disease

Neurodegeneration in AD leads to a marked reduction of brain tissue. Indeed, typical late-onset, amnestic AD is characterized by global atrophy on MRI. The medial temporal lobes, especially the hippocampus and entorhinal cortex, are among the earliest sites of structural damage [49]. Other severely affected regions include the posterior part of the cingulate gyrus, precuneus, and splenium of the corpus callosum on the medial surface, and the parietal, posterior superior temporal, and frontal regions on the lateral cerebral surfaces [49].

Interestingly (yet probably not coincidently), there is a remarkable overlap between the pattern of Aβ pathology and atrophy in AD and the DMN [50]. A decreased DMN connectivity has been described in patients with AD [51,52] as well as in patients with amnestic MCI [51,53–55] and in healthy elderly subjects harboring amyloid plaques (as measured by amyloid imaging) [56,57] or carrying the apolipoprotein E4 allele [58]. In addition, altered connectivity among the DMN nodes do occur regardless cortical damage [59], suggesting that functional deficits within the network may precede structural damage. As the disease progresses, DMN connectivity continues to decline as shown by cross-sectional studies across successive disease stages [60] and a few longitudinal studies [61].

Other brain networks are inevitably affected with AD progression. However, the sequence of involvement of functional systems outside the DMN is not well known. Resting-state fMRI studies demonstrated aberrant functional connectivity in the executive network and the salience network in patients with AD, along with loss of anticorrelation between the DMN and the executive network along the AD continuum [51,62].

Another compelling evidence supporting the notion that neurodegenerative diseases spread along networks comes from recent studies in patients with atypical AD forms, such as PCA and lvPPA. Recent studies combining structural MRI from patients with resting-state fMRI data from healthy subjects highlighted that the DMN is affected in all AD forms. In addition, there is a good anatomical correspondence between the patterns of atrophy in patients (i.e., of the visual network in PCA and language network in lvPPA), distinct brain functional networks in healthy subjects, and symptoms for each AD variant (Figure 2). Therefore, these recent multimodal analyses seem to suggest that atypical AD forms may reflect a different dissemination of pathology through specific interconnected neural networks relative to typical, late-onset AD [63,64].

White matter tracts that connect regions of the DMN, such as the cingulum (linking the medial temporal lobe with the posterior

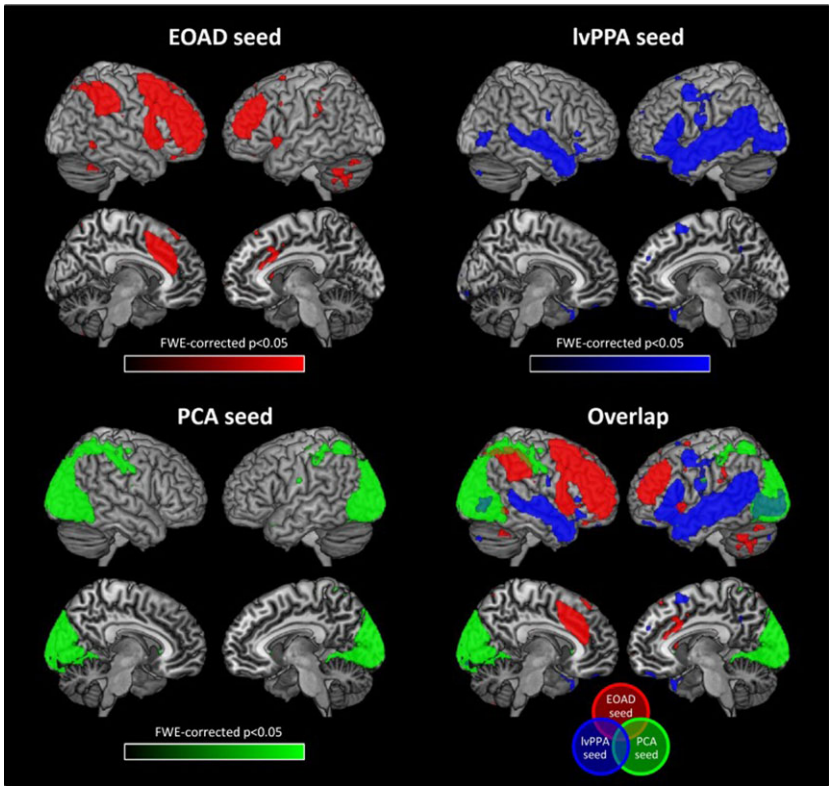

Figure 2 Resting-state functional connectivity network maps in healthy individuals produced by seeding three regions that were specifically atrophied in Alzheimer disease (AD) variants, that is, early-onset AD (EOAD), posterior cortical atrophy (PCA), and logopenic variant of primary progressive aphasia (lvPPA). Figure shows statistical *P* maps after correction for multiple comparisons ($P < 0.05$ family-wise-error corrected for multiple comparisons). Reproduced with permission from [64].

cingulate cortex and the medial frontal regions) and the corpus callosum, are widely affected in patients with AD [65,66]. Damage to these WM regions correlates with cognitive impairment and disease progression in patients with AD [67] and may be related to secondary degeneration. Nevertheless, another major finding of DT MRI studies in AD is that WM damage is more severe and widely distributed than expected on the basis of cortical atrophy. In addition, in MCI and healthy subjects, WM damage can be detected even before the development of cortical atrophy and overt dementia [68,69]. To date, the causes of WM degeneration in AD are still unknown. However, converging data support the notion that WM damage has a central role in how the disease strikes and progresses. Here again, DT MRI findings may reflect the dissemination of pathology from early damaged to yet unaffected cortical regions in AD, thus supporting pathological transmission of Aβ and tau aggregates from neuron to neuron along WM connections [1,2]. In keeping with this hypothesis, a DT MRI study of patients with AD and MCI suggested that microglia activation, which produces neurotoxic and oligodendrotoxic oligomers in the presence of Aβ in excess, can contribute to disease spreading to neighboring and connected areas through WM tracts [70]. In addition, one study investigating the patterns of WM damage in atypical AD variants suggested that the disease has targeted specific peripheral networks (memory, visual, language) at onset in different AD forms and then converged to medial and dorsal frontoparietal regions [71]. The spread of pathology in AD would occur through the corpus callosum and the main long-range WM fibers between the posterior and anterior brain regions [71]. Together with functional connectivity studies, DT MRI findings suggest that clinical heterogeneity of AD may be related to the fact that pathology starts from different medial temporal or lateral neocortical hubs and then eventually progresses along the same WM network to converge to a similar pattern of involvement matching the key hubs of the DMN. Longitudinal studies are needed to confirm such a model clarifying *in vivo* the direction of the pathology spreading through brain networks in AD.

Frontotemporal Lobar Degeneration

Behavioral Variant FTD

In bvFTD, early atrophy occurs in orbitofrontal/subgenual, medial frontal cortex (including anterior cingulate cortex), frontoinsula, anterior temporal lobe, and basal ganglia [72]. In bvFTD, atrophy maps strongly resemble a resting-state fMRI network called salience network [73]. This network is activated in tasks requiring attentional selection, task switching, and self-regulation of behavior, that is, events where we determine which inputs are salient for processing [74]. Within this network, two key nodes have been identified: the frontoinsula, an afferent hub which integrates

inputs coming from other networks with the interoceptive ones; and the anterior cingulate cortex, an efferent hub, which detects information from the previous hub and mobilizes visceroautonomic, emotional, cognitive, and behavioral responses [75]. Patients with bvFTD have reduced connectivity in the salience network when compared either with controls or with patients with AD [76–78]. In patients with bvFTD, the functional disconnectivity between these key nodes has been correlated with clinical severity, apathy, and disinhibition scores [76,78]. In addition, measures of salience network connectivity involving the left insula predict behavioral changes in patients with bvFTD [79].

White matter tracts connecting the key regions of the salience network are also altered [80–82], such as the uncinate fasciculus and genu of the corpus callosum. However, studies have shown that WM alterations may also go beyond the regions of cortical atrophy in a more distributed manner [80–82]. Indeed, with the disease progression, WM abnormalities involve the posterior temporal and parietal regions, reflecting distal propagation of the pathology [83]. It is worth noting that presymptomatic FTLD gene carriers present the same functional network alterations observed in patients with bvFTD without cortical atrophy but with considerable WM abnormalities in frontotemporal regions [84]. These results suggest that WM alterations might precede cortical tissue loss and that DT MRI metrics can be a marker of pathology spreading through WM tracts in FTLD cases.

Amyotrophic Lateral Sclerosis

MRI observations revealed cross-sectional brain atrophy in the motor and/or premotor cortices of patients with ALS [85]. Several resting-state fMRI studies of ALS reported significantly decreased functional connectivity within the sensorimotor network [86–89] in keeping with the structural damage. However, other studies have identified regions of increased functional connectivity in the somatosensory system [89–92]. Two scenarios have been described to explain increased connectivity patterns. First, increased functional connectivity might compensate for structural damage and exhaust with increasing burden of pathology [91,93]. Second, the high level of functional connectivity in ALS might be related to pathogenic loss of local inhibitory circuitry [94]. Indeed, increased functional connectivity was found over a large area spanning sensorimotor, premotor, prefrontal, and thalamic regions overlapping areas abutting WM tracts showing loss of integrity at DT MRI [92,95].

Diffusion tensor MRI studies of patients with ALS have consistently reported the involvement of the corticospinal tract and middle-posterior parts of the corpus callosum, correlating with disease severity and rate of disease progression [85]. Although diagnosed and classified on the basis of motor system involvement only, the growing body of evidence demonstrating a frontotemporal syndrome is undeniable. In keeping with pathological and clinical data, an altered (both decreased and increased) functional connectivity of brain networks associated with cognition and behavior was found in ALS, even in the absence of overt dementia [86,88,93]. Patients with ALS also show abnormalities in extramotor WM regions, especially in frontotemporal areas, in relation to the occurrence of cognitive impairment or ALS-FTD [96–99].

A recent study used DT MRI tractography to assess the pathways that are prone to be involved in ALS according to the different pTDP-43 stages [5], and revealed significant WM tract abnormalities in patients relative to controls in a sequential progression [100] (Figure 3), that is, the corticospinal tract (stage 1), the corticorubral and corticopontine tracts (stage 2), the corticostriatal pathway (stage 3), and the proximal portion of the perforant path (stage 4). These results mirror the proposed neuropathological propagation pattern of ALS [5], supporting *in vivo* the evidence of the progressive expansion of WM damage from the motor to the extramotor networks.

Parkinson Disease

Although conventional structural MRI remains normal in PD until the late stage, advanced techniques have shown abnormalities in the substantia nigra and the cortex [101]. Several studies assessed the resting-state fMRI pattern of the corticostriatal–thalamic–cortical circuits in patients with mild to moderate PD, most of which report reduced functional connectivity in some regions and decreased functional connectivity in others relative to healthy controls [102–105]. A levodopa-induced spatial remapping of the cortico-striatal connectivity has been detected in chronically treated patients with PD [103,104], suggesting that the clinical improvement associated with dopaminergic treatment could be related to the dopaminergic modulation of resting-state functional connectivity. A modulation of thalamocortical functional connectivity by levodopa administration has been demonstrated to occur also in drug-naïve PD cases [106–108].

Diffusion tensor MRI studies of patients with cognitively normal, early, idiopathic PD showed subtle WM alterations along the nigrostriatal projections, in the frontal regions, including premotor areas, and corpus callosum [109–112]. In early PD, diffusion changes precede atrophy that is detectable with conventional MRI, specifically within voxels containing the olfactory tracts [113]. WM damage is emerging as an important pathological substrate of cognitive deficits in patients with PD [114–118]. A large study of idiopathic nondemented PD cases at different disease stages showed that WM damage spreads predominantly to frontal and parietal regions with increasing PD severity and in association with the degree of cognitive impairment [115]. DT MRI studies exploring WM tract abnormalities in patients with PD-MCI showed a more severe involvement of the corpus callosum, cingulum, and major association WM tracts relative to those patients with no cognitive deficits [114,116,118].

Graph Theory and Network Properties in Neurodegenerative Diseases

Network-based analysis of brain structural and functional connections has provided a novel instrument to study the human brain in healthy and diseased individuals [119]. Using the theoretical framework of networks and graphs, the brain can be represented as a set of nodes (i.e., brain regions) joined by pairs by lines (i.e., structural or functional connectivity) [119]. Graph analysis has revealed important features of brain organization, such as an efficient "small-world" architecture (which combines a high level of segregation with a high level of global efficiency) and distributed,

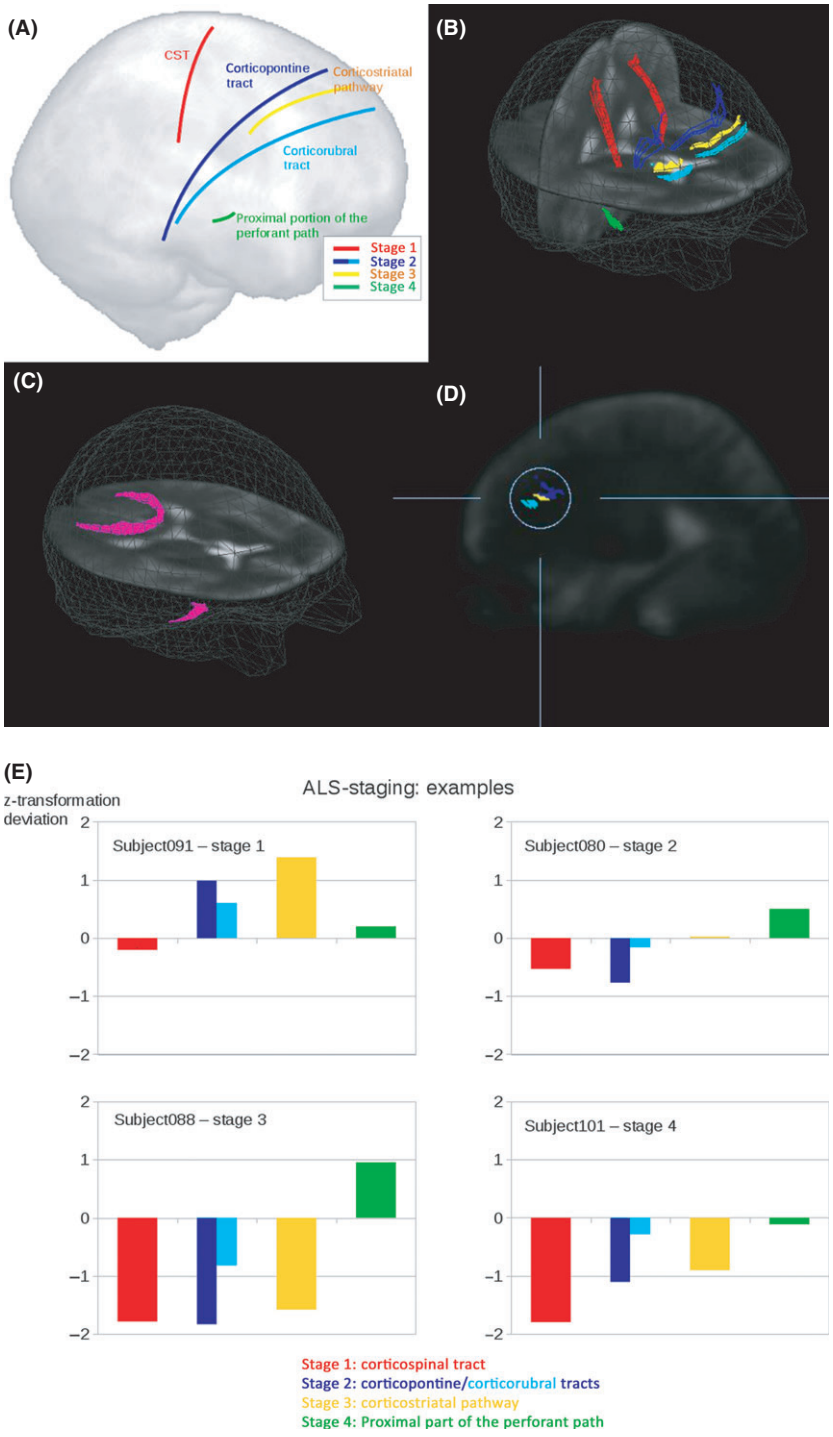

Figure 3 *In vivo* imaging of the disease stages in amyotrophic lateral sclerosis (ALS) using diffusion tensor tractography. (**A**) Schematic representation of the white matter tracts analyzed. (**B**) Three-dimensional images of the corticospinal tract (CST, red) corresponding to ALS stage 1 [5], corticopontine tract (dark blue) and corticorubral tract (light blue) corresponding to ALS stage 2 [5], corticostriatal pathway (yellow) corresponding to ALS stage 3 [5], and proximal portion of the perforant path (green) corresponding to ALS stage 4 [5]. (**C**) Reference paths (magenta) show starting points in the corpus callosum (area V) and starting points in the optic tract. (**D**) Sagittal slice for the illustration of the differences between the corticopontine tract (dark blue), corticorubral tract (light blue), and corticostriatal pathway (yellow). (**E**) Individual examples for the categorization of patients with ALS into ALS stages based upon deviations of z-transformed fractional anisotropy values from controls' values for different ALS stages. Modified with permission from [100].

highly connected network regions, called "hubs" [119]. In a small-world network, a high clustering coefficient indicates that nodes tend to form dense regional cliques, implying high efficiency in local information transfer/processing [119]. Path length and global efficiency are measures of network integration, which is the ability to combine specialized information rapidly from distributed brain regions [119]. Distinct modifications of brain network topology have been identified during development and normal aging, whereas disrupted functional and structural network properties have been associated with several neurological and psychiatric conditions, including dementia, ALS, multiple sclerosis, and schizophrenia [119].

Many studies used graph theoretical analysis in AD using both structural and functional MRI [120,121], pointing to a loss of highly connected areas in these patients [122]. A correlation between the site of Aβ deposition in patients with AD and the location of major hubs as defined by graph theoretical analysis of functional connectivity in healthy adults has been demonstrated [50]. These regions include the posterior cingulate cortex/precuneus, the inferior parietal lobule, and the medial frontal cortex, implying that the hubs are preferentially affected in the progression of AD. Although studies showed considerable variability in reported group differences of most graph properties, the average characteristic path length has been most consistently reported to be increased in AD, as a result of loss of connectivity, while the clustering coefficient is likely to be less affected by AD pathology [122]. The global architecture of MCI networks was found to be intermediate between patients with AD and normal elderly controls [122]. Additionally, compared with controls, patients with MCI retained their hub regions in the frontal lobe but lost those in the temporal lobe [123]. Increased interregional correlations within the local brain lobes and disrupted long-distance interregional correlations in MCI and AD were also detected [122]. In patients with AD and MCI, altered graph theory patterns were associated with cognitive deficits [124,125].

Graph theoretical analysis was recently applied to resting-state fMRI data from patients with bvFTD [126]. Global and local functional networks were altered in patients with bvFTD relative to normal subjects as indicated by reduced mean network clustering coefficient, and global efficiency and increased path length [126]. Altered brain regions were located in structures that are closely associated with neuropathological changes in bvFTD, such as the frontotemporal lobes and subcortical regions [126] (Figure 4).

Graph theoretical approach showed that overall functional organization of the motor network was unchanged in patients with ALS compared to healthy controls; however, the level of functional connectedness was correlated with disease progression rate, that is, stronger interconnected motor networks show a more progressive disease course [90]. The effects of ALS on structural brain topology were assessed using DT MRI and graph theoretical analysis [127,128]. While the organization of the global brain network was intact in ALS, an impaired subnetwork of regions with reduced WM connectivity was detected [127] centered on primary motor regions, including secondary motor regions (frontal cortex and pallidum) as well as high-order hub regions (posterior cingulate cortex and precuneus). A more recent study investigating the overlap between structural and functional connectivity abnormalities in patients with ALS showed coherent loss of structural and functional connections in the motor network [129].

Only two studies so far have investigated brain networks using graph analysis in patients with PD [130,131], suggesting a decreased global and nodal functional efficiency relative to healthy controls. In addition, one study indicated that the topological properties of brain functional networks are severely impaired in PD patients with cognitive deficits [130]. Patients with PD-MCI had connectivity reductions predominantly affecting long-range connections as well as increased local interconnectedness manifested as higher measures of clustering coefficient and small-worldness [130]. This latter measure also correlated negatively with cognitive performance in visuospatial and memory functions. Furthermore, normal hubs displayed reduced centrality and degree in these patients [130].

Recent graph theoretical MRI analyses tested various models of how neurodegenerative diseases spread across networks [128,132,133]. Combining atrophy patterns of patients with five different neurodegenerative diseases with resting-state fMRI data from healthy subjects, a first study revealed that, within each targeted network, neurodegenerative process spreads primarily between neurons according to the functional proximity of specific brain regions acting as critical hub-like "epicenters," rather than various alternative candidate mechanisms [133] (Figure 5). A second study modeled network diffusion based on brain structural connectivity networks obtained from DT MRI data of healthy subjects and derived robust spatial eigenmodes that correspond closely to known patterns of atrophy in patients with AD and bvFTD [132]. A longitudinal study of patients with ALS demonstrated no progressive impairment of the initially affected connections of the motor system, but a propagating loss of brain connections over time to frontal and parietal regions [128]. Therefore, all these sophisticated analyses best fit a transneuronal spread model of network-based vulnerability from initial disease epicenters to directly connected neighboring nodes in patients with different neurodegenerative diseases.

Conclusions

Neurodegenerative diseases feature characteristic patterns of early neuronal and regional vulnerability, with resulting neurological first symptoms. In turn, a common finding among neurodegenerative disease is that they show typical progressions of regional degeneration with associated downstream clinical disturbances. The cellular mechanisms underlying such a stereotypical progression of pathology in neurodegenerative diseases are incompletely understood, but increasing evidence indicates that misfolded protein aggregates can spread by a self-perpetuating process that leads to amplification, templating, and neuron-to-neuron transmission of these pathologies. Novel neuroimaging techniques can help elucidating how these disorders spread across brain networks. Recent knowledge from structural and functional connectivity studies suggests that the relation between neurodegenerative diseases and separate brain networks is likely to be a strict consequence of diffuse network dynamics. Furthermore, in the majority of these conditions, measurement of WM tract involve-

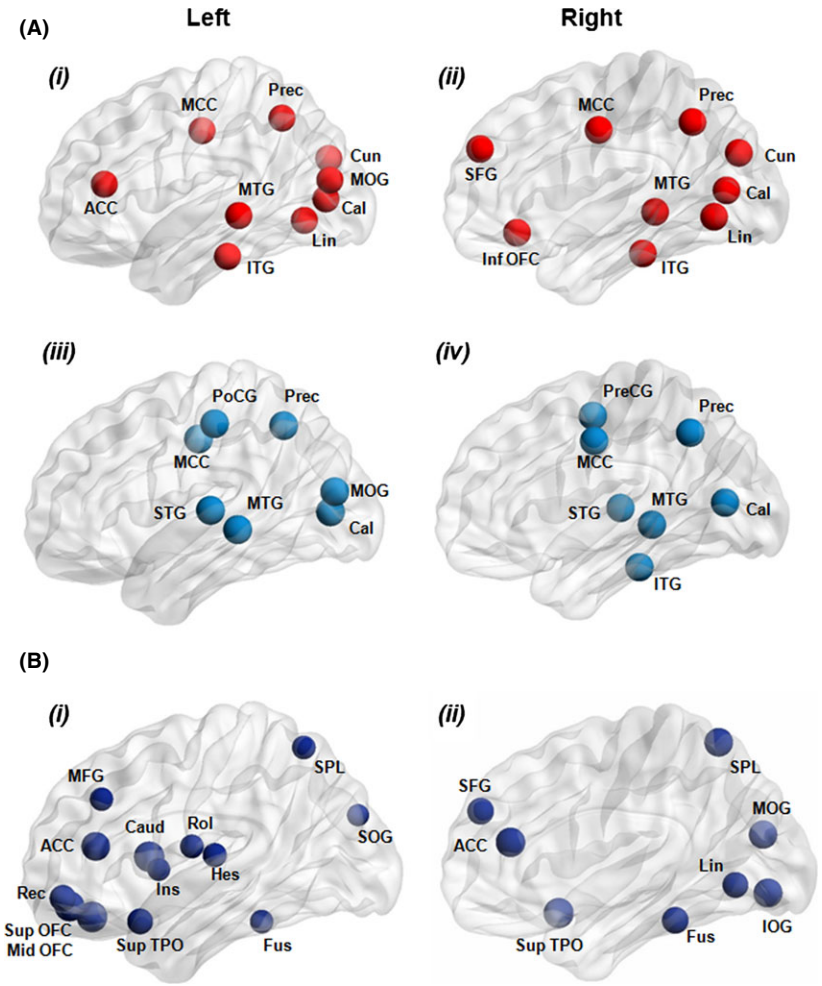

Figure 4 (**A**) Cortical hubs of brain functional networks in healthy controls (i, ii) and patients with the behavioral variant of frontotemporal dementia (bvFTD) (iii, iv). (**B**) Regions showing decreased integrated nodal degree (i, ii) in patients with bvFTD compared to healthy controls. Node size is proportional to the difference in the value of the integrated nodal parameters between the two groups. ACC, anterior cingulate cortex; Cal, calcarine cortex; Caud, caudate nucleus; Cun, cuneus; Fus, fusiform gyrus; Hes, Heschl gyrus; Ins, insula; IOG, inferior occipital gyrus; ITG, inferior temporal gyrus; Lin, lingual gyrus; MCC, middle cingulate cortex; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; OFC, orbitofrontal cortex; Prec, precuneus; PoCG, postcentral gyrus; PreCG, precentral gyrus; Rec, gyrus rectus; Rol, rolandic operculum; SFG, superior frontal gyrus; SOG, superior occipital gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; TPO, temporal pole. Reproduced with permission from [126].

ment seems to be a valid surrogate to assess the *in vivo* spreading of pathological proteins. Therefore, characterizing network breakdown in neurodegenerative diseases will help anticipate and perhaps prevent the devastating impact of these disorders. However, the reviewed literature also arises several burning questions. First, the direction of pathology spreading in each neurodegenerative disease is still not completely understood. Longitudinal analyses of multimodal imaging datasets, involving subjects in the preclinical phase of the diseases, are currently being acquired to allow for more explicit testing of the hypothesis of predictable disease spread. In addition, new analyses techniques that relate those changes to underlying pathology, for example, tau imaging, will shed new light on how neurodegenerative diseases develop and spread. Finally, limited information is available about how selective vulnerability works and how pathological proteins interact with disease-susceptible networks in these patients.

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Conflict of Interest

F. Agosta serves on the editorial board of the Journal of Neurology; has received speaker honoraria from Biogen Idec and EXCEMED—Excellence in Medical Education; and receives research supports from the Italian Ministry of Health, and AriSLA (Fondazione Italiana di Ricerca per la SLA). M. Weiler reports no disclosures. M. Filippi is Editor-in-Chief of the Journal of Neurology; serves on scientific advisory boards for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Bayer Schering Pharma, Biogen Idec,

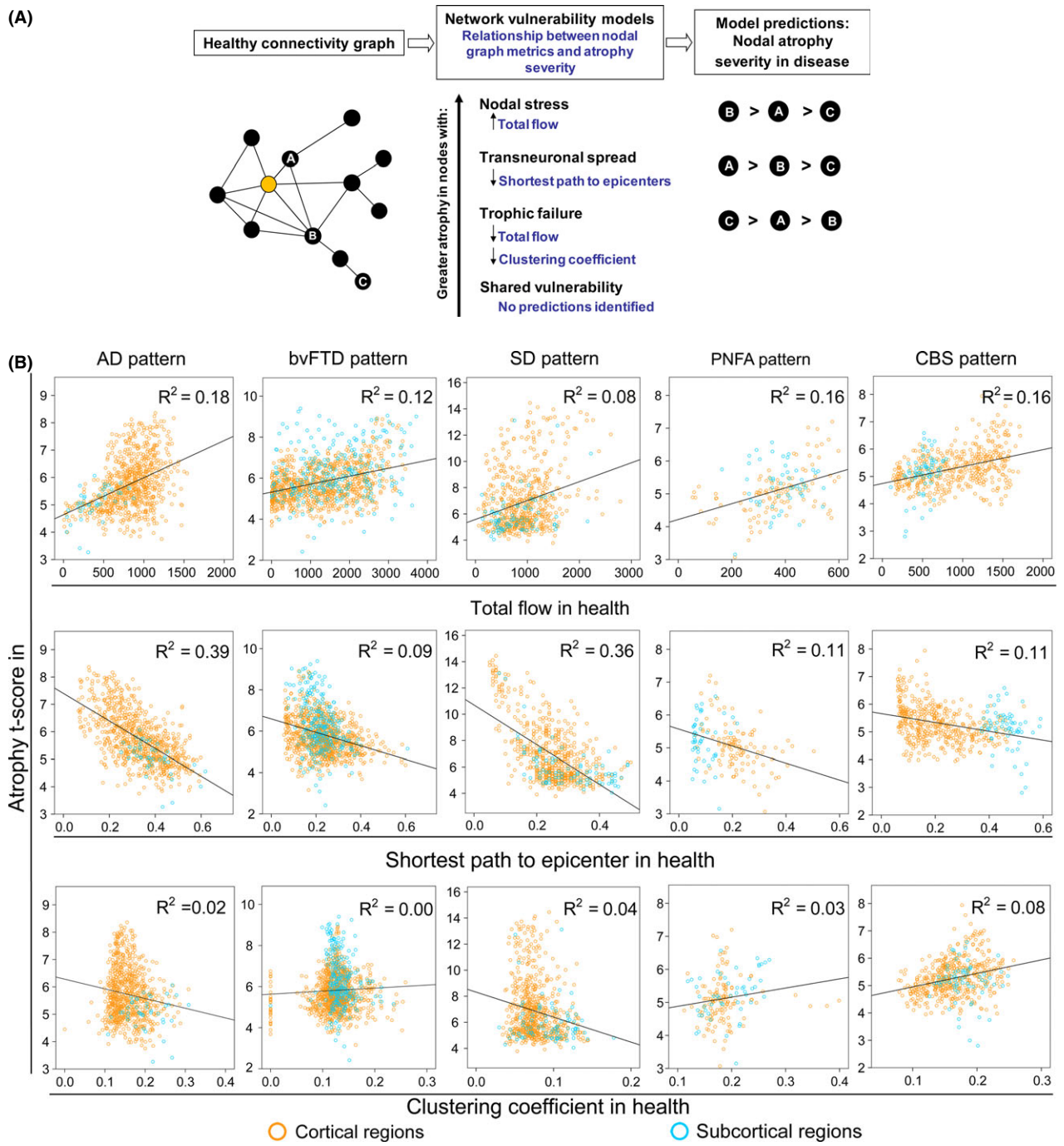

Figure 5 (**A**) Predictions made by network-based degeneration models: effects of healthy intrinsic connectivity graph metrics on atrophy severity in neurodegenerative diseases. A simplified healthy connectivity graph is shown (far left) for illustration purposes only; circles represent nodes (brain regions), lines represent edges (a connection between two nodes), and edge lengths represent the connectivity strength between nodes, with shorter edges representing stronger connections. The orange node represents an epicenter. Three nodes, labeled as "A", "B", and "C", feature contrasting graph theoretical properties to illustrate predictions made by the network-based vulnerability models (far right). Listed in the center column are the relationships predicted by each model. For example, the transneuronal spread model predicts that nodes with shorter (↓) paths to the epicenter in health will be associated with greater (↑) atrophy severity in disease. (**B**) Regions with high total connectional flow (row 1) and shorter functional paths to the epicenters (row 2) showed significantly greater disease vulnerability ($P < 0.05$ family-wise-error corrected for multiple comparisons) in Alzheimer disease (AD), behavioral variant of frontotemporal dementia (bvFTD), semantic dementia (SD), progressive supranuclear palsy (PNFA), and corticobasal degeneration (CBS), whereas inconsistent weaker or nonsignificant relationships were observed between clustering coefficient and atrophy (row 3). Cortical regions = blue circles; subcortical regions = orange circles. Modified with permission from [133].

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