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Recent update on the heterogeneity of the Alzheimer's disease spectrum

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Abstract

Alzheimer's disease (AD), the most common form of dementia worldwide, is a mixed proteinopathy (β-amyloid, tau and other proteins). Classically defined as a clinicopathological entity, AD is a heterogeneous, multifactorial disorder with various pathobiological subtypes showing different forms of cognitive presentation, currently referred to as the Alzheimer spectrum or continuum. Its morphological hallmarks are extracellular β-amyloid (amyloid plaques) and intraneuronal tau aggregates forming neurofibrillary tangles and neurites, vascular amyloid deposits (cerebral amyloid angiopathy), synapse and neuronal loss as well as neuroinflammation and reactive astrogliosis, leading to cerebral atrophy and progressive mental/cognitive impairment (dementia). In addition to "classical" AD, several subtypes with characteristic regional patterns of tau pathology have been segregated that are characterized by distinct clinical features, differences in age, sex distribution, disease duration, cognitive status, APOE genotype, and biomarker levels. In addition to four major subtypes based on the distribution of tau pathology and brain atrophy (typical, limbic predominant, hippocampal sparing, and minimal atrophy), several other clinical variants (non-amnestic, corticobasal, behavioral/dysexecutive, posterior cortical variants, etc.) have been identified. These heterogeneous AD variants are characterized by different patterns of key neuronal network destructions, in particular the default-mode network that is responsible for cognitive decline. Other frequent age-related co-pathologies, e.g., cerebrovascular lesions, Lewy and TDP-43 pathologies, hippocampal sclerosis, or argyrophilic grain disease, essentially influence the clinical picture and course of AD, and can challenge our understanding of this disorder including the threshold and causal relevance of each individual pathology. Unravelling the clinico-morphological heterogeneity among the AD spectrum entities is important for better elucidation of the pathogenic mechanisms affecting the aging brain that may enable a broader diagnostic coverage of AD as a basis for implementing precision medicine approaches and for developing preventive and ultimately disease-modifying therapies for this devastating disorder.

Keywords Alzheimer's disease · Neuropathology · Clinical subtypes · Regional lesion pattern · Co-pathologies

Abbreviations

AD	Alzheimer's disease
ADNC	Alzheimer's disease neuropathological changes
ADNI	Alzheimer's Disease Neuroimaging Initiative
Aβ	Amyloid-β
CAA	Cerebral amyloid angiopathy
CSF	Cerebrospinal fluid
CVD	Cerebrovascular disease
EOAD	Early-onset Alzheimer's disease
FAD	Familial Alzheimer's disease
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FTLD-TDP	Frontotemporal lobar degeneration with TDP-43
GVD	Granulovacuolar degeneration
HcSP-AD	Hippocampal-sparing Alzheimer's disease
HS	Hippocampal sclerosis
LATE	Limbic-predominant age-related TDP-43 encephalopathy
LATE-NC	LATE-neuropathological changes
LB	Lewy body
LOAD	Late-onset Alzheimer's disease
LP-AD	Limbic-predominant Alzheimer's disease
LPPA	Logopenic primary progressive aphasia
MA-AD	Minimal atrophy Alzheimer's disease

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MAPT	Microtubule-associated protein tau
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
MTL	Medial temporal lobe
NACC	National Alzheimer's Coordinating Center
NFT	Neurofibrillary tangle
NIA/AA	National Institute on Aging/Alzheimer's Association
NT	Neuropil thread
PART	Primary age-related tauopathy
PCA	Posterior cortical atrophy
PPA	Primary progressive aphasia
p-tau	Phosphorylated tau protein
SAD	Sporadic Alzheimer's disease
tAD	Typical Alzheimer's disease

Introduction

Alzheimer's disease (AD), the most common form of dementia in adults that currently affects around 50 million people worldwide, is clinically featured by a multidomain cognitive impairment with progressive decrease of daily living abilities. Its principal risk factor is age, with disease incidence increasing from 2/1000 at age 65–74 years to 337/1000 at age 85+, and doubling every 5 years after age 65, with peaks in the tenth decade and slight decrease afterwards. The overall AD duration varies between 24 years (age 66) and 15 years (age 80), with estimated preclinical durations of 10 years (prodromal 4 years and dementia 6 years) (Vermunt et al. 2019). With the disproportional increase of the elderly population, the prevalence of AD will approach around 132 million worldwide by 2050, and, thus, has become a tremendous public health and socioeconomic challenge of the twenty-first century (Alzheimer's-Association 2021). The scientific approach to AD suffers from mismatches between clinical, pathological and technological data, and from heterogeneity in cohort datasets impeding the reproducibility of results (Birkenbihl et al. 2021) and causing difficulties in conceiving diagnostic gold standards and creating models for drug discovery and screening (Ferrari and Sorbi 2021). As available treatments only target symptoms and neither slow nor reverse the progression of the disease, the development of disease-modifying therapies is urgent (Long and Holtzman 2019). The value of aducanumab, a monoclonal antibody targeting aggregated amyloid-β (Aβ), recently approved for AD treatment by the US Food and Drug Administration, is a matter of current discussion (Karlawish 2021; Barenholtz Levy 2021; Liu and Howard 2021; Musiek and Morris 2021; Nisticò and Borg 2021; Planche and Villain 2021; Schulman et al. 2021).

AD was originally defined as a clinicopathological entity, clinically characterized by progressive memory deficit involving multiple cognitive domains or skills, and a defining pathological substrate with deposition of Aβ in extracellular plaques and cerebral vasculature (cerebral amyloid angiopathy/CAA), neuritic plaques defined by the presence of phosphorylated tau protein (p-tau), intraneuronal aggregations of p-tau as neurofibrillary tangles (NFTs) in cell soma, and neuropil threads (NT), mainly in dendritic compartments and, to a lesser degree, in the axonal domain. These changes are accompanied by early synaptic loss, activated microglia, mitochondrial dysfunction causing energy loss, neuroinflammation, neurovascular dysfunction, disruption of the blood–brain barrier, neuronal loss, reactive astrogliosis, and brain atrophy (DeTure and Dickson 2019; Jellinger 2020; Trejo-Lopez et al. 2021). Clinical diagnosis of AD, according to the recommendations of the International Working Group, is to be restricted to people with positive biomarkers and specific AD phenotypes (Dubois et al. 2021), but despite the advent of more specific neuroimaging and reliable biomarkers, the final diagnosis of AD rests with postmortem neuropathology, using the updated National Institute on Aging/Alzheimer's Association (NIA/AA) "ABC" criteria (Montine et al. 2012). This score for AD neuropathological changes (ADNC) combines "A" for the phase of amyloid plaques (Thal et al. 2002), "B" for the NFT stages (Braak and Braak 1991), and "C" for the CERAD neuritic plaque score, which describes the density of neuritic plaques in certain key regions in the neocortex (Mirra et al. 1993). From this combination, it gives a likelihood for the degree of ADNC in an individual case. Table 1 shows how each of the three scores are transformed to state the level of ADNC on a four-tiered scale (non, low, intermediate, and high). Thus, the entire process of the neuropathological diagnosis of AD can be followed along the pathways shown in Fig. 1. Standard metrics for tangles and neuritic plaques are usually semi-quantitative (Hyman et al. 2012; Mirra et al. 1993; Montine et al. 2012) and, according to the BrainNet Europe consortium, good agreement can be reached in the diagnosis only when the lesions are substantial, e.g., when having reached isocortical structures (Braak stage V–VI with absolute agreement 91%), while for mild lesions the agreement was poorer (Braak stage I–II, agreement 50%) (Alafuzoff et al. 2008), thereby limiting the ability to make accurate correlation of antemortem cognitive status and morphological findings (Jellinger 2011; Nelson et al. 2012). These changes, which involve brain regions and neuronal cell types in a characteristic pattern as a result of selective cellular and regional vulnerability to pathological proteins and their spread through the brain (Fornari et al. 2020; Mattsson et al. 2016; Mrdjen et al. 2019), present clinically as progressive decline of cognition and other brain functions, including non-cognitive, behavioral and psychological symptoms, like

Table 1 ABC criteria for the diagnosis of Alzheimer's disease-related pathology. Modified from (Montine et al. 2012)

Level of AD neuropathologic change						
Thal phase for Aβ plaques	A	B			C	*CERAD*
		0 or 1	2	3		
0	0	Not	Not	Not	0	*neg*
1 or 2	1	Low	Low	Low	0 or 1	*neg or A*
1 or 2	1	Low	Intermediate	Intermediate	2 or 3	*B or C*
3	2	Low	Intermediate	Intermediate	any C	*neg or A to C*
4 or 5	3	Low	Intermediate	Intermediate	0 or 1	*neg or A*
4 or 5	3	Low	Intermediate	High	2 or 3	*B or C*
		Braak 0-II	*Braak III-IV*	*Braak V-VI*		

The level of AD neuropathologic change is determined by assessing A, B and C scores. A scores are related to phases of Aβ deposition (first column), B scores to neurofibrillary Braak stages (bottom row) and C scores to CERAD stages (last column). Superimposed on the AD classification are criteria for "definite PART" (yellow) and "possible PART" (blue) based on the same information

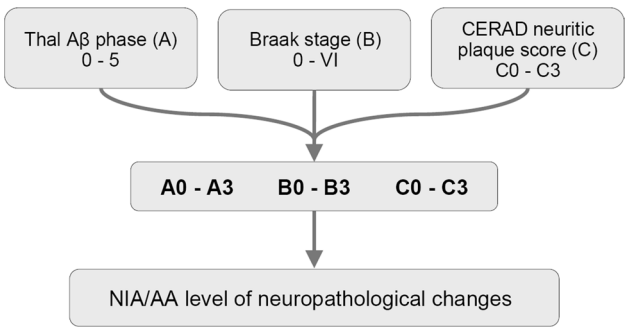

Fig. 1 Pathway of the combination of different pathological features that allows a classification of ADNC according to the NIA-AA guidelines (Jellinger 2020)

agitation, anxiety, depression, apathy, delusions, sleep and appetite changes (Casanova et al. 2011; Cerejeira et al. 2012; Gottesman and Stern 2019). Neuropsychiatric symptoms such as agitation, aggression, psychosis and activity disturbances increase as the dementia progresses, while affective symptoms (anxiety, depressive symptoms) remain stable throughout the cognitive spectrum, except for an increase in depression-dementia score in severe dementia (Wiels et al. 2021). Neuropsychiatric and cognitive symptoms are both prevalent across the Alzheimer clinical spectrum, but show different evolution during the course of disease. Cognitive function shows a uniform gradual decline, while large intraindividual heterogeneity of neuropsychiatric symptoms was seen over time across all AD groups (Eikelboom et al. 2021). These symptoms have been linked to multiple areas of neurodegeneration, including frontal and/or limbic regions as well as involvement of brainstem areas (serotonergic dorsal raphe nucleus, noradrenergic locus ceruleus), which may be early affected in AD (Grinberg et al. 2009; Matchett et al. 2021; Simic et al. 2009). However, not all persons who meet neuropathological criteria for AD exhibit cognitive impairment, and new criteria recognize the presence of preclinical pathology (Mehta and Schneider 2021). More detailed approaches for assessing comorbid conditions, such as Lewy and TDP-43 pathologies, vascular brain injury, and others, that frequently co-exist with ADNC and can complicate the pathological diagnosis, have also been considered (Montine et al. 2012). Current practice used in the AD Centers Program achieved an excellent agreement for the revised NIA/AA guidelines for the severity score for ADNC and, together with the National Alzheimer's Coordinating Center (NACC) database offers a robust and rapid method to evaluate newly identified conditions and provides carefully curated neuropathological information (Besser et al. 2018; Mock et al. 2020). Meta-analysis of 20 (out of 1189) studies to distinguish autopsy-verified AD from other dementias or healthy controls showed a sensitivity of 85.4% (95% CI 80.8–90) and a specificity of 77.7% (95% CI 70.2–85.1). Values were higher for neuroimaging procedures and slightly lower for cerebrospinal fluid (CSF) biomarkers, while the combination of both resulted in higher values (Plassman et al. 2006). These data are related to two factors: (1) the various subtypes or variants of AD, as described later, and (2) the high frequency of comorbidities in elderly persons that may cause difficulties in the clinical diagnosis of AD.

AD, a mixed proteinopathy (Aβ, tau, TDP-43, and others), is increasingly recognized as a pathologically heterogeneous, multifactorial and biologically multilayered disorder, currently referred to as the Alzheimer continuum (Jack et al. 2019), with several pathobiological phenotypes and various co-pathologies (Ferreira et al. 2020; Mehta and Schneider 2021). There are growing genetic, transcriptional, and proteomic data pointing to the complexity of AD pathogenesis, indicating that multiple distinct pathways can drive AD pathology (Wisniewski and Drummond 2019). Its variability in age and clinical presentation is well known, such as the

differences between early-onset AD (EOAD) and the more common late-onset AD (LOAD), both showing a different burden of ADNC, with significant heterogeneity in cognitive presentation and patterns of atrophy and hypometabolism (Phillips et al. 2019). Individuals with early AD show heterogeneity in disease progression, which increases when stratifying on risk factors associated with progression (Jutten et al. 2021). EOAD is associated with greater likelihood with an atypical, non-memory-dominant clinical presentation, including visual, language, executive, behavioral or motor dysfunctions (Graff-Radford et al. 2021), especially in the absence of APOE ε4, but it has faster cognitive and functional decline than LOAD, regardless of the APOE genotype (Smirnov et al. 2021), although APOE genotype varies by age at onset and clinical phenotype, highlighting the heterogenic nature of AD (Whitwell et al. 2021). Clustering analysis identified two clusters of patients in an EOAD cohort: cluster 1 had a predominant memory impairment and more frequent APOE ε4 allele; cluster 2 showed faster cognitive and functional decline and more severe posterior brain abnormalities (Pollet et al. 2021).

Clinicopathological features of AD variants

The main clinical phenotype of AD is the amnestic type targeting episodic memory, but the clinical spectrum of AD extends well beyond the classical amnestic-predominant syndrome (Villain and Dubois 2019). With the new definition of AD as a biological spectrum, using the NIA/AA research framework (Jack et al. 2019), it is now possible to review the different pathophysiologically defined subtypes of AD (Ferreira et al. 2020). Neuropathological criteria align with revised clinical framework for considering ADNC in living individuals according to a biologically based categorization termed "ATN" (Jack et al. 2019), which uses flexible combinations of in vivo biomarkers for Aβ deposition (A), tau pathology (T), and neurodegeneration (N). They include CSF or plasma biomarkers, positron emission tomography (PET), and functional and structural magnetic resonance imaging (MRI). The biomarker profiles and categories of the Alzheimer continuum referring to ADNC have been summarized recently (Jellinger 2020). The risk of progressive cognitive deterioration differs considerably between the various phenotypes: A−N− < A+N− < A+T−N+ < A+T+N+, the A+T−N+ cases with worse prognosis than the negative (A−T−N−) ones (Knopman et al. 2018). Some contributions are associated with preclinical AD (A+T+N−), symptomatic stages (A+T+N+), or non-AD diseases (A−T±N+) (Jack et al. 2018b). Several main diagnostic pathways with distinct biomarker sequences have been proposed. Neuroimaging can track neurodegeneration and other sources of network impairments, metabolomics provides a molecular snapshot that is sensitive to ongoing pathological processes, and genomics characterizes genetic risk factors representing key pathways associated with AD (Badhwar et al. 2020). In addition to amyloid and tau PET as well as $^{(18)F}$FDG-PET assessing glucose metabolism, emerging biomarkers able to measure synapse injury and loss in the brain are placed in different positions in the order of diagnostic evaluations, depending on clinical presentation (Chételat et al. 2020; Colom-Cadena et al. 2020; Dronse et al. 2017; Hanna Al-Shaikh et al. 2020). Comparison of the diagnostic accuracy of PIB (amyloid) PET versus 18F-FDG-PET in a series of autopsy-confirmed dementia cases revealed a higher sensibility of PIB-PET for intermediate-high ADNC, with similar specificity. When both modalities were congruent, sensibility and specificity approached 100% (Lesman-Segev et al. 2021). A recent study demonstrated that tau-PET is a promising prognostic marker in preclinical/prodromal stages of AD (Ossenkoppele et al. 2021) and can be used to identify the density and distribution of AD-type tau pathology, supporting a neuropathological diagnosis of AD (Fleisher et al. 2020).

A seminal clinicopathological study distinguished three AD subtypes based on postmortem NFT density: typical AD (tAD) with balanced NFT counts in the neocortex and hippocampus (75%), hippocampal-sparing (HcSP) forms with predominant involvement of association cortices (11%), and a limbic-predominant (LP) type with predominant involvement of the hippocampus (14%) (Murray et al. 2011). They corresponded to different clinical phenotypes with different ages at onset and progression rates: HcSP patients had earlier age at disease onset, higher proportion of men, and more rapid disease progression than tAD, while LP-AD patients were older at onset, involved more women, and progressed more slowly than the other groups. The disease duration of LP-AD and tAD cases was similar, age at death for LP-AD was highest and for HcSP forms lowest, which was coherent with the possible contribution of TDP-43 pathology, hippocampal sclerosis (HS) and the MAPT (microtubule-associated protein tau) H1H1 genotype to LP-AD, factors related to atrophy related to temporal lobe, older age and slower disease progression. APOE ε4 carriers more frequently had LP-AD and tAD than HcSP-AD in noncarriers, suggesting that APOE-negativity may increase resistance of the hippocampus against tau pathology (Mattsson et al. 2018). Vascular co-pathology was highest in LP-AD and lowest in HcSP-AD, while Lewy co-pathology was lowest in the latter subtype. These data were largely confirmed by a personal study of 933 autopsy cases of AD, all with Braak NFT stage > 4, although tAD was slightly more frequent than in the Mayo series (82.5 vs 75%) (Jellinger 2012). In both series, age at disease onset and death was significantly higher in LP-AD than in tAD ($p < 0.01$) and lower in HcSP-AD (Charil et al. 2019). While the final Mini Mental State

Examination (MMSE) scores in the Mayo series were lowest in HcSP-AD, in the Vienna series they were lowest in tAD. Among co-pathologies, cerebrovascular lesions in our cohort were most frequent in LP-AD and Lewy pathology in HcSP-AD, but slightly less frequent than in the Mayo series. Minimal AD was not considered in both series.

292 participants with autopsy-confirmed AD from the Religious Orders Study and Memory and Aging Project were categorized by neuropathological subtype based on regional NFT counts. There were 20% LP-AD, 8% HcSP-AD, and 73% tAD. People with HpSp-AD declined rapidly, but might not have a memory-sparing syndrome. Compared to tAD, they performed significantly worse in all cognitive domains and declined faster in memory, language, and globally, but did not have relatively preserved memory performance (Uretsky et al. 2021).

The AD subgroups, based on the distribution of tau pathology and corresponding brain atrophy have also been identified by neuroimaging studies using structural MRI (Byun et al. 2015; Park et al. 2017; Risacher et al. 2017; Sintini et al. 2020; Zhang et al. 2021b). Most severe medial-temporal atrophy was seen in LP-AD > tAD > HcSP-AD, and most severe cortical atrophy in HcSP-AD > tAD > LP-AD. tAD and non-amnestic forms had a significantly higher ratio of hippocampal to cortical volumes than those with an amnestic presentation (Whitwell et al. 2012). Recent MRI studies consistently identified four categories of brain atrophy: both hippocampal and neocortical forms, hippocampal only and no or minor gray matter atrophy (minimal atrophy AD/MA-AD), which shows comparable clinical severity (Dong et al. 2017; Ferreira et al. 2019; Oppedal et al. 2019; Poulakis et al. 2018), while others showed diffuse atrophy (32.2%), bilateral parietal, frontal and temporal atrophy (occipital sparing; 29.2%), left temporal dominant (22.4%), and MA-AD (16.1%) (Zhang et al. 2021a). Compared with the other groups, MA-AD showed an intermediate age at onset and a slower rate of disease progression. However, despite absence of significant brain atrophy, this group, due to positive AD CSF biomarker levels (increased p-tau and decreased Aβ), fulfilled the diagnostic criteria for AD, which was concordant with other studies (Hwang et al. 2015; Noh et al. 2014; Shiino et al. 2006). The MA-AD subtype was associated with an increased risk of developing clinical AD over time (Planche et al. 2019).

In prodromal AD, also four atrophy patterns were identified: (1) largely normal neuroanatomical profile with least abnormal cognitive and CBS biomarker profiles and slowest clinical progression; (2) classical AD with fastest clinical progression; (3) diffuse pattern of atrophy, less pronounced in medial-temporal lobe and greater executive impairment; (4) notable focal involvement of medial-temporal lobe and slow steady progression (Dong et al. 2017). Another study of prodromal AD using structural MRI identified the following four atrophy types: (1) medial-temporal predominant atrophy with worst memory and language function; (2) parieto-occipital atrophy with poor executive/attention and visuospatial functioning; (3) mild atrophy with best cognitive performance and language; (4) diffuse cortical atrophy with intermediate cognitive functions. The medial-temporal subtype showed fastest decline in memory and language, the parieto-occipital one declined fastest in the executive/attention domain and the diffuse subtype in visuospatial functioning, while the mild subtype showed intermediate decline in all subtypes (Ten Kate et al. 2018). FDG-PET data identified only three main hypometabolic AD subtypes: (1) typical AD (48.6%), showing classical posterior temporal-parietal patterns; (2) "limbic predominant" (44.6%), characterized by old age and a memory-predominant cognitive profile; and (3) a relatively rare "cortical-predominant" subtype (6.8%), characterized by younger age and more severe executive dysfunction (Levin et al. 2021).

A study using MRI, tau PET and amyloid PET also distinguished three subtypes of AD: medial temporal dominant (53%), parietal dominant (23%), and diffuse (24%), although Aβ deposition did not differ across the subtypes (Jeon et al. 2019), suggesting a typical pattern of tau spread with NFTs developing in the entorhinal cortex and then progressing to the association cortices. The MA-AD type shows the earliest presentation of the disease, which progresses via LP-AD finally to typical AD (Fig. 2).

According to studies on the cognitive relevance of atrophy subtypes in 2083 patients with mild cognitive impairment (MCI), typical/diffuse brain atrophy was associated with faster cognitive decline and higher risk of developing AD over time; HcSP and LP atrophy were also associated with incidental dementia with faster decline in the L-P atrophy group. DLB was more frequent in the HcSP- and minimal/no atrophy group (Planche et al. 2021). LP-AD and MA-AD subtypes show A+T−N− or A+T−N+ profiles (Cedres et al. 2020). Four tau atrophy subtypes were distinguished: medio-temporal predominant, LP, diffuse, and MA-AD. The medio-temporal predominant and diffuse subtypes showed intra-network connectivity reduction in the default-mode visual and limbic network and pronounced reduction of "global efficiency"; LP-AD showed only marginal global network failure, while MA-AD, in contrast, showed limited impairment in cognitive scores but prominent global network failure (Rauchmann et al. 2021). Recent studies in Aβ-negative and Aβ-positive individuals, all cognitively unimpaired, with and without MCI suggested that tau pathology may affect memory performance in cognitively unimpaired individuals via reduced functional connectivity in critical medial temporal lobe-cortical networks, while memory impairment in patients with MCI was associated with posterior hippocampal atrophy (Berron et al. 2021).

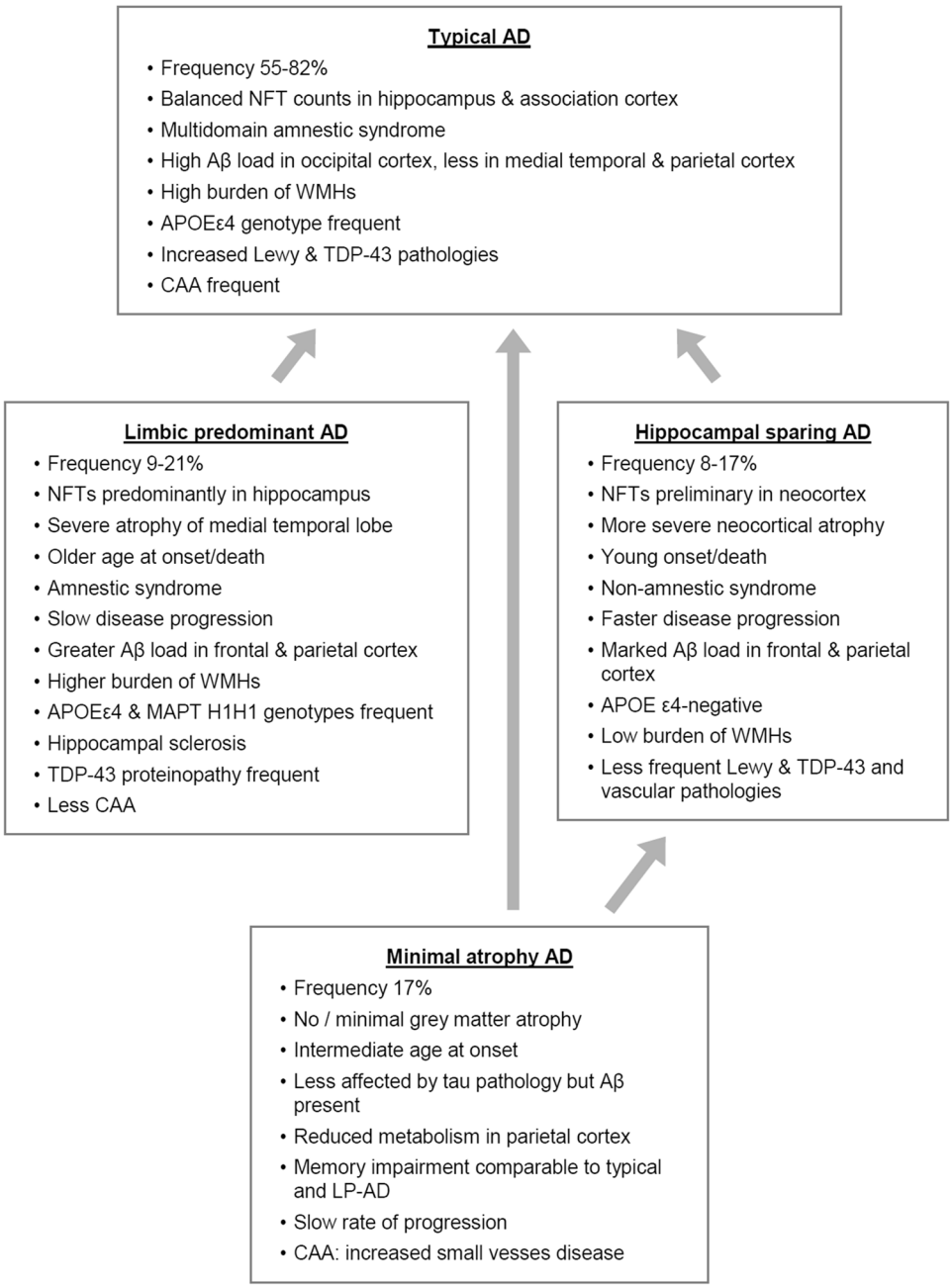

Fig. 2 Main factors and characteristics of the four major subtypes of AD. *AD* Alzheimer's disease, *NFT* neurofibrillary tangle, *WMH* white matter hyperintensity, *CAA* cerebral amyloid angiopathy, *EOAD* early-onset Alzheimer's disease, *LOAD* late-onset Alzheimer's disease, *LP-AD* limbic-predominant Alzheimer's disease (Jellinger 2020)

Tau PET studies in 260 Aβ-positive patients with MCI or dementia revealed the highest tau load in HcSP-AD and tAD, while LP patients showed significantly higher entorhinal tau load (Ossenkoppele et al. 2020), indicating that tau pathology is closely related to neurodegeneration (Das et al. 2021; Iaccarino et al. 2017; Tetzloff et al. 2018). They can significantly interrupt key brain networks, which could induce symptoms in the absence of overt cortical atrophy in the medial temporal lobe in MA-AD that shows memory impairment comparable to LP-AD and tAD (Ferreira et al. 2017, 2019; Risacher et al. 2017).

Distinct patterns of network destruction, which parallel the NFT (Braak stage V) and atrophy pattern of the four AD subtypes, have been documented (Ferreira et al. 2019), indicating that disruption of the default network is a consistent damage in heterogeneous AD groups (Byun et al. 2015; Varol et al. 2017). There are associated mechanisms underlying large-scale network disruption linking known molecular biomarkers and phenotypic variations in the AD spectrum (Wang et al. 2021). Amyloid is a partial mediator of the relationship between functional network failure and tau deposition in functionally connected brain regions, causing a cascading network failure in AD. Younger age

of disease onset was associated with 'non-Braak-like' patterns of tau, suggesting an association with atypical clinical phenotypes (Jones et al. 2017). There is a close relationship between gray matter network disruptions and tau pathology in individuals with abnormal amyloid, which may reflect a reduced communication between neighboring brain areas and an altered ability to integrate information from distributed brain regions with tau pathology, indicative of a more random network topology across different AD stages (Pelkmans et al. 2021).

Investigation of associations of ^{18}F-florbetapir (FBP) retention in the white matter with MRI-based markers of white matter degeneration AD, clinical progression, and fluid biomarkers showed that FBP retention in the white matter was associated with large-caliber axon degeneration. FBP uptake in normal-appearing white matter predicted clinical decline in preclinical or prodromal AD. Demyelination levels progressed across the AD continuum and were associated with clinical progression at early stages, suggesting that this process might be a relevant degenerative feature in the disease course (Moscoso et al. 2021). A meta-analysis of 24 studies calculated the pooled frequency of the four AD subtypes. tAD, characterized by tau pathology and atrophy of both hippocampus and association cortex, was most frequent with a pooled frequency of 55%; LP-AD, HcSP-AD and MA-AD had pooled frequencies of 21, 17 and 15%, respectively (Ferreira et al. 2020). These data depended on the algorithm used for biological and nonbiological subtyping, such as age at onset, disease duration, education years, MMSE, clinical dementia rating, APOE status, and CSF biomarkers.

These and other findings support the distinct subtype hypothesis, with pathology spreading through the brain in a different manner in these subtypes, as opposed to the staging hypothesis of brain pathology (Ferreira et al. 2019; Murray et al. 2011; Zhang et al. 2016). The assembly of mixtures of Aβ subtypes into different Aβ seeds leads to the formation of distinct subtypes having distinct physiochemical and biological properties which result in the generation of distinct AD molecular subgroups (Di Fede et al. 2018). Several studies suggest that conformational diversity of misfolded Aβ is a leading factor for clinical variability in AD, supporting the notion that AD subtypes are encoded in disease-associated Aβ-sheet heterogeneities (Confer et al. 2021; Duran-Aniotz et al. 2021). Moreover, certain types of Aβ aggregates exhibit key hallmarks of prion strains including divergent biochemical attributes and the ability to induce distinct pathological phenotypes when intracerebrally injected into mouse models. The evidence demonstrates that Aβ can assemble into distinct strains of aggregates and how such strains may be primary drivers of the phenotypic heterogeneity in AD (Lau et al. 2021). Amyloid spatially exceeds tau and neurodegeneration, with individual heterogeneities. Molecular pathology and neurodegeneration usually show progressive overlap along the AD course, indicating shared vulnerabilities or synergistic toxic mechanisms (Iaccarino et al. 2021). Although Aβ and tau might have differential downstream effects on synaptic and axonal function in a stage-dependent matter, recent findings suggest that amyloid-related changes occur first, followed by tau-related axonal degeneration (Pereira et al. 2021).

In PSEN1-carriers, altered γ-secretase activity and resulting Aβ accumulation are prerequisites for EOAD, However, tau hyperphosphorylation pattern, and its degradation by the proteasome, drastically influences disease onset in individuals with otherwise similar Aβ pathology, hinting towards a multifactorial model of familial AD (Sepulveda-Falla et al. 2021). Autosomal dominant AD (AD-AD), present in a younger population, is more likely to manifest with non-amnestic features in the prodromal phase or neurological signs, such as seizures or paralysis. The large variety of mutations associated with AD-AD explains the wide range of phenotypes, while in LOAD they are explained by age-associated co-morbidities (Rujeedawa et al. 2021). In sporadic AD, a wide range of heterogeneity, also influenced by tau pathology, has been identified (Dujardin et al. 2020; Murray et al. 2015). Cortical NFT burden was higher among atypical clinical variants relative to the amnestic syndrome.

Other recent studies evaluating cortical thickness and tau-PET in a cohort of cognitively impaired, amyloid-positive (A+) individuals revealed a T–N mismatch correlated with several underlying factors such as age and burden of WMH lesions. These data also indicate that tau-atrophy variability represents different biologically relevant subtypes, thus documenting the phenotypic heterogeneity of AD (Das et al. 2021). The propensity of a tau monomer to adopt distinct conformations appears to be linked to defined local motifs that expose different patterns of amyloidogenic amino acid sequences (Vaquer-Alicea et al. 2021). However, the molecular link between Aβ plaques and NFTs is still unclear. Recent studies have shown that PAX6 (a transcription factor essential for eye and brain development and increased in AD brain) signaling pathways plays a key role between Aβ toxicity and hyperphosphorylation (Zhang et al. 2021b).

HcSP-AD cases showed the highest levels of education, while MA-AD patients had the lowest, suggesting that high education may be one of the factors protecting the hippocampus and contributing to the fact that LP-AD may be unmasked and may contribute more to its clinical manifestation. Based on the cognitive reserve theory suggesting that education is beneficial for the brain by forming more pathology-resistant networks, it may act as surrogate for or act in synergy with cognitive or social engagement (Giovacchini et al. 2019; Stern 2012). Among Aβ-positive individuals, greater cognitive reserve relates to attenuated clinical progression in preclinical stages of AD, but accelerated

cognitive decline after the onset of dementia (van Loenhoud et al. 2019). More severe neurodegeneration and more aggressive disease progression in HcSP-AD (Byun et al. 2015; Murray et al. 2011; Na et al. 2016) and the absence of hippocampal atrophy in MA-AD, which has a lower level of reserve, support this hypothesis (Ferreira et al. 2020).

Higher functional MRI-assessed system segregation was associated with less decrement in global cognition and episodic memory per unit increase of temporal lobe tau PET, indicating that higher segregation of functional connections into distinct large-scale networks supports cognitive resilience in AD (Ewers et al. 2021).The AD-resilient group (pathological AD without cognitive impairment) showed preserved densities of synaptophysin-positive presynaptic terminals and dendritic spines and increased densities of GFAP-positive astrocytes compared to the AD-dementia group and normal controls (Arnold et al. 2013). Hence, greater amounts of presynaptic proteins and distinct protein–protein interactions may be components of cognitive reserve reducing the risk of dementia with aging (Honer et al. 2012). Data from a large population-based sample of older adults discovered genetic factors associated with differential cognitive resilience to brain amyloidosis determined by PET, supporting the hypothesis that genetic heterogeneity is one of the factors that explains differential cognitive resilience to brain amyloidosis (Ramanan et al. 2021).

All AD subtypes show reduced basal forebrain volumes: LP-AD had the fastest atrophy rate, while MS-AD did not show any significant volume decline over time; the atrophy rates of the hippocampus and precuneus also differed among subtypes (Machado et al. 2020). NFT accumulation in the nucleus basalis of Meynert (NBM) was lowest in HcSP-AD, higher in tAD, and highest in LP-AD. Both changes may underlie more severe cholinergic deficits in EOAD individuals, in particular in patients with HcSP-AD (Hanna Al-Shaikh et al. 2020).

In conclusion, AD is heterogenous in each aspect, such as amyloid composition, tau distribution, relation between Aβ and tau, resulting brain atrophy, clinical symptoms, and genetic background. Thus, it is impossible to explain AD with a single pathological process, but the pathogenic factors for its heterogeneity need further elucidation.

Rapidly progressive Alzheimer's disease

Among AD subtypes, a rapidly progressive form (rpAD), is characterized by rapidly progressive cognitive decline and/or short disease duration, and the possible occurrence of early focal neurologic signs (Schmidt et al. 2010, 2011). Early impairment in executive functions or language, motor disturbances, such as myoclonus (66–75%), gait impairment (66–887%), pyramidal (53–6%) or extrapyramidal (54%) signs, visual signs, such as hallucinations (44–62%), or psychiatric symptoms, frequently occurred in rpAD, either alone or in combination (Schmidt et al. 2012; Tosto et al. 2015). The mean duration of disease is between 2 and 3 years. Patients are younger at the time of death (60.0 vs 81.8 years) (Pillai et al. 2018).

Individuals with rpAD have more severe pathology, more comorbidities and lower baseline neuropsychology test scores of language and executive functions (Nance et al. 2019). Due to the rapid course of disease, rpAD mimics Creutzfeldt–Jakob disease (CJD), and represents a relatively frequent alternative diagnosis among cases referred to as possible or probable CJD to surveillance centers for prion diseases worldwide (Abu-Rumeileh et al. 2018a). The early clinical differential diagnosis between these two disorders can be challenging given the partial overlap in clinical features, although CSF biomarkers are within the range expected for classical AD except for protein 14-3-3, which was detectable in 43% of rpAD cases (Schmidt et al. 2012), whereas CSF neurofilament light chain protein (NfL) performs better than t-tau in the discrimination between rpAD and prion disease (Abu-Rumeileh et al. 2018b). Although rpAD and tAD seem to share the neuropathological core features, recent evidence suggests that a distinctive molecular signature involving the structure of Aβ aggregates and the proteomic landscape of amyloid plaques may distinguish rpAD from tAD. Studies using solid-state nuclear magnetic resonance measurements demonstrated a specific Aβ-40 fibril structure in t-AD and posterior cortical atrophy variant AD, whereas in rpAD they exhibited a significantly greater proportion of additional structures indicating differences in Aβ structure between different subtypes of AD (Qiang et al. 2017). Plaques from rpAD patients were abundant in synaptic proteins, in particular these involved in synaptic vesicle release, indicating the importance of synaptic dysfunction in accelerated plaque development in rpAD (Drummond et al. 2017). Recent proteomic studies indicated that the disregulation and dislocation factor proline and glutamine-rich protein (ASPQ), the subsequent DNA-related anomalies and aberrant function of TIA-A-positive stress granules in association with pathological tau represent a critical pathway which contributes to rapid progression of AD (Younas et al. 2020). Studies using conformation-dependent immunoassay (CDI) revealed distinct special attributes of diffuse and cored plaques in the temporal cortex of rapidly and slowly progressive AD, indicating a major conformational diversity of Aβ accumulating in the neocortex, with the most notable differences in the temporal cortex of rpAD (Liu et al. 2021), while spectroanalytic studies of Aβ proteoforms extracted from brain tissue detected the presence of highly hydrophobic Aβ seed in rpAD brains that seeded secretion at a slowed pace in comparison to t tAD (Noor et al. 2021). Previous studies showed a significant 1.2 decrease of di-glycosylated

Table 2 Hypothetical correlation between PART and AD (From Jellinger et al. 2015)

	No AD/no PART	Asymptomatic PART	p-preAD	NFT-predominant dementia (symptomatic PART)	Symptomatic AD
Aβ phase	0	0–2	1–5	0–2	3–5
Braak-NFT-stage	0	I–IV	0–VI	III, IV	III–VI
Degree of AD pathology	No AD	No or low AD	Low–high AD	No AD or low	Intermediate–high AD
Clinical signs of dementia or cognitive decline	No	No	No	Yes	Yes

PART vs. AD: symptomatic PART and symptomatic AD can be distinguished by Aβ pathology. Asymptomatic PART and p-preAD overlap in those cases with initial Aβ pathology (Aβ phases 1, 2)

prion protein (PrP) isoforms in rpAD, suggesting distinct PrP involvement in association with the altered PrP interacting protein in rpAD (Zafar et al. 2017). Involvement of high-density oligomers of PrP were isolated in frontal cortex tissues from rpAD brains that are suggested to be involved in destabilization of the neuronal actin/tubulin infrastructure, as a contributing factor for the rapid progression of rpAD (Shafiq et al. 2021).

Specific dementia phenotypes (PART and others)

The current guidelines for the pathological diagnosis of AD only consider the classical "plaque and tangle" phenotype, but not other forms such as the "plaque only but without tangle formation predominant" type with abundant amyloid or the "little or no tau pathology" type limited to the hippocampus and abnormal p-tau pathology in neocortical pyramidal cells. This latter type observed in 3–8% of demented subjects over age 85 years (Tiraboschi et al. 2004) represents a specific type of dementia with Lewy bodies (DLB-AD) (Hansen et al. 1990). Another phenotype is the recently described "primary age-related tauopathy" (PART), originally described as NFT-predominant dementia (Jellinger and Attems 2007), predominantly involving people aged 85 years and associated with MCI. It is morphologically characterized by tau pathology restricted to the medial temporal lobe (Braak NFT stages 0–4), relative absence of amyloid (Thal Aβ phases 0–2), and total absence of neuritic and rare CAA (Josephs et al. 2017), while NFT changes in PART with both 3 and 4 repeat (3R and 4R) tau isoforms are identical to those in tAD (Jellinger and Attems 2007). MAPT H1H1 genotype frequency is high in both PART and LP-AD and similar to tAD, while APOE ε4 is rare in PART (Bancher et al. 1997). In PART, the lack of Aβ oligomers is suggested to be responsible for lesser tau aggregation, lower Braak NFT stages, and less cognitive impairment, since they have been shown to potentiate tau aggregation by promoting tau seed uptake (Shin et al. 2019). The pattern of hippocampal tau pathology differs significantly between PART and AD (Jellinger 2018; Zhang et al. 2020). Whereas tau pathology in tAD usually displays relative sparing of the hippocampal subregion CA2 until later stages, early involvement and greater NFT intensity in this subregion than in CA1 has been demonstrated in PART that also frequently shows significant asymmetry of hippocampal tau pathology (Walker et al. 2021a, b). Positive correlations were reported in PART between the Braak NFT stage and TDP-43 stage and density (Zhang et al. 2019). AD and putative PART cases exhibited similar patterns of p-tau seeding activity that anticipated histopathology across all NFT stages. This suggests that pathological tau seeding activity begins in the transentorhinal/entorhinal region rather than in the locus ceruleus (Kaufman et al. 2018). PART is considered either a prodromal form or a subtype of AD (Jellinger et al. 2015) or a distinct tauopathic entity separate from tAD (Hickman et al. 2020) (Table 2). In contrast to tAD showing a slight decrease after age 85, the frequency of PART increases later (Jellinger and Attems 2010).

Analysis of PET data suggested that tau pathology is common among individuals without significant amyloidosis, since 45% of a sample of the Alzheimer's Disease Neuroimaging Initiative (ADNI) were categorized A−/T+ and only 6% as A+/T−, contrary to the amyloid cascade and ATN frameworks. A rather poor cognitive performance in the A−/T+ group and the association of Braak NFT I/II levels and cognition in these groups indicated that tau pathology is confined to the medial temporal lobe, and the absence of Aβ could be part of the AD developmental cascade rather than a feature of aging with no or only minor cognitive deficits, i.e., PART (Weigand et al. 2020). Mesial temporal tau in Aβ-negative, cognitively normal individuals, which are likely PART, is related to worse cognitive performance and greater neocortical tau load (Groot et al. 2021). Differentiating PART from tAD remains a diagnostic challenge (Nelson et al. 2016). Biomarker and neuroimaging studies will be important to define PART antemortem and to follow its natural history (Hickman et al. 2020). LP-AD cases shared some morphological features with PART (Crary et al. 2014), although later studies revealed significant differences versus LP-AD, emphasizing that PART may not be a variant of AD

(Janocko et al. 2012; Jellinger 2016), whereas others suggested that PART *is* a part of AD (Duyckaerts et al. 2015).

Another recently described disease entity mainly involving elderly people (age > 75 years), the limbic-predominant age-related TDP-43 encephalopathy (LATE), is associated with an amnestic dementia syndrome that may mimic AD (Besser et al. 2020; Nelson et al. 2019). It shows pathogenic mechanisms of both frontotemporal lobar degeneration with TDP-43 (FTLD-TDP) and AD, but there are different molecular patterns of TDP-43 pathology in various clinical phenotypes with a higher chance of frontotemporal dementia-like symptoms in AD + full-length TDP-43 cases (Tomé et al. 2020).

LATE-NC is predominantly age-related TDP-43 encephalopathy without other neuropathological changes. The recommended grading was divided into three: (1) amygdala only, (2) hippocampus, (3) middle frontal cortex. When compared with FTLD-TDP, it has a later age of onset and limbic predominance of pathological changes (Nelson et al. 2011). Clinically, LATE-NC was more associated with an amnestic syndrome rather than the behavioral aphasic syndrome typical for FTLD-TDP. Like AD, this entity correlated with the presence of APOE ε4 allele (Robinson et al. 2018; Yang et al. 2018). When comparing "pure" LATE-NC with "pure" AD, regarding neuropathological changes, those with "pure" LATE-NC showed a more gradual clinical decline (Murray et al. 2014). It is not uncommon that AD pathology occurs together with Lewy and TDP-43 pathologies causing neuropsychiatric syndromes (Bayram et al. 2019). Recent findings suggest that neocortical Lewy bodies (LBs) are associated with LATE-NC, specifically in the younger old and in women. Limbic/neocortical type LBs have additive effects on cognitive function in AD (Agrawal et al. 2021). Recent studies indicated that in most cases LATE-neuropathological changes (LATE-NC) and FTLD-TDP can be differentiated by applying single neuropathological criteria, e.g. the severity of cortical TDP-43 inclusions (Robinson et al. 2020). However, reliable biomarkers for antemortem diagnosis of LATE are currently not available (Teylan et al. 2019).

Pathobiology of other AD variants

The AD continuum shows a broad spectrum of clinical manifestations beyond the classical amnestic-predominant syndrome. Factor mixture analysis of neurocognitive changes in 230 patients with clinically diagnosed AD identified four groups: visuospatial AD, typical cognitive pattern (tAD), less impaired memory (mild AD), and non-amnestic AD with language/praxia deficits and relatively spared memory (Zangrossi et al. 2021).

The original ADNI distinguished five diagnostic clinical groups: AD ($n = 110$), late MCI ($n = 133$), early MCI ($n = 148$), significant memory concern ($n = 94$), and cognitive normal ($n = 173$) (Galili et al. 2014), while later studies of the same cohort even differentiated six clinical subtypes (Mitelpunkt et al. 2020). Another study classified more than 4000 people with LOAD into six subgroups according to their cognitive functions and genetic data, indicating that AD is not a single homogenous condition (Mukherjee et al. 2020). Based on patterns of grey matter (GM) volumes and hypometabolism, the following 4 AD subgroups were differentiated: AD-memory, AD-executive, AD-language, and AD-visuospatial. AD-memory showed mediotemporal lower GM volume and hypometabolism than all the subgroups; AD-language asymmetric GM volumes in temporal lobe (left > right), with prominent hypometabolism in lateral temporal lobe. AD-executive had lower fronto-parietal GM volumes, AD-visuospatial lower GM volumes in posterior areas and hypometabolism in parietal regions and precuneus compared to AD-memory. Thus, cognitively defined AD subgroups show specific reduction of GM volumes and hypometabolism pattern with differences in trajectories of metabolism over time (Groot et al. 2021b).

A number of non-amnestic syndromes generally referred to as atypical or focal AD have been identified (Galton et al. 2000; Lam et al. 2013). With regard to variable clinical presentation, a number of phenotypes have been determined based on consensus and accepted guidelines: besides the "typical" AD (the amnestic syndrome being more common than the non-amnestic one) (Sahoo et al. 2018), posterior cortical atrophy (PCA) (Crutch et al. 2017), showing greater NFT burden in the occipital and parietal lobes but lower in hippocampus (Levine et al. 1993), and a 4-R tauopathy clinically presenting as PCA (Jellinger et al. 2011). Higher NFT burden in the cingular gyrus and CA1 sector of hippocampus were independently associated with worsening visuospatial dysfunction, suggesting domain-specific functional consequences of regional NFT accumulation (Petersen et al. 2019). LPPA shows higher NFT density in the superior temporal gyrus but amyloid plaques similar to amnestic AD (Ahmed et al. 2012; Spinelli et al. 2017), the corticobasal syndrome subtype of AD (Di Stefano et al. 2016; McMillan et al. 2016), with atypical distribution of ADNC (a higher NFT density in the perirolandic cortices and greater neuronal loss in substantia nigra), which may contribute to parkinsonism that is uncommon in tAD (Sakae et al. 2019). Non-amnestic AD with TDP-43 pathology, showing little evidence that clinical or anatomical features are related to TDP-43 (Sahoo et al. 2018), and the rather rare behavioral variant of AD (bvAD) (Ossenkoppele et al. 2015) also showed heterogeneous distribution of ADNC (Singleton et al.

2021). It revealed temporo-parietal predominant atrophy in the Mayo series, where PCA, LPPA and bv-forms were more common in HcSP-AD than in LP and tAD (Josephs et al. 2015; Murray et al. 2011). The presence of left-sided NFT predominance and higher neocortical-to-entorhinal NFT ratio in primary progressive aphasia (PPA) establishes clinical concordance of ADNC with the aphasic phenotype, although these concordant clinicopathological relationships are not universal. PPA is a language disorder characterized by cortical atrophy, accumulation of both NFTs and hypertrophic microglia associated with lower neuron density in language-associated hemispheres targeting the language network (Ohm et al. 2021). PPA is subdivided into 3 subtypes: semantic variant (svPPA), non-fluent (nfvPPA), and logopenic variant (lvPPA). The latter progressed with broader language problems, nfvPPA to mutism, while semantic impairment was the major problem in svPPA. 83% of lvPPA were consistent with AD, while 54% of nfvPPA progressed to other tauopathies (Ulugut et al. 2021). Lobar cerebral microbleeds (CMB) in lvPPA affected temporal, frontal and parietal lobes with left side predominance, while CMB volume decreased in the left temporal area. Aberrant brain perfusion in lvPPA may be derived from brain atrophy and may involve aberrant microcirculation caused by lobar CMBs and cerebrovascular injuries (Ikeda et al. 2021). However, individual PPA cases with ADNC exist where distribution of plaques and NFTs do not account for this specific phenotype (Gefen et al. 2012).

The behavioral/dysexecutive variant of AD is a rare, atypical young-onset variant defined clinically by early impairments in executive and behavioral domains associated with multi-domain cognitive impairment. While it is hardly distinguishable from the behavioral variant of frontotemporal dementia (bvFTD) using clinical and cognitive features alone, CSF biomarkers and temporoparietal hypometabolism with relative sparing of mediotemporal (vs. amnestic), occipital (vs. visual phenotype) and left temporal (vs. language phenotype) help predict underlying pathology during life (Bergeron et al. 2020; Townley et al. 2020). Frontal variant of AD is a rare non-amnestic syndrome characterized by behavioral and/or dysexecutive impairments, mimicking bvFTD. Brain imaging showed diffuse Aβ deposition across the cerebral cortex, substantial tau pathology and hypometabolism in frontal and temporal lobes, while plasma biomarkers indicated an AD profile (Li et al. 2020; Paquin et al. 2020). PPA-AD is characterized by cortical atrophy and NFT densities concentrated in the language-dominant hemisphere. Stereological methods showed accumulation of NFTs and activated microglia associated with reduced neuronal densities, suggesting that they may collectively contribute to focal neurodegeneration characteristic of PPA-AD.

There is evidence linking different large-scale functional network abnormalities to distinct AD phenotypes: specifically, executive deficits in EO-AD link with dysfunctions of networks that support attention and executive functions. PCA, most commonly associated with loss of complex visuospatial functions, relates to the breakdown of visual and dorsal attentional circuits, while the PPA variant of AD is associated with dysfunction of the left-lateralized language network (Mesulam et al. 2021; Pini et al. 2021; Wong et al. 2019). Atypical clinical variants of AD often show a younger age at onset and fewer associations with the APOE ε4 genotype compared to typical amnestic forms (Murray et al. 2011), suggesting that APOE is a selective risk factor that increases the vulnerability of memory-related medial temporal areas, rather than language-related neocortices (Weintraub et al. 2020). Older age and APOE ε4 seem to affect expression by promoting a more medial-temporal lobe-prominent pattern of tau pathology (La Joie et al. 2021). APOE genotype contributes to heterogeneity in the rate of AD progression. Compared to APOE ε3/ε3 genotype, APOE ε2 and ε4 have opposite (slowing and accelerating, respectively) effects on the rate of cognitive decline, which are largely independent of the differential APOE allele effects on AD and co-morbid pathologies (PART and others) (Qian et al. 2021),

The pathogenic factors underlying AD subtypes are unclear and cannot be explained by Aβ pathology alone, because the distribution of Aβ PET retention is quite similar in all subtypes (Lehmann et al. 2013), with only subtle differences across phenotypes, while they are associated with differential patterns of tau pathology (La Joie et al. 2021). However, solid-state nuclear magnetic resonance measurements showed quantitative differences between Aβ-40 and Aβ-42 in the brain tissue of patients with two atypical clinical subtypes—PCA variant and a typical long duration AD—indicating that there are structural variations in Aβ fibers from clinical AD subtypes (Walker 2020). MA-AD, although Aβ positive, shows less tau pathology. Furthermore, it has been suggested that Aβ enhances tau pathology development in AD through increased tau spreading (Vergara et al. 2019), which may be accelerated via cellular prion protein (Gomes et al. 2019). The variations in sites of tau seeding between individuals could underlie differences in the clinical presentation and course of AD (Stopschinski et al. 2021). There is increasing evidence that Aβ, similar to prion protein, can assemble into distinct strains of aggregation, which may be the primary driver of the phenotypic heterogeneity of AD (Lau et al. 2021). These and other data indicate that AD "subtypes" may be linked to different tau protein modifications, suggesting that these patients may have multiple molecular drivers of an otherwise common phenotype.

A recent study using tau PET scans from 1612 individuals of the ADNI study identified four distinct spatiotemporal trajectories of tau pathology, ranging in prevalence from 18 to 33%. It replicated previously described LP and HcSP patterns, while also discovering posterior and lateral-temporal patterns resembling atypical clinical variants. These "subtypes" presented with distinct demographic and cognitive profiles and differing longitudinal outcomes. In addition, network diffusion models implied that pathology originates and spreads through distinct corticolimbic networks in the different subtypes, suggesting that variation in tau pathology is common and systematic. These and other data question whether "tAD" is a quantifiable entity, rather suggesting that several AD subtypes exist that may be influenced in their expression by genetic, cellular, developmental and other factors (Dujardin et al. 2020; Vogel et al. 2021).

Recent studies of 222 AD patients from The Religious Orders Study and Memory and Aging Project (ROSMAP) Study of molecular profiling and gene expression data, using consensus non-negative matrix factorization, identified two subtypes—synaptic and inflammatory: the synaptic type was more relevant in AD with APOE ε3/ε4 genotype, the inflammatory type more with the APOE ε3/ε3 genotype, being more prevalent in females (Zheng and Xu 2021). Molecular profiling measuring the brain levels of 25 inflammatory factors involved in neuroinflammation allowed a stratification of AD patients in three distinct "neuroinflammatory clusters". These findings strengthen the relevance of neuroinflammation in the pathogenesis of AD and that the differential involvement of neuroinflammatory molecules released by microglial cells during disease development may contribute to modulate the neuropathological changes, driving at least in part the AD phenotype diversity (Sorrentino et al. 2021). Recent proteomic studies highlight the molecular heterogeneity of AD and the relevance of neuroinflammation as major players in AD pathology (Velásquez et al. 2021).

Analysis of 1543 transcriptomes across five brain regions in two AD cohorts, using an integrative network approach, identified three major molecular subtypes of AD corresponding to different combinations of multiple dysregulated pathways, such as susceptibility to tau-mediated neurodegeneration, Aβ neuroinflammation, synaptic signaling, immune activity, mitochondrial organization, and myelination. This molecular subtyping of AD using RNA sequencing revealed novel mechanisms and targets (Neff et al. 2021). Gene expression data of 222 AD patients identified two molecular subtypes—synaptic and inflammatory: the synaptic type is characterized by disrupted synaptic vesicle priming and synaptic plasticity; the inflammatory type by disrupted IL2, interferon-α and -γ pathways. The synaptic type was more prevalent in males and the inflammatory type in females (Zheng and Xu 2021). Using CSF proteomics, three distinct pathophysiological subtypes of AD were discovered: one with neuronal hyperplasticity, a second with innate immune activation, and a third with blood–brain barrier dysfunction. These AD proteomic subtypes may already manifest in cognitively normal individuals and may predispose to AD before amyloid has reached abnormal levels (Tijms et al. 2021). This suggests that these multiple phenotypes are part of the same AD continuum (Ossenkoppele et al. 2015), which may have consequences for future personalized therapeutic approaches.

In conclusion, research into typical AD has revealed previously unrecognized neuropathological heterogeneity across the AD spectrum. Neuroimaging, genetics, biomarkers, and basic science studies provide key insights into the features that might drive selective vulnerability of differing brain networks, with potential implications for understanding typical and atypical forms of AD.

The impact of co-pathologies

The aging brain is vulnerable to a wide array of neuropathologies. AD pathology rarely occurs in isolation, while complex co-pathologies influence the clinical picture and may increase disease progression. The number of co-pathologies increases in the aging brain, causing complex mixed pathologies (Jellinger and Attems 2015; Matej et al. 2019; McAleese et al. 2021a; Power et al. 2018; Rahimi and Kovacs 2014; Robinson et al. 2021; Thomas et al. 2020; Tomé et al. 2020). However, highly prevalent co-morbidities are not restricted to the oldest-old but are common even in EOAD (Beach and Malek-Ahmadi 2021). The challenges of pathological mimics and concomitant pathologies in the neuropathological diagnosis of AD have been critically reviewed recently (King et al. 2020). The most frequent co-lesions are cerebrovascular diseases, Lewy- and TDP-43 proteinopathies (Agrawal et al. 2021; Besser et al. 2020; Boyle et al. 2021; DeTure and Dickson 2019; Schneider et al. 2007).

TDP-43 pathology was noted in particular in a very elderly subgroup of AD cases and was associated with an apparent worsening of cognitive decline (Josephs et al. 2014). A staging system was devised, where the earliest TDP-43 pathology in the context of AD was the amygdala, then entorhinal cortex and subiculum, then dentate gyrus of occipitotemporal cortex (stage 3), followed by the inferior temporal gyrus (stage 4), substantia nigra, inferior olive and midbrain tectum (stage 5), and finally, basal ganglia and middle frontal cortex (stage 6) of a different pattern and density than the typical FTLD-TDP. The different TDP-43 patterns were associated with typical AD symptoms in 80–100% of AD cases (Josephs et al. 2016; Tomé et al. 2020). A study of aged subjects (range 80–89 years) with cognitive impairments found 66% with "mixed pathology",

i.e., ADNC combined with TDP-43, α-synuclein or vascular brain lesions (Alafuzoff and Libard 2020).

In a consecutive autopsy series of 2060 elderly patients, ADNC was present in 82.9% of all demented and in 92.8% of clinically diagnosed patients, but only 33.6 and 47.6%, respectively, showed pure AD (ABC 3/3/3); atypical forms including PART (7 and 6%); additional cerebrovascular disease (CVD (24.3%), Lewy (12.5%) or other mixed pathologies. Vascular dementia accounted for 12.2 and 3.3%, respectively, while other non-AD pathologies were present in 7.2 and 3.3%, respectively (Jellinger 2006).

While a small study of demented elderly persons reported pure ADNC in only 31% and multiple pathologies in 63% (Wang et al. 2012), another one found at least one non-AD pathological diagnosis in 98% of patients with EOAD and in 100% in those with LOAD, with the number of co-pathologies predicting worse cognitive performance (Spina et al. 2021). A review of 12 clinico-pathological studies with 3,574 patients, irrespective of the clinical symptoms, reported ADNC between 19 and 67%, Lewy pathologies in 6–39%, vascular changes in 28–70%, TDP-43 proteinopathy in 19–78%, HS between 3 and 13%, and mixed pathologies between 8 and 70% (Rahimi and Kovacs 2014).

Among 447 patients with clinically probable AD, only 3.3% showed pure ADNC, 27.3% AD + CVD + other lesions, 7.6% ADNC + other degenerative lesions, and 47% AD + CVD and other neurodegenerative lesions (Kapasi et al. 2017). Neuropathological examination of 1164 deceased participants from two longitudinal clinicopathological studies provided 11 pathological including markers of AD and non-AD neurodegenerative diseases (like LATE-NC, HS, LBs, cerebrovascular lesions), most of them accounting for a large proportion in late life cognitive decline (Boyle et al. 2021). There is increasing association with LATE-NC, in younger age with LBs and increased Braak stage with CAA (Robinson et al. 2021). Among 670 aged individuals from the Brains for Dementia Research Program, more than three-quarters had multiple brain pathologies, ranging from low/intermediate levels of additional lesions (69.9%), to mixed severe pathology (7.5%), whereas only 22.7% had pure ADNC (McAleese et al. 2021a). In a data collection from the NACC assessing those at 39 NIA AD centers across the USA, 924 individuals had complete neuropathological data. 63% of individuals given the "gold standard" diagnosis of AD possessed either TDP-43 proteinopathy or CAA of sufficient severity to independently explain the majority of their cognitive impairment (Thomas et al. 2020). Aβ and/or tau burden, particularly in Braak NFT stages IV–VI, and small cerebral vessel disease may synergistically affect cognitive decline (Jang et al. 2020), and a significant interaction was found between Braak NFT stages, CAA status and cognitive decline (Malek-Ahmadi et al. 2020). Based on data from the NACC, 1854 participants with a clinical diagnosis of AD and ADNC at autopsy (confirmed AD) were studied. 204 with the clinical diagnosis of AD had no ADNC (AD-mimics), while 253 participants with negative clinical AD diagnosis had ADNC (unidentified AD). Compared to confirmed AD cases, AD mimics (FTLD, HS, cerebrovascular pathology, etc.) had less severe cognitive impairment (Gauthreaux et al. 2020).

Analysis of 522 individuals (> 50 years) from the Center for Neurodegenerative Disease Research (CNDR) autopsy and the NACC database found widespread distribution of CAA, LATE-NC and LBs that progressively accumulate alongside plaques and NFTs in AD. CAA interacted with plaques and NFTs especially in APOE ε4-positive cases, associated with higher NFT stages later in the disease course, while most LBs associated with moderate to severe plaques and NFTs (Robinson et al. 2021). Increased TDP-43 pathology in tAD and LP-AD compared to HcSP-AD (Murray et al. 2011) was due to a strong association between HS and TDP-43, but clinical presentation seemed to be driven by morphological subtypes rather than by TDP-43 pathology (Josephs et al. 2015). Among 172 autopsy-confirmed AD cases, 69% of which had typical ADNC, 31% were HcSP-AD and 36% TDP-43 positive, while there were no LP-AD cases (Sahoo et al. 2018).

Recent studies have revealed considerably different co-morbidities between EOAD and LOAD, the latter showing more frequent LATE, HS and argyrophilic grain disease (AGD), while Lewy pathology and CAA were common in both EOAD and LOAD. Thus, these co-pathologies may play an important role in the clinical phenotype of both forms, particularly in EOAD (Spina et al. 2021), although concomitant LATE in AD has shown not to be associated with increased tau or Aβ pathological burden or greater neuropsychiatric impairment (Liu et al. 2020; McAleese et al. 2020; Teipel et al. 2021). On the other hand, LATE-NC was independently associated with dementia and strongly associated with arteriolosclerosis in the oldest old (Harrison et al. 2021).

Several other pathological changes occur in the aging brain and may be associated with ADNC. AGD, a limbic predominant 4R tauopathy, with grain-like deposits in neuritic dendrites, oligodendroglial inclusions ("coiled bodies"), ramified astrocytes, and ballooned neurons in the amygdala, hippocampus and medial temporal lobes (Togo et al. 2002), has been reported in up to 25% of AD cases (Togo et al. 2002). It rarely occurs before the age of 75 years (Wurm et al. 2020). Granulovacuolar degeneration (GVD), characterized as 3–5 γm vesicles, occurs in the pyramidal neurons of the hippocampus, usually in association with NFTs. Their origin and significance are unclear. Despite the strong association between tau aggregation and GVD body formation (Wiersma et al. 2019), intracellular aggregates of proteins other than tau can also induce GVD formation, which needs

further elucidation (Wiersma et al. 2020). They correlate with NFT density, suggesting that they may represent a cellular response to neuronal damage of late-state autophagic vacuoles (Hou et al. 2018). Necrosome complex detected in granulovacuolar degeneration has been shown to be associated with neuron loss in AD (Koper et al. 2020).

Several co-morbidities may impact the integrity of cerebral white matter. In amyloid-negative amnestic type dementia, medial temporal atrophy was associated with high WMH due to greated CVD burden that may be important for development of hippocampal atrophy (Wong et al. 2019). In a recent study of 206 cases with ADNC, only 33 were without co-morbidities. White matter demyelination was more marked in AD with co-pathologies, which showed early alterations in oligodendrocytes and transcription of genes linked to myelin proteins, suggesting that oligodendrogliopathy is part of AD (Ferrer and Andrés-Benito 2020). Demyelination progresses across the AD continuum, suggesting that this pathologic process might be a relevant degenerative feature in the disease course (Moscoso et al. 2021). Recent studies indicated that anterior white matter lesions (WMLs) could be associated with both small vessel disease-associated and AD-associated cortical pathologies, while posterior WMLs may be associated with degenerative mechanisms secondary to AD pathology (McAleese et al. 2021b). Taken together, these and other recent findings highlight the relevance of multiple pathologies in the development of age-related dementias and suggest that they are "partners in crime". These concomitant pathologies may be harmful to individuals with low cognitive reserve such as patients with MA-AD. They can cause a number of challenges including the evaluation of the significance of each pathological entity in the manifestation of the clinical symptoms and the threshold of each individual pathology to cause dementia (King et al. 2020). The total burden of comorbid pathological abnormalities, rather than single lesions, is the most important cause of cognitive impairment often despite the clinical diagnosis of "only" or "pure" AD (White et al. 2016). The co-pathologies, multiple players, which may each account for so-called AD (Fig. 3), should be considered in the diagnosis and treatment of dementia in the elderly as part of an increasingly personal approach. Nevertheless, it should be borne in mind that all the additional pathologies may interact, although their mutual impact often remains unclear. Therefore, the reliability and clinical relevance of the current diagnostic criteria need better qualification and validation.

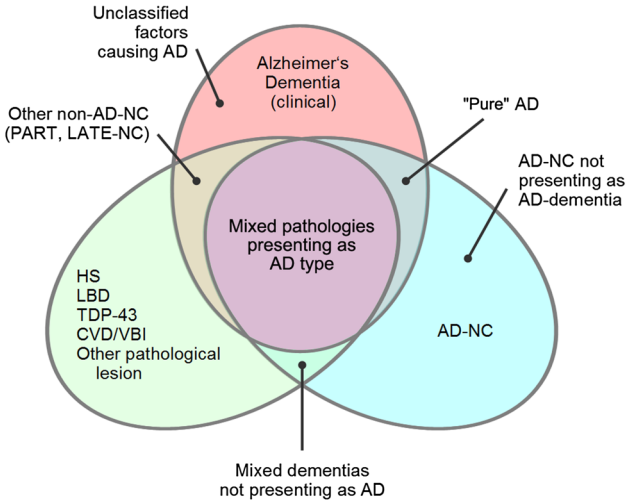

Fig. 3 Diagram showing the overlap between AD and other (co-) pathologies. Only a subset of individuals with the clinical symptoms of AD demonstrate "pure" ADNC. Other co-pathologies also contribute to dementia and may overlap with ADNC, while some persons with ADNC may not demonstrate dementia. Modified after (Mehta and Schneider 2021). *AD* Alzheimer disease, *ADNC* Alzheimer neuropathological changes, *CVD* cerebrovascular disease, *HS* hippocampal sclerosis, *LBD* Lewy body disease, *VBI* vascular brain injury, *LATE-NC* limbic-predominant age-related TDP-43 neuropathological changes, *PART* primary age-related tauopathy

Conclusions and perspectives

AD is a heterogeneous, multifactorial disorder, manifesting clinically and morphologically as several pathobiological phenotypes that have a distinctive signature of neuronal network disruptions associated with specific brain atrophy patterns and reflecting the different spread of NFT/tau pathology and neuronal loss due to different vulnerability patterns of affected brain regions, which relates to specific molecular-functional properties of the affected neuronal systems (Grothe et al. 2018; Wang et al. 2020). This is substantially related to three important factors, i.e., risk, protective factors, and concomitant pathologies. The balance between risk and protective factors determines brain cellular and regional vulnerability, which contributes to differential spatial manifestations of pathologies and potential disease-relevant lesion patterns, leading to divergent clinicopathological presentations of AD. The severity of lesions corresponds to the "N" category in the new A/T/N classification of biomarkers (Jack et al. 2018a), indicating that the AD clinical syndrome includes several pathobiologically defined entities or subtypes, which show both clinical and morphological differences. This heterogeneity of the Alzheimer continuum is due to multiple pathogenic factors, e.g., the "upstream" genotypes causing comorbidities, "downstream" disease-modifying gene variants (MAPT, H2 haplotype, PSEN1, APE, TREM, GRN and other variants), which induce misfolding tau, Aβ, TDP-43 and others, the synergetic or additive action of which results in various disease phenotypes (Nelson et al. 2016). Several factors such as brain resilience may help to compensate for these pathologies up to a certain

level, although their relevance is still poorly understood. It has been suggested that individuals should be identified who have connectivity patterns resistant to the initiation or spread of neurodegeneration. Furthermore, compensation strategies could be active in HcSP-AD and MA-AD, because the learning and encoding capacity in these subtypes is partially spared (Ferreira et al. 2017). The prevalence of biological AD with the various subtypes and variants is greater than clinical probable AD at any age, in particular at age 85 + (Jack et al. 2019). These problems and the increasing incidence of AD illustrate its consequences on public health and the resulting challenges for future medicine. Increased sensitivity and specificity of new A/T/N markers and more extensive clinicopathological studies in well-documented populations are needed, with postmortem studies using the updated NIA-AA criteria. The recent advent of tau PET and novel imaging and fluid-based (CSF and plasma) biomarkers will allow us to study the temporal progression of tau and other pathologies in vivo (Hampel et al. 2021; Koychev et al. 2020; Ricci et al. 2020; Wesenhagen et al. 2020). Although the current techniques do not yet have the resolution to assess the molecular mechanisms of Aβ and tau at the single neuron level, recent in vivo studies support the hypothesis that Aβ and tau have toxic effects on synaptic function and axonal integrity over the course of AD. By combining several established methods, it could be shown that early disease stages are characterized by Aβ-induced synaptic damages, memory impairment and functional connectivity changes, whereas later disease stages are characterized by tau-associated axonal damage, global cognitive decline and reduced connectivity. These results are consistent with axonal degeneration and disruption of synaptic physiology as central events in the pathogenesis of AD (Ahmad et al. 2021; Pereira et al. 2021).

It is essential to gain better understanding of the AD pathogenesis, subtype variety, and to develop several distinct therapeutic approaches tailored to address this diversity, as well as the common presence of mixed pathologies. Improving methods for disease detection and monitoring its progression may hopefully lead to the developmental refinement of tau-based therapies. Neuropathological studies should use a wide range of molecular methods and should evaluate multiple brain regions. Advances in digital pathology and technologies such as single cell sequencing and digital spatial profiling have opened novel ways for improving the neuropathological diagnosis and advancing our understanding of underlying molecular processes (Trejo-Lopez et al. 2021). An optimal and less cost-intensive strategy would be to screen specifically neurodegeneration-related proteins and to examine their cross reactions. A similar procedure was used to establish a new system, the Lewy pathology consensus criteria in postmortem brains, which showed good reproducibility and allowed the classification of all cases of LBD into distinct categories, irrespective of concomitant neurodegenerative diseases (Attems et al. 2021). Recent correlative studies on concomitant pathologies have provided insights into their interrelations with ADNC in causing various clinical symptoms. Interdisciplinary studies may further improve our knowledge about the pathogenesis of the heterogeneous manifestations of AD and promote methods for its early diagnosis as the basis for further preventive and successful disease-modifying therapeutic measures of this devastating disease.

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Declarations

Conflict of interest The author declares that he has no conflict of interest.

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