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A clinicopathological approach to the diagnosis of dementia

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Abstract

The most definitive classification systems for dementia are based on the underlying pathology which, in turn, is categorized largely according to the observed accumulation of abnormal protein aggregates in neurons and glia. These aggregates perturb molecular processes, cellular functions and, ultimately, cell survival, with ensuing disruption of large-scale neural networks subserving cognitive, behavioural and sensorimotor functions. The functional domains affected and the evolution of deficits in these domains over time serve as footprints that the clinician can trace back with various levels of certainty to the underlying neuropathology. The process of phenotyping and syndromic classification has substantially improved over decades of careful clinicopathological correlation, and through the discovery of *in vivo* biomarkers of disease. Here, we present an overview of the salient features of the most common dementia subtypes — Alzheimer disease, vascular dementia, frontotemporal dementia and related syndromes, Lewy body dementias, and prion diseases — with an emphasis on neuropathology, relevant epidemiology, risk factors, and signature signs and symptoms.

Dementia is a complex process involving an interplay between specific molecular pathways affecting cellular functions, leading to loss of synaptic connections, cell death, gliosis[1], inflammation, and disruption of functional networks underlying cognition, personality, behaviour and sensorimotor functions, eventually attacking an individual's autonomy[2]. Ageing is the most robust risk factor for dementia, with more than 90% of dementias presenting after the age of 65 years. With an increase in the mean age of the population, the incidence and prevalence of dementia continue to steadily increase worldwide. In 2015, the World Alzheimer Report[3], a comprehensive meta-analysis of population-based studies, estimated that 46.8 million people worldwide are living with dementia, and that number is expected to reach 131.5 million by 2050. In the USA alone, an intervention delaying onset of dementia by 5 years would reduce Medicare costs by US$283 billion in 2050 (REF. 4).

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Author contributions

F.M.E. researched data for the article and wrote the manuscript. Both authors made substantial contributions to discussions of the content, and reviewed and edited the manuscript before submission.

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SUPPLEMENTARY INFORMATION

See online article: S1 (box)

Historically, definitions of dementia have been weighted toward prominent deficits in memory, as observed in typical amnestic Alzheimer disease (AD)[5]. The definition was revised in 2011 to reflect the plethora of cognitive and behavioural changes that can cause decline from baseline levels of functioning[6]. The revised definition requires impairments in at least two neuropsychiatric or cognitive domains that are not better explained by nondegenerative or primary psychiatric disorders, or systemic conditions such as delirium. The diagnostic process requires a history taken from the patient and a reliable informant, as well as objective measures of impairment through a neuropsychiatric and neuropsychological assessment[6].

Definitive classification of dementia is based on the underlying neuropathology, as noted on autopsy or — in rare cases — biopsy. However, with various degrees of certainty, dementias can be sorted into syndromic categories on the basis of distinct clinical features, evolution over time (symptomatic progression), and other ancillary diagnostic information. Different pathologies can cause similar clinical syndromes, although rigorous syndromic classification can often predict the underlying pathology. The accuracy of clinicopathological diagnoses is improved by the use of imaging, biofluid and genetic biomarkers. In addition, simple treatable causes of cognitive impairment, such as hypothyroidism, vitamin B_{12} deficiency, infection or medication-induced problems, must be sought and ruled out.

In this Review, we highlight key elements that distinguish the most common dementia subtypes. We offer an overview of dementia classification and diagnosis, with an emphasis on salient clinical features, neuropathology, relevant epidemiology, risk factors, and *in vivo* biomarkers. We conclude with a summary of where the field stands with regards to the diagnostic process, and where it is heading.

Dementia classification

Dementias are classified on the basis of their underlying pathologies, which are largely defined by accumulation of abnormal protein aggregates in neurons and glia, as well as in the extracellular compartment, in vulnerable regions of the brain[7]. The vast majority of non-vascular dementias fall into six main categories of neurodegenerative proteinopathy: amyloid-β (Aβ), microtubule-associated protein tau, TAR DNA-binding protein 43 (TDP-43), fused in sarcoma (FUS), α-synuclein, and prion protein (FIG. 1). Often, the presence of proteinopathies precedes clinical deficits by years. Whether these proteins are simply biomarkers reflecting the toxic molecular milieu, active agents of toxicity, or a combination of the two is open to debate.

The prion protein propagates along neuronal networks and can seed healthy cells[8,9]. Evidence emerging in recent years suggests that other neurodegenerative proteinopathies — in particular, tau and α-synuclein — share similar mechanisms of propagation[10–13]. Indeed, pathological and *in vivo* functional studies indicate that the majority of neurodegenerative diseases begin focally in a subset of vulnerable neurons or glia, with subsequent spread throughout the brain along specific paths[7,14]. Moreover, rather than being a homogeneous disease process, dementias seem to constitute a continuum of pathophysiological change, in turn giving rise to a spectrum of symptoms of varying severity. Therefore, definitions of the

underlying pathologies, incorporating information from *in vivo* biomarkers of disease, are changing to reflect asymptomatic (or presymptomatic) and symptomatic phases of disease, also referred to as preclinical and clinical, respectively.

Three dichotomous clinical categories — early versus late, gradual versus rapid, and sporadic versus familial — apply distinctly or in combination to the spectrum of dementing processes. The age cut-off for early versus late onset of dementia is arbitrarily set at 65 years, which is historically the typical age for retirement. However, the incidence of many pathologies increases with age, frequently resulting in coexistence of more than one pathology (mixed pathology), which blurs syndromic delineations in the latter decades of life[15].

Dementia epidemiology remains challenging: the accuracy of incidence and prevalence estimates is hampered by diagnostic challenges, and the absence of pathological confirmation in most of the published literature[16]. Globally, AD accounts for approximately 60% of all dementias[17,18]. However, when dementias are subdivided into early versus late, frontotemporal dementia (FTD) seems to be at least equally prevalent to AD before the age of 65 years[19–23]. Many patients diagnosed with AD also show multiple non-AD pathologies involving tau, TDP-43 and α-synuclein[24,25]. Sex differences between syndromes are observed, with over-representation of AD in females after age 75 years[26]. Survival after diagnosis ranges from months to decades. Regardless of the disease specificity, as dementia progresses, vegetative functions eventually become affected, with death frequently ensuing from swallowing difficulties, falls and infections.

It should be noted that established diagnostic criteria are primarily aimed at homogenizing clinical research cohorts, although they also have value for the clinician in establishing certainty around a specific diagnosis. In clinical practice, every patient presents with a unique story of decline. The work of the clinician lies in translating the patient's story into a dynamic neuroanatomical map of the underlying pathology and its associated proteinopathy, supported by *in vivo* biomarkers of disease.

Alzheimer disease

Pathology: a dual proteinopathy

AD pathology is a dual proteinopathy defined by the coexistence of extracellular aggregates of $A\beta_{42}$ fibrils — and, to a lesser extent, $A\beta_{40}$ fibrils — that form neuritic Aβ plaques (hereafter referred to as amyloid), and intracellular aggregates of hyperphosphorylated tau (P-tau), termed neurofibrillary tangles (NFTs)[27,28]. The gradual spread of NFTs (Braak stages I–VI)[29] correlates better with progression of cognitive deficits[30,31] than does amyloid deposition[32], which is often diffuse at the time of symptom presentation[33,34].

The order in which these proteinopathies develop, and their potentially synergistic relationship with neurodegeneration, continue to be investigated. In sporadic AD, both proteinopathies precede symptom onset by years[31]. In an autopsy series of 2,332 brains[35], Braak and colleagues found NFTs in the absence of amyloid in the early stages of AD. By contrast, with the exception of one individual with an autosomal dominant genetic cause of

amyloidopathy (amyloid precursor protein (*APP*) gene triplication in Down syndrome), the researchers did not detect amyloid plaques in the absence of NFTs. The observation of tau pathology early in the disease course and its close association with the severity of neurodegeneration has prompted reconsideration of AD as a tauopathy. Nevertheless, by definition, AD-related dementia remains a dual proteinopathy with postulated synergy between tau and amyloid in the progression toward dementia.

From an anatomical standpoint, the abnormal intracellular aggregation of tau may begin subcortically in noradrenergic projection neurons of the locus coeruleus[36–39], extending along functional networks subserving the limbic system. Noradrenergic deficiency, and ensuing symptoms such as attentional deficits, are intimately connected to the neuroanatomical substrates of AD. In addition, involvement of cholinergic neurons in the nucleus basalis of Meynert results in an important cholinergic deficit, and loss of serotonergic neurons in the dorsal raphe nucleus is thought to contribute to psychiatric changes. The first cortical regions displaying accumulation of abnormal tau include the transentorhinal cortex of the medial temporal lobes, the hippocampal formation and the basal forebrain, followed by the allocortex and the rest of the neocortex.

From a molecular standpoint, abnormally phosphorylated tau no longer binds to microtubules, leading to misfolding and aggregation, forming ‘pretangles’ that gradually fill affected neurons. Pretangles transform into insoluble fibrillary and argyrophilic neuropil threads, and eventually NFTs. In addition, tau is extensively involved in neuronal signalling pathways, which become affected with disease progression. Affected cells survive for years, eventually undergoing premature apoptosis, which results in loss of grey matter and symptomatic progression. With increasing age, other co-pathologies, such as vascular disease and Lewy body disease (LBD), are found post mortem[24].

Additional dimensions to AD proteinopathies continue to be uncovered. For instance, several structurally diverse molecular subtypes of Aβ fibrils that have differential associations with AD subtypes (phenotypes) have been reported[40–43].

The current model of AD is based on distinct but related pathological and clinical continua. AD pathology progresses through disease states, with spread of NFTs, neurodegeneration, and phases of amyloid. These states are reflected in progression of clinical symptoms[44], from prodromal AD or mild cognitive impairment (MCI)[45,46] to mild, moderate or severe dementia[6].

Risk factors

In autosomal dominant AD (ADAD), mutations in known disease-related genes, including *APP*, presenilin-1 (*PSEN1*) and presenilin-2 (*PSEN2*), contribute directly to increased $A\beta_{42}$ production, amyloid formation and inflammation[47–49]. Sporadic AD is a genetically complex disease, for which the strongest monogenic risk factor remains the apolipoprotein E ε4 allele (*APOE*ε4*): homozygosity for this allele increases the odds of AD 15-fold, compared with threefold in heterozygotes[50]. Genome-wide association studies have identified over 20 risk and protective genetic variants, with modest individual effect sizes[51]. Recent work using genotype data from over 70,000 patients with AD and age-matched

controls has shown that a polygenic hazard score composed of AD-associated risk genotypes and *APOE* status can predict the age-specific risk of developing AD[52].

Additional risk factors for AD include age, family history of AD, cerebrovascular disease (CVD) and its associated risk factors (including hypertension and diabetes), chronic inflammation, obstructive sleep apnoea, traumatic brain injury (TBI), and low education[53,54]. In fact, emerging data-driven models suggest that vascular disease and dysregulated inflammation are early risk factors in the pathophysiological cascade leading to AD[55]. The mechanisms of vascular disease — especially small vessel disease (SVD) — and AD-related neurodegeneration might be intricately interrelated[56].

Biomarkers

The most commonly used *in vivo* biomarkers of AD neuropathology are cerebrospinal fluid (CSF) levels of $A\beta_{42}$, tau and P-tau (BOX 1; TABLE 1). Decreases in CSF $A\beta_{42}$ can be observed in the early stages of disease, before overt neurodegeneration occurs, and can precede increases in CSF tau and P-tau by years[30], or even decades in the case of ADAD[49]. Of the various biomarker combinations under investigation, the $A\beta_{42}$:$A\beta_{40}$ ratio shows the best correlation with amyloid deposition at the MCI stage, and the highest diagnostic accuracy for AD versus other dementias[57].

AD states can only be determined with certainty post mortem, although advances in structural and molecular neuroimaging are making ante-mortem determination a possibility[58–60]. Several tau PET ligands show promise, with tracer uptake matching the predicted topographic Braak staging of NFTs in AD[61–64]. However, only amyloid PET, using the ^{18}F-labelled tracers florbetapir, flutemetamol and florbetaben, is available clinically[65]. Other amyloid ligands, such as ^{11}C-labelled Pittsburgh compound B, are available for research. Studies in ADAD suggest that CSF $A\beta_{42}$ levels are more sensitive than amyloid PET, which can lag behind by a decade in ADAD[49].

Structural MRI and ^{18}F-FDG–PET are topographical methods of assessing neurodegeneration and neuronal dysfunction (for example, synaptic loss), respectively. Antecedent to atrophy, hypometabolism characteristically involves the medial temporal and medial parietal (precuneus) lobes, posterior cingulate cortex, and temporo parietal association cortices[66]. In typical, amnestic AD, atrophy is first noted in the medial temporal lobes, gradually involving the broader temporoparietal cortices with disease progression[67] (FIG. 2).

From a clinical perspective, biomarkers should be used to confer confidence on the clinical diagnosis or to determine disease state, with their interpretation being contingent on clinical phenotype. Biomarkers diminish in utility with age, as the incidence of asymptomatic AD neuropathology increases dramatically from 70 years of age. Consequently, they are most useful in diagnosing early-onset AD (EOAD), or in the presence of atypical features, such as rapid rate of progression, prominent behavioural symptoms, or motor dysfunction. In late-onset AD (LOAD), structural neuroimaging (MRI or CT) remains useful in determining contributing factors, such as vascular disease, and assessing the presence of alternative pathologies such as strokes or malignancies.

From a research perspective, the combination of tau with amyloid PET[60] offers the possibility of ante-mortem disease state determination, and clarification of the temporospatial relationship between the proteinopathies as individuals transition into the symptomatic stage of disease. However, in-depth clinical phenotyping and assessment of functional status continue to serve as gauges of disease progression.

Biomarker findings can conflict with the clinical picture: even a 'typical' progressive amnestic AD phenotype can be associated with negative amyloid biomarkers. Combined with an atypical pattern of atrophy or hypometabolism, and possibly increased CSF tau levels, negative amyloid biomarkers can be suggestive of other neurodegenerative diseases, such as FTD with TDP-43 neuropathology (see below), argyrophilic grain disease, LBD, or tangle-only dementia[68].

Clinical syndromes

A diagnosis of AD dementia requires insidious onset and gradual progression of deficits in two cognitive domains, one being memory. These original diagnostic criteria have been revised to incorporate *in vivo* biomarkers of the disease process as well as genetics. The new criteria[6] distinguish between levels of certitude, with probable and possible AD categories, as well as probable or possible AD with *in vivo* evidence of the AD pathophysiological process or genetic risk factors.

AD clinical diagnoses can be sporadic (the majority of cases) or familial. Sporadic AD is predominantly a late-onset dementia, presenting after the sixth to seventh decade of life, whereas familial AD usually presents earlier. Among individuals affected by AD, an estimated 1–5% present with EOAD[69]. EOAD is genetically complex, and only an estimated 10–20% of individuals with this condition have a clear family history showing a Mendelian inheritance pattern. The genes most commonly implicated in EOAD are *PSEN1*, *PSEN2* and *APP.*

A few syndromes that classically present early are discussed below. However, presentation of early EOAD as a whole and the spectrum of ADAD syndromes is a vast topic, outside the scope of this Review, and the interested reader is directed to previously published work[70,71].

Typical Alzheimer disease—Sporadic LOAD is the prototypical AD syndrome. Amnestic MCI, defined as isolated difficulties with formation of new episodic memories, with preserved functional independence[46], is frequently the first clinical presentation of typical — or amnestic — AD[6]. Decreased semantic fluency can also be noted on neuropsychological testing. Overall, typical AD is defined by prominent early episodic memory deficits, reflecting neurodegeneration of the limbic system and the medial temporal lobe. Additional deficits such as acalculia and visuospatial dysfunction localize to parietal lobes (FIG. 2). Noradrenergic and cholinergic deficits can be prominent, affecting mood and frontal lobe functions, with diminished attention and concentration. Early and prominent involvement of cognitive domains other than memory is suggestive of atypical or variant AD, detailed below.

Atypical or variant Alzheimer disease—In variant AD, deficits in language, visual processing and executive and/or behavioural functions constitute the first presenting symptoms, and frequently overshadow milder disturbances in episodic memory in the initial stages of the disease. These focal cortical presentations occur with higher frequency in patients with EOAD[72].

The three well-described syndromes — logopenic variant primary progressive aphasia (lvPPA), posterior cortical atrophy (PCA), and behavioural dysexecutive AD — begin in the inferior parietal lobule or superior temporal gyrus, the occipitoparietal lobes, and the frontoparietal neuronal networks, where peak atrophy can be seen.

As lvPPA is an aphasia syndrome, the earliest and most debilitating symptom must be impairment in language, even in the presence of other deficits, including episodic memory[73–75]. Frequently, patients present with anomia due to single-word retrieval difficulties, with frequent pauses and hesitations in spontaneous speech, and loss of fluency (Supplementary information S1 (box)). As patients attempt to circumvent word-retrieval blocks through simplifications, substitutions and circumlocutions, use of indefinite or demonstrative pronouns and unspecified nouns such as ‘stuff’ increase with greater imprecision in language. Limitation in auditory working memory can lead to difficulties in repetition and comprehension of long sentences. Phonemic paraphasias also occur.

At onset of lvPPA, routine ‘small talk’ may sound normal, with deficits becoming apparent when access to infrequently used words is sought. With disease progression, patients develop features common to other aphasias, as well as verbal episodic memory deficits, typical of limbic AD. Concordant presence of atrophy (FIG. 2) and hypoperfusion or hypometabolism in the posterior perisylvian region and/or parietal lobe on MRI, single-photon emission CT (SPECT) and PET supports this diagnosis[66,67]. In addition, AD biomarkers (CSF or PET) have high utility for increasing confidence in the diagnosis, as well as for distinguishing lvPPA from FTD language syndromes that are much less frequently caused by AD pathology[76] (see FTD section below).

PCA, historically referred to as visual AD[77,78], involves a plethora of signs and symptoms that reflect degeneration of the occipitoparietal and sometimes the posterior temporal lobes (FIG. 2). Deficits include higher-order visual processing impairments, such as visual agnosia, dressing apraxia, alexia, elements of Balint and Gerstmann syndromes, ideomotor apraxia, and prosopagnosia. Some patients experience visual field cuts early in the disease course, and many eventually become cortically blind. By contrast, memory and verbal fluency impairments are typically more modest. The preservation of insight in the setting of severe impairments can contribute to depression. Topographic changes in the posterior cortex, noted on ancillary testing, are supportive of the diagnosis[72,79].

PCA and dementia with Lewy bodies (DLB) both target posterior cortical regions and, therefore, share noted changes in higher-order visual processing. However, these conditions differ with regard to typical age of onset and other specific core and supportive diagnostic criteria. On average, symptom onset for PCA is in the fifth or sixth decade of life — earlier than for DLB, which is typically a late-onset dementia. AD is the most common pathology

associated with PCA, although cases with Lewy bodies, prions or primary tau pathology have been reported.

The behavioural dysexecutive variant of AD[80], also referred to as frontal variant AD, can present with predominance of behavioural and/or executive dysfunction[81–85]. In the behavioural subtype, voxel-based morphometric studies reveal temporoparietal atrophy with relative preservation of frontal grey matter (FIG. 2). Consequently, Rabinovici and colleagues have favoured the use of the term behavioural dysexecutive variant, rather than frontal variant[80]. The behavioural variant can easily be mistaken for possible behavioural variant FTD (bvFTD, see below); however, it is characterized by a more dampened and restricted behavioural disturbance. Although memory deficits can lag behind behavioural dysfunction, they still tend to occur earlier than in sporadic bvFTD[80]. In the University of California, San Francisco (UCSF) series, amyloid PET and post-mortem evaluations indicated a rate of 10–40% for the misdiagnosis of behavioural variant AD as bvFTD[86–88].

Autosomal dominant Alzheimer disease—Overproduction of amyloid, caused by mutations in *APP*, *PSEN1* or *PSEN2*, is thought to be an important aspect of ADAD pathophysiology. This phenomenon is intricately linked to certain complications that are prevalent in ADAD, including cerebral amyloid angiopathy, and the related microbleeds, progressive white matter disease and microinfarcts. Although non-cognitive manifestations of disease affect only a fraction of individuals with ADAD[70], they occur with higher frequency than in sporadic EOAD[71]. Besides early age of onset[64], profound amnesia and a family history, certain features, such as psychiatric symptoms (including hallucinations and delusions), parkinsonism, gait abnormality, pseudobulbar affect and early prominent myoclonus, have been reported in mutation carriers[71,89]. Overall, the reported ADAD phenotypes are highly variable, possibly owing to other genetic modifiers that influence the molecular effects of mutated gene products.

Vascular dementia

Pathology, risk factors and epidemiology

CVD affecting vessels of various calibres can cause infarcts and haemorrhages, as well as chronic progressive white matter disease, including demyelination, axonal injury, astrocytosis and oedema, with infiltration of macrophages and activation of microglia[90]. In contrast with other neurodegenerative diseases, vascular cognitive impairment (VCI) and vascular dementia (VaD)[91,92] are not characterized neuropathologically by accumulation of abnormal proteins. Nonetheless, vascular disease tends to be progressive and degenerative, with cognitive impairment following clinical stroke or resulting from subclinical vascular brain injury[93].

The Newcastle pathological categorization distinguishes six vascular injury subtypes that can cause a dementia syndrome[94]. Chronic cerebral SVD, the most insidious subtype, shows the strongest association with cognitive impairment. From a microstructural perspective, SVD is associated with blood–brain barrier (BBB) compromise, resulting in leakage of fluid and macromolecules, and chronic white matter disease[95,96]. SVD can cause cortical and subcortical microinfarcts, lacunar strokes, a chronic state of cerebral hypoperfusion,

hippocampal atrophy, and sclerosis. Interestingly, SVD is also an important risk factor for large vessel disease[97]. The histopathological substrate of SVD includes lipo-hyalinization of vessels, formation of microatheromas within vessels, fibroid necrosis, enlarged Virchow–Robin spaces (eVRS), pallor of perivascular myelin, and astrocytic gliosis[98]. In addition to age-related and possibly synergistic interactions between SVD and AD pathology, cerebral amyloid angiopathy can cause a vigorous inflammatory and non-inflammatory SVD, with microbleeds and infarcts.

Risk factors for poststroke dementia[99], which include age, low education, female sex, vascular risk factors, and global and medial temporal lobar atrophy on structural imaging, overlap extensively with those identified for AD, suggesting possible mechanistic interactions and cumulative risk of these two pathologies. Hereditary vascular disease syndromes such as CADASIL are associated with specific patterns of change, as well as a more aggressive disease process. In general, the spatial variability in manifestation of vascular disease echoes the principle of selective vulnerability seen in neurodegenerative diseases with underlying proteinopathy. The extent of overlap between molecular mechanisms of sporadic and genetic disease remains to be determined.

Population-based clinicopathological studies have yielded prevalence estimates of 2.4–23.7% for pure VaD and 4.1–21.6% for mixed AD and VaD[100,101]. A large number of dementia patients with prominent CVD show multiple pathologies, most frequently including AD and LBD[102]. The variability in types and location of vascular disease, existence of mixed pathology, and lack of internationally accepted consensus criteria for VaD neuropathology might explain the limited sensitivity and specificity of ante-mortem clinical diagnostic criteria, and the variability in prevalence estimates reported in autopsy series[92]. Nevertheless, the consistent decrease in pure VaD and the related increase in mixed pathologies with age are well established, and imply intricate relationships between vascular disease, cerebral ageing and accumulation of abnormal proteins in neurodegeneration[99,103].

Clinical syndromes and biomarkers

The VCI–VaD spectrum encompasses a heterogeneous group of clinical presentations. Numerous diagnostic criteria have been drafted for sporadic VaD to date. The modified Hachinski Ischemic Scale (HIS), which includes 13 features aimed at obtaining a global ischaemic score, can be easily applied in clinical practice[104]. The HIS was specifically designed to enhance the distinction between VaD and AD[105]. The scoring system includes risk factors such as history of hypertension, as well as symptoms of small and large vessel disease that localize to white and grey matter, such as stepwise cognitive decline, abrupt onset, a history of stroke, focal neurological signs and symptoms, emotional lability, and somatic complaints. The criteria are limited by lack of integration of neuroimaging information, but the sensitivity (70%) and specificity (80%) for separating VaD from AD remain acceptable.

The most widely used criteria in VaD clinical trials research were formulated by the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS–AIREN)[106]. Emphasis was placed on neuroimaging evidence of disease in key areas involved in VaD (frontal, temporal

or parietal cortices, thalamus, and basal ganglia), and visual quantification of abnormal white matter signal. In 2014, the International Society of Vascular Behavioural and Cognitive Disorders (VASCOG) drafted a new set of criteria addressing the breadth of symptoms, high variability in severity of deficits and rate of progression, and frequent occurrence of mixed CVD and AD pathologies[107].

Early changes at the prodromal VCI stage include deficits in cognitive flexibility and verbal memory retrieval[108]. As the frontal white matter is particularly vulnerable to SVD[56], typical cognitive deficits with disease progression include executive dysfunction, with diminished attention and concentration and impaired spontaneous retrieval of stored memory. Behavioural changes such as irritability are common, and parkinsonism (frequently symmetrical) can also be noted.

Vascular disease is necessary but not sufficient for the development of VaD. Biomarker predictors of clinical deficits include the volume and pattern of white matter disease, as well as the patient's cognitive reserve[109]. White matter disease, microbleeds and eVRS all constitute imaging biomarkers of SVD[110].

In research, new imaging techniques, including diffusion tensor imaging (DTI), proton magnetic resonance spectroscopy and dynamic contrast-enhanced MRI, are being used to quantify white matter disease and BBB disruption. In addition, CSF and peripheral biomarkers of inflammation and BBB dysfunction show promise for improving the diagnosis of SVD and VaD[109,111].

Frontotemporal dementia

Pathology: tau, TDP-43 and FUS

FTD syndromes arise from frontotemporal lobar degeneration (FTLD), a gross pathological term denoting the degeneration of cortical and subcortical structures within frontal and temporal regions of the brain. Affected structures include the frontoinsular cortices, anterior temporal poles, basal ganglia, brainstem and thalamus, as well as the cerebellum in certain genetic forms of the disease. Gradually, neuronal networks that subserve personality, behaviour, executive functions, language and motor abilities are disrupted, with relative sparing of memory and visuospatial functions[112,113]. FTLD and the clinical syndromes of FTD have diverse molecular pathologies, risk factors and genetic foundations.

Most FTLD cases (90–95%) are FTLD-tau or FTLD-TDP, caused by intracellular aggregates of tau or TDP-43, respectively[114–117] (BOX 2). Most of the remaining 5–10% of cases are FTLD-FUS, caused by intracellular FUS inclusions[118,119] (BOX 2). Alternative splicing of microtubule-associated protein tau (*MAPT*) pre-mRNA gives rise to tau isoforms containing three or four microtubule-binding domain repeats (3R and 4R). Therefore, FTLD-tau is further subdivided into 3R, 4R and 3R/4R tauopathies. Pick disease is a 3R tauopathy, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are 4R tauopathies, and AD is a mixed 3R/4R tauopathy. Mixed FTLD pathologies and unclassifiable tauopathies are also encountered.

Each FTLD pathological subtype can cause several FTD syndromes (FIG. 3). There are three core FTD syndromes, including the most common — behavioural variant FTD (bvFTD) — and two language syndromes, namely, nonfluent/agrammatic variant PPA (nfvPPA) and semantic variant PPA (svPPA)[120]. In addition, three FTD motor syndromes are recognized: FTD with motor neuron disease (FTD–MND), and two variants with parkinsonism, namely, corticobasal syndrome (CBS), and PSP syndrome (PSP-S) (FIG. 1).

The heterogeneity in clinical presentations of FTLD molecular pathologies renders ante-mortem pathological predictions difficult. In familial FTLD, however, the affected genes are associated with homogenous pathological signatures. Mutations in the *C9orf72*, progranulin (*GRN*), valosin-containing protein (*VCP*) and TDP-43 (*TARDBP*) genes are associated with TDP-43 pathology, whereas *MAPT* mutations are consistently associated with tau pathology (BOX 2). In addition, a few non-familial clinical syndromes have homogenous pathological substrates. Approximately 90% of individuals with svPPA have FTLD-TDP type C pathology, and Steele– Richardson–Olszewski syndrome (PSP-RS) is linked to 4R tau pathology (FIG. 3). FTD–MND is almost always associated with TDP-43 pathology (usually type B), and around 85% of all nfvPPA cases show either 4R (CBD or PSP) or 3R tau pathology. By contrast, all molecular subtypes are seen with bvFTD: at UCSF, 60% of cases show TDP-43 aggregates, 30% show some form of tau pathology, and 10% show FUS neuropathology (D. C. Perry *et al.*, unpublished observations).

Approximately one-third of patients with FTD have a family history of dementia, although the proportion varies between FTD subtypes. Investigation of familial FTD has revealed notable variability in penetrance of mutations and associated phenotypes, including age of onset and rate of progression[121]. FTD–MND is the most heritable subtype, and svPPA — notwithstanding a few cases associated with *GRN* mutations — is the least heritable[122–126].

Expansion of an intronic hexanucleotide repeat in *C9orf72* is the most common hereditary cause of FTLD-TDP[127], as well as the most frequent genetic aetiology of familial and sporadic amyotrophic lateral sclerosis (ALS) (BOX 3). TANK-binding kinase 1 (*TBK1*) mutations have also been reported to cause FTD–MND spectrum disorders[128]. *GRN* mutations cause about 25% of familial cases of FTLD-TDP[129], and typically give rise to a bvFTD syndrome or, less commonly, CBS, language or mixed behavioural–language FTD[130,131]. *TARDBP* mutations are responsible for 4% of familial ALS cases reported, and only rarely cause FTD. *VCP* mutations can cause FTLD pathology with a syndrome including hereditary inclusion body myopathy and Paget disease of bone[132,133]. The *MAPT* H1 haplotype is a genetic risk factor for PSP and CBD[134].

Clinical syndromes and biomarkers

FTLD molecular pathologies give rise to degeneration in vulnerable neuronal networks subserving cognitive, behavioural and sensorimotor functions. Psychiatric symptoms such as depression occur with varying frequency across different FTD subtypes[135]. Early in the clinical course, self-awareness and insight commonly diminish, so despite disabling deficits affecting social and interpersonal relationships, patients report depression less frequently than in other dementia syndromes. However, important behavioural and personality changes contribute to a high caregiver burden[136].

Each FTD syndrome is characterized by a chronology of deficits partially dictated by the underlying proteinopathy[7]. In bvFTD and right-sided svPPA (svPPA-R), global hemispheric differences, with right-predominant patterns of atrophy, lead to striking behavioural symptoms, whereas patients with left-predominant atrophy, such as nfvPPA and svPPA-L, tend to present with language-related deficits (FIG. 4). Consequently, prototypical findings on formal neuropsychological evaluation vary depending on the syndrome, stage of disease, and individual factors, such as baseline cognitive function, or disease resilience[137]. However, deficits in executive function — possibly including face and emotion recognition — and changes in language, with relative preservation of episodic memory and visuospatial functions, can generally be noted. With disease progression, the mesiotemporal and parietal lobes also become involved, with corresponding impairment in episodic memory and visuospatial functions.

The reported age of FTD onset ranges from the 20s to the 90s, with most patients presenting between 45 and 65 years of age. Motor FTD syndromes can present later, with mean age of onset in the seventh decade of life[120,138,139].

Behavioural variant frontotemporal dementia—The earliest symptoms of bvFTD include progressive changes in emotion, personality and behaviour, especially relating to interpersonal interactions and social conduct, localizing to disrupted paralimbic networks including the anterior cingulate, insular, medial frontal and orbitofrontal cortices[140]. Dysfunction of the dorsolateral prefrontal cortices contributes to impairment in executive functions. Most patients present with early changes in empathy; apathy or inertia; disinhibition; stereotypic behaviour; alteration in food preference and eating behaviour; and dysexecutive symptoms[113,141] (Supplementary information S1 (box)). Among these early symptoms, loss of empathy seems to have special diagnostic value, but is challenging to ascertain in practice. In relation to disinhibition and loss of insight, transgression of social and moral rules is common, giving rise to criminal and sociopathic behaviour[142]. Memory and visuospatial deficits are unusual early in the illness, although a subset of patients exhibit early problems with episodic memory. An amnestic phenotype is more frequently observed in individuals harbouring expansions in *C9orf72* (REF. 143). The underlying neuropathology in amnestic FTD is thought to be TDP-43-related hippocampal disease and sclerosis[144]. The differential diagnosis in such cases includes typical LOAD or mixed pathology. Amyloid biomarkers can be helpful in cases of pure FTLD-related hippocampal disease.

Patients with bvFTD frequently present with psychiatric symptoms, at onset or during the course of their illness. Distinguishing behavioural features from primary psychiatric disorders, such as depression, borderline personality disorder, bipolar disorder and schizophrenia, can be challenging[145,146] In a large case series including 751 individuals with bvFTD, 6% of patients presented with psychosis early in their disease course[146]. Approximately 20% of patients have delusions and 10% have hallucinations. These symptoms are more common in genetic cases caused by mutations in *C9orf72* (REF. 147) (BOX 3) and *GRN*. Mania has also been reported[148]. Using voxel-based morphometry, Rosen and colleagues demonstrated that core neuropsychiatric symptoms of bvFTD, such as apathy, disinhibition, eating disorders and aberrant motor behaviour, localized to right

frontal structures (FIG. 4). Severity of symptoms correlated with extent of atrophy in the right-hemispheric anterior cingulate cortex, ventromedial superior frontal gyrus, posterior ventromedial prefrontal cortex, lateral middle frontal gyrus, caudate head, orbitofrontal cortex, and anterior insula[149]. In addition to psychiatric symptoms, parkinsonism with axial rigidity often emerges in bvFTD.

Progression of symptoms, and neurodegeneration demonstrated by atrophy on MRI, provide important clues for the differential diagnosis of bvFTD. The diagnostic criteria were revised in 2011 to incorporate the extended spectrum of psychiatric and motor symptomatology, as well as topographical biomarkers of disease[113] (TABLE 1). Currently, the pattern of neurodegeneration seen on structural MRI constitutes the most helpful biomarker of disease (FIG. 4). However, hypoperfusion on SPECT and hypometabolism on ^{18}F-FDG–PET precede atrophy, and have potential utility early in the disease before overt neurodegeneration. When the differential diagnosis includes the behavioural variant of AD, AD biomarkers can be helpful, as dual pathology is uncommon in early-onset dementias.

The clinical phenotype of bvFTD is influenced by the underlying molecular pathology. For instance, in comparison with bvFTD patients who have Pick disease, those with CBD pathology tend to have more dorsal than ventral frontal atrophy, and relative preservation of the frontoinsular rim. Consequently, executive dysfunction and anxiety are more prominent than disinhibition, emotional dysregulation, social misconduct and changes in eating behaviour[150]. bvFTD associated with *C9orf72* expansion also has distinct clinical features and patterns of neurodegeneration[151] (BOX 3).

A subgroup of patients meet the core diagnostic criteria for bvFTD at presentation, but show little or no symptom progression, and have — at most — modest atrophy on brain MRI. The neurodegenerative basis of this ‘phenocopy’ syndrome has been debated. Some individuals with bvFTD phenocopies carry *C9orf72* expansions[152]. Moreover, a slowly progressing subgroup with predominant subcortical atrophy and FTLD-TDP pathology was recently identified, almost one-quarter of whom had mutations in FTD-related genes[153].

Language-centred frontotemporal dementias—The language-centred FTDs generally show focal onset but, with disease progression, deficits eventually arise in all language functions. Therefore, the different subtypes are distinguished by the chronology and severity of deficits in specific linguistic functions. Neurodegenerative diseases targeting the language circuitry often present asymmetrically, with dominant (frequently left) hemispheric disease manifesting as language syndromes[154–156] (FIG. 4).

Patients with nfvPPA present with fluency impairment and/or agrammatism, and most eventually develop both features. These deficits localize to the disrupted frontoinsular language network, with atrophy noted most frequently in the left inferior frontal and insular cortices[157] (FIG. 4). Speech becomes nonfluent, gradually more telegraphic and less melodic (aprosodic). Apraxia emerges, with inconsistent sound errors and distortions, especially with pronunciation of consonant clusters, as well as effortful, halting speech with groping of the tongue and lips (Supplementary information S1 (box)). Deficits in grammar, which can be first noted in writing, eventually limit comprehension, especially of the passive

voice or complex syntax. Anomia is not a central deficit, but delayed naming, with hesitations, and word-finding pauses are frequently noted. Repetition is less impaired than spontaneous speech, and semantic language typically remains preserved well into the disease process. Progressive deficits resemble the lesion-based model of Broca aphasia. Motor deficits, including asymmetric parkinsonism and/or pyramidal signs, occur in most patients, even early in the illness.

Differentiating nfvPPA from lvPPA can be challenging, with commonalities including preserved object meaning in the presence of progressive anomia and loss of fluency. In such instances, AD biomarkers such as CSF analyses or amyloid PET can be helpful; in comparison with lvPPA, only a small fraction of nfvPPA cases are caused by AD pathology. The diagnostic criteria for nfvPPA are supported by markers of neurodegeneration and neuronal dysfunction, as measured by MRI, PET or SPECT, in the left posterior frontoinsular region (TABLE 1).

In svPPA, degeneration of the anterior temporal lobes (FIG. 4) disrupts access to semantic memory[75]. Anomia and single-word comprehension deficits, starting with low-frequency items, are essential for diagnosis[158]. Difficulties in confrontation naming are present in other language-dominant neurodegenerative diseases, but are most severe in semantic variants (Supplementary information S1 (box)). Critically, the loss of semantic knowledge in svPPA encompasses all sensory modalities, including visual, tactile, olfactory and gustatory, in addition to auditory. Moreover, the deficits extend to reading and writing, with the emergence of surface dyslexia and dysgraphia[75]. Although motor speech production and grammar are initially unaffected, communication becomes gradually more difficult, with impoverishment of content and increasingly vague speech. Among all the FTD syndomes, svPPA is associated with the longest survival times.

In addition to prosopagnosia and associative agnosia, right anterior temporal variants of svPPA (svPPA-R) present with prominent behavioural and personality changes that frequently overshadow more-subtle linguistic deficits[159,160]. Compulsions, loss of empathy with ensuing ‘coldness’, and child-like behaviour can be observed. A decline in semantic knowledge regarding people familiar to the patient, graded by frequency of interactions with those people, has been reported[161]. Affected individuals can also display features of Geschwind syndrome[162], including rigidity in philosophical beliefs or religious dogmatism, hypergraphia, hyposexuality, and a tendency to inappropriately prolong conversations, termed ‘viscosity’ (REF. 159). Selective tissue loss in the anterior temporal lobes can help distinguish svPPA-R from bvFTD. The svPPA-R variant presents an exception to the coherence of the current PPA nosology, as the development of language deficits is delayed until the pathology extends into the dominant hemisphere[159,163].

The neuropathological substrate of svPPA is almost always TDP-43 type C[164], but other possible pathologies include TDP-43 type B and Pick disease. For atypical presentations in which other pathological processes are suspected, AD biomarkers can diminish uncertainty regarding the underlying pathology.

A mixed PPA bridging the two main FTD language phenotypes, characterized by concomitant onset and progression in agrammatism and semantic deficits, has also been described[165]. However, this condition is more frequently associated with AD[166], although cases of tauopathy have also been reported[76].

Progressive deficits in language can arise as a secondary feature of other syndromes[167], but such presentations do not meet the core PPA diagnostic criteria and cannot, therefore, be classified as PPA subtypes.

Motor frontotemporal dementias—The spectrum of FTD extends to syndromes with pyramidal and/or extrapyramidal impairments. These 'motor FTD syndromes' can present later than nonmotor syndromes, with mean age of onset in the seventh decade of life[120,138,139].

FTD and MND are increasingly perceived along a clinicopathological continuum with shared fundamental biology. ALS and FTD–MND are mostly associated with TDP-43 pathology, and FTD–MND is frequently caused by *C9orf72* mutations (BOX 3). Approximately 60% of patients with FTD have evidence of MND on electromyography, with 10–15% of patients developing clinical signs of MND[168,169]. Conversely, around 50% of patients with MND develop cognitive decline without meeting the research diagnostic criteria for FTD[170]. The MND clinical phenotype is typically ALS, although upper motor neuron (primary lateral sclerosis) and lower motor neuron (progressive muscular atrophy) disorders have also been described[171]. Early bulbar dysfunction is observed more frequently in FTD–MND than in isolated ALS, and patients with FTD–MND show the shortest survival among individuals with FTD syndromes. The clinical course of FTD–MND can be very aggressive, with acceleration at the onset of MND.

PSP-S refers to a range of clinical syndromes that are mainly — but not exclusively — caused by 4R FTLD-tau pathology (FIG. 3). Other than PSP pathology, PSP-S is associated with CBD and Pick disease. PSP-S can manifest with a combination of features, including atypical parkinsonism with axial, symmetrical rigidity; a stare with furrowing of the brow (procerus sign); supranuclear gaze palsy; and prominent frontal lobe dysfunction[172] (Supplementary information S1 (box)). Limited to no response to dopaminergic therapy is typical. PSP-S invariably involves atrophy of the midbrain tegmentum and the pons[173], although the timing and, therefore, the symptomatic chronology varies across subtypes. The classic PSP-S presentation, PSP-RS, is characterized by early involvement of the midbrain with ensuing supranuclear gaze palsy, gait instability and falls. PSP-parkinsonism and PSP-pure akinesia and gait freezing closely resemble PD[174]. Of these two conditions, PSP-parkinsonism is the more responsive to dopaminergic medications. Psychiatric symptoms (depression and anxiety), and profound sleep disruption associated with hyperarousal often precede PSP-S and can remain prominent once the parkinsonian features emerge.

PSP-RS has the highest predictive value for underlying PSP pathology. Although saccade abnormalities, including increased latency, decreased velocity and decreased gains, are associated with numerous neurodegenerative pathologies, including CBD, Pick disease, and AD, patients with PSP-RS display the most severe visually guided saccade abnormalities[175].

Therefore, careful examination of eye movement abnormalities can be diagnostically valuable. Decreased vertical saccade velocity correlates with dorsal midbrain atrophy (TABLE 1). Moreover, quantification of anteroposterior midbrain to pons ratio has high specificity for PSP pathology, and has potential diagnostic utility[176]. PSP-S due to PSP (4R FTLD-tau) pathology is associated with shorter survival.

CBD is another 4R FTLD-tau pathology, and is implicated in approximately 35% of cases of CBS. A UCSF study found that patients with pathologically proven CBD presented with bvFTD, nfvPPA or executive–motor syndrome with early extrapyramidal motor symptoms such as ridigity and akinesia[177]. CBS is a pathologically diverse syndrome that involves progressive neurodegeneration of dorsal posteromedial frontal, perirolandic and insular cortices. The syndrome typically includes motor, behavioural and cognitive changes[177]. Alien limb phenomena occur in a minority of cases, usually in the later stages[178] (Supplementary information S1 (box)). CBS, as defined by the diagnostic criteria, has low pathological predictive value[177,178].

CBS can be associated with FTLD-tau (CBD, PSP or, less frequently, Pick disease), FTLD-TDP or AD pathology (FIG. 3). Extension of atrophy into frontal cortices is suggestive of FTLD-tau pathology, whereas posterior extension into the precuneus and temporoparietal regions is predictive of CBS due to AD (CBS-AD). In addition, individuals with CBS-CBD display pronounced dorsal frontal atrophy, whereas patients with CBS-AD tend to have more posterior involvement (TABLE 1). From a neuropsychological perspective, group comparisons demonstrate greater visuospatial and memory deficits, concordant with greater temporoparietal degeneration, in patients with CBS-AD in comparison with CBS associated with underlying FTLD[179].

The pathological heterogeneity of CBS limits its clinical and research utility. Diagnostic criteria for CBD syndromes, or clinical phenotypes predictive of possible or probable underlying CBD pathology, may be more useful[178].

Lewy body dementia

Pathology: α-synucleinopathy

Lewy body dementias include DLB and Parkinson disease (PD) dementia (PDD), which lie along a clinicopathological continuum defined by characteristic intracellular α-synuclein aggregates (Lewy bodies) that cause dysfunction of cerebral neuronal networks.

Traditionally, PD pathology is thought to originate in the caudal brainstem, typically involving the dorsal IX/X motor nucleus and the intermediate or magnocellular reticular zone of the caudal medulla, before extending, possibly transynaptically[180], to the rostral brainstem — resulting in prodromal REM sleep behaviour disorder (RBD), mood disorders and anxiety — the substantia-nigra and, eventually, the basal ganglia, and cortex[36,181]. However, recent evidence suggests that the pathology actually originates in the enteric nervous system[182], progressing to involve the CNS via the vagus nerve[183]. The pathological progression of DLB remains unclear.

DLB and PDD typically manifest symptomatically between the ages of 60 and 90 years. Most patients with DLB show mixed pathology, with concomitant presence of vascular disease and/or AD pathology[184–186]. Similarly, the cortical pathology observed in patients with PDD is often mixed[187,188], with coexisting AD pathology leading to more-advanced dementia[189]. Not surprisingly, the genetics of AD pathology and LBD overlap to some extent[190]: the *APOE*ε4* genotype is overrepresented in sporadic LBD[191], whereas the *APOE*ε2* allele seems to be protective against DLB as well as sporadic AD[192]. Other genetic risks for LBD include mutations in *SNCA* and *LRRK2* (REF. 193). Mutations in *SCARB2* (REF. 194) and *GBA* specifically increase the risk of DLB, and result in younger age of onset[195]. Risk factors for DLB, other than genetic modifiers, remain to be discovered. Pesticide exposure, TBI and a history of melanoma are overrepresented in patients with PD, and are possible risk factors for PDD and DLB.

Clinical syndromes

The main difference between DLB and PDD hinges on the temporal relationship of cognitive decline and neuropsychiatric symptoms to parkinsonism, with the two conditions showing early and late onset of cognitive symptoms, respectively[196]. Original descriptions of PD emphasized an absence of cognitive deficits[197–199]; however, recent observations support insidious spread of pathology along cognitive networks, with approximately one-fifth of patients diagnosed with at least MCI at the time of presentation[200].

Dementia with Lewy bodies—The defining clinical features of DLB localize to cortical and subcortical structures, with the ensuing characteristic combination of cognitive and motor dysfunction[196]. The disease typically progresses slowly; however, a rapidly progressive dementia syndrome is also possible[201]. The core diagnostic features of DLB include fluctuating cognition, recurrent visual hallucinations, and parkinsonism. The fluctuations in mental status, conceived as a low-grade chronic delirium, may be due to profound cholinergic deficits in addition to neocortical Lewy body pathology[202]. Visuospatial and constructional deficits are frequently seen in early AD, but are also suggestive of Lewy body pathology[203,204], where they foreshadow more-rapid decline and visual hallucinations[205]. In comparison with AD, however, memory functions are often preserved in the early stages of DLB, although episodic memory deficits are frequently reported with older age, possibly due to mixed Lewy body and AD pathology[24]. Other features include anxiety and depression[206], autonomic symptoms[207] (including constipation and hypersialorrhea), olfactory dysfunction[208,209], and severe neuroleptic sensitivity, causing exacerbation of parkinsonism. RBD has great diagnostic utility due to its high positive predictive value (>80%) for α-synuclein-related neurodegeneration[210,211].

Parkinson disease dementia—Most patients with PD develop MCI[212,213] (labelled as MCI-PD) and can progress to dementia[214–217]. Cognitive deficits are routinely missed in clinical practice, as motor symptoms are frequently the focus of diagnosis and treatment[218,219]. Although patients with PDD primarily present with executive dysfunction, localizing to disrupted dorsolateral prefrontal–striatal networks[220], the cognitive profile can be diverse[200]. The best predictors of further cognitive decline seem to be deficits in verbal and visual memory, semantic fluency, and visuospatial abilities[221].

Biomarkers

^{18}F-FDG–PET typically reveals reduced metabolism and perfusion in occipital cortices in patients with DLB[222], with additional involvement of frontal and parietal lobes noted in patients with PDD[223] (TABLE 1). One distinguishing feature between DLB and AD is the relative sparing of the posterior cingulate cortex — the so-called posterior cingulate 'island sign' — in DLB[224]. Studies suggest that CSF markers can also help to distinguish these dementia syndromes from AD, with lower CSF α-synuclein levels being observed in patients with DLB[225]. By contrast, *in vivo* detection of amyloid pathology through CSF analysis or molecular imaging has not proven useful for distinguishing these diseases, owing to the frequent coexistence of AD and Lewy body pathology[226,227].

Low dopamine transporter (DAT) uptake in the basal ganglia, as shown by SPECT or PET, is suggestive of DLB. An autopsy-based study that compared neuroimaging with clinical diagnosis alone showed that 123I-*N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (123I-FP-CIT) SPECT dopaminergic imaging increased specificity and overall diagnostic accuracy[228]. Though clinically available, DAT scans are seldom necessary in the presence of supportive clinical features. Should ancillary studies be necessary, a characteristic marked reduction in tracer uptake is seen on myocardial ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) SPECT in patients with diffuse LBD.

MRI has limited ability to discriminate between DLB and PDD, as atrophy can be modest and/or lack focality in the early stages of LBD.

Prion disease

Pathology and risk factors

Prion diseases, also known as transmissible spongiform encephalopathies, are rapidly progressive neurodegenerative diseases caused by propagation of misfolded prion proteins in the nervous system[229]. A histopathological hallmark is the protease-resistant amyloid-containing prion protein, also known as scrapie prion protein (PrP^{Sc}). PrP^{Sc} shows a high degree of β-pleated sheet structure, in contrast to PrP^{C}, the nonpathogenic, mostly α-helical and protease-sensitive cellular isoform[230]. In the majority of cases, misfolding of this protein occurs spontaneously, possibly via *de novo* structural changes in the PrP gene *PRNP*. This subtype is referred to as sporadic CJD (sCJD)[231]. Less frequently, CJD cases are familial, exhibiting an autosomal dominant pattern of inheritance. Over 20 known causative mutations have been identified worldwide[232]. Familial cases of CJD are subdivided into three clinicopathologically distinct categories: familial CJD (fCJD), fatal familial insomnia (FFI) and Gerstmann–Straussler–Scheinker syndrome (GSS). In rare cases, prion disease is acquired, giving rise to variant CJD (vCJD). The majority of these cases (about 200) occurred in the UK and France in the past two decades, and were associated with consumption of cattle affected by bovine spongiform encephalopathy[233]. Finally, prion disease can be acquired iatrogenically via cadaveric transplants, human-derived hormones (growth hormone) or medical instrumentations[234], or via cannibalism — a condition known as kuru, the historic disease of the Fore tribe in Papua New Guinea[235]. Importantly, the incubation period for acquired CJD can be several decades[232].

Astrocyte proliferation, gliosis, and neuronal loss are found in all prion diseases, but other histopathological features allow distinction between four major pathological subtypes: diffuse spongiosis (or vacuolation, due to focal swelling of axonal and dendritic processes) of grey more than white matter neuropil, with minimal PrP-amyloid plaques, characteristic of sCJD and fCJD; 'florid' PrP-amyloid plaques surrounded by a vacuole or halo, characteristic of vCJD[232]; multicentric PrP plaques extensively affecting the molecular layer of the cerebellum, pathognomonic of GSS; and focal and relatively isolated anterior and dorsomedial thalamic nuclear gliosis, as seen in FFI. In addition, some mutations leading to GSS were shown to be associated with cortical NFTs[236,237].

The peak incidence of sCJD occurs between 55 and 75 years of age, whereas fCJD typically presents before age 55, and vCJD commonly occurs even younger, in the late teens or young adulthood[232].

Clinical syndromes and biomarkers

sCJD has a protean presentation, reflecting the variety of neuropathological subtypes[238] and the extent of the CNS territory affected. The condition most often presents with rapidly progressive dementia (mean disease duration 4.0–6.5 months), featuring behavioural abnormalities, cerebellar ataxia, pyramidal and/or extra pyramidal signs, and myoclonus as the disease progresses. The two main modes of onset are cognitive deficits (usually memory impairment, but sometimes also deficits in language, executive function or visual processing) and cerebellar ataxia, predominantly limiting gait[231]. These presentations are sometimes preceded by neuropsychiatric symptoms, such as agitation, aggressiveness, depression, apathy or anxiety, or vague constitutional symptoms, such as dizziness, fatigue or sleep disturbances[239–242]. If not already present in the early stages of the disease, about half of patients with sCJD will develop behavioural changes, including psychiatric symptoms and higher cortical deficits, such as aphasia, neglect, acalculia, apraxia or astereognosis, followed in frequency by visual or oculomotor dysfunctions. Other deficits commonly affect motor (extrapyramidal, pyramidal) and sensory (pain, paraesthesia) functions. Depending on the initial presentation of the disease, sCJD can resemble other non-rapidly progressive neurodegenerative syndromes, such as the language forms of FTD, AD or CBS; however, the rapid emergence of new deficits often in a matter of days to weeks, as well as the pace of general decline, should raise concern for prion disease. The symptoms can occasionally progress more slowly: in one subtype of sCJD, mean disease duration is 17 months[243].

sCJD phenotypes are in part determined by a polymorphism at codon 129 (methionine or valine) in the *PRNP* gene and the pattern of PrP^{Sc} cleavage by protease K, giving rise to six molecular subtypes — MM1, MV1, VV1, MM2, MV2 and VV2 (REFS [244,245]). The MM2 molecular subtype is further divided into a thalamic and a cortical subtype on the basis of the distribution of pathology in the CNS. The most common subtypes, MM1 and MV1 (about 40% of cases), are pathologically and clinically identical and are, therefore, known as MM1/MV1. These subtypes are associated with more-rapid clinical progression than MV2. VV2, which presents with rapidly progressive ataxia, is another common subtype. The MM2-thalamic subtype has features of FFI, and is also referred to as sporadic fatal insomnia[232].

Compared with most cases of sCJD, vCJD shows slightly slower progression (mean disease duration 14.5 months)[233], with a prolonged prodromal phase typically dominated by psychiatric symptoms. At more-advanced stages, however, vCJD is clinically indistinguishable from sCJD. All but one of the reported cases of vCJD were homozygous for methionine (MM) at codon 129 (REF. 233).

fCJD may progress more slowly than its sporadic counterpart, but otherwise presents with similar clinical phenomenology. FFI and GSS have distinctive clinical features. The initial symptoms of FFI are severe insomnia followed by dysautonomia, with cognitive and motor dysfunctions typically lagging. GSS manifests as a slowly progressive dementia associated with cerebellar ataxia or a parkinsonian syndrome that commonly starts in the fifth decade of life; however, the age of onset, symptomatic progression, and disease duration vary greatly, even within a given family.

Routinely available ancillary diagnostic tests for CJD include EEG, MRI, and CSF biomarkers (BOX 1; TABLE 1). In addition, because the lymphoreticular system is invaded in vCJD, tonsillar biopsy is considered to be a sensitive test for PrP^{Sc} (REF. 246). EEG findings of frequent periodic sharp-wave complexes (1–2 Hz) with occasional triphasic morphology are supportive of a CJD diagnosis, but can manifest at a late stage[247] — if at all — so are of limited diagnostic utility.

Classic MRI findings in CJD include hyperintense signal along various segments of the cortical ribbon, as well as in the thalamus, on diffusion-weighted imaging, often corroborated by evidence of fluid restriction on apparent diffusion coefficient sequences. These findings have an estimated diagnostic accuracy of 97%[248]. Symmetrical involvement of both pulvinar and medial thalami — the so-called ‘double hockey stick sign’ — is not specific for any particular form of CJD[249]; however, involvement of the pulvinar nuclei alone is pathognomonic for vCJD.

Despite good sensitivity, CSF biomarkers show limited specificity in CJD[250]. A combination of elevated concentrations of 14-3-3, total tau, neuron-specific enolase and S100β increase the diagnostic accuracy, but remain inferior to MRI[251]. These tests are best used as a complement to neuroimaging, and in the work-up of the differential diagnosis[248,252]. An emerging CSF real-time quaking-induced conversion (RT-QuIC) test shows high specificity (98.5%) and sensitivity (92%)[253] for the diagnosis of CJD, with close concordance between laboratories[254]. Though more accurate than any combination of the usual CSF biomarkers, RT-QuIC has yet to be directly compared with MRI, which has the disadvantage of being dependent on the reader’s skills and expertise.

Network-based biomarkers

In the past few years, network-based neuroimaging techniques, including resting state functional MRI and DTI, have provided research-based biomarkers for neurodegenerative diseases, with promise for the classification of syndromes on the basis of unique structural and functional network alterations (TABLE 1). For instance, the salience network, which integrates limbic, autonomic and higher-order perceptual functions, and has intimate links to

emotional processing, sense of self and rapport with others — critical for social behaviour — shows decreased connectivity and activation in patients with bvFTD compared with healthy controls or patients with AD[7]. In AD, the default mode network (DMN) seems to be especially affected, with AD variants showing decreased connectivity in this network, as well as specific differences in connectivity outside the DMN, such as the visuospatial network in PCA, the language network in lvPPA, and the frontoparietal network in behavioural dysexecutive AD[255].

Conclusions

Amid the tangled web of neurodegenerative disease, common schemas are emerging. Misfolding of proteins — forming aggregates, disrupting cellular functions, and propagating across functionally and structurally connected vulnerable neuronal networks — seems to lie at the heart of neurodegenerative diseases causing dementia. The pathological cascade can begin years or decades before symptomatic presentation, and clinical deficits eventually arise from irreversible damage within functional networks. Causative genetic factors promote specific proteinopathies, and modifier genes can influence variability in phenotypic presentation.

With disease progression, syndromes converge, and syndromic frontiers efface. In advanced stages of dementia, the footprints of disease extend beyond the initial regions of vulnerability, affecting symptom specificity and diagnostic yield. Therefore, detection of incipient signs and symptoms, or a history that allows early symptoms to be deciphered, is critical for the clinical classification of disease and prediction of the underlying proteinopathy. Nonetheless, despite detailed pre-mortem phenotyping, clinicopathological correlations remain imperfect.

The use of biomarkers has become crucial for *in vivo* dissection of neurodegenerative syndromes into distinct molecular and structural subtypes, with the ultimate goal of uncovering the factors that are necessary and sufficient to cause neurodegenerative disease. Currently, among the clinically available biomarkers, those for prion disease and AD have the highest predictive values. Patterns of atrophy on structural MRI (FIGS 2,4) can assist in the diagnosis of other neurodegenerative diseases, with high specificity for certain syndromes and pathologies. Tau PET, functional MRI and DTI, which are currently limited to research, show promise for the detection of mild or prodromal stages of disease.

The incidence of dementia increases with age, but some neurodegenerative diseases — in particular, those with a strong heritable component, such as FTLD — can present early. Taken together with the fact that subclinical structural changes can precede symptomatic disease by decades, vulnerability to dementia might be partially dictated by developmental differences in the brain.

Decades of careful phenotyping and clinical observations, as well as intensive molecular investigations, have culminated in discoveries that have launched a new era in dementia research and patient care. The discovery of causative mutations and related proteinopathies, as well as vulnerable large-scale structurally and functionally related neural networks, is

offering molecular windows into the study of disease processes, with opportunities for the development of pathway-specific therapies that could be administered at prodromal or preclinical stages to patients selected on the basis of biomarker positivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Glossary

Acalculia
Inability to perform calculations

Phonemic paraphasias
Errors in speech resulting in substitution of parts of the intended word by other phonemes, leading to generation of a — sometimes non-existent — word sounding similar to the target word (for example, pipe for pile, loan for moan, or papple for apple)

Visual agnosia
Inability to recognize or interpret visual stimuli despite intact vision

Alexia
Inability to read, which comprises inability to read out loud and/or comprehend

Ideomotor apraxia
Deficit in the ability to voluntarily plan or complete a motor task, with preservation of involuntary (automatic) motor planning when the subject is cued. This preserved ability to perform automated motoric responses to cuing contrasts with ‘ideational apraxia’, in which the ability to select the appropriate motor programme or sequencial steps, even in the presence of cuing, is lost

Prosopagnosia
Inability to recognize faces, also known as ‘face blindness’

Pseudobulbar affect
Also referred to as marked emotional lability or emotional incontinence. This symptom is characterized by uncontrollable episodes of crying or laughter, proportionately in excess of the valence of an emotional stimulus

Virchow–Robin spaces
Perivascular spaces surrounding the penetrating vessels that arise from the subarachnoid space and perforate the brain parenchyma. Prominence — in terms of visibility and numbers — of enlarged Virchow–Robin spaces has been associated with cognitive ageing, small vessel disease, and neurodegeneration

CADASIL
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominantly inherited small vessel

disease, with notable dysregulation of inflammatory markers and pathognomonic T2/FLAIR white matter hyperintensities in anterior temporal lobes

Anticipation
Genetic phenomenon relating to the gradual expansion of a mutation with each generation, usually resulting in earlier age of onset and more-severe symptoms when passed on to the next generation

Surface dyslexia and dysgraphia
Impairment in the ability to read and write words that are considered ‘irregular’ with regard to their spelling-to-sound correspondence (for example, friend, island or yacht), as opposed to ‘regular’ words (for example, fire, lemon or computer). This impairment can result in regularization errors, that is, words are erroneously spelled according to the regular phonetic rules

Associative agnosia
Impaired recognition of visually presented objects despite intact visual perception of these objects. Also known as ‘visual object agnosia’

Hypergraphia
Compulsive and overwhelming urge to write, with potential intraindividual variability in style and content during the disease course

Astereognosis
Inability to recognize an object by active touch alone, in the absence of primary sensory deficit

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Box 1

Biomarker-based diagnostic algorithms for dementia syndromes

Alzheimer disease

- MRI to evaluate pattern of atrophy, concomitant vascular disease, and nondegenerative lesions (mimics)
- Alzheimer disease (AD) molecular biomarkers (cerebrospinal fluid (CSF) or PET) for early-onset AD, atypical clinical features or possibility of frontotemporal lobar degeneration; ^{18}F-FDG–PET if patient is amyloid-negative according to CSF or PET studies and MRI is inconclusive
- Genetic testing: *PSEN1*, *PSEN2* and *APP* if familial or genetic causes of AD are suspected; *C9orf72* in the case of an amyloid-negative amnestic phenotype

Frontotemporal dementia

- MRI to evaluate pattern of atrophy and nondegenerative lesions (mimics)
- Amyloid biomarkers (CSF or PET) if AD is included in the differential diagnosis
- Can consider genetics in the case of a family history or certain clinical features
  - *C9orf72*: family history of frontotemporal dementia with or without motor neuron disease (MND), MND, or atypical clinical features (for example, hallucinations or delusions)
  - *GRN*: extensive white matter damage, striking asymmetry in atrophy, or prominent parietal lobe involvement
  - *VCP*: if inclusion body myopathy, with or without Paget disease, is present
  - *MAPT*: family history and extrapyramidal motor dysfunction

Lewy body dementia

- MRI to evaluate pattern of atrophy and nondegenerative lesions (mimics)
- AD molecular biomarkers (CSF or PET) to test for mixed disease if atrophy patterns or clinical features are suggestive
- In-laboratory sleep study to evaluate for REM sleep without atonia; may also find evidence of dream-enactment behaviour on video recording

Prion disease

- MRI: abnormalities on diffusion-weighted imaging, and apparent diffusion coefficient sequences abnormality; T1-weighted and T2-weighted sequences to test for mimics

- CSF: real-time quaking-induced conversion (RT-QuIC) preferred; 14-3-3, tau and neuron-specific enolase (alternative)
- Paraneoplastic panel (serum and/or CSF) if diagnosis not reached in the first two steps (mimics)

Vascular dementia

- MRI for subtype and severity of disease, and atrophy pattern suggestive of mixed disease
- AD molecular biomarkers (CSF or PET) if clinical features or atrophy patterns suggest mixed disease
- Genetic testing (for example, *NOTCH3* for CADASIL) if familial disease suspected, or atypical features are seen, such as white matter disease in anterior temporal lobes

Box 2

FTLD proteinopathies

Frontotemporal lobar degeneration (FTLD) is caused predominantly by intracellular aggregates of tau, TAR DNA-binding protein 43 (TDP-43) or fused in sarcoma (FUS).

Tau

Tau is encoded by the microtubule-associated protein tau (*MAPT)* gene. Alternative splicing of *MAPT* mRNA leads to production of six tau isoforms with differential expression across the brain. Tau binds to and stabilizes microtubules, which are important for cellular morphology and function. In neurodegenerative disorders, the normally phosphorylated tau becomes aberrantly hyperphosphorylated, dissociates from microtubules, and forms aggregates within neurons and glia. *MAPT* mutations mainly cause FTLD-tau pathology, giving rise to syndromes such as nonfluent/agrammatic variant primary progressive aphasia. Patients with frontotemporal dementia (FTD) syndromes who harbour *MAPT* mutations tend to be relatively young (<50 years), present with disinhibition rather than apathy, display ritualistic behaviour, and develop features of semantic impairment.

TDP-43

TAR DNA-binding protein 43 (TDP-43) is encoded by the *TARDBP* gene. *TARDBP* mutations typically cause amyotrophic lateral sclerosis (ALS), but are also, in rare cases, implicated in FTLD-TDP types A–D and U. TDP-43 pathology is subclassified according to patterns of TDP-43-containing neuronal cytoplasmic inclusions and dystrophic neurites in diseased neurons. All FTD syndromes except for progressive supranuclear palsy syndrome can be caused by FTLD-TDP. The TDP-43 C-terminus has been shown to contain a prion-like domain that permits formation of TDP-43 oligomers, and is a hotspot of disease-causing mutations in ALS.

FUS

Fused in sarcoma (FUS) is an RNA-binding protein involved in splicing and nuclear export of mRNA. FTLD-FUS has three subtypes: atypical FTLD with ubiquinated inclusions, basophilic inclusion body disease, and neuronal intermediate filament inclusion disease. *FUS* mutations are mainly associated with ALS, but can give rise to behavioural variant FTD, FTD with motor neuron disease, or language FTD phenotypes. A specific phenotype related to sporadic FTLD-FUS pathology has emerged, with young onset (22–46 years), prominent caudate atrophy, and unique phenotypic features of marked obsessiveness, social withdrawal, hyperorality (often with pica), and stimulus-bound and repetitive, ritualistic behaviours. The cognitive profile consists of subcortical executive dysfunction in the absence of cortical language, perceptual and praxis impairments.

Box 3

C9orf72

Intronic hexanucleotide (GGGGCC) repeat expansions in *C9orf72* are the most common genetic cause of familial and sporadic frontotemporal dementia (FTD) plus or minus motor neuron disease (MND)[127], with a suspected single-founder effect in Northern Europe[256]. Molecular pathologies, in descending frequency, include TAR DNA-binding protein 43 (TDP-43) type B, TDP-43 type A and corticobasal degeneration (rare). Common syndromes (with or without MND) in descending frequency include behavioural variant FTD, mixed behavioural and semantic language deficits, nonfluent/agrammatic variant primary progressive aphasia, and behavioural and nonfluent language symptoms[257]. Symptoms more frequently observed in mutation carriers in comparison to individuals with sporadic FTD[147,257] include greater disinhibition and less apathy; psychosis (~30%); paranoia and delusional and/or irrational thoughts (~25%), such as somatoform delusions of infestation (<4% of nongenetic FTD cases); complex repetitive delusion-related behaviours (as opposed to simple motor stereotypies); and amnesia, with or without TDP-43-related hippocampal sclerosis[144,145]. In fact, progressive amnesia can cause misdiagnosis as ‘atypical’ early-onset Alzheimer disease. Concomitance of FTD and amyotrophic lateral sclerosis in *C9orf72* carriers can be associated with prominent bulbar dysfunction. Atrophy on MRI is variable and can be modest in comparison to the severity of clinical deficits. In addition to the frontotemporal lobes, cerebellar, parietal and thalamic atrophy can be noted[158]. White matter atrophy has been reported at preclinical stages. Variability in penetrance, clinical features and age of onset is suggestive of potential anticipation mechanisms and modifying factors (including epigenetic factors and other genes). For a more detailed review on *C9orf72*, see Yokoyama *et al.*[121].

Key points

- Definite classification of dementia is based on the underlying neuropathology
- Accumulation of abnormally folded proteins lies at the heart of dementia neuropathology
- Alzheimer disease pathology can give rise to subtypes with focal onset in functional networks outside the memory system, such as language, visuospatial and behavioural executive domains
- Frontotemporal lobar degeneration, associated with aggregates of tau, TDP-43 or FUS, can give rise to three core frontotemporal dementia syndromes and three associated syndromes
- Clinical classification of dementia syndromes is based on diagnostic criteria that rely heavily on the specificity of affected domains and the evolution of deficits in these domains
- *In vivo* biomarkers of disease include imaging findings of morphological, molecular and functional changes, both upstream and downstream of the disease processes

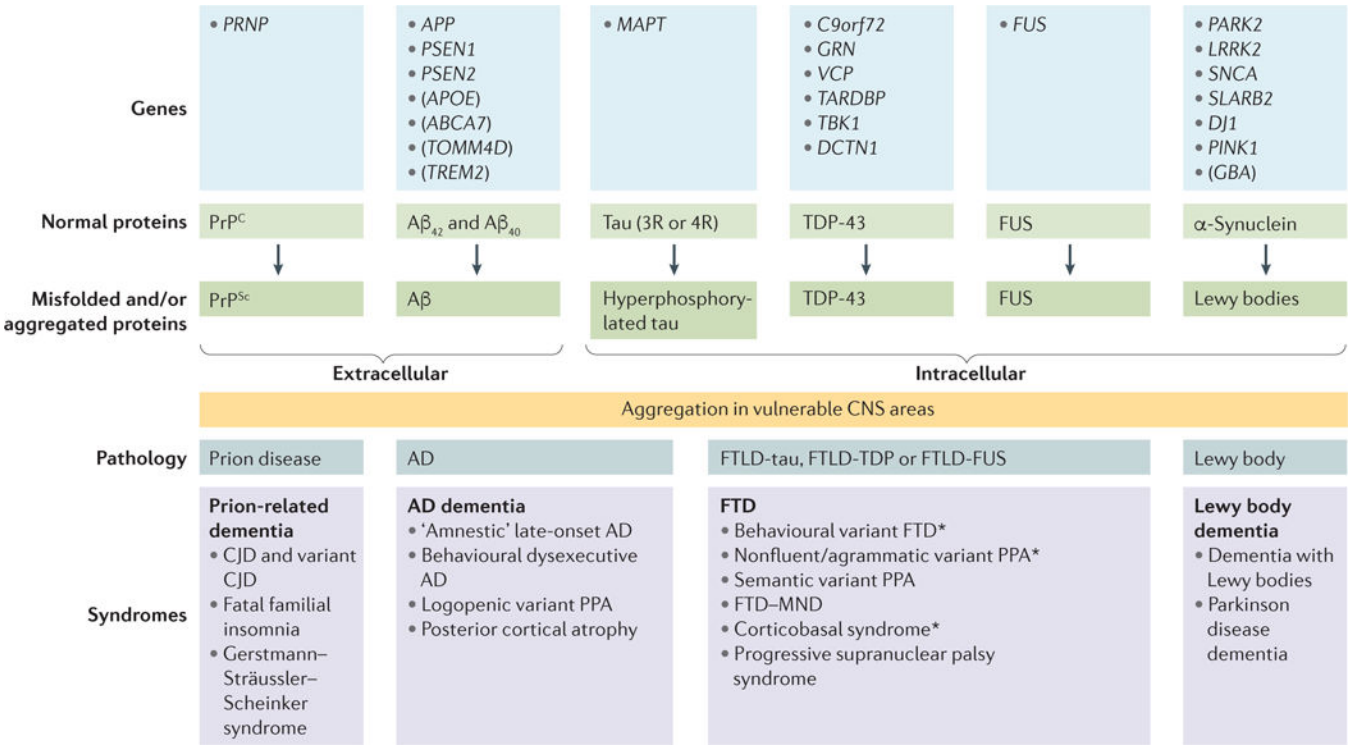

Figure 1. Clinicopathological spectrum of neurodegenerative proteinopathies

Schematic representation of the molecular underpinnings of neurodegenerative diseases and their main clinical manifestations. The figure lists genes with full penetrance that are considered causative and risk genes (in parentheses) that influence molecular processes culminating in the misfolding and/or aggregation of six fundamental proteins: cellular prion protein (PrP^C), $A\beta_{42}$ (and, to a lesser extent, $A\beta_{40}$), tau, TAR DNA-binding protein 43 (TDP-43), fused in sarcoma (FUS), and α-synuclein. These normal proteins misfold and/or accumulate in intracellular or extracellular compartments in specific areas of the CNS. Four major pathological disease categories are recognized: prion disease, Alzheimer disease (AD), frontotemporal lobar degeneration (FTLD) and Lewy body diseases (LBD). The pathologies can involve multiple molecules; for example, AD is a dual proteinopathy with Aβ and tau aggregates. Also, in some cases of prion disease, Aβ in seen in addition to the principal aggregates of misfolded scrapie prion protein (PrP^{Sc}). The majority of FTLD cases are associated with three different proteinopathies: tau, TDP-43 and FUS. Each pathological entity can in turn manifest as a variety of clinical syndromes, sometimes featuring symptoms that bridge syndromes. Asterisks indicate frontotemporal dementia (FTD) syndromes that, in addition to FTLD, can be associated with AD neuropathology. Genetic pleiotropy is also at play: mutations in certain genes — for example, *GRN* — have full penetrance for one pathology (FTLD-TDP) and associated FTD syndromes, while representing a risk factor for another pathology (AD). In addition, certain fully penetrant genetic mutations (for example, *VCP* mutations), are associated with additional systemic disease manifestations. The rich and diverse clinical expression of neurodegenerative processes is best illustrated in FTLD, a pathological category with six distinct clinical syndromes. Of note, FUS pathology causing FTLD is typically not associated with *FUS* mutations, which more often cause amyotrophic

lateral sclerosis. Aβ, amyloid-β; CJD, Creutzfeldt–Jakob disease; FTD–MND, FTD with motor neuron disease; PPA, primary progressive aphasia.

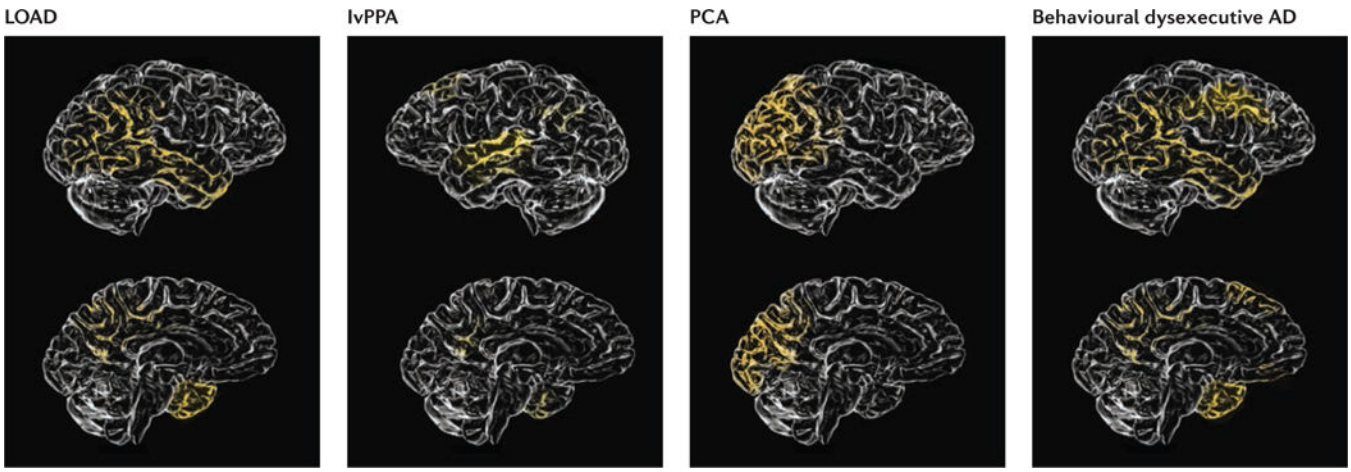

Figure 2. Patterns of brain atrophy in Alzheimer disease

The images show patterns of atrophy on structural neuroimaging observed in various clinical syndromes associated with Alzheimer disease (AD) pathology. In typical amnestic late-onset Alzheimer disease (LOAD), atrophy is first noted in the medial temporal lobes, and gradually spreads to involve the broader temporoparietal and posterior cingulate cortices. Logopenic variant primary progressive aphasia (lvPPA) is characterized by atrophy in the posterior perisylvian region or parietal lobe. For lvPPA, the left (dominant) hemisphere is represented here to indicate that the left-hemispheric cortical areas are predominantly affected. In posterior cortical atrophy (PCA), degeneration of the occipitoparietal and sometimes the posterior temporal lobes is observed. In the behavioural dysexecutive variant of AD, voxel-based morphometric studies reveal temporoparietal atrophy with relative preservation of frontal grey matter.

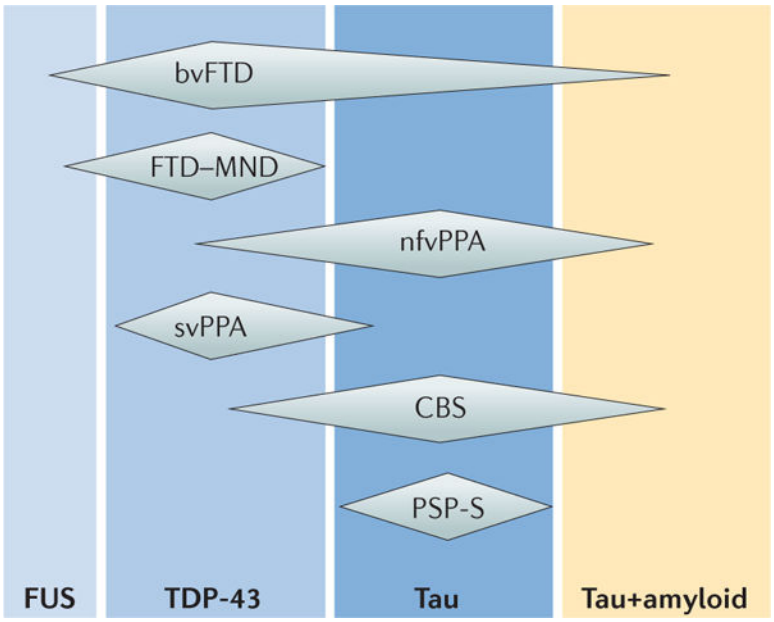

Figure 3. Possible clinicopathological correlations for frontotemporal dementia syndromes

The figure shows the pathologies associated with each frontotemporal dementia (FTD) syndrome. The three main frontotemporal lobar degeneration (FTLD) molecular pathologies — FTLD-tau, FTLD-TDP and FTLD-FUS — are represented in different shades of blue, and Alzheimer disease (AD) pathology is in yellow. The areas of crossover between syndromes and pathologies are qualitative rather than quantitative. The centre of the rhombus indicates the most frequent pathology for each syndrome. bvFTD, behavioural variant FTD; CBS, corticobasal syndrome; FTD–MND, FTD with motor neuron disease; FUS, fused in sarcoma; nfvPPA, nonfluent/agrammatic variant PPA; PPA, primary progressive aphasia; PSP-S, progressive supranuclear palsy syndrome; svPPA, semantic variant PPA; TDP-43, TAR DNA-binding protein 43.

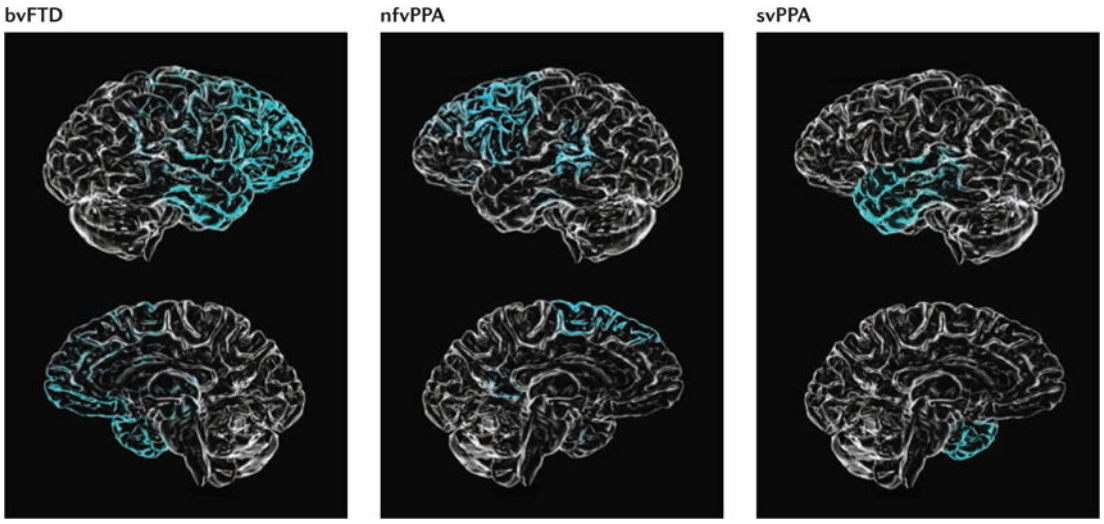

Figure 4. Patterns of brain atrophy in frontotemporal dementia syndromes

The images show the patterns of atrophy observed on structural imaging in various frontotemporal dementia (FTD) syndromes, which arise from frontotemporal lobar degeneration. The core neuropsychiatric symptoms of behavioural variant FTD (bvFTD), such as apathy, disinhibition, eating disorders and aberrant motor behaviour, localize to right frontal structures. Patients with nonfluent/agrammatic variant primary progressive aphasia (nfvPPA) present with fluency impairment and/or agrammatism. These deficits localize to the frontoinsular language network, with atrophy noted most frequently in the left inferior frontal and insular cortices (the entire network is not depicted on this figure). In semantic variant PPA (svPPA), degeneration of the anterior temporal lobes disrupts access to semantic memory.

Table 1

Biomarkers of dementia syndromes

Clinical syndrome	Molecules		Imaging			
	Pathology	Cerebrospinal fluid	MRI (typical areas of peak atrophy)	Metabolic (^{18}F-FDG-PET) and perfusion (SPECT) imaging	Functional networks (resting state functional MRI)	Molecular imaging and emerging techniques
Alzheimer disease (AD)						
Typical/amnestic AD	NFTs (3R/4R tau) and amyloid plaques	Reduced Aβ ($Aβ_{42}Aβ_{40}$ ratio); increased tau and P-tau	MTL (hippocampus and entorhinal cortex), PCC, temporoparietal cortex, precuneus	Reduced perfusion and metabolism in MTL, precuneus, PCC, temporoparietal	Reduced DMN and anterior temporal network activation	• ^{18}F-based amyloid tracer (for example, florbetapir, flutemetamol, and florbetaben) uptake is typically diffuse in the neocortex • Tau ligand uptake is closely associated with post-mortem NFT distribution and peak areas of atrophy
Behavioural dysexecutive AD	NFTs (3R/4R tau) and amyloid plaques	Reduced $Aβ_{42}$ ($Aβ_{42}$:$Aβ_{40}$ ratio); increased tau and P-tau	Temporoparietal cortex > dorsolateral prefrontal cortex	Reduced metabolism in medial and orbital frontal regions	Reduced DMN and frontoparietal network activation	
Posterior cortical atrophy (PCA)	NFTs (3R/4R tau) and amyloid plaques	Reduced $Aβ_{42}$ (Aβ42A40 ratio); increased tau and P-tau	MTL, PCC, occipital and parietal lobes	Reduced signal in parieto-occipital lobes	Reduced DMN and visual network activation	
Logopenic variant PPA (lvPPA)	NFTs (3R/4R tau) and amyloid plaques	Reduced $Aβ_{42}$ (Aβ42Aβ40 ratio); increased tau and P-tau	Temporal lobe (superior temporal gyrus), parietal lobe (inferior parietal lobule)	Reduced signal in inferior parietal lobule	Reduced DMN and language network activation	
Frontotemporal dementia (FTD)						
Behavioural variant FTD (bvFTD)	TDP-43 type B > Pick disease (3R tau)	Nonspecific increase in tau due to neurodegeneration	Frontoinsular and anterior temporal lobes right > left	Reduced perfusion and metabolism in frontal and temporal lobes	Reduced salience network and increased DMN activation	Ongoing efforts to develop PET tracers that bind the conformations of abnormal tau characteristic of frontotemporal lobar degeneration tauopathies, while minimizing off-target binding
Nonfluent/agrammatic variant PPA (nfvPPA)	4R tau > TDP-43 type A	Nonspecific increase in tau due to neurodegeneration	Grey matter atrophy: left > right posterior frontoinsular cortex, including inferior frontal gyrus; white matter atrophy: aslant tract and arcuate fasciculus	Reduced metabolism in inferior frontal gyrus	Reduced language network activation	
Semantic variant PPA (svPPA)	TDP-43 type C	Nonspecific increase in tau due to neurodegeneration	Atrophy of anterior temporal lobe(s) and inferior temporal gyrus	Reduced metabolism in anterior temporal lobe	Reduced language network activation	
Progressive supranuclear palsy syndrome (PSP-S)	PSP (4R tau)	Nonspecific) increase in tau due to neurodegeneration	Classic Richardson: midbrain tegmentum (hummingbird or penguin	Variable, with reduced metabolism reported in frontal,	Reduced cerebello-thalamocortical	

Clinical syndrome	Molecules		Imaging			
	Pathology	Cerebrospinal fluid	MRI (typical areas of peak atrophy)	Metabolic (^{18}F-FDG-PET) and perfusion (SPECT) imaging	Functional networks (resting state functional MRI)	Molecular imaging and emerging techniques
			sign), pons, thalamus and striatum, with minimal involvement of the frontal lobe	caudate, midbrain and thalamic regions in 4R tauopathies	network activation	
Corticobasal syndrome (CBS)	Corticobasal degeneration (CBD) and AD most common	Nonspecific increase in tau due to neurodegeneration	Perirolandic cortex and posterior extension (AD); perirolandic cortex and prefrontal extension (CBD)	Early changes can be seen typically in the same pattern as the atrophy that follows	NA	
Lewy body dementia						
Dementia with Lewy bodies (DLB)/Parkinson disease dementia (PDD)	Lewy body disease (LBD)	Reduced α-synuclein	Inferior frontal lobe, visual cortex, insula, hypothalamus, midbrain, caudate, putamen and anterior hippocampus	Reduced perfusion in striatum, reduced perfusion and metabolism in visual cortex. Sparing of PCC ('island sign') helps when mixed disease or AD are in the differential diagnosis	Reduced cerebello-thalamocortical network activation	Reduced dopamine transporter uptake in basal ganglia, reduced tracer uptake on cardiac-^{123}I-MIBG SPECT
Prion disease						
Creutzfeldt–Jakob disease (CJD)	Scrapie prion protein (PrP^{Sc})	RT-QuIC test (most accurate); increased 14-3-3, neuron-specific enolase and tau (specificity increases when more than one cerebrospinal fluid marker is elevated)	Diffusion-weighted imaging and T2 hyperintensity in the striatum, hypothalamus and cortices ('cortical ribboning'), posterior (pulvinar) and medial thalamus ('double hockey stick sign', nonspecific) or pulvinar alone ('pulvinar sign', in variant CJD only)	NA	NA	NA
Vascular dementia (VaD)						
VaD (small and large vessel disease)	White matter and grey matter lesions, mixed pathology (most commonly AD or LBD)	NA	Frontal subcortical and periventricular white matter hyperintensities, microhaemorrhages, lacunar strokes, prominent Virchow-Robin spaces, cortical infarcts and haemorrhage	Reduced perfusion and metabolism in frontal subcortical and periventricular regions	NA	NA

3R/4R, three/four microtubule-binding domain repeats; Aβ, amyloid-β; DMN, default mode network; MTL, medial temporal lobe; NA, not applicable; NFTs, neurofibrillary tangles; PCC, posterior cingulate cortex; PPA, primary progressive aphasia; P-tau, hyperphosphorylated tau; RT-QuIC, real-time quaking-induced conversion; SPECT, single-photon emission CT; TDP-34, TAR DNA-binding protein 43.