Synapse vulnerability and resilience underlying Alzheimer's disease

Raquel N. Taddei[a,b,*] and Karen E. Duff[b]

[a]Neurology Department, Massachusetts General Hospital, Harvard Medical School, Boston, USA
[b]UK Dementia Research Institute at UCL, Institute of Neurology, University College London, UK

eBioMedicine
2025;112: 105557
Published Online 31 January 2025
https://doi.org/10.1016/j.ebiom.2025.105557

Summary

Synapse preservation is key for healthy cognitive ageing, and synapse loss represents a critical anatomical basis of cognitive dysfunction in Alzheimer's disease (AD), predicting dementia onset, severity, and progression. Synapse loss is viewed as a primary pathologic event, preceding neuronal loss and brain atrophy in AD. Synapses may, therefore, represent one of the earliest and clinically most meaningful targets of the neuropathologic processes driving AD dementia. The synapse loss in AD is highly selective and targets particularly vulnerable synapses while leaving others, termed resilient, largely unaffected. Yet, the anatomic and molecular hallmarks of the vulnerable and resilient synapse populations and their association with AD neuropathologic changes (e.g. amyloid-β plaques and tau tangles) and memory dysfunction remain poorly understood. Characterising the selectively vulnerable and resilient synapses in AD may be key to understanding the mechanisms of cognitive preservation versus loss and enable the development of robust biomarkers and disease-modifying therapies for dementia.

Keywords: **Alzheimer's disease; Synapse loss; Resilience; Vulnerability; Cognition; Biomarkers**

Introduction

AD is the most frequent form of dementia, accounting for around two-thirds of all dementias, which cumulatively affect >55 million people worldwide (*World Health Organisation, 2023*). The classical clinical syndrome of AD is characterised by hippocampal-driven episodic memory loss together with temporoparietal dysfunction signs. Synapse dysfunction and loss are viewed as critical pathologic hallmarks of AD and other dementias and are further supported by the notion that synapse protein mutations account for more neurological diseases than mutations in any other known proteins in the brain.[1] Synapses are nanomolecular structures that contain up to 6'000 proteins per synapse, are present at around 10'000 synapses per neuron, have a density of 1 trillion synapses per cm^3 in the human brain, and show intimate associations with glial cells.[2,3] In AD and other dementias, synapse pathology is considered one of the earliest events with clinical significance, and it shows cell-, region-, and network-specific patterns preferentially targeting a subset of so-called vulnerable synapses while leaving others, termed resilient synapses, remarkably unaffected.[3,4] These highly selective synapse susceptibilities complemented with resiliencies may form the anatomic basis of the clinical phenotypes underlying each dementia and offer alternative insights into the potential mechanisms driving different cognitive syndromes. Unravelling the molecular signatures of the most and the least affected synapses in AD and understanding their association with the AD-defining neuropathologies, amyloid-β and tau, and the clinical syndrome may be key to discovering cognition-relevant biomarkers and alternative synapse-protective therapies that by promoting synapse resilience could effectively treat dementia. This review defines the concepts of classical and local vulnerability and resilience, provides an overview of the known vulnerable and resilient synapse proteins in typical AD, and explores the association between the classical disease-defining neuropathologies and the synapse and cognitive dysfunction in AD. A detailed glossary of terms of the synaptic protein abbreviations used throughout the text can be found in the Table legend.

AD symptoms versus AD lesions

AD dementia classically affects individuals above the age of 65 and forms part of the so-called slowly progressive dementias with a clinical course that typically progresses over 8–10 years. AD can be divided into six clinical stages, as recently defined by the National Institute on Ageing and Alzheimer's Association (NIA-AA), which initiate with genetic and/or biomarker evidence of underlying AD pathology in cognitively unimpaired individuals (stage 1), followed by minimally detectable functional changes that still fall within normal performance and can be documented either by subjective cognitive decline or subtle change in longitudinal

*Corresponding author.
E-mail address: raquel.taddei.20@ucl.ac.uk (R.N. Taddei).

cognitive testing (stage 2), progressing to prodromal or mild cognitive impairment (MCI) (stage 3), ultimately reaching the formal dementia stages, which are subdivided into mild (stage 4), moderate (stage 5), and severe (stage 6).[5] The duration of the MCI stage is variable, typically ranging from a few years to potentially decades, the mild dementia stage is estimated at 2 years, the moderate dementia stage at 2–4 years, and the severe stage is the shortest, with an average duration of 1–2 years (*Alzheimer's Society UK, 2023*). The amnestic presentation of AD is characterised by early episodic memory dysfunction associated with hippocampal and entorhinal cortical affection, and variable presentations of aphasia, agnosia, and apraxia underlying different degrees of temporoparietal dysfunction. The clinical development of symptoms is closely paralleled by the sequential affection of brain anatomic structures displaying neuronal loss and brain atrophy, which initiates in the hippocampus and amygdala (stage 1), progresses to the middle temporal gyrus (stage 2), next affects the entorhinal, parahippocampal, and other temporal regions (stage 3), followed by striatum and thalamus (stage 4), and lastly affects the middle frontal, cingular, and insular cortices (stage 5).[6] Interestingly, the so-called atypical variants of AD are clinically characterised by frontal-executive (behavioural variant), language (logopenic variant), and/or prominent visuospatial dysfunctions (posterior cortical atrophy variant) and their brain structural changes differ from typical AD in that they are usually most pronounced in regions corresponding to clinical symptoms.[7] The broad spectrum of clinical presentations encompassed within the umbrella term of AD dementia thus suggests that the disease process is remarkably multifaceted and that vulnerable and resilient brain structures exist and may result from distinct mechanisms which target select synaptic and neuronal populations that ultimately shape the clinical syndrome.

Notably, the term AD is currently a neuropathologic and not a clinical diagnosis that is defined by the accumulation of amyloid-β plaques and neurofibrillary tangles (NFTs) in the brain. AD is viewed as a continuum that initiates with the appearance of neuropathologic lesions in asymptomatic individuals and progresses to increasing pathologic burdens, eventually leading to the emergence of clinical symptoms.[5] Neurocognitive symptoms are considered a result of the disease process but are not strictly necessary to diagnose AD. Hence, there is an important disconnect between AD symptoms and AD lesions, and the association between cognitive dysfunction and neuropathologic changes is not invariably required.[8] In fact, autopsy studies of cognitively unimpaired elderly have demonstrated the presence of amyloid-β and NFT deposits in around one-third of individuals without dementia, a striking finding that has been termed resilience[8–10] and reinforces the important discrepancy between clinical symptoms and AD neuropathologic lesions (Fig. 1).

Defining vulnerability and resilience to AD

Resilience is classically defined by the absence of dementia in an individual with AD pathologic brain changes.[8–10] Importantly, resilience is not limited to AD pathology, as it has also been described in individuals without dementia who contain alpha-synuclein and/or TDP43 pathology at autopsy.[9,11–13] In contrast, vulnerability refers to critically affected brain structures and functions in individuals with AD neuropathologic changes (Fig. 1). A related concept termed resistance refers to the absence of brain neuropathologic lesion accrual, irrespective of cognitive status, and the concept of frailty to individuals with dementia in the absence of evident neuropathologic deposits (Fig. 1). These two related terms are distinct yet complementary to vulnerability and resilience and may offer additional insights into neuropathology-related brain anatomic and functional changes.

A more recent and interesting subset of resilience, referred to as regional or local resilience, involves the selective preservation of cognitive functions in an individual with AD neuropathologic changes and global cognitive decline (Fig. 1). Hence, local resilience represents an interesting phenomenon that is emerging as a complementary term to classical resilience.[10,14–17] This novel concept highlights that not only can individuals remain globally resilient and display no signs of dementia in the presence of AD pathology, but also that within the brain of an individual with AD dementia, some regions remain remarkably resilient even though other so-called vulnerable brain regions are functionally impacted causing clinical symptoms (Fig. 1). While most studies of resilience have focused on the important phenomenon of global resilience[8–10,13] and/or on the regional assessment of vulnerable brain regions,[4,18] much less attention has been directed at the purposeful study of resilient brain regions in individuals with AD dementia. A few studies assessing resilient brain regions have highlighted lower AD pathology burdens, distinct glial cell profiles with reduced inflammatory activation, maintenance of metabolic functions, and preservation of synaptic proteins[16,19–21] which may be critical for the primary preservation of select neurological functions, such as motor and sensory ones, in individuals with AD dementia. One important driver of local resilience may derive from the preservation of synapses, or local synapse resilience[10,16,17] (Fig. 1). This local form of resilience can be regional and entail the preservation of synapses in clinically relatively silent brain regions, such as the posterior cortical regions and basal ganglia,[22,23] and/or be subregional and involve the maintenance of select synapses within clinically affected brain regions, such as synapses in layer V of the anterior cingulate and layers III and V of the entorhinal cortex.[3] This regional and subregional maintenance and/or respective dysfunction of synapses may ultimately determine which clinical functions

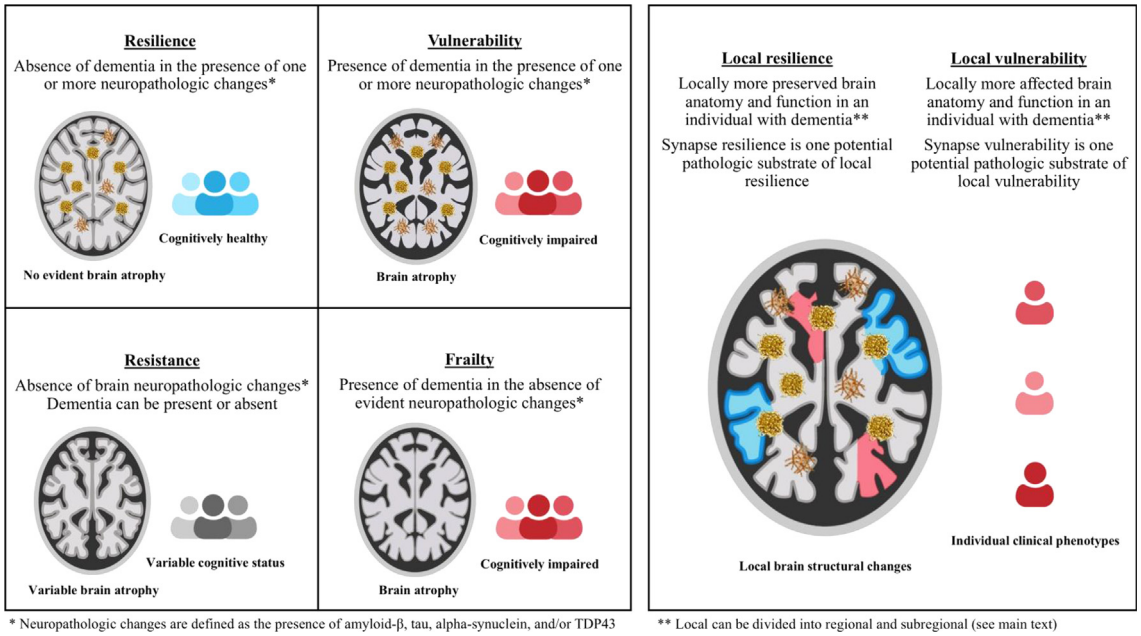

***Fig. 1:* Glossary of terms: resilience, vulnerability, resistance, and frailty.** Definition and concept of resilience, vulnerability, resistance, and frailty. The terms local resilience and vulnerability are explained separately. Representative brains showing higher or lower amounts of brain atrophy and Alzheimer's disease (AD) neuropathologic changes (amyloid-β plaques and tau neurofibrillary tangles), where applicable. Local resilience and local vulnerability are exemplified with a brain depicting randomly chosen areas coloured in blue to showcase more preserved and/or in red for more affected brain structures. The small figures in red indicate individuals with dementia, in blue individuals without dementia, and in grey variable and/or undefined cognitive performance. The colour gradients indicate individual phenotypic expressions of dementia and/or variability in the cognitive performance of resilient individuals globally still falling within normal limits. Of note, the neuropathologic changes depicted in the Figure refer primarily to AD pathology, but resilience, vulnerability, resistance, and frailty can also be observed with other brain neuropathologic changes, including alpha-synuclein and TDP43 deposits.

remain relatively intact and which ones become affected, driving the diverse clinical manifestations of AD dementia (Fig. 1). Importantly, the determinants of resilience are viewed as intrinsically distinct from the drivers of vulnerability, and they do not simply represent opposite effects counteracting the same mechanism.[24] Rather, they may involve unique processes that complement each other and form part of a continuum, in which the loss of critical resilience mechanisms combined with the emergence of sufficient vulnerability traits may ultimately precipitate the emergence of anatomic and functional changes. Understanding resilience mechanisms may, hence, be crucial to uncovering the pathologic processes leading to dementia development. For example, recent discoveries have suggested resilience-specific pathways that were different from known vulnerability-associated mechanisms.[25,26] In addition, the study of locally resilient brain regions in individuals with AD dementia has revealed selective synapse modules that differed from locally vulnerable brain regions,[17] pointing to unique molecular hallmarks associated with synapse resilience or vulnerability.

Dementia drivers in genetic and sporadic forms of AD

AD is considered a sporadic disease in around 95% of cases, in which the apoE4 allele represents the strongest known genetic risk factor. In rare instances, accounting for around 5% of AD cases, genetic mutations in autosomal dominantly inherited genes (e.g. APP, PSEN1, PSEN2) are observed.[27] In these familial forms of AD, the clinical course usually starts earlier (<65 years of age) and shows a more aggressive trajectory that is often accompanied by atypical clinical features.[28] While the exact underlying mechanisms in genetic and sporadic subtypes of AD likely differ, the ultimate outcome often converges in a common synapse dysfunction. Genomic analyses in sporadic AD have associated >80 genetic risk loci with increased dementia risk, and an important subset of them have been found to play critical roles in synapse homeostasis.[29] Interestingly, around 50% of the described genetic risk loci are prominently expressed in glial cells, suggesting an intricate association between synapse and glial cell dysfunction in AD.[30] Moreover, recent gene co-expression analyses have shown close associations of the known causative genes of AD with

synaptic transmission genes,[31] proposing that the downstream effects of familial AD may be intimately linked with synapse dysfunction.[29,32] Close associations have also been observed between the ApoE4 gene variant and synapse loss.[33] Moreover, recent studies have proposed that epigenetic modifications may be key to allowing the detrimental effects of genetic susceptibility alleles on AD dementia development,[34] with the highest epigenomic changes observed in the clinically most affected brain regions.[35] The three known causative as well as the main risk genes of AD thus converge on underlying synapse dysfunction, that may be further determined by environmentally-driven epigenomic modifications.

The role of AD neuropathology on synapse function

Amyloid-β plaques and NFTs represent the defining hallmarks of AD. Amyloid-β and tau deposition occur in a highly stereotypical pattern following the Thal phases and Braak stages, respectively.[5] Amyloid-β plaques start to form in the neocortex (Thal phase 1), then progress to the allocortex (Thal phase 2), subsequently affecting the diencephalon, striatum, and basal forebrain (Thal phase 3), the brainstem nuclei (Thal phase 4), and the cerebellum (Thal phase 5). Tau deposits develop in the transentorhinal region (Braak stage I), followed by the entorhinal region (Braak stage II), fusiform and occipitotemporal gyrus (Braak stage III), medial temporal gyrus (Braak stage IV), occipital lobe and peristriate areas (Braak stage V), and they lastly affect the striate areas (Braak stage VI). Overall, amyloid-β plaques develop predominantly in neocortical and limbic brain regions (Fig. 2), with relative preservation of the cerebellum (Supplementary Fig. S1). Tau preferentially accumulates in the entorhinal cortex, hippocampus, and neocortical association cortices (Fig. 2), largely sparing the primary sensory cortices (Supplementary Fig. S1). Tau distribution relates more closely with the clinically most affected brain regions in AD, and it accumulates in discrete brain regions that coincide with areas of highest neurodegeneration, whereas amyloid-β distribution is more widespread[36] (Fig. 2). Hence, NFTs are overall better correlates of memory dysfunction than amyloid-β plaques,[37] but the association of classical AD neuropathology with dementia is not always present,[8–10] and neurodegeneration and cognitive dysfunction can occur in the absence of AD lesions.[38]

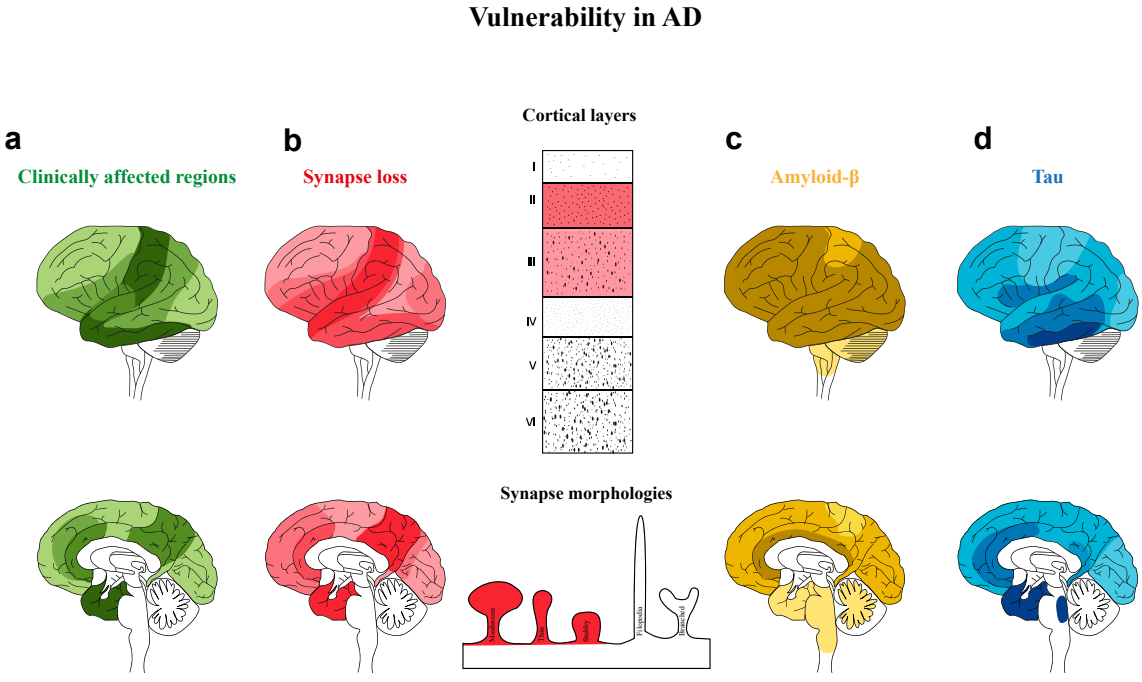

Fig. 2: **Vulnerable brain regions to clinical, synaptic, and AD neuropathologic changes in AD dementia.** Brains representative of Alzheimer's disease (AD) showing the clinically most affected brain regions (green) (a), the regions with the highest synapse loss (red) (b), and the brain areas of highest neuropathologic burden accumulation (amyloid-β in yellow, tau in blue) (c). Colour gradients indicate the highest (most intense) to lowest (least intense) affected brain regions, respectively. AD brains show the highest overlap between clinical and synaptic vulnerability, while tau partly overlaps but amyloid-β does not closely associate with the clinically affected and the most severely impacted regions of synapse loss in AD. Synapse vulnerability is highest in cortical layers II and III (b), and affects mushroom, thin, and stubby spines (b). Overall, clinical symptoms overlap more closely with synapse changes than with amyloid-β and/or tau distributions.

Synapse loss is particularly high in the immediate vicinity, the so-called penumbra, of amyloid-β plaques, which contains high amounts of toxic oligomeric amyloid-β.[39,40] In contrast, synapse densities are largely preserved in the immediate vicinity of NFTs, which presumably sequester toxic tau oligomers intracellularly.[40,41] Recent *in vitro* and *in vivo* studies have shown that amyloid-β oligomers, but not monomers or fibrils, disrupt synaptic structure and function[42,43] and induce neuroinflammatory activation preferentially targeting excitatory presynapses[44] also affecting a subset of inhibitory synapses.[43] The selective vulnerability of excitatory synapses may underlie the higher activity of excitatory neurons, which induces amyloid-precursor protein (APP) processing and oligomeric amyloid-β production in the synapse.[45] Although the mechanisms of synapse dysfunction induced by amyloid-β oligomers remain unknown, pathways involving postsynaptic NMDA receptors have been proposed.[46] Memantine, one of the two classes of oral drugs approved for the symptomatic treatment of AD, targets and modulates the NMDA receptor. However, its efficacy on cognitive symptoms is modest and may be limited by additional synaptic dysfunctions and by its relatively late application in the moderate to severe disease stages.[47]

Tau oligomers are potent synaptotoxic molecules that alter synaptic vesicle and synaptic receptor expression and lead to neuronal death in cell culture.[48,49] Tau oligomers accumulate in synapses from the prodromal disease stages, and they are better predictors of neuronal loss and dementia severity than NFTs.[41,50] Accumulation of putative toxic tau species has been observed at the presynapse and postsynapse of individuals with AD dementia,[51] and synapse dysfunction has been suggested to be a key driver of the spread of AD pathology in critical brain regions.[52] Moreover, recent *in vitro* studies in primary tauopathy models have proposed that synapse dysfunction may precede the buildup of toxic tau and neurodegeneration.[53] Notably, severe and region-specific synapse loss has also been described in a subset of primary tauopathies in which synapse degeneration is a strong determinant of disease severity and progression.[54,55] The drivers of selectively vulnerable synapses to accumulating tau remain largely unknown, and the mechanisms by which tau proteins attach to cellular and synaptic membranes are an important topic of ongoing exploration.[56] Recent studies have found that vulnerable neurons contain lower axonal and synapse plasticity-associated gene transcripts when compared with resistant neurons[45] and that an imbalance in the 3R–4R ratio may further contribute to selective neuronal vulnerability to tau.[57] Neurons in layers II of the entorhinal cortex and excitatory neurons are more likely to develop tau inclusions, while neocortical pyramidal and inhibitory neurons appear more resistant to tau pathology.[57] Interestingly, some brain regions seem particularly resistant to accumulating tau deposits, such as the primary sensory cortices (Supplementary Fig. S1), and they coincide with areas of relatively preserved synapse densities, which could be parsimoniously attributed to the absence of NFTs. However, the potential synaptotoxic effects of tau oligomers, which may develop ahead of NFTs,[50] still suggest the presence of efficacious synapse resilience mechanisms in these brain regions despite the virtual absence of NFTs.

Recent evidence has shown that amyloid-β and tau oligomers are synaptotoxic by themselves but that their toxic effects are enhanced by the presence of both.[58] Brains of individuals with dementia more commonly contain multiple oligomeric species in their synapses compared with resilient and healthy control brains,[41] and the convergence of synaptic oligomers leads to a hastened cognitive decline and a faster disease progression. In fact, the interplay between oligomeric amyloid-β and tau at the synapse may be a critical step leading to synapse dysfunction.[58] Importantly, synaptic amyloid-β and tau oligomers can also induce the release of cytokines and promote aberrant astroglial activation,[59,60] which may, among others, drive the targeted elimination of oligomer-containing synapses by glial cells.[50] The distribution of synapse loss is partly associated with amyloid-β plaques and NFTs (Fig. 2), but AD deposits offer overall limited predictive value for determining cognitive dysfunction in AD.

Vulnerable synapses in AD

Synapse loss is considered a closer predictor of dementia severity than amyloid-β plaque burden, NFTs, neuronal loss, and brain atrophy.[50,61–63] Healthy elderly display largely preserved synapse densities during normal ageing, exhibiting only minor synaptic losses of at most 15%, which are not associated with a relevant functional change. However, individuals with dementia lose 15–25% of synapses in the mild dementia stages, and 20–50% in the advanced dementia stages, and synapse loss closely correlates with the onset and progression of cognitive decline.[3,64–67] The synapse dysfunction in AD has been associated with a severe loss of neuronal connectivity networks, which may culminate in the neurodegeneration observed in these brains. Yet, the temporality of events between synaptic and neuronal loss remains a topic of ongoing debate.[68] While several studies have highlighted selectively vulnerable neuronal populations in AD brains,[6] the detailed study of vulnerable synapses remains substantially less explored.[2,16]

Synapse loss is typically observed in the clinically most expressive brain regions in AD, including the hippocampus, cingulate, entorhinal, and temporal cortex, whereas brain regions less clinically affected, such as the primary motor and sensory cortices, cerebellum, and basal ganglia, show a lesser or undetectable degree of early synapse loss (Fig. 2 and Supplementary

Fig. S1).[2,3] Recent *in vivo* assessments of synapse densities with presynapse-targeting SV2A PET have shown synapse loss patterns that closely mimicked the clinically most relevant brain structures and were closely associated with the severity of dementia.[63] In contrast, neurons and synapses of primary sensory cortices remained relatively unaffected until the late disease stages[10] (Supplementary Fig. S1). Within the cortex, vulnerable synapses are particularly high in layer II neurons of the transentorhinal, entorhinal, and parietal cortex,[3,69] and layers II and III of the frontal neocortex,[10] while other synapses, such as synapses located in layer V, remain overall less affected[4] (Fig. 2 and Supplementary Fig. S1). Synapse vulnerability has been described both at the presynapse and postsynapse, and postsynaptic spines, which play a key role in excitatory input, seem to be particularly affected. Excitatory synapse transmission occurs on postsynaptic spines, and preserved spine morphology and structure are necessary for intact synapse and cognitive function.[70] Accordingly, spine changes have been observed early in AD brains involving lower spine densities with larger spine volumes in cortical layer II,[71] and fewer mushroom, stubby, and thin-shaped spines in individuals with dementia when compared with cognitively unimpaired controls.[10,72] Recent studies have also proposed that inhibitory synapses, which comprise around 10–20% of the total synapse population, are significantly reduced in AD brains and that their loss occurs across the six cortical layers.[43]

Studies of AD brains have found selectively reduced synapse proteins which showed a close association with dementia severity (e.g. synaptophysin, synapsin 1, neurogranin)[2,50,73–78] (Table 1). A meta-analysis of ten human brain studies has recently revealed another subset of vulnerable synapse proteins in AD brains (e.g. neuronal pentraxin 2, synaptotagmins, GFRA2) (Table 1).[79] Two large studies have identified modules of genes related to synaptic and neuronal dysfunction, which were strongly associated with dementia development and severity.[75,95] Several other studies have highlighted the downregulation of synapse genes and synaptogenesis pathways, especially of synaptic signalling and synaptic vesicle-related genes.[92] Interestingly, some synaptic genes are selectively upregulated in the early disease stages and ahead of the formation of AD-typical brain deposits in clinically affected regions, such as the hippocampus, and they become downregulated only in the later disease stages.[74] This has been attributed to an early synapse dysfunction, which may induce a compensatory upregulation of synapse transcription in an effort to maintain synapse function. Despite this paradox in differing brain synaptic gene expression levels between early (MCI) and late (formal dementia) stages, at the protein level, there is a global and progressive loss of brain synapses in all disease stages. The mechanisms driving the dysfunction and loss of vulnerable synapse populations in AD remain largely unknown. Recent evidence has pointed to the critical role of missorted amyloid-β and tau oligomers to synaptic compartments[41,96] and the detrimental effects of glial cells,[50,93] in particular of inflammatory microglia and astrocytes in excessively eliminating synapses in the brains of individuals with dementia compared with resilient.[50] The innate immune system, including macrophages and complement proteins, may be critical in facilitating the deleterious crosstalk between microglia, astrocytes, and synapses,[97–99] and interesting evidence of peripheral inflammation and its effect on central neuroinflammation, AD pathology, and synapse dysfunction[100] has been recently proposed.

Synapse dysfunction in the clinical continuum of AD dementia

The dysfunction and loss of brain synapses represent a central hallmark of AD and other dementias. The term synapse dysfunction refers to the disruption of synapse structure and function, which may render a synapse ineffective but not invariably lead to its loss.[90] In contrast, synapse loss is considered a major neuropathologic event characterised by the irreversible degeneration of synaptic proteins in the brain. As such, synapse loss is considered the terminal outcome of synapse dysfunction, and both concepts are closely associated with the presence and severity of cognitive symptoms in AD.[90] The dysfunction of synapse proteins in AD and their nanomolecular size facilitate their diffusion across extracellular space and measurement in peripheral biofluids such as cerebrospinal fluid (CSF) and plasma, providing an unprecedented tool to study longitudinal brain synapse changes in AD *in vivo*. Although the mechanisms of synapse decay and translocation to peripheral biofluids remain unknown, the changes in synapse protein levels measured in CSF and plasma of individuals with AD dementia are thought to reflect a primary brain synapse dysfunction with the subsequent release of synapse proteins from neuronal structures.[101]

Synapse proteins measured in CSF and plasma show stage-specific changes in AD that are closely associated with cognitive dysfunction and progression[89] (Fig. 3). Interestingly, individuals with MCI show, on average, higher synapse protein changes in biofluids compared with healthy controls and individuals with dementia (Fig. 3). This paradoxical effect has been attributed to an enhanced synapse turnover to compensate for the incipient synapse dysfunction in the early MCI stages to help maintain cognitive function. Yet, in the brains of individuals with MCI, there is already a significant albeit mild loss of synapse proteins, which may explain their cognitive symptoms[3] (Fig. 3). Interestingly, individuals with MCI and higher CSF synaptic protein levels, which possibly reflect an enhanced synapse dysfunction, also

Synapse proteins	Vulnerability		Resilience	Sample	References
	Early AD	Late AD			
AP2B1				B, CSF	79,80
Beta-synuclein				CSF, P	64,81
Calsyntenin1				CSF	68
CC2D1A				CSF	82
CPLX1				B	3,21,80
Drebrin				B	74,78
GABAR				B	2,74
GAP-43				CSF	64,74,83–86
GFRA2				B	79,80
GluR4				CSF	68
GRIA2				B	79,80
HOMER1				B, CSF	74,75,87
Neuregulin 1				B, P	80,88
Neurexin 2A				CSF	68
Neurexin 3A				CSF	68
Neurexin 2				B	73
Neurogranin				B, CSF	73,83–86,89
NPTX2				B, CSF	79,80,90,91
Neuritin 1				B	21,80
PPP3R1				CSF	82
PSD95				B, CSF	2,10,50,74,84–86
RPH3A				B	21,87
SHANK2				B	80
SNAP-25				B, CSF	2,10,83,87,90,92
SV2A				B	76
Synapsin 1				B, CSF, P	2,10,50,64,74,93
Synaptophysin				B, CSF, P	3,10,74,85
Synaptotagmin 1				B, CSF	79,83
Synaptotagmin 7				B	79
Synaptotagmin 11				B	79
Synaptotagmin 12				B	77,87
SYNGAP1				B	80
Syntaxin 1A				B	10,74,77
Syntaxin 1B				B, CSF	10,68,94
Thy 1				CSF	68
VAMP2				B, CSF	10,89

Table showing a compilation of synapse proteins associated with cognitive vulnerability and/or resilience in Alzheimer's disease (AD). The synapse proteins included in this Table derive from human brain (B), cerebrospinal fluid (CSF), and/or plasma (P) samples, as indicated. The most common direction of change in synapse protein levels is highlighted in blue (increase) and/or green (decrease) when data was obtained from biofluids; when data was exclusively obtained from brain samples, the field is marked in grey, indicating a decrease in the respective brain synapse protein. Synapse proteins associated with resilience are labelled in purple and derive from studies evaluating human brain tissue. Early AD (prodromal and/or mild cognitive impairment), and late AD (formal dementia stages) are shown separately. Synapse proteins included in this Table are limited to recent literature and human-derived samples. B: brain, CSF: cerebrospinal fluid, P: plasma. Glossary of synapse protein abbreviations: AP2B1: adaptor related protein complex 2 subunit beta 1; CC2D1A: coiled-coil and C2 domain containing 1A; CPLX1: complexin1; GABAR: gamma-aminobutyric acid B receptor; GAP-43: growth-associated protein 43; GFRA2: GDNF family receptor alpha 2; GluR4: glutamate receptor 4; GRIA2: glutamate ionotropic receptor AMPA type subunit 2; NPTX2: neuronal pentraxin 2; PPP3R1: protein phosphatase 3 regulatory subunit B; PSD95: postsynaptic density 95; RPH3A: rabphilin-3A; SHANK2: SH2 and Multiple Ankyrin-Repeat Domains: SNAP-25: synaptosomal-associated protein 25; SV2A: synaptic vesicle glycoprotein 2A; SYNGAP1: synaptic Ras GTPase activating protein 1; VAMP2: vesicle-associated membrane protein 2.

Table 1: **Synapse proteins associated with vulnerability and resilience in AD.**

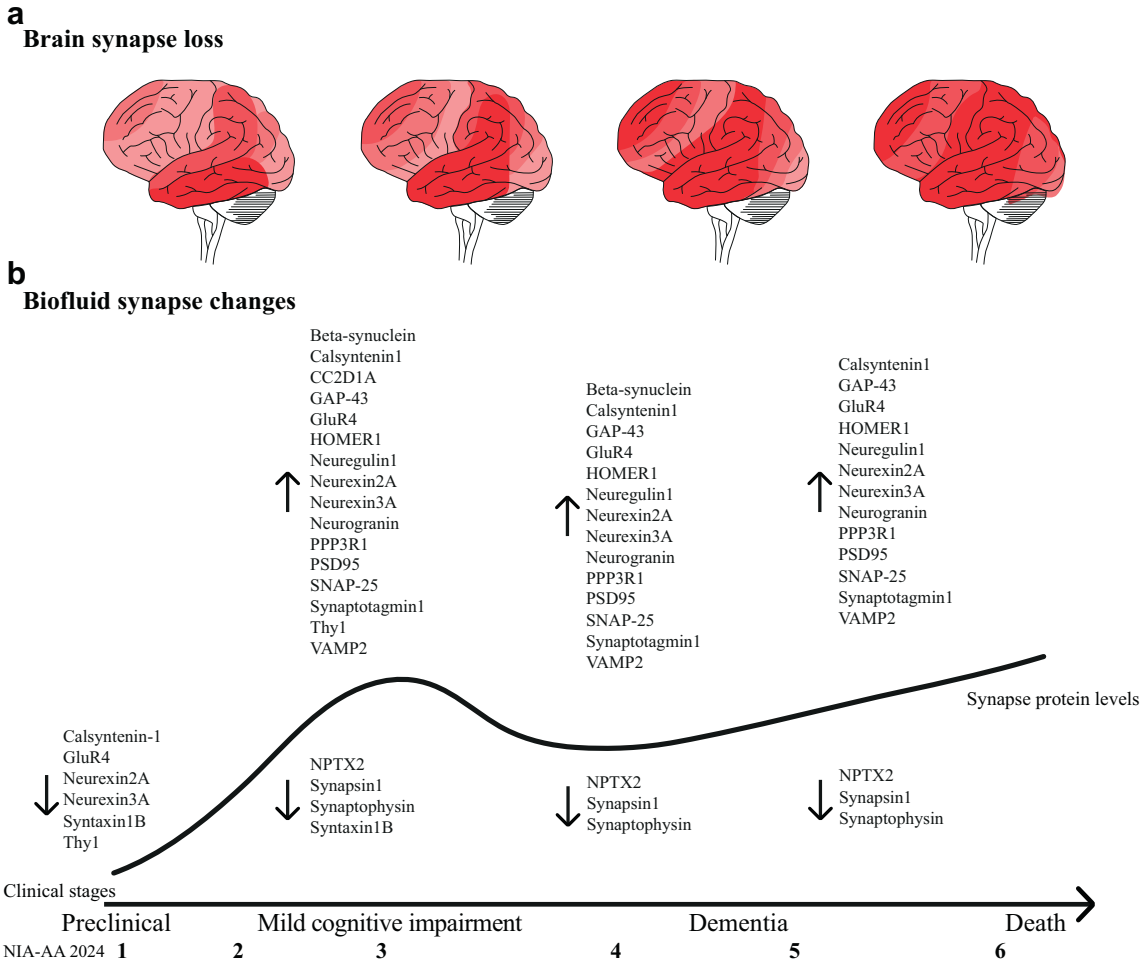

***Fig. 3:* Synapse changes in the clinical continuum of AD dementia.** Temporal trajectory of synapse loss in individuals with AD dementia (a) and synapse protein changes measured in the cerebrospinal fluid and/or plasma in the different clinical stages of AD (preclinical, mild cognitive impairment, and dementia) (b). The direction of synapse protein changes (e.g. increase and/or decrease) as measured in biofluids are indicated with an arrow, respectively. The clinical stages are shown as preclinical (NIA-AA stages 1–2), prodromal or MCI (NIA-AA stage 3), mild dementia (NIA-AA stage 4), moderate dementia (NIA-AA stage 5), and severe dementia (NIA-AA stage 6). The respective references are in Table 1. NIA-AA: National Institute on Ageing and Alzheimer's Association.

show higher rates of progression to dementia.[68] In the MCI stages, increases in several synaptic proteins have been observed in the CSF (e.g. neurogranin, SNAP-25, synaptotagmin-1, GAP-43)[64,83] and in plasma (e.g. neuregulin 1, beta-synuclein)[81,88] (Fig. 3). Early synapse protein changes have also been found in the CSF of autosomal dominant AD mutation carriers (e.g. CC2D1A and PPP3R1).[82] In the formal dementia stages, synapse loss progresses in parallel to increasing dementia severity, and most synaptic protein changes in CSF keep increasing[84–86] (Fig. 3). Paradoxically, subsets of synapse proteins measured in biofluids (e.g. neuronal pentraxins) have shown a steady decrease throughout the dementia course starting from the MCI stages, despite their concomitant loss in the brain (Fig. 3).[68,91] This paradoxical decrease has been attributed to the dysfunction of a very discrete subpopulation of brain synapse proteins that may get lost (e.g. due to their very low numbers) and/or eliminated (e.g. by glial cell engulfment) prior to reaching the CSF and/or plasma.[91] To date, the best characterised synaptic proteins for reflecting cognitive dysfunction in AD include SNAP-25, GAP-43, neurogranin, and neuronal pentraxin 2 measured in CSF[90] (Fig. 3).

Notably, synapse dysfunction is increasingly recognised as an important feature of AD, and the recently revised NIA-AA framework guidelines for the biological definition of AD, which include measures of amyloid (A category), tau (T category), and neurodegeneration (N category), have incorporated the clinical use of

neurofilament light measured in CSF or plasma as a marker of axonal damage, and the use of presynaptic SNAP-25 and GAP-43, postsynaptic neurogranin, and pan-synaptic neuronal pentraxin 2 measured in CSF together with presynaptic SV2A-PET to assess synaptic dysfunction and/or loss in research settings.[5] This important advancement reinforces the relevance of synapse pathology in AD and the promising avenue of discovering more and better synaptic biomarkers for the clinical definition of AD dementia.

Resilient synapses in AD

Resilience refers to the absence of dementia in individuals with AD neuropathologic changes and has been associated with the robust preservation of synapses in the brain.[10,50,95] Resilient brains show strikingly preserved subsets of inhibitory interneurons, axonal structures, and thin and mushroom-shaped synaptic spines[10,38] (Supplementary Fig. S1). They also contain lower inflammatory glial responses and cytokine levels compared to individuals with dementia,[8,102] and substantially less glia-mediated synapse engulfment.[50] Lower amounts of oligomeric amyloid-β and tau in synaptic terminals have been reported in the brains of resilient when compared with individuals with dementia, even when both displayed similar amounts of AD neuropathologic aggregates.[50,102] Resilient brains also show lower DNA damage responses and preservation of various synapse gene transcripts compared with individuals with dementia.[92]

Studies of resilient brains have revealed >180 proteins related to synapse formation and remodelling that were strongly associated with the maintenance of cognitive function.[103] Several studies have described synapse-related proteins in the cortex and/or CSF[21,80,94,95] of cognitively unimpaired that were strikingly preserved when compared with individuals with dementia (Table 1). A recent study assessing the brains of resilient, demented, and frail individuals (e.g. participants without AD neuropathology at autopsy but with antemortem dementia, Fig. 1), has highlighted the preservation of synapse-relevant cytoskeletal proteins and inhibitory neurons in resilient individuals compared with individuals with dementia.[38] Moreover, the brains of frail individuals showed higher dysfunction in secretory synaptic proteins when compared with controls, proposing common but also unique pathways of dementia development in the presence and absence of AD lesions, both converging at the synapse. Yet, studies comparing synapse transcriptomic and proteomic changes in AD brains have highlighted reductions in synapse gene transcripts in both individuals with dementia and resilient, while synapse protein densities showed a significant reduction only in individuals with dementia.[104] This important finding suggests that post-translational synapse protein modifications may ultimately determine the loss of synapses and cognitive function, supporting the primarily proteopathic nature of AD.[87]

Genetic resilience variants have been recently discovered in an ApoE3 Christchurch[25] and Reelin[26] mutation. In the autopsy reports of the individuals carrying these protective mutations, amyloid-β burdens were exceedingly high, but tau loads remained low, particularly in the entorhinal cortex. Other protective gene variants have been reported in a KIBRA mutation,[105] which was associated with protective effects against cognitive decline in the presence of tau pathology, and in fibronectin,[106] which was linked to cognitive protection in the presence of the ApoE4 risk allele. Genome-wide association studies have revealed additional genetic resilience variants, including bile acid metabolism-associated pathways, variants on chromosomes 1, 5, 13, and 18,[107] and protective effects of BDNF and DLGAP.[108] Moreover, primarily resilient brain regions in individuals with AD dementia, such as the primary motor and sensory cortices (Supplementary Fig. S1), have been shown to harbour >270 differentially expressed gene profiles, among which the synapse regulation module significantly differed between the more and less clinically affected brain regions.[17]

Mechanistic insights gained from the intriguing phenomenon of resilience represent an emerging area of interest for novel therapeutic drug discovery. Compounds to downregulate selective neuroinflammatory pathways,[104] avoid oligomeric protein tethering to synapse membranes[109] and limit glia-mediated synapse elimination[93] hold promising potential. Other interesting resilience-derived targets involve enhancing synaptic spine strength and neurotrophic factor expression,[110] and clinical trials are currently testing additional resilience-associated pathways for therapeutic use.[105]

Conclusions

Synapses are central to maintaining intact cognitive function, and synapse loss is closely associated with the presence and severity of dementia. The intimate association between synapses and cognitive dysfunction highlights the pivotal role of synaptic changes in the clinical manifestations of AD. Synapses may, therefore, represent the primary target of the underlying processes driving AD dementia. Yet, the complexity of synapse biology challenges our current understanding of the drivers of synapse dysfunction. A novel approach to studying the relevant synapses in AD dementia entails the detailed exploration of the most affected (e.g. vulnerable) and the least affected (e.g. resilient) synapses, which may be critical to identifying alternative disease mechanisms and targetable pathways.

The disease-defining signatures of AD, amyloid-β and tau, exert a differential impact on synaptic and

cognitive function, underscoring their convoluted association with AD dementia. Although the effects of AD lesions on cognition are not always present, as exemplified by resilient individuals, their contribution may be fundamental to promoting the deleterious effects of the dementing process on synapse and cognitive function. The critical role of select protein species, in particular oligomers mistargeted to synaptic compartments may be a key determinant of the local synapse dysfunction underlying AD dementia. The exploration of mechanisms driving synaptic oligomer mislocalisation and their local synaptotoxicity may unravel promising treatment targets to effectively halt dementia symptoms.

Resilience, both classical and local, showcases the remarkable ability of the brain to maintain cognitive function despite the presence of neuropathologic lesions. The interesting concept of local resilience with a focus on synapses opens avenues for the discovery of highly effective local synapse protection mechanisms to preserve cognition when challenged with global dementia. A promising target involves the emerging role of glial cells and inflammatory responses on synapse dysfunction, which remains substantially reduced in resilient individuals. Glial cells are intimately linked with synapses and play a crucial role in synapse formation, maintenance, and elimination, and their involvement in synapse pathology may be fundamental for the development of dementia. Targeting the detrimental crosstalk between glial cells and synapses, and/or interfering with the signals leading to an enhanced glia-mediated synapse elimination may offer promising therapeutic avenues to mimic resilience and thereby, alter the course of dementia. Intriguingly, resilience is not exclusive to AD but also exists for alpha-synuclein and TDP43 pathology, expanding the potential of resilience studies to other dementias.

Synapse proteins can be associated exclusively with vulnerability or with resilience, or be associated with both (Table 1), and within synapse protein families (e.g. synaptotagmins), differing synapse outcomes can be observed. This suggests time and region-specific mechanisms targeting discrete synapse protein components that may determine the fate of that local synapse protein and its function, shaping the AD dementia syndrome. Resilience and vulnerability may ultimately form part of the same continuum where the eventual emergence of cognitive symptoms may arise from the respective combination of phenomena. While some synapse proteins may primarily lose resilience-associated pathways, others may succumb to vulnerability-associated mechanisms, or be ultimately impacted by both. Although the exploration of synapse proteins associated with AD dementia and/or resilience is evolving, many vulnerable synapse proteins have not yet been studied in resilient individuals and/or brain regions, and this represents an important future direction. Notably, some of the exclusively biofluid-measured synapse proteins may not accurately capture the local brain changes and, instead, yield a global measure of combined brain processes. Complementing biofluid-measured synapse proteins with neuropathologic evaluations will remain critical for future studies.

Emerging evidence suggests the key role of synapse dysfunction in the clinical trajectory of AD dementia, underscoring the importance of understanding selective synaptic changes associated with the different dementia stages and expanding the study of vulnerable to also include resilient synapses in the temporal course of AD. Unique synapse changes may be linked with specific dementia subtypes and disease stages, and targeting the selective synapse dysfunction at the right clinical time may be crucial to developing stage-specific biomarkers to accurately detect, track, and predict cognition, and time-critical therapeutic interventions to effectively treat dementia.

In summary, shifting the focus towards preserving synaptic integrity in AD, rather than primarily addressing amyloid-β and tau pathologies alone, may potentially transform the clinical approach to AD dementia. Deepening our knowledge of synapse diversity, vulnerability, and resilience in AD offers promising prospects for breakthrough discoveries in dementia diagnosis and treatment. A selective but multi-targeted approach to reduce synapse vulnerability, enhance synapse resilience, limit the toxicity of amyloid-β and tau proteins, and modulate neuroinflammation may be a promising approach to effectively halt dementia development and progression.

Outstanding questions

Synapse pathology is increasingly recognised as a central driver of AD dementia, and synapse vulnerability and resilience represent a novel direction to better understand the underlying mechanisms of cognitive preservation and loss. The exploration of locally preserved synapses may help uncover alternative molecular mechanisms and complement the insights gained from classical resilience and vulnerability to provide novel synapse-protective treatment targets. The timing of synapse changes in the dementia course is important, and the detailed study of vulnerable synapses in the temporal continuum of AD may unravel stage-selective biomarkers and personalised therapeutic targets for early intervention. The toxic effects of amyloid-β and tau oligomers and their accumulation in synaptic compartments remain an area of high impact and exploring the detrimental oligomer–synapse interactions may lead to breakthrough discoveries in AD and beyond, helping develop synapse-protective strategies for various neurologic diseases with underlying synapse pathology. The exploration of neuroinflammation, in particular the interactions of microglia and astrocytes with resilient and vulnerable synapses may lead to the discovery of compounds to modulate glial-synapse

Search strategy and selection criteria

We searched PubMed and the Cochrane databases for English-language studies published from March 2019 to August 2024. A small subset of relevant and seminal literature >5 years old was also included. Search terms included: *AD, synapse dysfunction, synapse loss, synapse biomarkers, resilience, vulnerability, locoregional, clinical, anatomical*. We included meta-analyses, systematic reviews, and observational studies. We also manually searched the references of selected meta-analyses, reviews, articles, and practice guidelines. Selected articles were mutually agreed upon by the authors. Emphasis was given to a selection of meta-analyses and observational studies and to information of interest to a general medical readership. The studies included in this work derived from human samples, unless otherwise indicated.

signalling and effectively protect synapses from the detrimental effects of neuroinflammatory processes. Addressing these unmet needs may revolutionise the field of dementia and shape future advancements to effectively preserve synaptic integrity and halt or, ideally, reverse cognitive decline in AD.

Contributors

RNT and KD contributed to the concept and design of this review. RNT performed the literature search and selected the papers for inclusion. RNT wrote and edited the manuscript. RNT created the figures. KD critically revised the manuscript, the figures, and the table. RNT and KD read and approved the final version of the manuscript.

Declaration of interests

RNT and KD declare no conflicts of interest.

Acknowledgements

RNT and KD declare no funding sources. No funders had any role in the paper design, data collection, data analysis, interpretation, or writing of the paper.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2025.105557.

References

1 Grant SGN. Synapse diversity and synaptome architecture in human genetic disorders. *Hum Mol Genet*. 2019;28:R219–R225.
2 de Wilde MC, Overk CR, Sijben JW, Masliah E. Meta-analysis of synaptic pathology in Alzheimer's disease reveals selective molecular vesicular machinery vulnerability. *Alzheimers Dement*. 2016;12:633–644.
3 Griffiths J, Grant SGN. Synapse pathology in Alzheimer's disease. *Semin Cell Dev Biol*. 2023;139:13–23.
4 Mrdjen D, Fox EJ, Bukhari SA, Montine KS, Bendall SC, Montine TJ. The basis of cellular and regional vulnerability in Alzheimer's disease. *Acta Neuropathol*. 2019;138:729–749.
5 Jack JrCR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: alzheimer's Association Workgroup. *Alzheimers Dement*. 2024;20(8):5143–5169.
6 Planche V, Manjon JV, Mansencal B, et al. Structural progression of Alzheimer's disease over decades: the MRI staging scheme. *Brain Commun*. 2022;4:fcac109.
7 Graff-Radford J, Yong KXX, Apostolova LG, et al. New insights into atypical Alzheimer's disease in the era of biomarkers. *Lancet Neurol*. 2021;20:222–234.
8 Gómez-Isla T, Frosch MP. Lesions without symptoms: understanding resilience to Alzheimer disease neuropathological changes. *Nat Rev Neurol*. 2022;18:323–332.
9 Latimer CS, Burke BT, Liachko NF, et al. Resistance and resilience to Alzheimer's disease pathology are associated with reduced cortical pTau and absence of limbic-predominant age-related TDP-43 encephalopathy in a community-based cohort. *Acta Neuropathol Commun*. 2019;7:91.
10 de Vries LE, Huitinga I, Kessels HW, Swaab DF, Verhaagen J. The concept of resilience to Alzheimer's Disease: current definitions and cellular and molecular mechanisms. *Mol Neurodegener*. 2024;19:33.
11 Melikyan ZA, Corrada MM, Leiby A-M, et al. Cognitive resilience to three dementia-related neuropathologies in an oldest-old man: a case report from the 90+ Study. *Neurobiol Aging*. 2022;116:12–15.
12 Meneses A, Koga S, O'Leary J, Dickson DW, Bu G, Zhao N. TDP-43 pathology in alzheimer's disease. *Mol Neurodegener*. 2021;16:84.
13 Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology*. 2006;66:1837.
14 Wang M, Roussos P, McKenzie A, et al. Integrative network analysis of nineteen brain regions identifies molecular signatures and networks underlying selective regional vulnerability to Alzheimer's disease. *Genome Med*. 2016;8:104.
15 Vilkaite G, Vogel J, Mattsson-Carlgren N. Integrating amyloid and tau imaging with proteomics and genomics in Alzheimer's disease. *Cell Rep Med*. 2024;5(9):101735.
16 Mathys H, Boix CA, Akay LA, et al. Single-cell multiregion dissection of Alzheimer's disease. *Nature*. 2024;632(8026):1–11.
17 Siebert M, Carello-Collar G, Bastiani MAD, Zimmer ER. Transcriptomic similarities in vulnerable and resilient brain regions of Parkinson's disease and Alzheimer's disease. *Alzheimers Dement*. 2023;19:e080097.
18 O'Neill N, Stein TD, Olayinka OA, et al. Cognitive resilience to Alzheimer's disease characterized by cell-type abundance. *Alzheimers Dement*. 2024;20:6910–6921.
19 Huang Z, Merrihew GE, Larson EB, et al. Unveiling Resilience to alzheimer's disease: insights from brain regional proteomic markers. *J Exp Neurosci*. 2023;18:26331055231201600.
20 Zammit AR, Yu L, Petyuk V, et al. Cortical proteins and individual differences in cognitive resilience in older adults. *Neurology*. 2022;98:e1304–e1314.
21 Yu L, Tasaki S, Schneider JA, et al. Cortical proteins associated with cognitive resilience in community-dwelling older persons. *JAMA Psychiatr*. 2020;77:1172–1180.
22 Fang XT, Raval NR, O'Dell RS, et al. Synaptic density patterns in early Alzheimer's disease assessed by independent component analysis. *Brain Commun*. 2024;6:fcae107.
23 O'Dell RS, Higgins-Chen A, Gupta D, et al. Principal component analysis of synaptic density measured with [11C]UCB-J PET in early Alzheimer's disease. *Neuroimage Clin*. 2023;39:103457.
24 Dumitrescu L, Mahoney ER, Mukherjee S, et al. Genetic variants and functional pathways associated with resilience to Alzheimer's disease. *Brain*. 2020;143:2561–2575.
25 Arboleda-Velasquez JF, Lopera F, O'Hare M, et al. Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch homozygote: a case report. *Nat Med*. 2019;25:1680–1683.
26 Lopera F, Marino C, Chandrahas AS, et al. Resilience to autosomal dominant Alzheimer's disease in a Reelin-COLBOS heterozygous man. *Nat Med*. 2023;29:1243–1252.
27 Seo J, Byun MS, Yi D, et al. Genetic associations of in vivo pathology influence Alzheimer's disease susceptibility. *Alzheimers Res Ther*. 2020;12:156.
28 Rujeedawa T, Carrillo Félez E, Clare ICH, et al. The clinical and neuropathological features of sporadic (Late-Onset) and genetic forms of alzheimer's disease. *J Clin Med*. 2021;10(19):4582.
29 Fu W-Y, Ip NY. The role of genetic risk factors of Alzheimer's disease in synaptic dysfunction. *Semin Cell Dev Biol*. 2023;139:3–12.
30 Andrews SJ, Renton AE, Fulton-Howard B, Podlesny-Drabiniok A, Marcora E, Goate AM. The complex genetic architecture of Alzheimer's disease: novel insights and future directions. *EBioMedicine*. 2023;90:104511.
31 Giau VV, Bagyinszky E, Yang YS, Youn YC, An SSA, Kim SY. Genetic analyses of early-onset Alzheimer's disease using next generation sequencing. *Sci Rep*. 2019;9:8368.
32 Dourlen P, Kilinc D, Malmanche N, Chapuis J, Lambert J-C. The new genetic landscape of Alzheimer's disease: from amyloid

cascade to genetically driven synaptic failure hypothesis? *Acta Neuropathol*. 2019;138:221–236.
33 Zhao J, Fu Y, Yamazaki Y, et al. APOE4 exacerbates synapse loss and neurodegeneration in Alzheimer's disease patient iPSC-derived cerebral organoids. *Nat Commun*. 2020;11:5540.
34 Sharma KV, Mehta V, Singh GT. Alzheimer's disorder: epigenetic connection and associated risk factors. *Curr Neuropharmacol*. 2020;18:740–753.
35 Smith RG, Pishva E, Shireby G, et al. A meta-analysis of epigenome-wide association studies in Alzheimer's disease highlights novel differentially methylated loci across cortex. *Nat Commun*. 2021;12:3517.
36 Pereira JB, Janelidze S, Ossenkoppele R, et al. Untangling the association of amyloid-β and tau with synaptic and axonal loss in Alzheimer's disease. *Brain*. 2021;144:310–324.
37 DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. *Mol Neurodegener*. 2019;14:32.
38 Morgan G, Carlyle B. Interrogation of the human cortical peptidome uncovers cell-type specific signatures of cognitive resilience against Alzheimer's disease. *Sci Rep*. 2024;14:7161.
39 O'Dell RS, Mecca AP, Chen M-K, et al. Association of Aβ deposition and regional synaptic density in early Alzheimer's disease: a PET imaging study with [11C]UCB-J. *Alzheimers Res Ther*. 2021;13:11.
40 Spires-Jones TL, Hyman BT. The intersection of amyloid beta and tau at synapses in Alzheimer's disease. *Neuron*. 2014;82:756–771.
41 Colom-Cadena M, Davies C, Sirisi S, et al. Synaptic oligomeric tau in Alzheimer's disease — a potential culprit in the spread of tau pathology through the brain. *Neuron*. 2023;111(14):2170–2183.e6.
42 Sackmann C, Hallbeck M. Oligomeric amyloid-β induces early and widespread changes to the proteome in human iPSC-derived neurons. *Sci Rep*. 2020;10:6538.
43 Kurucu H, Colom-Cadena M, Davies C, et al. Inhibitory synapse loss and accumulation of amyloid beta in inhibitory presynaptic terminals in Alzheimer's disease. *Eur J Neurol*. 2022;29:1311–1323.
44 He Y, Wei M, Wu Y, et al. Amyloid β oligomers suppress excitatory transmitter release via presynaptic depletion of phosphatidylinositol-4,5-bisphosphate. *Nat Commun*. 2019;10:1193.
45 Leng K, Li E, Eser R, et al. Molecular characterization of selectively vulnerable neurons in Alzheimer's disease. *Nat Neurosci*. 2021;24:276–287.
46 Martinez Tyler P, Larsen Matthew E, Sullivan Emily, Woolfrey Kevin M, Dell'Acqua Mark L. Amyloid-β-Induced dendritic spine elimination requires Ca^{2+}-permeable AMPA receptors, AKAP-calcineurin-NFAT signaling, and the NFAT target gene Mdm2. *eNeuro*. 2024;11. ENEURO.504-20.2021.
47 Ortiz-Sanz C, Balantzategi U, Quintela-López T, et al. Amyloid β/PKC-dependent alterations in NMDA receptor composition are detected in early stages of Alzheimer's disease. *Cell Death Dis*. 2022;13:253.
48 Wu M, Zhang M, Yin X, et al. The role of pathological tau in synaptic dysfunction in Alzheimer's diseases. *Transl Neurodegener*. 2021;10:45.
49 Pampuscenko K, Morkuniene R, Krasauskas L, Smirnovas V, Tomita T, Borutaite V. Distinct neurotoxic effects of extracellular tau species in primary neuronal-glial cultures. *Mol Neurobiol*. 2021;58:658–667.
50 Taddei RN, Perbet R, Mate de Gerando A, et al. Tau oligomer–containing synapse elimination by microglia and astrocytes in alzheimer disease. *JAMA Neurol*. 2023;80(11):1209–1221.
51 Tai H-C, Wang BY, Serrano-Pozo A, Frosch MP, Spires-Jones TL, Hyman BT. Frequent and symmetric deposition of misfolded tau oligomers within presynaptic and postsynaptic terminals in Alzheimer's disease. *Acta Neuropathol Commun*. 2014;2:146.
52 Franzmeier N, Dehsarvi A, Steward A, et al. Elevated CSF GAP-43 is associated with accelerated tau accumulation and spread in Alzheimer's disease. *Nat Commun*. 2024;15:202.
53 Bowles KR, Silva MC, Whitney K, et al. ELAVL4, splicing, and glutamatergic dysfunction precede neuron loss in MAPT mutation cerebral organoids. *Cell*. 2021;184(17):4547–4563.e17, 2021.
54 Holland N, Jones PS, Savulich G, et al. Longitudinal synaptic loss in primary tauopathies: an in vivo [C]UCB-J positron emission tomography study. *Mov Disord*. 2023;38:1316–1326.
55 Malpetti M, Jones PS, Cope TE, et al. Synaptic loss in frontotemporal dementia revealed by [11C]UCB-J positron emission tomography. *Ann Neurol*. 2023;93:142–154.
56 Fowler SL, Behr TS, Turkes E, et al. Tau filaments are tethered within brain extracellular vesicles in Alzheimer's disease. *Nat Neurosci*. 2025;28:40–48.
57 Carroll T, Guha S, Nehrke K, Johnson GVW. Tau post-translational modifications: potentiators of selective vulnerability in sporadic alzheimer's disease. *Biology*. 2021;10(10):1047.
58 Marcatti M, Fracassi A, Montalbano M, et al. Aβ/tau oligomer interplay at human synapses supports shifting therapeutic targets for Alzheimer's disease. *Cell Mol Life Sci*. 2022;79:222.
59 d'Errico P, Ziegler-Waldkirch S, Aires V, et al. Microglia contribute to the propagation of Aβ into unaffected brain tissue. *Nat Neurosci*. 2022;25:20–25.
60 Amro Z, Yool AJ, Collins-Praino LE. The potential role of glial cells in driving the prion-like transcellular propagation of tau in tauopathies. *Brain Behav Immun Health*. 2021;14:100242.
61 Henstridge CM, Tzioras M, Paolicelli RC. Glial contribution to excitatory and inhibitory synapse loss in neurodegeneration. *Front Cell Neurosci*. 2019;13:63.
62 Colom-Cadena M, Spires-Jones T, Zetterberg H, et al. The clinical promise of biomarkers of synapse damage or loss in Alzheimer's disease. *Alzheimers Res Ther*. 2020;12:21.
63 Mecca AP, O'Dell RS, Sharp ES, et al. Synaptic density and cognitive performance in Alzheimer's disease: a PET imaging study with [11C]UCB-J. *Alzheimers Dement*. 2022;18:2527–2536.
64 Camporesi E, Nilsson J, Brinkmalm A, et al. Fluid biomarkers for synaptic dysfunction and loss. *Biomark Insights*. 2020;15:1177271920950319.
65 Martínez-Serra R, Alonso-Nanclares L, Cho K, Giese KP. Emerging insights into synapse dysregulation in Alzheimer's disease. *Brain Commun*. 2022;4:fcac083.
66 DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. *Ann Neurol*. 1990;27:457–464.
67 Terry RD, Masliah E, Salmon DP, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann Neurol*. 1991;30:572–580.
68 Lleó A, Núñez-Llaves R, Alcolea D, et al. Changes in synaptic proteins precede neurodegeneration markers in preclinical Alzheimer's disease cerebrospinal fluid. *Mol Cell Proteomics*. 2019;18:546–560.
69 Lauterborn JC, Scaduto P, Cox CD, et al. Increased excitatory to inhibitory synaptic ratio in parietal cortex samples from individuals with Alzheimer's disease. *Nat Commun*. 2021;12:2603.
70 Walker CK, Herskowitz JH, Dendritic Spines. Mediators of cognitive resilience in aging and Alzheimer's disease. *Neuroscientist*. 2021;27:487–505.
71 Domínguez-Álvaro M, Montero-Crespo M, Blazquez-Llorca L, et al. 3D analysis of the synaptic organization in the entorhinal cortex in Alzheimer's disease. *eNeuro*. 2021;8. ENEURO.175-23.2024.
72 Pchitskaya E, Bezprozvanny I. Dendritic spines shape analysis—classification or clusterization? Perspective. *Front Synaptic Neurosci*. 2020;12:31.
73 Hesse R, Hurtado ML, Jackson RJ, et al. Comparative profiling of the synaptic proteome from Alzheimer's disease patients with focus on the APOE genotype. *Acta Neuropathologica Communications*. 2019;7:214.
74 Paasila PJ, Aramideh JA, Sutherland GT, Graeber MB. Synapses, microglia, and lipids in Alzheimer's disease. *Front Neurosci*. 2022;15:778822.
75 Johnson ECB, Dammer EB, Duong DM, et al. Large-scale proteomic analysis of Alzheimer's disease brain and cerebrospinal fluid reveals early changes in energy metabolism associated with microglia and astrocyte activation. *Nat Med*. 2020;26:769–780.
76 Kumar A, Scarpa M, Nordberg A. Tracing synaptic loss in Alzheimer's brain with SV2A PET-tracer UCB-J. *Alzheimers Dement*. 2024;20:2589–2605.
77 Ramos-Miguel A, Jones AA, Petyuk VA, et al. Proteomic identification of select protein variants of the SNARE interactome associated with cognitive reserve in a large community sample. *Acta Neuropathol*. 2021;141:755–770.
78 Pelucchi S, Stringhi R, Marcello E. Dendritic spines in Alzheimer's disease: how the actin cytoskeleton contributes to synaptic failure. *Int J Mol Sci*. 2020;21(3):908.
79 Haytural H, Benfeitas R, Schedin-Weiss S, et al. Insights into the changes in the proteome of Alzheimer disease elucidated by a meta-analysis. *Sci Data*. 2021;8:312.
80 Hurst C, Pugh DA, Abreha MH, et al. Integrated proteomics to understand the role of neuritin (NRN1) as a mediator of cognitive resilience to Alzheimer's disease. *Mol Cell Proteomics*. 2023;22:100542.
81 Oeckl P, Janelidze S, Halbgebauer S, et al. Higher plasma β-synuclein indicates early synaptic degeneration in Alzheimer's disease. *Alzheimers Dement*. 2023;19(11):5095–5102.

82 van der Ende EL, In't Veld SGJG, Hanskamp I, et al. CSF proteomics in autosomal dominant Alzheimer's disease highlights parallels with sporadic disease. *Brain*. 2023;146:4495–4507.
83 Milà-Alomà M, Brinkmalm A, Ashton NJ, et al. CSF synaptic biomarkers in the preclinical stage of Alzheimer disease and their association with MRI and PET. *Neurology*. 2021;97:e2065.
84 Zhang H, Lyu D, Jia J. For the Alzheimer's disease neuroimaging initiative. The trajectory of cerebrospinal fluid growth-associated protein 43 in the Alzheimer's disease continuum: a longitudinal study. *J Alzheim Dis*. 2022;85:1441–1452.
85 Utz J, Berner J, Muñoz LE, et al. Cerebrospinal fluid of patients with Alzheimer's disease contains increased percentages of synaptophysin-bearing microvesicles. *Front Aging Neurosci*. 2021;13:682115.
86 Kivisäkk P, Carlyle BC, Sweeney T, et al. Increased levels of the synaptic proteins PSD-95, SNAP-25, and neurogranin in the cerebrospinal fluid of patients with Alzheimer's disease. *Alzheimers Res Ther*. 2022;14:58.
87 Askenazi M, Kavanagh T, Pires G, Ueberheide B, Wisniewski T, Drummond E. Compilation of reported protein changes in the brain in Alzheimer's disease. *Nat Commun*. 2023;14:4466.
88 Vrillon A, Mouton-Liger F, Martinet M, et al. Plasma neuregulin 1 as a synaptic biomarker in Alzheimer's disease: a discovery cohort study. *Alzheimers Res Ther*. 2022;14:71.
89 Das S, Goossens J, Jacobs D, et al. Synaptic biomarkers in the cerebrospinal fluid associate differentially with classical neuronal biomarkers in patients with Alzheimer's disease and frontotemporal dementia. *Alzheimers Res Ther*. 2023;vol. 15:62.
90 Nilsson J, Pichet Binette A, Palmqvist S, et al. Cerebrospinal fluid biomarker panel for synaptic dysfunction in a broad spectrum of neurodegenerative diseases. *Brain*. 2024;147(7):2414–2427.
91 Libiger O, Shaw LM, Watson MH, et al. Longitudinal CSF proteomics identifies NPTX2 as a prognostic biomarker of Alzheimer's disease. *Alzheimers Dement*. 2021;17:1976–1987.
92 Williams JB, Cao Q, Yan Z. Transcriptomic analysis of human brains with Alzheimer's disease reveals the altered expression of synaptic genes linked to cognitive deficits. *Brain Commun*. 2021;3:fcab123.
93 Tzioras M, Daniels MJD, Davies C, et al. Human astrocytes and microglia show augmented ingestion of synapses in Alzheimer's disease via MFG-E8. *Cell Rep Med*. 2023;4(9):101175.
94 Nilsson J, Cousins KAQ, Gobom J, et al. Cerebrospinal fluid biomarker panel of synaptic dysfunction in Alzheimer's disease and other neurodegenerative disorders. *Alzheimers Dement*. 2023;19:1775–1784.
95 Johnson ECB, Carter EK, Dammer EB, et al. Large-scale deep multilayer analysis of Alzheimer's disease brain reveals strong proteomic disease-related changes not observed at the RNA level. *Nat Neurosci*. 2022;25:213–225.
96 Chen Y, Fu AKY, Ip NY. Synaptic dysfunction in Alzheimer's disease: mechanisms and therapeutic strategies. *Pharmacol Ther*. 2019;195:186–198.
97 Wiatrak B, Jawień P, Szeląg A, Jęśkowiak-Kossakowska I. Does inflammation play a major role in the pathogenesis of Alzheimer's disease? *NeuroMolecular Med*. 2023;25:330–335.
98 Batista AF, Khan KA, Papavergi M-T, Lemere CA. The importance of complement-mediated immune signaling in Alzheimer's disease pathogenesis. *Int J Mol Sci*. 2024;25(2):817.
99 De Schepper S, Ge JZ, Crowley G, et al. Perivascular cells induce microglial phagocytic states and synaptic engulfment via SPP1 in mouse models of Alzheimer's disease. *Nat Neurosci*. 2023;26:406–415.
100 Liang N, Nho K, Newman JW, et al. Peripheral inflammation is associated with brain atrophy and cognitive decline linked to mild cognitive impairment and Alzheimer's disease. *Sci Rep*. 2024;14:17423.
101 Goossens J, Cervantes González A, Dewit N, et al. Evaluation of cerebrospinal fluid levels of synaptic vesicle protein, VAMP-2, across the sporadic Alzheimer's disease continuum. *Alzheimers Res Ther*. 2023;15:186.
102 Perez-Nievas BG, Stein TD, Tai H-C, et al. Dissecting phenotypic traits linked to human resilience to Alzheimer's pathology. *Brain*. 2013;136:2510–2526.
103 Huang Z, Merrihew GE, Larson EB, et al. Brain proteomic analysis implicates actin filament processes and injury response in resilience to Alzheimer's disease. *Nat Commun*. 2023;14:2747.
104 King D, Holt K, Toombs J, et al. Synaptic resilience is associated with maintained cognition during ageing. *Alzheimers Dement*. 2023;19:2560–2574.
105 Kauwe G, Pareja-Navarro KA, Yao L, et al. KIBRA repairs synaptic plasticity and promotes resilience to tauopathy-related memory loss. *J Clin Invest*. 2024;134(3):e169064–e169106.
106 Bhattarai P, Gunasekaran TI, Belloy ME, et al. Rare genetic variation in fibronectin 1 (FN1) protects against APOEε4 in Alzheimer's disease. *Acta Neuropathol*. 2024;147:70.
107 Phillips J, Dumitrescu L, Archer DB, et al. Longitudinal GWAS identifies novel genetic variants and complex traits associated with resilience to Alzheimer's disease. *Alzheimers Dement*. 2022;18:e067816.
108 Seto M, Weiner RL, Dumitrescu L, Hohman TJ. Protective genes and pathways in Alzheimer's disease: moving towards precision interventions. *Mol Neurodegener*. 2021;16:29.
109 van Dyck CH, Mecca AP, O'Dell RS, et al. A pilot study to evaluate the effect of CT1812 treatment on synaptic density and other biomarkers in Alzheimer's disease. *Alzheimers Res Ther*. 2024;16:20.
110 Pham AQ, Dore K. Novel approaches to increase synaptic resilience as potential treatments for Alzheimer's disease. *Semin Cell Dev Biol*. 2023;139:84–92.