

Brain connectivity in neurodegenerative diseases—from phenotype to proteinopathy

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Abstract | Functional and structural connectivity measures, as assessed by means of functional and diffusion MRI, are emerging as potential intermediate biomarkers for Alzheimer disease (AD) and other disorders. This Review aims to summarize current evidence that connectivity biomarkers are associated with upstream and downstream disease processes (molecular pathology and clinical symptoms, respectively) in the major neurodegenerative diseases. The vast majority of studies have addressed functional and structural connectivity correlates of clinical phenotypes, confirming the predictable correlation with topography and disease severity in AD and frontotemporal dementia. In neurodegenerative diseases with motor symptoms, structural—but, to date, not functional—connectivity has been consistently found to be associated with clinical phenotype and disease severity. In the latest studies, the focus has moved towards the investigation of connectivity correlates of molecular pathology. Studies in cognitively healthy individuals with brain amyloidosis or genetic risk factors for AD have shown functional connectivity abnormalities in preclinical disease stages that are reminiscent of abnormalities observed in symptomatic AD. This shift in approach is promising, and may aid identification of early disease markers, establish a paradigm for other neurodegenerative disorders, shed light on the molecular neurobiology of connectivity disruption and, ultimately, clarify the pathophysiology of neurodegenerative diseases.

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Introduction

Neurodegenerative disorders are believed to be attributable to the deposition of abnormal toxic proteins in the brain (Figure 1).¹ These proteins might activate a cascade of biochemical, metabolic, functional and structural changes that precede clinical symptoms by years, if not decades.² Thus, clinical symptoms are just the final manifestation of a long-standing disease process and, traditionally, were the only aspects of the disease process that clinical neurologists could appreciate and study. Unfortunately, clinical symptoms are also nonspecific, in the sense that the same clinical phenotype can have different underlying molecular pathology (Figure 1). Given the extended time frame and the lack of clinical specificity, identification of biomarkers linking proteinopathies to symptoms is critical for early disease detection and better understanding of disease pathophysiology.

Imaging techniques offer an invaluable tool to assess pathology *in vivo*. For example, brain atrophy as assessed on structural MRI is a good biomarker of downstream neurodegeneration in Alzheimer disease (AD) and frontotemporal lobar degeneration (FTLD).^{3,4} Brain connectivity markers are believed to represent reliable candidate biomarkers of downstream cognitive deficits and, more importantly, of upstream neuronal dysfunction and disease spread.^{5,6} The interest in this field is

documented by the exponential growth of studies on brain connectivity in disorders in the past decade (around 2,300 papers published overall, and over 16,000 citations).

This article aims to review key findings on functional and structural connectivity, assessed with imaging techniques, as intermediate biomarkers for the main neurodegenerative disorders. Specifically, we will evaluate the evidence that connectivity biomarkers are associated downstream with clinical phenotypes and topographic brain imaging markers of neurodegeneration, and upstream with molecular determinants of neurodegeneration and susceptibility genes. After a brief description of traditional imaging methods used to assess brain connectivity in neurodegenerative diseases, we will extensively review connectivity studies in AD, frontotemporal dementia (FTD), Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), progressive supranuclear palsy (PSP), and Huntington disease (HD). This section will be divided into two parts: connectivity correlates of clinical phenotypes, and connectivity correlates of molecular pathology. Dementia with Lewy bodies will not be addressed, as too few studies are available to draw any meaningful conclusions. Finally, we will briefly discuss future directions of research in the field.

Methods to assess brain connectivity

Functional connectivity

The main focus of the early era of functional imaging was on the identification of functional segregation—the localization of brain regions specialized in a specific

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Competing interests

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Key points

- Abnormal functional and structural connectivity are candidate biomarkers for Alzheimer disease (AD) and other neurodegenerative diseases
- The topography of abnormal functional and structural connectivity maps onto the clinical phenotype, and its severity correlates with clinical disease severity in AD and frontotemporal dementia
- Structural—but, as yet, not functional—connectivity signatures of neurodegenerative diseases with a primary motor phenotype (for example, amyotrophic lateral sclerosis, Parkinson disease and Huntington disease) have been consistently identified
- Functional connectivity signatures are related to specific molecular pathology in preclinical AD, and could serve as early disease markers

function—as a principle of organization of the human brain. The concept of functional integration, that is, the integration of segregated areas, started with the application of statistical approaches assessing distributed brain activation changes,^{7,8} and was developed by Friston and colleagues with methods assessing functional and effective connectivity.⁹ Functional connectivity was originally defined as the “temporal correlations between remote neurophysiological events” as assessed on functional MRI (fMRI), PET or EEG.⁹ While these concepts were initially designed to assess task-related functional integration, with the emergence of resting-state fMRI¹⁰ the approach was applied to the investigation of task-free functional integration.

Resting-state (or ‘task-free’) fMRI measures the spontaneous low-frequency (<0.001–0.100 Hz) fluctuations of the blood oxygen level-dependent (BOLD) signal while

the individual rests in the scanner without performing any specific task. According to Friston’s definition, functional connectivity is measured by identifying temporal correlations in the low-frequency BOLD signal between brain regions.¹⁰ Seed-based and data-driven approaches are commonly used to identify brain regions that share a common time course of spontaneous fluctuations (commonly termed ‘networks’). The potential value of using task-free fMRI has been demonstrated in clinical population studies,^{11–13} and has the advantage of not relying on any explicit temporal model or the choice of a specific task.

Multiple task-free networks have been consistently observed across individuals,¹⁴ sessions,¹⁵ and functional brain imaging modalities.^{16,17} Similar topographic mappings have been identified across multiple networks, notwithstanding the different analytical methods.¹⁸ The topography of task-free networks commonly investigated in neurodegenerative disorders is shown in Figure 2. The default mode network (DMN) is the network most consistently found in people of any age, and is also present during sleep,¹⁹ and in anaesthetized monkeys²⁰ and rats.²¹ The DMN incorporates various brain regions, including the anterior and posterior cingulate, the lateral parietal lobes, and the medial and lateral temporal regions, and has been proposed to be involved in self-referential functions.¹⁷ Some DMN regions (posterior cingulate and precuneus) are highly connected with the rest of the brain, and recent studies have better elucidated the roles of DMN core regions as key components of specific subnetworks and functions. In a recent review, Leech *et al.* presented

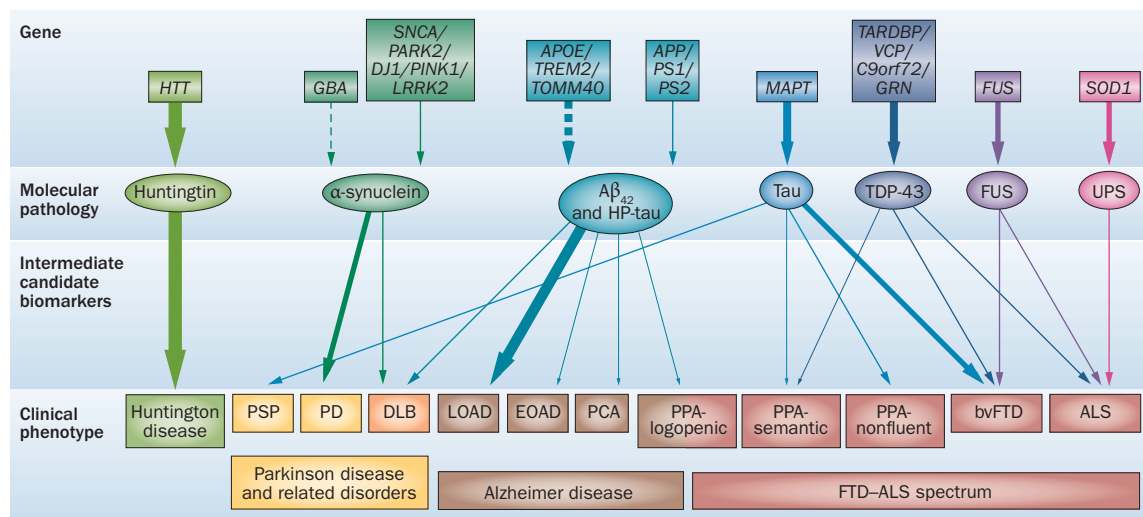


Figure 1 | Upstream determinants (genes and molecular pathology) and downstream effects (clinical phenotypes) for the main neurodegenerative disorders. Functional and structural brain connectivity might act as intermediate biomarkers. Causative genetic mutations are shown by solid arrows and genetic risk factors by dotted arrows. The size of the arrow is roughly proportional to the population attributable fraction. The size of arrows linking molecular pathology to clinical phenotypes are roughly proportional to the prevalence of the clinical phenotype in the pertinent molecular pathology. Abbreviations: Aβ₄₂, amyloid-β₄₂; ALS, amyotrophic lateral sclerosis; APOE, apolipoprotein E; APP, amyloid precursor protein; bvFTD, behavioural variant frontotemporal dementia; DJ1, parkinson protein 7; DLB, dementia with Lewy bodies; EOAD, early-onset Alzheimer disease; FUS, fused in sarcoma; GBA, glucocerebrosidase; GRN, granulin; HP-tau, hyperphosphorylated-tau; LOAD, late-onset Alzheimer disease; LRRK2, leucine-rich repeat kinase 2; MAPT, microtubule-associated protein tau; PARK2, parkin RBR E3 ubiquitin protein ligase; PCA, posterior cortical atrophy; PD, Parkinson disease; PINK1, PTEN induced putative kinase 1; PPA, primary progressive aphasia; PS, presenilin; PSP, progressive supranuclear palsy; SNCA, α-synuclein; SOD1, superoxide dismutase 1; TARDBP/TDP-43, TAR DNA-binding protein 43; TOMM40, translocase of outer mitochondrial membrane 40 homologue; TREM2, triggering receptor expressed on myeloid cells 2; UPS, ubiquitin proteasome system; VCP, valosin containing protein.

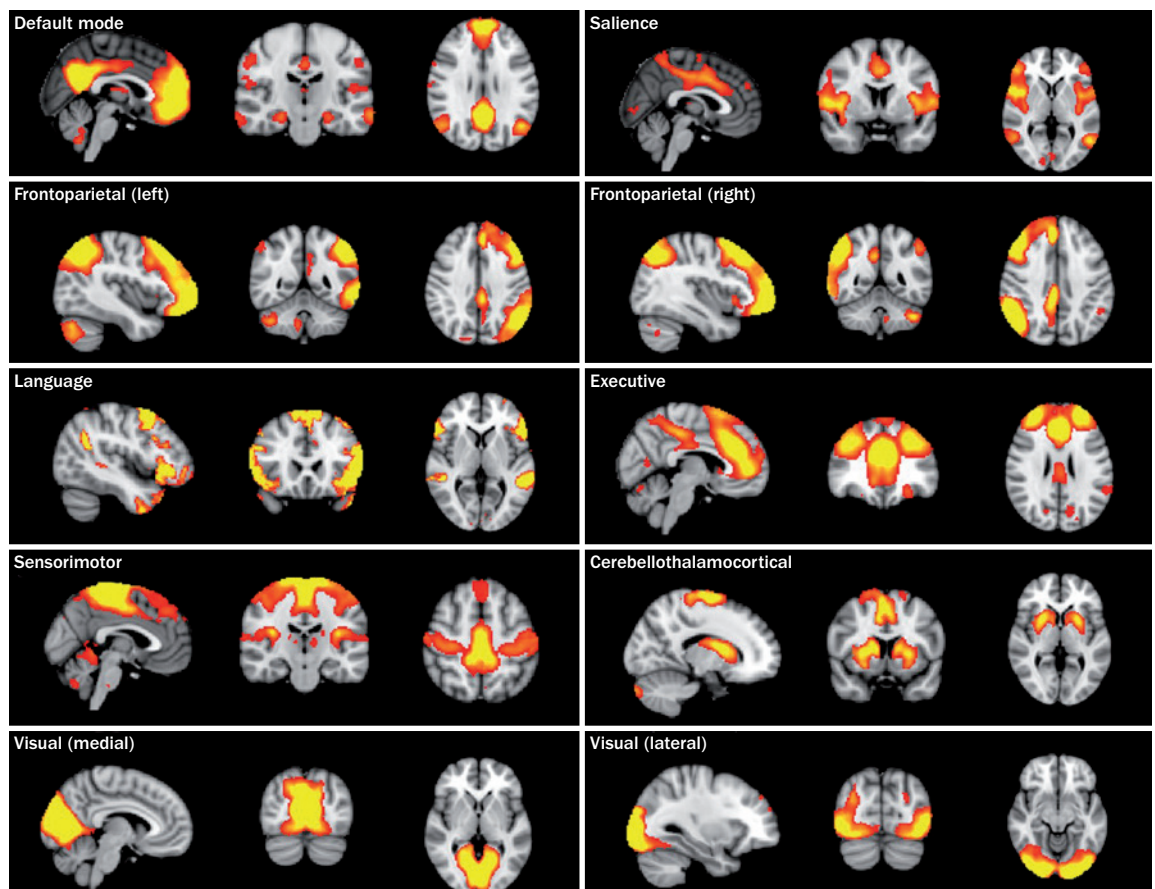


Figure 2 | Spatial patterns of task-free networks commonly investigated in neurodegenerative disorders. Images represent group maps of 30 healthy young adults (20–40 years old) obtained using a data-driven approach. Networks are shown superimposed on the MNI152 standard space template image. All spatial maps are shown in radiological convention and are thresholded at $z=3$. Red to yellow colours represent z -scores >3 .

evidence that the posterior cingulate serves as a major hub involved in monitoring of the arousal state, and is particularly active in people who are prone to daydreaming, or during the retrieval of autobiographical memories.²² Utevsky *et al.*, using a variety of cognitive tasks, observed increased connectivity between the precuneus and the frontoparietal network during task conditions, suggesting that the precuneus interacts with multiple brain networks depending on the cognitive status.²³

Other task-free networks that are commonly investigated in neurodegenerative diseases show good correspondence with the functional networks activated during the performance of a task. The salience network, comprising the dorsal anterior cingulate, bilateral orbitofrontal and insular cortices, guides behaviour by integrating limbic and autonomic information and relating it to social rules.²⁴ The frontoparietal network, commonly segregated into left and right components, includes the dorsolateral prefrontal cortex, lateral parietal cortex and contralateral cerebellum, and subserves multiple cognitive paradigms, including memory, language and perception.^{24,25} This network can be further partitioned into a subnetwork, including prefrontal, temporal and parietal areas, that is associated with the language function. The executive network, which includes bilateral

dorsolateral and medial prefrontal cortices, is associated with cognition, action inhibition and emotion.²⁵ The sensorimotor network is anchored to the motor cortex (bilateral precentral and postcentral gyri, and supplementary motor area), and guides motor planning, execution and control.²⁵ The visual network, which is commonly separated into medial and lateral portions of the occipital pole, is involved in visuoperceptual and visual control processing.²⁵ A less well-characterized task-free network, potentially relevant to PD, is the cerebellothalamocortical network. This network includes the basal ganglia, the motor and premotor cortex and the cerebellum, and has a role in motor control.²⁶

The correspondence between task-free and task-activated networks suggests that functional networks used by the brain when performing a task are continuously and dynamically active even when an individual is at rest and, therefore, reflect properties of functional brain organization.

Structural connectivity

Structural brain connectivity is generally assessed by means of diffusion tensor imaging (DTI). This technique measures the net diffusion of water molecules in brain tissues, revealing details about microstructural organization of white

Table 1 | Connectivity correlates of clinical phenotypes

Clinical phenotype	Network	Connectivity changes	Correlation with symptom severity	Changes track disease stage*	Changes track disease progression†	Connectivity changes in other networks
Functional connectivity						
AD ^{29–35,42,43}	DMN	↓↓↓	+++	+++	+	↓/↑
bvFTD ^{35,42,44,49}	Salience	↓↓	++	NA	NA	↓/↑
PSP ^{50,51}	Cerebellothalamocortical	↓↓	++	NA	NA	↓
ALS ^{56–61,76–78}	Sensorimotor	↓/↑	+/-	NA	NA	↓/↑
PD ^{79–87,90}	Cerebellothalamocortical	↓/↑	+/-	NA	NA	↓
HD ^{91–94}	Sensorimotor	↓/↑	+/-	NA	NA	↓/↑
Structural connectivity						
AD ^{37–41}	Limbic	↓↓↓	+++	++	+	↓↓↓
bvFTD ^{41,45–48}	Frontal	↓↓↓	+++	NA	NA	↓↓↓
PSP ^{51,53–55}	Cerebellothalamocortical	↓↓↓	+/-	NA	NA	↓↓↓
ALS ^{60–77}	Sensorimotor	↓↓↓	+++	NA	+++	↓↓
PD ^{88,89}	Cerebellothalamocortical	↓↓	++	++	NA	↓↓
HD ^{96–100}	Sensorimotor	↓↓↓	+++	+++	NA	↓↓↓

*Cross-sectional studies. †Longitudinal studies. Evidence from cross-sectional and longitudinal studies indicates that functional connectivity biomarkers are associated with the clinical phenotype and disease severity in AD and bvFTD. These biomarkers seem to be specific to the clinical phenotype. In PSP, the evidence is similar but still preliminary. In ALS, PD and HD, no functional connectivity signature was consistently identified. Structural connectivity biomarkers are strongly associated with clinical phenotype and disease severity in all neurodegenerative diseases. Key: ↓, reduced connectivity; ↑, increased connectivity; +, yes; -, no; ++, consistent evidence from multiple studies; +++, overall consistent evidence from multiple studies; +, ↓, evidence from single study; +/-, conflicting evidence. Abbreviations: AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; bvFTD, behavioural variant frontotemporal dementia; CST, corticospinal tract; HD, Huntington disease; NA, not assessed; PD, Parkinson disease; PSP, progressive supranuclear palsy.

matter tissue. DTI can delineate white matter fibre orientation and provide indirect measures of tissue integrity. The two most widely used metrics of structural connectivity in neurodegenerative disorders are fractional anisotropy (FA) and mean diffusivity. These indices measure the anisotropy of the diffusion process and the magnitude of the diffusion, respectively. In the presence of damage to white matter fibres, such as axonal loss, Wallerian degeneration and demyelination, molecule diffusion is less hindered and FA is reduced. Tissue loss (including demyelination) can reduce local barriers to the movement of molecules in brain tissue, causing an increase in mean diffusivity.²⁷ The main brain white matter tracts extracted with DTI are the cingulum, the fornix, the corpus callosum, the corticospinal tract (CST), the uncinate, the superior longitudinal fasciculus, and the inferior and fronto-occipital fasciculi.²⁸ Recent advances in structural connectivity measurements, like high angular resolution diffusion imaging and diffusion kurtosis imaging, may provide additional markers of structural connectivity with more-detailed information about white matter microstructure.

Connectivity correlates of disease

Connectivity correlates of clinical phenotypes

Table 1 summarizes the available evidence that neurodegenerative diseases affect distinct functional and structural connectivity networks. Overall, evidence indicates that functional network abnormalities are associated with the topography and clinical severity of AD, behavioural variant FTD (bvFTD) and PSP, but in ALS, PD and HD, no clear association has yet emerged. Structural connectivity abnormalities correlate with the clinical phenotypes

and disease severity in all major neurodegenerative diseases, but are topographically less specific.

Alzheimer disease

Task-free fMRI studies have identified consistent involvement of the DMN in AD.^{29–35} This network shows good topographic overlap with areas affected by pathology and neurodegeneration, that is, the posterior cingulate and preuneus, parietal cortex, hippocampus, and medial prefrontal cortex.⁵ Reduced connectivity (lower synchrony in the spontaneous BOLD fluctuations) in the DMN correlates with disease severity, as measured by the Clinical Dementia Rating (CDR) scale^{29,32,35} and cognitive-behavioural scores.³¹ There is consistent evidence that DMN damage tracks disease progression, as measured by cross-sectional studies at different disease stages,^{29,31–33} or longitudinal studies (Table 1).³⁶

Structural connectivity changes also show good agreement with DMN topography in AD patients: significantly reduced FA and increased mean diffusivity values have been observed in limbic white matter tracts connecting the medial temporal lobe with the posterior cingulate.^{37–40} Moreover, damage to these regions has been shown to correlate with symptom severity and disease progression.^{37–40} White matter damage in AD is not confined to the DMN, however, and typically extends to frontal regions.^{37–41}

Whether other networks are affected in AD is less clear. Considerable heterogeneity exists in terms of the networks investigated and findings across studies. It was initially suggested that the connectivity within the salience network is increased in AD.³⁵ However, to date, this finding has not been replicated; indeed, two studies

found reduced rather than increased salience network connectivity,^{32,42} and another showed no difference.³⁰ The only network showing consistently enhanced connectivity in AD is the executive network.^{30,34,42} Several studies assessed the frontoparietal network in AD, but the findings were conflicting, variously showing reduced connectivity,³² mixed patterns^{30,42} or increased connectivity.³⁴ Notwithstanding this uncertainty, an emerging feature seems to be the disruption of internetwork connectivity,^{32,43} possibly underlying functional disconnection and spread of pathology across interlinked networks.

Behavioural variant frontotemporal dementia

The salience network is consistently involved in bvFTD.^{35,42,44} As in AD, good topographical overlap is observed between this network and areas of grey matter atrophy, namely, the anterior cingulate and frontolimbic cortex.⁵ Reduced salience network connectivity has been shown to correlate with disease severity, as measured on the CDR scale³⁵ and via behavioural scores.⁴⁴ No study has yet investigated whether connectivity in the salience network tracks disease progression (Table 1).

Structural changes in bvFTD are congruent with salience network topography: frontal white matter tracts such as the uncinate fasciculus and the anterior cingulate show massive FA reduction, and damage to these tracts correlates with disease severity.^{41,45–48} As in AD, white matter damage extends beyond the salience network and involves posterior white matter tracts.^{41,45–48}

Increased DMN connectivity in bvFTD has been reported by two studies,^{35,44} but two other studies found either reduced connectivity⁴² or mixed changes (both increased and reduced connectivity).⁴⁹ Internetwork connectivity also seems to be disrupted in bvFTD.⁴²

Progressive supranuclear palsy

In PSP, preliminary evidence from two studies supports the hypothesis of reduced cerebellothalamocortical network connectivity,^{50,51} in line with the topography of neurodegeneration in PSP.⁵² Damage to this network is associated with dementia severity,⁵⁰ motor symptoms⁵¹ and cognitive impairment;⁵¹ however, further studies are required to confirm these associations. Multiple DTI studies have shown severe structural damage in PSP, which is not restricted to the cerebellothalamocortical network but involves all white matter tracts.^{51,53,54}

There is conflicting evidence that reduced FA correlates with clinical symptoms in patients with PSP.^{51,54} A recent study suggests that whole-brain FA may be useful for the differential diagnosis of PSP, as it is very sensitive to white matter damage at the individual level.⁵⁵

Amyotrophic lateral sclerosis

In ALS, the sensorimotor network has been investigated with task-free fMRI. Two studies found reduced connectivity in this network,^{56,57} while another reported a mixed pattern of both increased and reduced connectivity.^{58,59} Findings in ALS populations have been more consistent in terms of structural connectivity disruption. There is extensive evidence of reduced FA in the CST and

corresponding motor network,^{60–68} and of an association between sensorimotor network damage and disease severity.^{63,66–68} Consistent with these data are the findings from two studies investigating ALS patients carrying superoxide dismutase 1 mutations, a dominantly inherited form of ALS associated with a less-severe clinical course and longer survival. Both studies showed relatively preserved CST connectivity in mutation carriers compared with sporadic cases.^{69,70} DTI changes in nonmotor tracts were reported by a recent study, and have been related to changes in social and emotional processing.⁷¹ Motor network damage has been suggested as a potential marker to track disease progression in ALS, with progressive expansion of white matter damage from the CST to extramotor areas.^{72–74} One recent longitudinal study examining sensorimotor network topology in ALS reported an expanding network of affected connectivity centralized to a motor disease epicentre.⁷⁵

Four studies have combined functional and structural connectivity to assess sensorimotor disruption more comprehensively,^{60,61,76,77} and they all reported reduced structural connectivity. One study reported structural network deterioration with overall preserved functional connectivity.⁶⁰ Two subsequent studies reported increased sensorimotor network connectivity.^{61,76} These studies also questioned whether increased connectivity reflected pathogenic or compensatory processes, and they reached opposite conclusions.^{61,76} Specifically, Agosta *et al.* showed that higher connectivity was associated with lower disease severity, suggesting compensatory mechanisms,⁷⁶ whereas Douaud *et al.* found that increased connectivity was associated with a higher rate of disease progression, suggesting a pathogenic mechanism.⁶¹ A more recent study, examining the direct overlap between structural and functional connectivity changes, reported coherent loss of anatomical and functional interactions in the motor system in patients with ALS.⁷⁷ No functional study has yet assessed whether functional sensorimotor network changes are sensitive to disease progression. Other networks investigated include the DMN and frontoparietal network, and reports mostly indicate increased connectivity in the DMN.^{56,57,78}

Parkinson disease

Multiple task-free studies have investigated connectivity of the thalamocortical network in patients with PD, but the results have been mixed (Table 1). However, when patients were distinguished on the basis of their medication state (drug-naïve PD, PD off levodopa, PD on levodopa), a more coherent picture emerged. Two studies scanned drug-naïve PD patients and showed that thalamocortical connectivity was reduced in patients compared with controls,^{79,80} and administration of levodopa increased connectivity.⁷⁹ A different pattern was observed in treated PD patients who were scanned in the 'off' state: studies found either increased connectivity^{81,82} or mixed patterns of both increased and reduced connectivity compared with controls.^{83–85} As in drug-naïve PD, administration of levodopa normalized thalamocortical connectivity.^{81,83} Overall, these findings do not identify a connectivity signature for PD but suggest that acute levodopa administration restores normal thalamocortical connectivity.

Table 2 | Connectivity correlates of clinical subtypes

Clinical subtype	Specific network	Overlapping networks or pathways
AD variants		
Early-onset AD ^{101–103}	Salience, frontoparietal	DMN
Late-onset AD ^{102,103}	Anterior temporal	DMN
Posterior cortical atrophy ^{101,104,105}	Visual	DMN
PPA-logopenic ^{101,106–108}	Language	DMN, uncinate
FTD variants		
PPA-semantic ^{44,106–108}	Language	Uncinate
PPA-nonfluent ^{106–108}	Language	Uncinate
Behavioural variant FTD ^{35,41,42,44–48}	Salience	Uncinate

Preliminary evidence shows that AD variants are associated with damage to specific functional networks, but evidence for the involvement of specific structural pathways is poor. FTD variants show consistent and specific involvement of distinct functional and structural networks (frontolimbic and language, respectively). Networks and pathways commonly affected across variants are also detected, for example, the DMN for AD variants, and the uncinate fasciculus for FTD variants. For the major variants of progressive supranuclear palsy and amyotrophic lateral sclerosis, evidence is still limited (see main text). Abbreviations: AD, Alzheimer disease; DMN, default mode network; FTD, frontotemporal dementia; PPA, primary progressive aphasia.

Finally, two studies assessed patients with PD under stable levodopa in the 'on' state and reported conflicting results, that is, either reduced⁸⁶ or unchanged⁸⁷ thalamocortical connectivity. Only two studies reported significant associations between connectivity abnormalities and disease severity (as assessed with the Unified PD Rating Scale),^{83,86} the majority failed to find such an association.^{81,82,84}

Structural connectivity studies in patients with PD produced more-consistent results, indicating that white matter damage is initially confined to the brainstem and thalamus and subsequently spreads predominantly to frontal white matter tracts, paralleling the clinical⁸⁸ and cognitive⁸⁹ decline. Extramotor networks have been assessed by two studies, which showed reduced connectivity in the DMN⁹⁰ and visual network.⁸⁷ Two studies have revealed DTI changes in nonmotor tracts,^{88,89} and one of these studies related these changes to cognition.⁸⁹ No longitudinal studies have been conducted to assess whether thalamocortical connectivity is sensitive to disease progression in PD.

Huntington disease

In HD, several resting-state networks have been investigated;^{91–94} however, a clear hypothesis on the possible 'target' networks is still lacking. Given the strong motor component in this disease, sensorimotor and basal ganglia–thalamocortical networks might be preferentially affected, although studies assessing these networks have provided mixed findings, some reporting reduced connectivity^{91,92} and others reporting increased connectivity or mixed patterns.^{93,94} These observations are not easy to interpret in view of the clear-cut and selective localization of HD pathology in the caudate nucleus, and the established role of this nucleus in large and well-defined corticostriatal loops (oculomotor, dorsolateral and ventral–orbital circuits).⁹⁵

Structural connectivity studies in HD have been more consistent. FA reductions that correlate with disease severity have been reported in the basal ganglia and motor pathways.^{96–98} Nonmotor tracts have also been found to

be affected in HD, and these changes seem to relate to cognition.^{96,97,99,100}

Connectivity correlates of clinical subtypes

Table 2 summarizes the evidence that functional and structural connectivity biomarkers are associated with specific clinical subtypes within each neurodegenerative disease.

Alzheimer disease variants

In AD, the typical clinical phenotype is represented by late-onset amnesic AD. A proportion of patients, however, present with atypical phenotypes, for example, early-onset AD, or focal nonamnesic presentations such as posterior cortical atrophy or the logopenic variant of primary progressive aphasia (PPA). Preliminary evidence indicates that AD subtypes are associated with disruption of specific functional and structural networks. Two studies independently reported that early-onset AD is associated with damage to frontal networks—that is, the frontoparietal and salience networks^{101,102}—in line with the neocortical phenotype associated with these forms. The involvement of frontal networks might also explain why these forms are difficult to distinguish from FTD in early disease stages. One study assessing structural connectivity in early-onset AD, however, did not find specific frontal involvement.¹⁰³ Posterior cortical atrophy has been consistently associated with reduced connectivity to the visual network,^{101,104,105} and logopenic PPA with language network disruption.^{101,106–108} One study investigating functional networks in late-onset AD identified the anterior temporal network as being specifically involved in this form,¹⁰² although further confirmation is required.

Overall, these data indicate good topographical correspondence between affected networks and symptoms for each variant. Interestingly, the DMN is significantly affected in all variants^{101,102} and could, therefore, aid discrimination between AD and non-AD dementias in prodromal stages. An interesting question arising from these findings is whether the DMN represent an initial or final target of the disease, that is, whether pathology initially targets variant-specific networks and subsequently converges to the DMN, or vice versa.¹⁰¹ The answer to this question has important consequences for a better understanding of disease pathophysiology, and for biomarker development.

Frontotemporal dementia variants

FTD variants include behavioural (bvFTD) and language (semantic and nonfluent PPA) subtypes. Evidence indicates that each subtype is associated with distinct networks. As shown in the previous section, bvFTD is consistently associated with reduced connectivity of the salience network and frontolimbic white matter tracts.^{35,41,42,44–48} DTI studies have provided consistent evidence for reduced structural connectivity in frontotemporal pathways in semantic PPA, and fronto–parietotemporal pathways in nonfluent PPA.^{106–108} Evidence from task-free fMRI for the involvement of the language network in PPA variants is lacking,⁴⁴ but it is reasonable to predict that this network will be markedly affected in all PPA variants. Finally, the

Table 3 | Effects of molecular pathology and susceptibility genes on connectivity biomarkers

Feature	Factor	Associated pathology	Study group	Connectivity	Effect on connectivity biomarkers
AD					
Molecular pathology	Amyloid (Pittsburgh compound B) ^{113–115} or amyloid and tau (cerebrospinal fluid) ^{116,117}	AD	Asymptomatic cognitively normal	Functional	↓ DMN
Susceptibility gene	Apolipoprotein E ε4 (APOE ε4) allele	AD	Asymptomatic cognitively normal	Functional ^{119,120,124,125}	↓ DMN and ↑ frontal in elderly individuals, ↑ DMN in younger individuals
				Structural ^{121–123,127–129}	↓ In AD regions in elderly individuals
FTD					
Molecular pathology	Tau and TDP-43 (autopsy or genetic confirmation) ¹³⁰	FTLD-tau, FTLD-TDP	Symptomatic FTD	Structural	Greater damage in FTLD-tau than in FTLD-TDP
Susceptibility gene or polymorphism	TMEM106B ¹³²	FTLD-TDP	Asymptomatic GRN+	Functional	Greater damage in TMEM+ than in TMEM–
	rs1768208 (MOBP) ¹³¹	FTLD-tau	Symptomatic FTD	Structural	↓ Midbrain, ↑ SLF
	rs646776 (near SORT1) ¹³¹	FTLD-TDP	Symptomatic FTD	Structural	↓ Midbrain, ↑ SLF
	rs5848 (PGRN) ¹³¹	FTLD-TDP	Symptomatic FTD	Structural	↓ Midbrain and SLF
In AD, molecular pathology and susceptibility genes affect connectivity biomarkers from the preclinical stages, the effects mirroring those observed in symptomatic stages. Studies in FTD are preliminary and mostly confined to symptomatic stages: factors associated with younger age at onset (tau and TMEM106B) might modulate the severity of connectivity damage; susceptibility factors recently identified via genome-wide association studies might modulate structural connectivity. For other neurodegenerative disorders, evidence is lacking. Key: ↑, increased connectivity; ↓, reduced connectivity. Abbreviations: AD, Alzheimer disease; DMN, default mode network; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; GRN+, granulin mutation carriers; SLF, superior longitudinal fasciculus; TDP, TAR DNA-binding protein; TMEM+, TMEM106B T/T; TMEM–, TMEM106B */C.					

uncinate fasciculus shows significant involvement across all FTD variants,^{41,103–106} suggesting that this biomarker may be central to understanding disease propagation across networks and variants.

Amyotrophic lateral sclerosis variants

For the main variants of ALS, data are still preliminary. The classic phenotype is characterized by upper and lower motor neuron signs, although a proportion of patients present, in addition, with behavioural and cognitive deficits compatible with a diagnosis of FTD (ALS–FTD). No task-free fMRI study has yet investigated whether these forms are associated with disruption of distinct functional networks.

Two recent anatomical studies assessed white matter abnormalities in these subtypes. One reported that reduced FA in the CST is specific to classic ALS, whereas reduced FA in the frontotemporal white matter tends to be more specific to ALS–FTD.¹⁰⁹ While these findings are in line with clinical phenotypes, they need further replication, as a second study found no FA differences between subgroups.¹¹⁰

Progressive supranuclear palsy variants

In PSP, the most common presentation is Richardson syndrome (PSP–RS), characterized by early postural instability and falls, and supranuclear vertical gaze palsy. A smaller proportion of cases present with parkinsonian signs and generally show a less aggressive disease course (PSP–P). Only one DTI study has compared structural connectivity between PSP variants, reporting that infratentorial fibres and thalamic radiations are severely affected in PSP–RS and relatively spared in PSP–P,¹¹¹ in line with disease topography and aggressiveness.

Connectivity correlates of molecular pathology

Whereas clinical phenotypes are ‘downstream’ events in disease pathophysiology, molecular pathology is ‘upstream’ (Figure 1). The pathological process starts many years prior to clinical onset,² and identification of ‘upstream’ markers is critical for the development of effective interventions. Currently, the nature of the association between connectivity markers and molecular pathology in preclinical stages is largely unknown. This section reviews evidence on the relationships between connectivity abnormalities and molecular pathology in AD and FTD. Other diseases (PSP, ALS, PD and HD) will not be addressed owing to a lack of literature.

Alzheimer disease

Molecular pathology in AD is characterized by the deposition of two toxic proteins, amyloid-β (Aβ) and hyperphosphorylated tau.¹ Cognitively normal elderly individuals with abnormal Aβ or tau levels are at a heightened risk of developing AD, and represent the ideal group to investigate preclinical AD.¹¹² A large body of literature supports the view that amyloid pathology in these individuals, as assessed with PET or cerebrospinal fluid analysis, is associated with reduced DMN connectivity (Table 3).^{113–117} Similarly, carriers of the ε4 allele of the apolipoprotein E gene (*APOE*), by far the strongest genetic risk factor for sporadic late-onset AD,¹¹⁸ show DMN abnormalities that mirror those observed in clinical AD.^{119,120} These individuals also showed increased connectivity in frontal regions of the DMN and salience network, a finding that was not observed in those with amyloidosis.^{119,120} DTI studies showed lower structural connectivity in AD regions in elderly carriers of the *APOE* ε4 allele.^{121–123} The *APOE* ε4 allele is also associated

with cortical A β deposition, and in order to tease out the independent contribution of this allele, one study investigated DMN changes in elderly *APOE* $\epsilon 4$ carriers who were A β -negative.¹²⁴ The results confirmed the presence of DMN abnormalities similar to those observed in AD, as well as increased frontal connectivity.

These data raise the question of whether connectivity abnormalities reflect neuropathological or neurodevelopmental changes. Recent studies assessing structural and functional connectivity at a younger age seem to partially support the latter hypothesis, as they demonstrate that the *APOE* $\epsilon 4$ allele modulates connectivity strength decades before any clinical expression of neurodegenerative and/or ageing processes emerges. One study assessed the DMN in young adults (20–35 years of age), and found increased connectivity in *APOE* $\epsilon 4$ carriers.¹²⁵ The findings of this study were subsequently independently confirmed.¹²⁶ Similarly, a DTI study showed higher structural connectivity in *APOE* $\epsilon 4$ carriers than in noncarriers,¹²⁷ although this finding was not confirmed by an independent study.¹²⁸ Finally, a recent study assessing structural connectivity in infants showed lower connectivity in regions typically affected by AD, and increased connectivity in frontal regions.¹²⁹ Overall it is difficult to reconcile this complex pattern of developmental and neurodegenerative connectivity changes into a unified framework, although these findings raise the possibility that the *APOE* $\epsilon 4$ allele is associated with a specific endophenotype.

Frontotemporal dementia

The pathological process underlying FTD—that is, frontotemporal lobar degeneration (FTLD)—has been elucidated in the past decade with the identification of two abnormal proteins, TAR DNA-binding protein 43 (TDP-43) and fused in sarcoma, which account for about 50–60% of FTD cases. The remaining cases are characterized by the presence of hyperphosphorylated tau (FTLD-tau), with only a small percentage of cases remaining unclassified.

To date, only one study has investigated the connectivity correlates of molecular pathology in FTD (Table 3).¹³⁰ This study assessed structural connectivity in FTD patients with tau or TDP-43 pathology, defined on the basis of autopsy or genetic confirmation (*MAPT* for FTLD-tau, *GRN* or *C9orf72* for FTLD-TDP), and showed greater damage in the superior longitudinal fasciculus in FTLD-tau than in FTLD-TDP.¹³⁰ FA values in the superior longitudinal fasciculus discriminated molecular subtypes with 96% sensitivity and 100% specificity.¹³⁰ Because the study was carried out in symptomatic patients, these results could indicate either a phenotypic difference or more-severe pathology in FTLD-tau.

A subsequent study by the same group selected 21 single nucleotide polymorphisms (SNPs) previously implicated in FTLD and investigated the structural connectivity correlates of these SNPs.¹³¹ The study identified three susceptibility SNPs, two conferring risk of the FTLD-TDP subtype (rs646776 and rs5848) and one for FTLD-tau pathology (rs1768208). The study included patients with sporadic FTD, and demonstrated that the three SNPs

were associated with reduced connectivity of the mid-brain and a mixed pattern of superior longitudinal fasciculus connectivity (Table 3). These preliminary data suggest a modulation effect of these susceptibility SNPs on structural connectivity.

With regard to functional connectivity, only one study to date has investigated connectivity changes associated with susceptibility genes in preclinical stages.¹³² The study included asymptomatic *GRN* mutation carriers (that is, with FTLD-TDP pathology) and focused on *TMEM106B*, a susceptibility factor associated with younger age at onset. The study showed that individuals carrying a risk polymorphism in *TMEM106B* (T/T) had reduced salience network and frontoparietal connectivity, a pattern of abnormalities similar to that observed in full-blown dementia.

Enhanced functional connectivity

As shown in the previous sections and in Table 1, enhanced functional connectivity (that is, increased synchrony of spontaneous BOLD fluctuations) is a common finding in task-free fMRI studies across a range of neurodegenerative diseases. This phenomenon has frequently been observed in motor diseases (for example, in PD and ALS), and occasionally also in cognitive-behavioural diseases (AD and FTD). The mechanism underlying these changes, however, is still unclear. Some authors have claimed compensatory mechanisms when increased connectivity was found associated with lower symptom severity.^{30,44,58,76,78,102} Other authors have also endorsed the ‘compensatory theory’, but with little evidence.^{57,84,87} Importantly, some studies showed an inverse relationship; that is, higher connectivity correlated with more-severe clinical symptoms^{35,44} or faster disease progression,^{58,60,61,83} suggesting a maladaptive and/or pathogenic mechanism rather than a compensatory phenomenon. A maladaptive response might reflect an unsuccessful attempt to recruit preserved neuronal areas to compensate for pathology, as well as a disrupted excitatory-inhibitory balance of damaged networks due to impending pathological processes. Overall, these findings indicate that enhanced connectivity is not a useful biomarker of disease severity in symptomatic individuals.

To better clarify the potential of enhanced connectivity as a disease biomarker at preclinical disease stages, we reviewed evidence from presymptomatic individuals with autosomal dominant forms of neurodegenerative diseases. According to the available literature (Table 4), evidence of over-recruitment is generally found in areas affected at late stages of the disease. In presymptomatic AD, one study reported greater connectivity in the frontal areas of the DMN,¹³³ whereas another found no evidence of enhanced connectivity in this network.¹³⁴ In FTD, one study found increased salience network connectivity in presymptomatic *GRN* mutation carriers,¹³⁵ but others reported either reduced salience network connectivity¹³⁶ or no changes.¹³⁷ Whitwell *et al.*⁴⁹ found increased connectivity in the posterior DMN of *MAPT* mutation carriers, a pattern similar to that observed in symptomatic bvFTD.³⁵ In PD, only one study has assessed connectivity in mutation carriers

Table 4 | Evidence of network over-recruitment from genetic studies

Clinical disease	Genes	Target network	Effect on connectivity in preclinical stages
Functional connectivity			
AD ^{133,134}	PS1, APP	Default mode network	↓/↑
FTD ^{49,135–137}	GRN, MAPT	Saliency	↓/↑
PD ¹³⁸	SCA2	Cerebellothalamocortical	↑
HD ^{91,139}	HTT	Sensorimotor	↔
Structural connectivity			
AD ^{140–142}	PS1, APP	Whole-brain white matter	↓/↑
FTD ^{136,137,143}	GRN, MAPT	Whole-brain white matter	↔
ALS ¹⁴⁴	SOD1	Sensorimotor	↓
HD ^{145,146}	HTT	Sensorimotor	↔

Evidence of functional over-recruitment is conflicting in AD and FTD, and extremely limited in PD. Structural connectivity biomarkers consistently show reduced connectivity at preclinical stages. Key: ↑, increased connectivity; ↓, reduced connectivity; ↔, evidence from multiple studies; ↑ or ↓, evidence from single study; ↓/↑, conflicting evidence. Abbreviations: AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; FTD, frontotemporal dementia; GRN, granulin; HD, Huntington disease; HTT, huntingtin; MAPT, microtubule-associated protein tau; PD, Parkinson disease; PS1, presenilin 1; SCA2, spinocerebellar ataxia type 2; SOD1, superoxide dismutase 1.

(SCA2 gene), and showed reduced connectivity in the basal ganglia–thalamocortical network but enhanced connectivity in other networks affected later by the disease.¹³⁸ Two studies conducted in presymptomatic HD showed no areas of increased connectivity in the sensorimotor⁹¹ or basal ganglia¹³⁹ networks. At presymptomatic stages, FTD, ALS and HD were associated with reduced structural connectivity in regions affected early in the disease process (Table 4).^{136,137,140–146} Interestingly, in individuals with presymptomatic AD, two studies reported paradoxically lower mean diffusivity in the precuneus and cingulum,^{141,142} a pattern opposite to that observed in symptomatic mutation carriers.

With regard to the possible underlying mechanisms, as studies in presymptomatic individuals cannot investigate the association with cognitive or clinical decline, it is not possible to clarify whether changes in connectivity represent a pathogenic or compensatory mechanism, or simply a distinct endophenotype. However, the relatively stable finding of enhanced connectivity in areas affected by pathology at late stages of the disease process, concurrently with reduced connectivity in areas affected early on, might indicate a pathogenic mechanism such as disrupted excitatory–inhibitory balance between networks. A maladaptive mechanism is an unlikely explanation because of the lack of cognitive and clinical deficits. Caution is needed when interpreting these findings, however, because they are not consistently reported by all studies.

Future perspectives

Filling gaps in the field

The reviewed literature identifies two major gaps in the study of brain connectivity that should be addressed by future investigations. First, the trajectory of connectivity changes over the disease course is largely unclear. Cross-sectional and longitudinal studies in symptomatic individuals suggest that pathology spreads along brain connections,^{5,75} leading to the hypothesis

that neurodegenerative diseases might be ‘networkopathies’.¹⁴⁷ However, a rigorous demonstration of when, where and how the pathology deposits and spreads along brain connections is still lacking, and will be an important goal of future research. The best approach would be a serial study covering the entire disease spectrum from normal to preclinical and clinical stages. Clearly, this is not a trivial undertaking in terms of resources, costs, and preclinical disease identification. In some cases, the latter issue is facilitated by the availability of *in vivo* disease markers, for example, markers of amyloidosis in AD, or susceptibility factors such as the APOE ε4 allele. Two large-scale population initiatives assessing individuals at risk of AD—Anti-Amyloid Treatment in Asymptomatic AD and the Alzheimer’s Prevention Initiative—have recently commenced, and could serve as a reference for other studies. Alternatively, autosomal dominant forms of neurodegenerative diseases could represent a valid approach: studying these rare populations would enable inclusion of presymptomatic individuals who will certainly develop the disease. The Dominantly Inherited Alzheimer Network¹⁴⁸ and the Genetic Frontotemporal Dementia Initiative¹⁴⁹ are two examples of such an approach.

Second, future studies should aim to integrate multiple imaging modalities to address the possible interplay between structural and functional connectivity changes.¹⁵⁰ Functional and structural connectivity are strongly linked: structural connectivity can predict functional connectivity; however, functional connections are also observed between regions that lack direct anatomical connections, possibly reflecting multisynaptic communication.¹⁵¹ To date, only a few studies have combined task-free fMRI and DTI to investigate network connectivity in neurological disorders.^{60,61} More-sophisticated approaches to combine structural and functional connectivity and more-complex measures of structural connectivity have recently been proposed,^{152,153} but have yet to be tested in the major neurodegenerative diseases. Furthermore, recent advances in the application of *in silico* simulations to model the effects of disease spread and structural damage on brain function provide a promising approach to examine neurodegenerative diseases.^{6,154} These methods may enable the creation of future predictive models to assess progressive disease effects in neurodegenerative disorders.

New targets

Neuronal communication has high metabolic costs.¹⁵⁵ Brain ‘hubs’ receive a disproportionately high number of connections, and have been suggested to form a central ‘rich-club’ or ‘core’ in the brain, creating a central anatomical infrastructure for neuronal communication and integration of information across distal regions and networks.^{153,156} Brain hubs include core nodes of all major task-free networks,¹⁵³ and these areas are disproportionately costly in terms of brain wiring and metabolic demand.^{155,157,158} These features could make the hubs especially vulnerable to pathology, either as a primary effect of the disease or as a secondary effect during disease progression. Indeed, simulation of damage to these

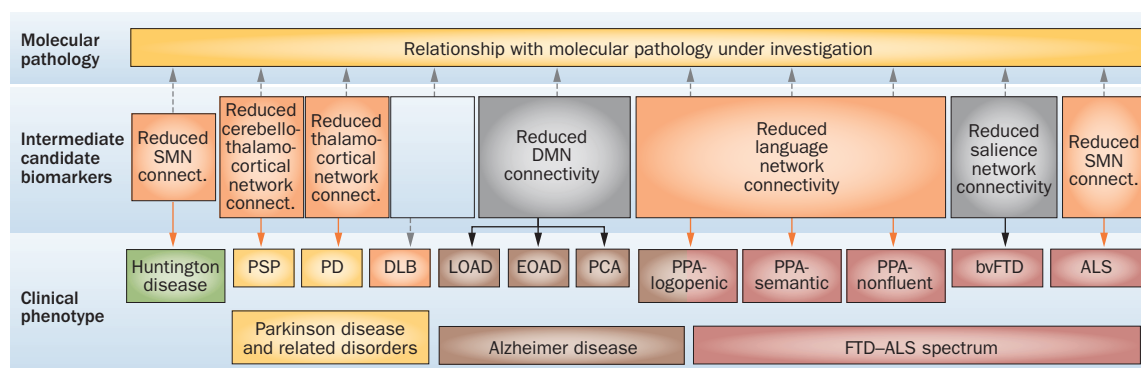


Figure 3 | Brain connectivity signatures for major neurodegenerative disorders. Functional connectivity signatures are shown in solid grey squares, and structural connectivity signatures are shown in orange squares. Brain signatures of molecular pathology are the subject of current research and are shown in dotted arrows. Abbreviations: ALS, amyotrophic lateral sclerosis; bvFTD, behavioural variant frontotemporal dementia; DLB, dementia with Lewy bodies; DMN, default mode network; EOAD, early-onset Alzheimer disease; LOAD, late-onset Alzheimer disease; PCA, posterior cortical atrophy; PD, Parkinson disease; PPA, primary progressive aphasia; PSP, progressive supranuclear palsy; SMN, sensorimotor network.

regions was demonstrated to be especially disruptive for whole-brain connectivity.^{155,156} This finding is in line with the hypothesis of selective neuronal vulnerability, which suggests that certain well-defined neuronal circuits are specifically targeted by neurodegenerative processes.¹⁵⁹ Related to this topic, an important question to address in AD is whether the higher functional connectivity observed in AD-specific brain regions in young adult *APOE ε4* carriers¹²⁵ may predispose these individuals to AD pathology through a network disruption mechanism starting decades before disease onset. Hubs and rich-club formation have been hypothesized to be involved in psychiatric disorders such as schizophrenia,¹⁶⁰ but whether they have a primary role in neurodegenerative disorders, and in AD in particular, has yet to be established.

Vital insights might come in the near future from the availability of MRI sequences directly assessing brain metabolic costs and/or vascular contribution, such as arterial spin labelling. This sequence was designed in the early 1990s to measure cerebral blood flow, and it provides a more direct and quantitative physiological measurement than fMRI, without the drawbacks of PET. Perfusion-related alterations have been observed across a variety of neurodegenerative disorders,¹⁶¹ and these changes may reflect, or be prodromal to, pathophysiological processes. To date, arterial spin labelling has been infrequently used in research due to issues such as the low signal-to-noise ratio and the lack of standard sequences. These limitations are likely to be overcome in the near future owing to technical and harmonization efforts that are currently underway.¹⁶²

Technical considerations

Technical factors such as field strength and the analytical method might account for the lack of consistent functional connectivity markers in PD, HD and ALS. The BOLD contrast is known to be significantly higher at 3 T than at 1.5 T, so scanners at lower field strength might be less sensitive to connectivity changes. Also, analytical approaches such as seed-based analysis might be less sensitive and specific than ICA-based approaches for identifying functional networks. When these differences

are taken into account, however, no systemic bias emerges across studies that could explain the inconsistencies described above (Supplementary Table 1 online). Indeed, findings in AD and bvFTD seemed to be consistent even when different approaches were used.

Alternatively, the conflicting findings might be attributable to the presence of motion that is not detected by standard post-processing controls. Motion is one of the most important factors affecting fMRI studies: researchers have noted that motion induces spurious functional relationships between cortical regions,¹⁶³ potentially influencing functional connectivity differences in patient studies. This phenomenon seems especially true for long-distance functional connections. As patients with neurodegenerative disease are more prone to movement than are healthy controls, and some disorders such as PD and ALS involve movement disturbances, general caution is needed in interpreting these findings, and methods to correct for these potential artefacts are advised.¹⁶³ Furthermore, local atrophy may affect the fMRI signal and, thus, the computation of connectivity. This is a well-established issue, and correction for the contribution of atrophy is generally recommended as part of the statistical analysis. Of note, these issues are less of a concern in studies on preclinical disease stages, since atrophy is minimal and patients tend to move less. Other possible explanations for the conflicting findings might be the small sample sizes, and functional connectivity variability related to the internal status of the patient.

Because the BOLD signal is an indirect measure of neuronal activity, and depends largely on vascular components (cerebral blood flow, cerebral blood volume and vascular compliance), brain oxygen metabolism and the coupling between these measures, any change in one of these factors may affect both the amplitude and the magnitude of the signal. While this is not a major problem when BOLD fMRI is used for anatomical localization of neuronal activity, quantitative interpretation of the signal in diseased populations is less straightforward. Baseline perfusion measures and a more comprehensive fMRI analysis model may be essential for inferring group differences.¹⁶⁴

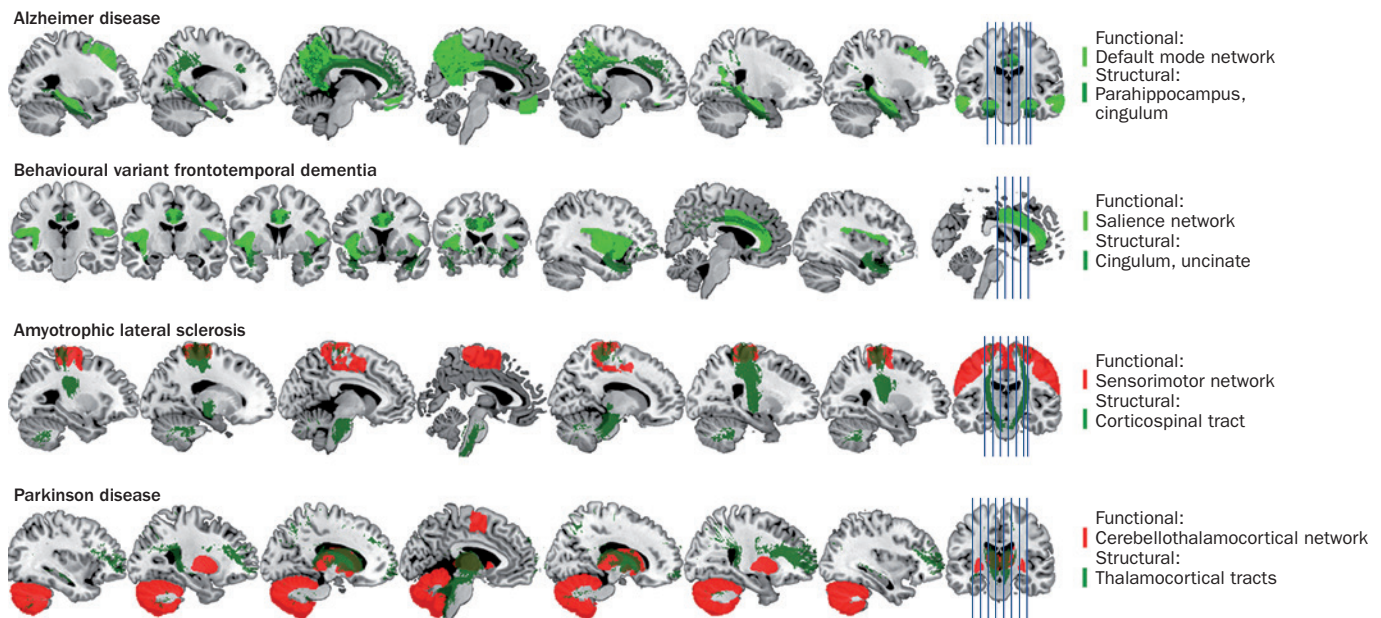


Figure 4 | Correspondence between structural and functional connectivity findings in four neurodegenerative diseases. For each disease, the panel shows the predicted pattern of functional and structural connectivity disruption. The predicted pattern is defined on the basis of the pathophysiology of the disease. Green corresponds to functional networks and structural pathways (light green and dark green, respectively) that fulfil the prediction, whereas red corresponds to networks and pathways that do not fulfil the prediction, according to the reviewed evidence.

Finally, test–retest reliability is critical in view of future longitudinal studies. Several task-free networks discussed in this Review (DMN, sensorimotor, frontoparietal and visual) and the major white matter tracts show good reliability over 12 months.^{165,166} However, reliability figures vary largely across networks and pathways, and future studies will need to demonstrate sufficient reliability for clinical use.

Conclusions

A summary of the reviewed literature is provided in Figure 3. Overall, current evidence supports the validity of task-free fMRI functional connectivity as a marker of clinical phenotype and disease severity in AD and bvFTD. However, evidence is still weak on its validity in ALS, PD and HD. In these latter neurodegenerative diseases, which are characterized by motor phenotypes, structural connectivity markers are stronger candidate biomarkers of clinical phenotype and disease severity. Figure 4 illustrates the correspondence between structural and functional connectivity findings in some of the neurodegenerative diseases discussed in this Review.

From a translational perspective, several factors, which could limit the clinical use of connectivity markers, should be mentioned. First, the current literature is largely based on group-level comparisons, and the specificity and sensitivity of these biomarkers must be established. A few studies carried out in patients with AD and bvFTD showed that the added value of these markers might be only incremental compared with standard markers of neurodegeneration.^{40,167} Future studies in patients at preclinical stages will indicate whether connectivity markers can outperform structural

MRI markers early in the disease course. Second, functional connectivity findings are inconsistent in motor phenotypes. As mentioned above, structural connectivity markers might be more useful for these diseases.

Finally, owing to the increasing availability of *in vivo* markers of pathology, such as cerebrospinal fluid-derived or PET-derived amyloid and tau signatures, the molecular correlates of abnormal connectivity can now be studied. As shown in the section on connectivity correlates of molecular pathology in AD, findings in this area are very promising. The molecular correlates of connectivity abnormalities in the FTD spectrum are largely unexplored, but future studies in this field will enable identification of the determinants of the spread of pathology across distinct neuronal networks, and possibly shed light on the mechanisms underlying phenotypic variability.

Review criteria

Articles were identified by searching PubMed for the following terms: “brain connectivity”, “structural connectivity”, “functional connectivity”, “resting-state functional MRI”, “diffusion tensor imaging”, “dementia”, “neurodegenerative disorders”, “Alzheimer”, “frontotemporal dementia”, “Parkinson”, “amyotrophic lateral sclerosis”, “progressive supranuclear palsy”, and “Huntington”. Articles were also identified through searches of the authors’ own files. Reference lists of the identified papers were examined for further leads. The search was limited to full-text manuscripts published in English between 2004 and 2014 (except for theoretical or methodological papers). The final selection was based on originality and relevance, as judged by the authors.

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Author contributions

M.P. and G.B.F. developed the architecture of the manuscript. M.P. wrote the initial draft, which was completed, edited and reviewed for important intellectual content by N.F., M.P.v.d.H., S.F.C. and G.B.F. M.P. and G.B.F. prepared Figure 1, Figure 3 and Figure 4, and N.F. prepared Figure 2. All the authors have seen and approved the final version.

Supplementary information is linked to the online version of the paper at www.nature.com/nrneuro.