



New insights into atypical Alzheimer's disease in the era of biomarkers

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Most patients with Alzheimer's disease present with amnestic problems; however, a substantial proportion, over-represented in young-onset cases, have atypical phenotypes including predominant visual, language, executive, behavioural, or motor dysfunction. In the past, these individuals often received a late diagnosis; however, availability of CSF and PET biomarkers of Alzheimer's disease pathologies and incorporation of atypical forms of Alzheimer's disease into new diagnostic criteria increasingly allows them to be more confidently diagnosed early in their illness. This early diagnosis in turn allows patients to be offered tailored information, appropriate care and support, and individualised treatment plans. These advances will provide improved access to clinical trials, which often exclude atypical phenotypes. Research into atypical Alzheimer's disease has revealed previously unrecognised neuropathological heterogeneity across the Alzheimer's disease spectrum. Neuroimaging, genetic, biomarker, and basic science studies are providing key insights into the factors that might drive selective vulnerability of differing brain networks, with potential mechanistic implications for understanding typical late-onset Alzheimer's disease.

Introduction

Alzheimer's disease is defined by amyloid β plaques and neurofibrillary tangles, which can be detected post mortem or in vivo with biomarkers.¹ The most common clinical presentation of sporadic Alzheimer's disease (ie, typical Alzheimer's disease dementia) is a slowly progressive amnestic disorder reflecting predominant early distribution of neurofibrillary tangle pathology in medial temporal lobe structures that eventually evolves into an amnestic-predominant, multidomain dementia. However, non-amnestic phenotypes are characterised on the basis of initial, dominant difficulties in visual, language, executive, behavioural, and motor domains. These presentations (atypical Alzheimer's disease) disproportionately affect individuals with young-onset dementia whose symptoms begin before age 65 years.²

Younger patients with Alzheimer's disease dementia with non-amnestic symptoms or lacking typical hippocampal volume loss might be misdiagnosed or receive a delayed diagnosis. In a neuropathologically confirmed cohort of patients with young-onset Alzheimer's disease, 53% with atypical presentations were misdiagnosed compared with 4% of patients with typical symptoms.^{3,4} Given their younger age and unusual symptoms, patients with non-amnestic Alzheimer's disease might have their symptoms attributed to life stresses, or new-onset psychiatric illness. Neuropsychological assessment should be individualised for atypical Alzheimer's disease and interpreted in the context of the overall profile. For example, memory or executive-function tests with visual or numerical demands present particular challenges to patients with visual-spatial phenotypes.

Beyond diagnostic delays and deployment of unnecessary tests, non-memory symptoms of Alzheimer's disease correlate with significant morbidity and consequential decrease in autonomy and quality of life, often in working-age people with dependants. Alzheimer's disease services are typically tailored to the needs of older patients,

often not addressing the specific needs of atypical patients with Alzheimer's disease who require treatment plans tailored to their symptoms and stage of life.

Biomarkers allow for improved detection of non-amnestic phenotypes in vivo. Biomarker studies, in addition to emerging findings from neuropathologically defined Alzheimer's disease subtypes, provide insights into the pathogenesis of both typical and atypical Alzheimer's disease, including regional vulnerability and opportunities for earlier diagnosis.

We review clinical features of atypical Alzheimer's disease and common scenarios regarding delayed diagnosis; advances in biomarkers and quantitative neuropathology; key aspects of individualised treatment approaches; and unique opportunities provided by atypical phenotypes to better understand Alzheimer's disease.

Epidemiology

Age-standardised prevalence of dementia over age 60 years is approximately 5–7% worldwide.⁵ To date, no population-based studies of atypical Alzheimer's disease exist. Limited studies from dementia clinics estimate a prevalence of Alzheimer's disease of 15–65 per 100 000 in the 45–64 year age range.⁶ Approximately 8–13% present with visual or motor difficulties, 7–9% with language difficulties, and 2% with behavioural or executive dysfunction.^{7,8} Atypical variants represent one third of patients with young-onset compared with 6% of late-onset Alzheimer's disease;⁸ however, patients with atypical late-onset disease might be less likely to be referred to academic centres. Although the proportion of patients with atypical disease might be lower in older populations than in younger populations, larger numbers of people with late-onset Alzheimer's disease suggest the absolute number of atypical cases might be higher in the older population than in the younger population. There are few studies comparing young-onset versus late-onset atypical Alzheimer's disease.

Sex distributions might vary by phenotype with evidence of modest overrepresentations of women in visual-spatial and motor presentations, possibly reflecting increased prevalence of Alzheimer's disease in women.^{9,10} Behavioural presentations might be more common in men, while there is little evidence of either sex being overrepresented for language and executive presentations.^{7,11} There is scarce evidence on survival in atypical Alzheimer's disease.

Atypical clinical phenotypes of Alzheimer's disease

Visual-spatial

Posterior cortical atrophy (PCA) refers to a clinical-radiological syndrome previously termed Benson syndrome, most commonly attributable to Alzheimer's disease pathology (75–100% of cases).^{12,13} Patients with PCA typically present in their sixth or seventh decade. In a study of 302 patients with PCA, 82% had young-onset dementia.¹⁰ Core features of PCA include difficulty with space and object perception; simultanagnosia, optic ataxia, and oculomotor apraxia (Balint syndrome); dyscalculia, dysgraphia, left-right confusion, and finger agnosia (Gerstmann syndrome); constructional, dressing, or limb apraxia; environmental agnosia; and alexia, with relative preservation of other cognitive domains (panel 1).^{13,14} A dorsal, visuospatial-led variant of PCA with elements of simultanagnosia predominates, with ventral (visuo-perceptual) variants exhibiting letter-by-letter reading or apperceptive prosopagnosia and caudal (primary visual) variants less commonly documented.¹⁴ Predominant right lateralised atrophy in PCA is associated with dressing apraxia,¹⁵ whereas left lateralised PCA is associated with elements of Gerstmann syndrome. Early symptoms include problems with driving including minor damage to one side of the car, dressing, judging distances, and negotiating familiar environments and stairs, escalators, and patterned flooring.¹⁶ Visual impairments include difficulties perceiving objects in the periphery or among clutter, and becoming lost on a page while reading.^{17,18} Incongruent findings on visual acuity and field testing might prompt suspicion of functional illness.

Recent consensus criteria introduced syndromic-level and disease-level descriptions. Syndromic-level descriptions specify key neuropsychological criteria and supportive neuroimaging features comprising occipital-parietal or occipito-temporal atrophy or hypometabolism on MRI and FDG-PET. Disease-level descriptions incorporate molecular biomarker or neuropathological evidence to classify individuals by underlying pathology—eg, distinguishing PCA due to Alzheimer's disease from PCA due to non-Alzheimer's disease pathology. Motor features, including limb rigidity, myoclonus, and tremor, might reflect underlying non-Alzheimer's disease pathology but are also seen in PCA due to Alzheimer's disease,^{13,15} while early hallucinations and rapid eye movement sleep behaviour disorder might be suggestive of PCA due to

Lewy body disease. Rapid clinical progression and cortical restricted diffusion on MRI suggest underlying prion disease. The FDG pattern in PCA overlaps with Lewy body disease, which can lead to diagnostic confusion.¹⁹ The pattern of amyloid PET deposition in PCA resembles typical Alzheimer's disease, in contrast to regional, particularly occipital involvement, on FDG and tau PET. As PCA progresses, deficits in episodic and working memory and language emerge, although early word-finding difficulties might be apparent.^{16,20} Depression, anxiety, and other neuropsychiatric symptoms in PCA overlap with those occurring in typical Alzheimer's disease.²¹

Language

Patients with progressive aphasia, which can occur in isolation for years before the development of impairments in other domains, are defined as having primary progressive aphasia (PPA). Frontotemporal lobar degeneration and Alzheimer's disease were the most common underlying pathologies in early PPA studies. Current clinical PPA diagnostic criteria emphasise progressive language impairment with relatively spared memory, visual abilities, and behaviour.²² There are three major PPA subtypes: non-fluent/agrammatic, semantic, and logopenic variants. Alzheimer's disease pathology is most associated with the logopenic variant. A large amyloid PET study in PPA provided data consistent with neuropathological studies, with amyloid PET positivity in 86% of 443 patients with logopenic variant, 20% of 333 with non-fluent/agrammatic, and 16% of 401 with semantic. Across all three variants most patients were under 70 years and 49% were female, consistent with typically young onset presentation in these syndromes.²³

Patients with logopenic variant often have word-finding difficulty, sentence-repetition deficits, and phonological impairments without impairments of motor speech and single-word comprehension (panel 1).²⁴ In logopenic variant, anomia is common but, unlike in the semantic variant, object knowledge and single-word comprehension are typically preserved. Speech might appear hesitant but, in contrast to patients with non-fluent/agrammatic variant, those with logopenic Alzheimer's disease do not have prominent agrammatic or telegraphic speech or motor speech deficits. MRI and FDG-PET scans typically show evidence of left hemisphere-lateralised, posterior temporal, and inferior parietal atrophy or hypometabolism. The presence of posterior temporal and parietal atrophy distinguishes logopenic variant from frontotemporal lobar degeneration, which can also have asymmetric temporal atrophy. Tau PET studies show asymmetric, left-hemisphere predominant temporoparietal signal in most patients with logopenic variant.²⁵

Although some patients with PPA have clear, isolated language problems, others have varying degrees of additional memory and executive dysfunction, particularly later in the disease course. The initial logopenic neuropsychological profile might ultimately evolve into

Panel 1: Clinical features of atypical phenotypes and common scenarios regarding delay or misdiagnosis**Posterior cortical atrophy Alzheimer's disease***Clinical features*

- Space or object perception difficulties
- Simultanagnosia (the inability to perceive more than one object at a time), optic ataxia, and oculomotor apraxia
- Dyscalculia, dysgraphia, left-right confusion, finger agnosia
- Constructional, dressing, or limb apraxia
- Environmental agnosia
- Reading difficulties
- Face perception difficulties
- Visual field defect
- Relatively spared anterograde memory, speech, non-visual language, executive function, and behaviour

Diagnostic red flags

- Repeated appointments with eye specialists
- Repeatedly changing prescription of glasses
- Diagnosed incorrectly with an ocular condition
- Might undergo unnecessary surgeries (eg, cataract removal)
- Might be diagnosed as functional

Logopenic variant primary progressive aphasia*Clinical features*

- Impaired single-word retrieval
- Impaired sentence repetition
- Phonological errors
- Spared single-word comprehension
- Spared motor speech
- Absence of frank agrammatism

Diagnostic red flags

- Due to aphasia, might be misdiagnosed as having a stroke, even in the absence of neuroimaging changes
- Might be misdiagnosed as another form of primary progressive aphasia

Behavioural Alzheimer's disease*Clinical features*

- Progressive deterioration of behaviour and cognition
- Features of behavioural variant frontotemporal dementia (apathy, disinhibition, loss of empathy, and less commonly, perseverative or compulsive behaviour, hyperorality, and dietary changes)
- Executive deficits with relative sparing of memory and visuospatial functions

Diagnostic red flags

- Might be misdiagnosed as behavioural variant frontotemporal dementia
- Might receive a psychiatric diagnosis

Dysexecutive Alzheimer's disease*Clinical features*

- Predominant decline in core executive cognitive function: working memory, cognitive flexibility, inhibition in the absence of predominant behavioural features

Diagnostic red flags

- Might receive a psychiatric diagnosis
- Mimics dysexecutive problems seen in vascular dementia with coexisting Alzheimer's disease

Corticobasal syndrome Alzheimer's disease*Clinical features*

- Parkinsonism
- Myoclonus
- Apraxia
- Cortical sensory deficit
- Alien limb
- Executive, visuospatial, and language dysfunction

Diagnostic red flags

- Might be misdiagnosed as Parkinson's disease or other parkinsonian disorder

multidomain Alzheimer's disease dementia²⁶ featuring memory, executive, and visuospatial dysfunction, often with limb apraxia, acalculia, and other elements of Gerstmann syndrome. Behavioural symptoms including anxiety might be accompanied by depression, irritability, or agitation.

Executive and behavioural

Frontal Alzheimer's disease originally described patients with primary executive dysfunction and frontal-lobe neurofibrillary tangle pathology compared with typical Alzheimer's disease, noting that none of these patients had major behavioural change.²⁷ Frontal or frontal-variant Alzheimer's disease has since described patients presenting with either dysexecutive or behaviour-predominant syndromes.^{7,28,29} Two distinct clinical phenotypes, dysexecutive and behavioural Alzheimer's disease, were subsequently informed by case series.^{11,30}

Dysexecutive Alzheimer's disease primarily presents with a dysexecutive syndrome involving working memory, cognitive flexibility or set shifting, inhibitory control deficits, and rarely behavioural symptoms (panel 1).^{11,30} Early features include impaired multi-tasking, planning, and project completion—eg, problems playing board games, following directions and recipes, and organising calendars. The disease is now recognised as a distinct, predominantly young-onset atypical Alzheimer's phenotype in patients with positive Alzheimer's disease biomarkers.³⁰

Dysexecutive Alzheimer's disease is associated with parieto-frontal atrophy and relatively preserved medial temporal regions compared with amnestic phenotypes.^{11,30} These parieto-frontal brain regions overlap with the working-memory network corresponding to spatial patterns of tau PET signal.³¹ Atrophy occurs in the parietal lobe but might be subtle. In patients with dysexecutive Alzheimer's disease, FDG-PET scans show frontal and

parietal hypometabolism. The frontal hypometabolism might lead to diagnostic confusion with frontotemporal degeneration. Unique executive profiles are observed: in Alzheimer's disease it is disproportionate working memory and in behavioural-variant frontotemporal dementia inhibition deficits.³²

Impaired core executive functions lead to a multidomain dysfunctional pattern on neuropsychological testing. Depression and anxiety are common in dysexecutive Alzheimer's disease, and neuropsychiatric symptoms might be more evident relative to typical Alzheimer's disease,¹¹ but behavioural and personality changes are typically not reported, the exception being apathy.

A primary behavioural syndrome mimicking behavioural-variant frontotemporal dementia³³ is a relatively rare clinical manifestation of Alzheimer's disease.^{7,12,34–37} Of 532 consecutive patients with Alzheimer's disease presenting to an academic memory clinic, 2% reported predominant frontal behavioural features. 75% of patients with predominantly behavioural manifestation were male with a mean age of onset of 49 years.⁷ Clinicoopathological series determined Alzheimer's disease as the causative neuropathology in 7–20% of patients with clinically diagnosed behavioural-variant frontotemporal dementia.^{12,34–37} Subsequent studies describe demographic, clinical, and neuroimaging features of patients with a behaviour-predominant clinical presentation and autopsy or biomarker confirmation of underlying Alzheimer's disease (behavioural Alzheimer's disease).^{11,12,34,35,37,38} Symptoms typically start between the fifth and seventh decade. In contrast with behavioural-variant frontotemporal dementia, cognitive symptoms often pre-date behavioural change,³³ apathy is more common than disinhibition or loss of empathy, perseverative or compulsive and eating changes are relatively uncommon, and behavioural changes are generally less marked (panel 1). Conversely, delusions and hallucinations are more common in behavioural Alzheimer's disease than in behavioural-variant frontotemporal dementia.³⁶

Paradoxically, atrophy or hypometabolism on MRI or FDG-PET primarily focuses on classic Alzheimer's disease regions, including posterior cingulate, precuneus, and medial temporal lobe.^{11,37} Variable frontal involvement, intermediate between behavioural-variant frontotemporal dementia and typical amnestic Alzheimer's disease, shows more predilection for dorsal than ventral frontal regions,³⁷ consistent with clinical changes (apathy is more common than disinhibition or executive dysfunction).

An intermediate behavioural profile, including prominent apathy, early cognitive deficits, and temporo-parietal predominant involvement on MRI or FDG-PET, characterises behavioural Alzheimer's disease (compared with behavioural-variant frontotemporal dementia).

Amyloid and tau biomarkers (biofluid or PET) allow distinction of dysexecutive Alzheimer's disease and behavioural Alzheimer's disease from dysexecutive and behavioural presentations due to frontotemporal degeneration.

Motor dysfunction

Corticobasal syndrome, characterised by motor and sensory symptoms, typically correlates with corticobasal degeneration pathology. However, 15–50% of cases are attributable to Alzheimer's disease.^{12,39–42}

Proposed core clinical features for corticobasal syndrome include limb rigidity, bradykinesia, dystonia, myoclonus, apraxia, cortical sensory deficit, and alien limb phenomenon (panel 1).^{40,42,43} Executive, visuospatial, and language dysfunction are proposed core or supportive features of corticobasal syndrome.^{40,42,43} Corticobasal syndrome might be due to several pathologies; prominent episodic memory and visuospatial or visuoperceptual deficits, frequent myoclonus, and logopenic type aphasia are suggestive of Alzheimer's disease, whereas prominent executive dysfunction, non-fluent/agrammatic aphasia, and supranuclear gaze palsies suggest non-Alzheimer's disease pathology.^{9,42,44} Autopsy and neuroimaging studies have found relative preservation of superior frontal regions contrasted by greater occipital and temporo-parietal volume loss in corticobasal syndrome due to Alzheimer's disease compared with corticobasal degeneration.^{9,41} Asymmetric clinical syndromes or atrophy patterns do not distinguish Alzheimer's disease from corticobasal degeneration or other causes of corticobasal syndrome. Biofluid and PET biomarkers of amyloid and tau support identification of underlying Alzheimer's disease pathology *in vivo*, with tau PET showing asymmetric involvement of perirolandic cortex, often spared in other Alzheimer's disease variants.

Over the course of corticobasal syndrome due to Alzheimer's disease, variable initial signs might progress to apraxia, myoclonus, gait disorder, visuospatial, language, and memory symptoms. Although prominent apathy and disinhibition might be suggestive of non-Alzheimer's disease pathology,^{42,44} the neuropsychiatric profile of corticobasal syndrome due to Alzheimer's disease has yet to be characterised comprehensively.

Overlapping presentations

Phenotype overlap is recognised in criteria (eg, PCA-plus¹⁴). Both PCA and corticobasal syndrome involve limb apraxia and visuospatial dysfunction^{13,14,38,40,43} and might encompass biparietal, apraxic, and dyscalculic Alzheimer's disease variants.¹⁴ The language profile of corticobasal syndrome^{40,42} overlaps with logopenic. Verbal working-memory difficulty features prominently in logopenic and dysexecutive Alzheimer's disease.

Biomarkers to diagnose atypical Alzheimer's disease

The extent and regional deposition of the neuropathological hallmarks of both typical and atypical Alzheimer's disease differ. Contemporary criteria for both typical and atypical Alzheimer's disease dementia^{45,46} require molecular evidence for these neuropathologies, which, *in vivo*, depends on imaging or fluid biomarkers. These biomarkers are particularly relevant in atypical Alzheimer's

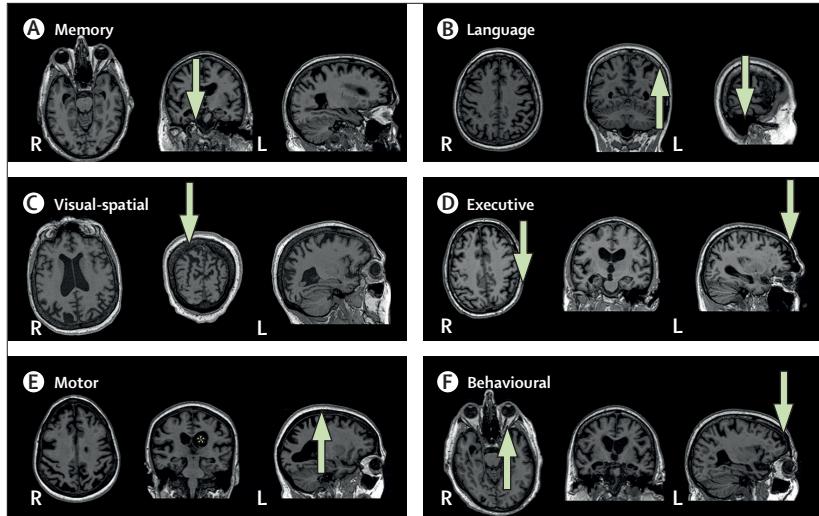


Figure 1: MRI across Alzheimer's disease phenotypes

(A) Memory (typical amnesia); arrow indicates hippocampal atrophy. (B) Language (logopenic variant primary progressive aphasia); arrows highlight left temporal-parietal atrophy. (C) Visual-spatial (posterior cortical atrophy); arrow indicates parieto-occipital atrophy. (D) Executive (also known as dysexecutive); arrows indicate frontotemporal atrophy. (E) Motor (corticobasal syndrome); asterisk highlights greater left than right hemisphere atrophy, and arrow indicates atrophy around the motor cortex. (F) Behavioural; arrows point to greater temporal than frontal atrophy. R=right. L=left.

disease, where the underlying pathology is challenging to recognise clinically. With predominantly younger patients, false positives (ie, asymptomatic age-related Alzheimer's disease pathology) are less likely to occur compared with older patients presenting with cognitive problems.

On structural MRI, typical Alzheimer's disease atrophy begins in the medial-temporal lobe and spreads to the lateral-temporal and parietal cortices. In atypical Alzheimer's disease atrophy is usually most prominent in regions corresponding to clinical symptoms, often sparing the hippocampus early in the disease. See figure 1 for patterns.

FDG-PET can aid in the diagnosis of Alzheimer's disease dementia, particularly in differentiating Alzheimer's disease from frontotemporal dementia. Hypometabolism patterns on FDG-PET reflect clinical deficits across atypical Alzheimer's disease variants and distinguish between typical and atypical Alzheimer's disease (figure 2).

Although amyloid PET is clinically approved as a diagnostic test, it is predominantly used in research settings. In typical Alzheimer's disease, amyloid deposition occurs diffusely throughout neocortex, with early involvement of posteromedial cortices and relative sparing of medial temporal, primary sensorimotor, and visual cortices. Importantly, unlike other imaging modalities, amyloid distribution is similar between atypical and typical Alzheimer's disease.

The US Food and Drug Administration approved F18-flortaucipir to image tau pathology in Alzheimer's disease. Although flortaucipir and several other tau-specific tracers are available, imaging is rarely accessible outside the research setting. As opposed to amyloid PET, tau PET

deposition patterns reflect the anatomical areas producing the clinical phenotype and overlap with regional FDG-PET hypometabolism and atrophy. Figure 2 illustrates example tau PET patterns across phenotypes. In atypical Alzheimer's disease, tau PET does not conform to the pattern seen in amnestic presentations and the pattern might have use in distinguishing typical and atypical phenotypes. Tau negative cognitive disorders, even in the context of a positive amyloid scan, might suggest different underlying non-Alzheimer's disease pathologies.³¹

On longitudinal imaging, atrophy patterns diverge by phenotype with greatest medial temporal atrophy in typical Alzheimer's disease, occipito-parietal or occipito-temporal atrophy in PCA,²⁰ and left temporal atrophy in logopenic variant. Across PCA, logopenic and behavioural or dysexecutive Alzheimer's disease, regions of greatest baseline atrophy are particularly affected over time, although converge across temporoparietal and dorsolateral prefrontal regions.⁴⁷ Although baseline tau PET corresponds closely to clinical phenotype and atrophy pattern, longitudinal tau accumulation occurs in frontal regions in atypical variants and typical Alzheimer's disease.⁴⁸

Fluid biomarkers

Tau and amyloid PET give information on regional distribution and burden of tau and amyloid β . In contrast, CSF or plasma biomarkers allow for indirect detection of these pathologies: CSF A β 42 concentration and A β 42 to A β 40 ratios correlate inversely with cerebral amyloid β plaque burden, and concentrations of total and phosphorylated tau (p-tau) correlate with intensity of neurodegeneration and neurofibrillary-tangle pathology respectively, both in typical and atypical Alzheimer's disease.⁴⁹ Combining CSF A β 42 and p-tau181 gives a sensitivity and specificity of approximately 90% for distinguishing Alzheimer's disease from non-Alzheimer's disease pathologies.⁵⁰ Although fluid and imaging molecular diagnostics correlate fairly well, CSF and plasma biomarkers might show changes earlier in the disease course than amyloid or tau PET, and conversely show earlier plateau with disease progression.⁵¹

Few studies have directly compared the profiles of typical and atypical Alzheimer's disease. CSF differences might include increased tau in atypical phenotypes,⁵² with mixed evidence of whether p-tau differs between variants.^{53,54} CSF concentrations of synaptic proteins (neurogranin, SNAP-25, synaptotagmin-1) and neurofilament light protein (NfL) increase in atypical Alzheimer's disease,^{54,55} although normal age-related rise in NfL needs to be considered.⁵⁶ CSF proteomics approaches reveal various biological pathways involved in Alzheimer's disease varying from haemostasis, lipoprotein, and extracellular matrix,⁵⁷ possibly underpinning phenotypic Alzheimer's disease variation. Recent advances in blood-based biomarkers of amyloid β , tau, p-tau, and NfL, and proteomic approach biomarkers in plasma require further validation in atypical Alzheimer's disease.

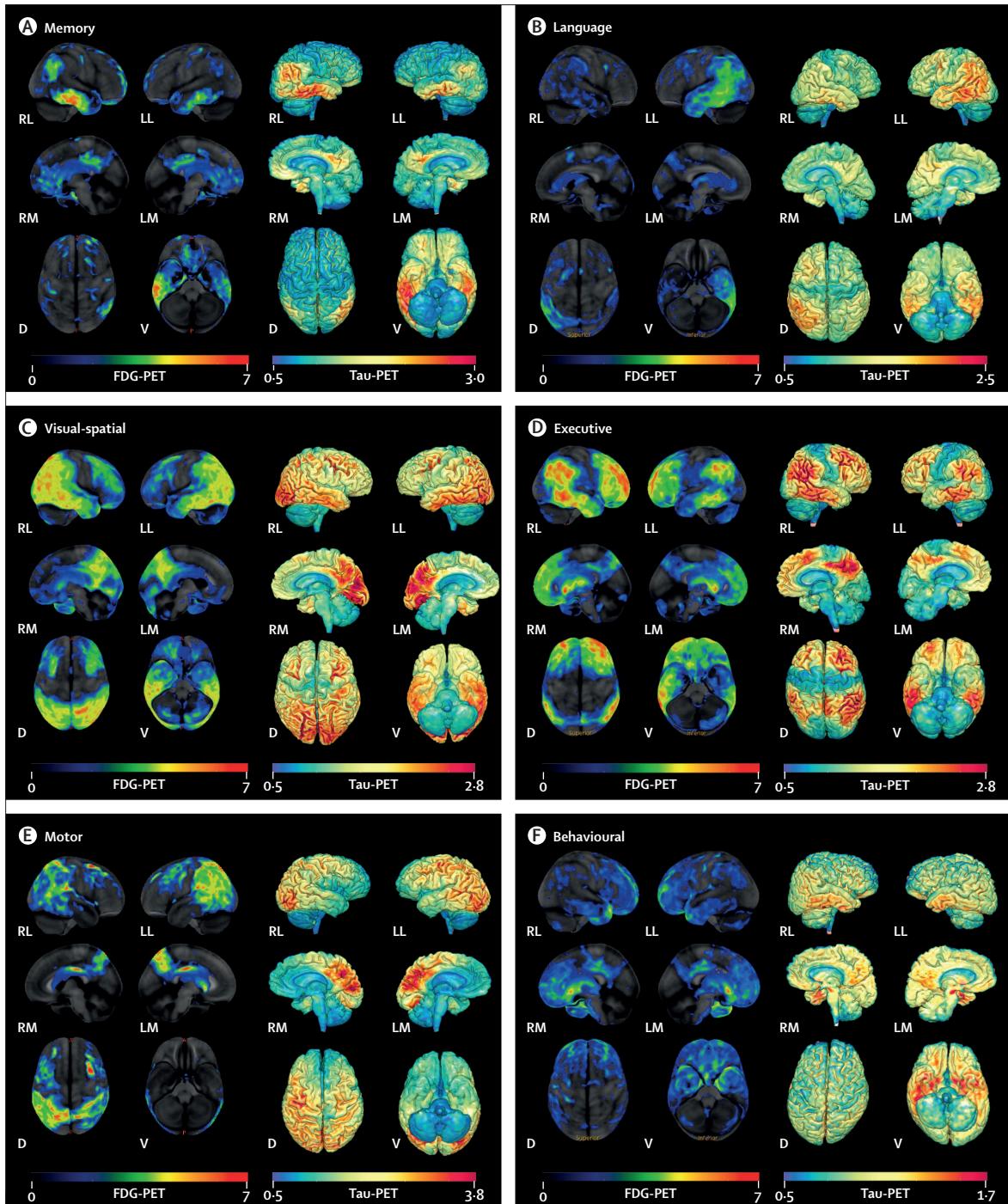


Figure 2: FDG and tau PET across Alzheimer's disease phenotypes

FDG-PET is shown on the left and tau PET on the right of each panel, presenting representative cases of each Alzheimer's disease phenotype: (A) memory (typical amnestic); (B) language (logopenic variant primary progressive aphasia); (C) visual-spatial (posterior cortical atrophy); (D) executive (dysexecutive); (E) motor (corticobasal syndrome); and (F) behavioural. The Z-scores, relative to a normative database, of pons intensity normalised FDG-PET scans for each individual are displayed on stereotactic surface projections using Cortex ID (GE Healthcare Waukesha, WI, USA). Red colour indicates greater hypometabolism. The cerebellar crus intensity normalised Tau-PET scan (Tauvid; AV1451; floratacipur F18; Avid Radiopharmaceuticals, Philadelphia, PA, USA) is overlaid on the grey matter segmentations of each patient's own T1 weighted structural MRI scan. Red colour indicates higher intensity of tracer. RL=right lateral. LL=left lateral. RM=right medial. LM=left medial. D=dorsal. V=ventral.

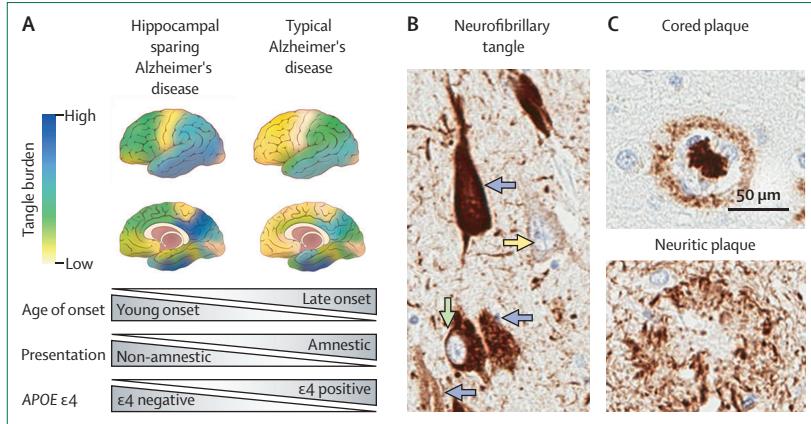


Figure 3: Clinicopathological features of Alzheimer's disease subtypes

(A) Neuropathological subtypes of Alzheimer's disease are characterised by distribution of neurofibrillary tangle pathology. Illustrations depict the hippocampal sparing subtype with greater cortical pathology relative to sparing of the hippocampus. The typical Alzheimer's disease subtype shows expected patterns of both limbic and cortical involvement. Disproportionate differences in age of onset, clinical presentation, and APOE ε4 positivity are observed between hippocampal sparing Alzheimer's disease and typical Alzheimer's disease. (B) Abnormal accumulation of intracellular tau pathology is observed with increasing severity from pre-tangles (yellow arrow) to mature tangles (green arrow). As the neuron dies, a remnant of the tau pathology remains in the extracellular space as ghost tangles (blue arrow). (C) Top: classic cored plaques are typically observed in brains of patients with Alzheimer's disease. Bottom: neuritic plaques can be readily observed using tau antibodies, but might be more easily distinguished by silver stain or thioflavin-S microscopy (not shown).

Alzheimer's disease and the US National Institute on Aging and Alzheimer's Association (NIA-AA) research criteria and the Second International Working Group (IWG-2) criteria

Although traditional Alzheimer's disease criteria focused on amnestic deficits, the NIA-AA dementia 2011 and IWG-2 Alzheimer's disease 2014 criteria acknowledged non-amnestic (ie, atypical) phenotypes.^{45,46} The IWG-2 criteria describe posterior, logopenic, and frontal variants of Alzheimer's disease and require biomarker confirmation of Alzheimer's disease pathology (CSF, PET, or mutation status), whereas the NIA-AA criteria describe executive, visual, and language presentations with different levels of certainty based on biomarker abnormalities. Applying these criteria requires adoption of diagnostic algorithms extending beyond detection of amnestic deficits and use of biomarkers where possible.

Neuropathological underpinnings

Despite differences in their extent and regional deposition, accumulation of amyloid β plaques and neurofibrillary tangles are neuropathological hallmarks of both typical and atypical Alzheimer's disease (figure 3).⁵⁸ Although clinical criteria subdivide atypical Alzheimer's disease into several canonical syndromes, neuropathological studies have also investigated the Alzheimer's disease spectrum predicated on regional neuropathological involvement.

Neuropathological Alzheimer's disease criteria use scoring systems for severity of cortical neuritic plaques (CERAD)⁵⁹ and topography of amyloid β plaque pathology using Thal phase,⁶⁰ with tangle distribution scored using

Braak staging.⁶¹ These scoring systems designed for typical Alzheimer's disease rely on a predictable sequence of neuropathological spread not always observed in atypical Alzheimer's disease. Quantitative assessment of tangle density in a larger Alzheimer's disease cohort identified several subtypes including limbic predominant (not shown) and hippocampal sparing (figure 3).^{4,62} Non-amnestic presentations are relatively uncommon at 11% in typical Alzheimer's disease, compared with 38% of patients with hippocampal sparing Alzheimer's disease.⁶² The tangle density in the cortex and nucleus basalis of Meynert (ie, cholinergic hub) in hippocampal sparing Alzheimer's disease exceeds that in the relatively spared hippocampal-amygdala region.⁶² Furthermore, an inverse relationship exists between younger onset and greater neuronal loss in the nucleus basalis of Meynert. Given widespread cholinergic projections throughout cortico-limbic structures,⁶³ pathologies in specific nuclei within the cholinergic hub might confer vulnerability to neocortical tangle pathology in non-amnestic Alzheimer's disease phenotypes.^{62,64}

Atypical, non-amnestic Alzheimer's disease phenotypes are most commonly observed in the hippocampal sparing Alzheimer's disease subtype, although typical Alzheimer's disease patterns at autopsy might reflect late-stage concurrent hippocampal involvement.⁴ Contribution of oligomeric amyloid β species cannot be ruled out; however, overwhelming evidence points to tau pathology as the major contributor to domain-specific functional consequences in Alzheimer's disease.^{53,62,65} Tangle density in PPA is greatest in primary visual cortex and visual association areas, with lesser hippocampal involvement relative to typical Alzheimer's disease.¹³ In PPA due to Alzheimer's disease, neuronal loss and tau pathology are seen in temporoparietal structures.⁶⁶ Asymmetry of Alzheimer's disease pathology was inconsistently observed at the individual level in people with PPA but, when observed, it appears to be more specific to tangle than neuritic plaque pathology.⁶⁷ Patients with corticobasal syndrome with underlying Alzheimer's disease pathology have greater perirolandic tau and nigrum neuronal loss with less temporal pathology than typical Alzheimer's disease.⁹ Although asymmetric clinical presentation of motor symptoms was observed, the relationship to asymmetry of pathology was precluded by routine unavailability of both hemispheres.⁹ This finding highlights the mutually beneficial relationship between the macroscopic information provided by neuroimaging and the microscopic details provided by neuropathology studies.⁶⁸

Some patients with atypical dementia syndromes and Alzheimer's disease pathology exhibit coexisting cerebrovascular disease and Lewy body disease pathology, that are not thought to have a major role in atypical Alzheimer's disease.^{53,62,69} The frequency of Lewy body disease is lower in hippocampal sparing Alzheimer's disease (14%) compared with typical Alzheimer's disease (26%),⁶² but these estimates do not account for amygdala predominant

Lewy bodies often seen in end-stage Alzheimer's disease. TDP-43 pathology in limbic regions is often found in typical Alzheimer's disease (60%),⁷⁰ more so than non-amnestic phenotypes (42%) or individuals with hippocampal sparing Alzheimer's disease (21%).^{4,67,69} The lower frequency of coexisting pathologies in non-amnestic phenotypes or in people with hippocampal sparing Alzheimer's disease might be age-related, as patients with atypical Alzheimer's disease are often younger than those with typical Alzheimer's disease.⁶² Microscopic inspection often reveals an overall greater burden of tangle pathology of vulnerable cortical regions compared with typical Alzheimer's disease.^{13,30,62} This occurrence probably reflects the fact that atypical forms of Alzheimer's disease are more common in younger patients, who generally have a greater tau burden.⁷¹ The reasons for this are not well understood, but younger individuals might exhibit greater inflammatory reactions to amyloid or a different genetic profile, resulting in more tangles, or increasing age might correlate with higher risk of multiple co-pathologies, that might result in dementia accompanied by a lesser burden of specific pathologies. Morphological differences of amyloid β plaque pathology might have a role in atypical Alzheimer's disease, as the newly identified coarse-grained plaques in young-onset Alzheimer's disease do not contain the classic amyloid β core and have a poorly organised microglial response.⁷²

Causes of atypical Alzheimer's disease

Genetics

A small proportion of patients with autosomal dominant Alzheimer's disease, have atypical phenotypes.⁷³ Beyond case reports, canonical atypical Alzheimer's disease phenotypes apparently do not associate with autosomal dominant mutations, and to offer clinical genetic testing without a compelling family history is not common practice. Despite the *APOE* $\epsilon 4$ allele being the strongest genetic risk factor for sporadic Alzheimer's disease and lowering the age of symptom onset, patients with atypical phenotypes^{10,74} are less likely to carry *APOE* $\epsilon 4$ than those with a typical presentation.⁷⁵ The relative rarity of these presentations render it challenging to conduct large-scale genetic studies with adequate power; however, a GWAS in PCA identified candidate genes implicated in developmental and intercellular communication processes in visual systems and the CNS, with findings requiring replication and validation.¹⁰

Functional brain networks

Alzheimer's disease-phenotypic extremes highlight our limited understanding of the disease mechanism underlying such heterogeneity. Amyloid β deposition is thought to precede accumulation of tau, regional atrophy, and clinical symptoms, but the clinical phenotype broadly corresponds to regional atrophy and tau deposition, not amyloid β deposition.⁷⁶ These spatiotemporal discrepancies suggest that mechanisms leading to amyloid

deposition are distinct from those leading to tau deposition, neurodegeneration, and symptom development. Well documented cognitive variability is reflected in differential network disruptions between clinically defined phenotypes.⁷⁰ Variability in tau patterns coincide with functional networks,³¹ suggesting heterogeneity in symptoms, atrophy, and tau might be explained by differential effects on functional brain networks.⁷⁷ A widely accepted model explaining the relationship between tau and networks is the seed-based templating or prion-like spread of tau across functionally connected brain regions.⁷⁸ For such a mechanism to account for phenotypic heterogeneity, there must be variable initiation, selective spread, or a common site with diverse connections with variable, complex spreading patterns (eg, locus coeruleus).⁷⁹

Although amyloid is also associated with functional network properties of the brain,⁸⁰ these network properties are more general (eg, hubness or overall connectivity) and do not directly relate to variably impaired cognitive abilities in Alzheimer's disease. The association between hubness and amyloid β might relate to variations in metabolic or other local tissue factors, imparting selective vulnerability.⁸¹ In line with seed-based templating for amyloid, others report observing sequential spread in cortical amyloid β ,⁸² but this finding contrasts with pathological observations.⁶⁰ If both amyloid β and tau accumulate via the same seed-based mechanism within functional brain networks, why they have variable relationships to clinical phenotypic heterogeneity is uncertain. One possible explanation is that oligomeric species of amyloid align with neurodegeneration,⁸³ but extracellular amyloid plaque deposition measured with PET⁶² does not.

The cascading network-failure theory of Alzheimer's disease is an alternative model that explains both the uniform amyloid β and variable tau distributions via functional networks, but allows different network properties to account for the observed spatiotemporal differences.³¹ The large-scale neural networks associated with clinical phenotype are marked by tau, but general compensatory network functions done by brain hubs are marked by amyloid. Such modular failure and global compensation are features of complex networks like power grids and might be a general disease mechanism in the brain.⁸⁴ Such models do not preclude the co-existence of seed-based templating, but they are also not dependent upon them.

Amyloid β might also potentiate tau pathology and neurodegeneration potentially explaining temporal differences, but the mechanistic link between amyloid β and tau accounting for regional and phenotypic discrepancies between them is currently unknown.

Other associations or molecular mechanisms

The global amyloid β distribution seen in both atypical and typical Alzheimer's disease prompts consideration of additional factors influencing the clinicoradiological

Panel 2: Phenotype-specific considerations and non-pharmacological treatment approaches in atypical Alzheimer's disease**Posterior cortical atrophy Alzheimer's disease****Phenotype-specific considerations**

- Early discussion of driving safety is a priority; most patients with posterior cortical atrophy will not be safe to drive
- Patients might have a high risk of becoming lost
- Occupational and daily routines might be severely affected by progressive visual loss, despite preserved insight
- Patients might be eligible for registration as severely sight impaired or legally blind, to obtain appropriate services
- Most patients become functionally blind leading to a high risk of falls

Non-pharmacological treatment

- Treatment from an occupational therapist experienced in dealing with low vision can assist in identifying compensation strategies for vision issues
- Aids and adaptations to support diminished reading and navigation based on minimising visual clutter and strategic use of contrast might help
- Adaptive equipment designed for those with low vision might be appropriate (talking watch, cane, tyoscope, audiobooks) with careful appreciation of concurrent non-visual symptoms

Logopenic variant primary progressive aphasia**Phenotype-specific considerations**

- Patients might have difficulty communicating their diagnosis and needs, prompting use of aphasia awareness and medical cards
- Communication difficulties might lead to social isolation due to increased anxiety

Non-pharmacological treatment

- Speech and language therapy can help maximise independence in communication and lessen frustration
- Evidence supports use of lexical retrieval based on self-cueing, reading, repetition, and recall
- Patients might use repetition for words that present the biggest challenge
- Practice talking around words might improve symptoms

Behavioural Alzheimer's disease**Phenotype-specific considerations**

- Increased risk of financial losses and susceptibility to scams
- Driving safety should be determined, considering relevant skills (judgement or inhibition, praxis, visuospatial function)

Non-pharmacological treatment

- Counselling can help the patient and family to focus on simple instructions (ie, one step rather than multistep commands)
- Redirection techniques can mitigate and prevent behavioural symptoms

Dysexecutive Alzheimer's disease**Phenotype-specific considerations**

- Most patients will develop symptoms during working years; referral to occupational medicine or counselling regarding job loss or disability might be needed

Non-pharmacological treatment

- Counselling can help the patient and family to focus on simple instructions (ie, one step rather than multistep commands)
- Multi-tasking as well as environmental and emotional distractions should be avoided
- Emphasis should be placed on approaches to facilitate sequential processing and reliance on highly learned strategies to improve daily task performance

Corticobasal syndrome Alzheimer's disease**Phenotype-specific considerations**

- Mobility and balance difficulties might lead to a high risk of falls
- Motor and visual symptoms have particular implications for daily functioning
- Communication and swallowing difficulties might pose challenges to maintaining social function and nutrition

Non-pharmacological treatment

- Interdisciplinary teams might include physical therapy, occupational therapy, and speech and language therapy-based approaches, with an emphasis on risk management and maximising functional status

profile. Altered inflammatory response has received increased attention. Relative to typical Alzheimer's disease, a small study of PCA due to Alzheimer's disease documented C11-PBR28 PET binding (a marker of activated microglia and astrocytes) increased in parietooccipital and reduced in entorhinal regions.⁸⁵ Genes implicated in immune processes and phagocytosis might carry comparable or reduced risk for PCA compared with typical Alzheimer's disease.¹⁰ Disproportionate glial activation in superior parietal-versus-temporal regions was noted in atypical relative to typical Alzheimer's disease.⁸⁶ Yet, evidence is limited for differential glial burden or abnormality between individual language-predominant or corticobasal syndromes compared with typical phenotypes.^{9,87}

Treatment of atypical Alzheimer's disease

Pharmacological management strategies for atypical and typical Alzheimer's disease overlap. Acetylcholinesterase inhibitor medications are indicated. Limited studies of young-onset Alzheimer's disease, in which these phenotypic variants are overrepresented, suggest a similar treatment response relative to late-onset Alzheimer's disease.⁸⁸ Less data for memantine exist, but a trial of memantine is reasonable when indicated at the moderate-to-severe dementia stage. As with other dementias, antidepressant drugs might alleviate patients' depression, behavioural symptoms, or anxiety, but evidence is scarce. Treatment for parkinsonism, seizures, dystonia, or myoclonus might be appropriate for individual patients.

Resources for typical Alzheimer's disease often do not cover the unique challenges faced by patients with atypical Alzheimer's disease. A multidisciplinary approach targeted to individual patients' symptoms and specific phenotype can improve functional status and quality of life.⁸⁹ Approaches to maximise function in atypical Alzheimer's disease are largely derived from small studies. Compensatory strategies might mitigate reading loss and environmental disorientation in PCA,^{17,90} and word-retrieval interventions can benefit patients with logopenic variant (panel 2).⁹¹ Many patients with atypical Alzheimer's disease might find research participation empowering, particularly given delays to diagnosis and lack of public and professional understanding, although appropriate study outcomes are required.

Individuals living with young-onset dementia and their families or households often experience challenges compared with late-onset dementia. Given the substantial overlap with young-onset Alzheimer's disease, such challenges affect many individuals with atypical Alzheimer's disease. Patients are still likely to be working, more likely to have children living at home, and more likely to also be providing care for their own parents. These needs are frequently unaddressed by government services targeting older individuals, which are often only available to those over ages 60–65 years. Providing access to important services regardless of age is a necessary step that will benefit patients with atypical Alzheimer's disease. Rare Dementia Support is a resource used by patients with atypical Alzheimer's disease worldwide that offers syndrome-specific support and education for patients and their families.⁹²

Conclusions and future directions

Although recognised for many years, Alzheimer's disease biomarkers and novel neuropathological approaches have refined our understanding of the phenotypic breadth of atypical Alzheimer's disease. Increasing use of Alzheimer's disease biomarkers in clinical practice and greater recognition of diverse phenotypes can ensure early diagnosis, timely treatment, and appropriate support. Atypical Alzheimer's disease overlaps with young-onset Alzheimer's disease, and there is increasing focus on ensuring appropriate resources and support for these individuals. Studying phenotypic heterogeneity in Alzheimer's disease is key to disentangling mechanisms underlying clinico-radiological as well as neuropathological variability, particularly regarding relative sparing of memory function and medial temporal regions. Although patients with atypical Alzheimer's disease are in many ways ideal for clinical trials (eg, having fewer co-pathologies), current trials in Alzheimer's disease typically emphasise memory dysfunction and patients with atypical Alzheimer's disease might not fulfil entry criteria. Like typical Alzheimer's disease research, nearly all atypical Alzheimer's disease studies disproportionately feature white populations. Forthcoming research should

Panel 3: Current gaps in knowledge

Why focal onset?

Evidence from prospective studies on location initiation is scarce, largely owing to challenges of investigating atypical Alzheimer's disease during the preclinical phase. Neuropathological studies of atypical Alzheimer's disease provide preliminary evidence of selective vulnerability. Selective spread has received support from longitudinal multicentre investigations estimating regional atrophy differences between atypical versus typical Alzheimer's disease persisting across disease stages. Further research is required on the role of common sites, such as the locus caeruleus, mediating disease spread. There are age-related changes in large-scale network configurations that are associated with Alzheimer's pathophysiology; therefore, there might be windows of vulnerability for networks associated with atypical Alzheimer's disease at younger ages, in contrast to typical Alzheimer's disease where the network problem is focused on the hippocampus that occurs at a later age.

Is there a link to brain development or other factors?

Greater frequency of self-reported learning disabilities have been documented in atypical Alzheimer's disease, including language-learning disabilities in logopenic variant primary progressive aphasia and mathematical or visual impairments in posterior cortical atrophy, implying that networks subserving these abilities might be developmentally vulnerable to age-related pathology.^{94,95} The link between learning disabilities and later life neurodegenerative disease in a corresponding neural network suggests a vulnerability or compensation might predispose to later life neurodegeneration. Work in this area is still preliminary and further research is necessary. Regarding other associations, further investigations might relate exogenous factors and neuroinflammation to coexisting pathology and regional vulnerability.

Response to pharmacological therapy and appropriate outcomes for trials

Information on differential response to acetylcholinesterase inhibitors in atypical relative to typical Alzheimer's disease is limited, although might be of key interest given differential involvement of the nucleus basalis of Meynert in neuropathologically defined subtypes. Although patients with atypical Alzheimer's disease might be good candidates for clinical trials, these trials largely emphasise memory outcomes and atypical Alzheimer's disease patients might not fulfil inclusion criteria. Questions on appropriate outcomes include whether these should reflect deficits that are relatively common across atypical phenotypes (eg, working memory) or be adapted to mitigate confounds presented by atypical symptoms (eg, joint visual or verbal presentation of episodic memory stimuli). The Longitudinal Early-onset Alzheimer's disease Study and other international studies plan to answer these questions in the years to come.

Search strategy and selection criteria

We searched PubMed between Jan 1, 2014, and March 1, 2020, and references from relevant articles, using search terms "atypical Alzheimer(s) disease," "posterior cortical atrophy," and "logopenic primary progressive aphasia," "corticobasal syndrome," "frontal or dysexecutive or behavioural Alzheimer's disease". For this Review, we selected only studies on sporadic Alzheimer's disease. There were no language restrictions. The final reference list was generated based on relevance to the topics covered in this Review.

For Rare Dementia Support see
<https://www.raredementiasupport.org/>

describe these syndromes in more diverse, representative populations (panel 3).^{93,94} Multicentre studies, such as the Longitudinal Early-onset Alzheimer's disease Study

For more on the Longitudinal Early-onset Alzheimer's disease Study see www.leads-study.org

are now underway, but more research into atypical Alzheimer's disease is needed in this important patient group to determine the mechanisms behind the focal onset, whether there is a link to early brain development, and the appropriate outcome measures to facilitate clinical trials.

Contributors

All authors contributed equally.

Declaration of interests

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