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Review

Synapse pathology in Alzheimer's disease

Jessica Griffiths [a,b], Seth G.N. Grant [a,*]

[a] Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh EH16 4SB, UK
[b] Dementia Research Institute at Imperial College, Department of Brain Sciences, Imperial College London, London W12 0NN, UK

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ABSTRACT

Synapse loss and damage are central features of Alzheimer's disease (AD) and contribute to the onset and progression of its behavioural and physiological features. Here we review the literature describing synapse pathology in AD, from what we have learned from microscopy in terms of its impacts on synapse architecture, to the mechanistic role of Aβ, tau and glial cells, mitochondrial dysfunction, and the link with AD risk genes. We consider the emerging view that synapse pathology may operate at a further level, that of synapse diversity, and discuss the prospects for leveraging new synaptome mapping methods to comprehensively understand the molecular properties of vulnerable and resilient synapses. Uncovering AD impacts on brain synapse diversity should inform therapeutic approaches targeted at preserving or replenishing lost and damaged synapses and aid the interpretation of clinical imaging approaches that aim to measure synapse damage.

1. Introduction

Around the turn of the 19th century, the neuroanatomists Santiago Ramón y Cajal and Alois Alzheimer laid the foundations for the present concept that synapse damage underlies many of the symptoms of neurodegenerative disease. Cajal revealed that nerve cells contact each other at structures we now call synapses [151] and Alzheimer observed the presence of plaques and tangles in the brain of patients with dementia [3]. The evidence that synapses were lost or damaged in Alzheimer's disease (AD) was first reported in the 1980s and since then studies have shown that synapse loss correlates with cognitive decline in AD [127,136,140,23,147,29].

Until relatively recently, synapses were considered to function as simple connectors between neurons. Connectionist theories, including Hebb's influential theory of learning [51], emphasised the importance of ensembles of synaptically connected neurons as building blocks for behavioural representations. Disruption of these ensembles in neurodegenerative disease by either synapse or neuronal loss offered a plausible explanation for the behavioural deficits. However, molecular biological and proteomic studies in the last two decades have revealed that synapses are far from simple connectors. Instead, they contain thousands of proteins with complex cell biological and signalling properties [112,133,4,56]. Moreover, these proteins are differentially distributed into each synapse, producing a vast diversity of synapse types defined by their molecular composition, protein lifetime and subsynaptic nanoarchitecture [100,14,154,22,90]. These findings potentially add a further layer to synapse pathology in AD, raising the possibility that cognitive impairments could arise by altered molecular composition in particular synapse types or by alterations in the populations of synapse types in neurons and brain regions.

Here we review the literature on synapse pathology in AD, starting with key observations of synapse loss and morphological and molecular impacts from microscopy. We then discuss how pathogenic mechanisms of AD involving Aβ, tau, mitochondria and glial cells may play a role in synapse pathology, as well as the link to AD risk genes. We then consider how our current understanding of synapse molecular diversity and the brain synaptome may inform the impact and progression of AD. We also address the potential value of synapse diversity to clinical studies that utilise brain imaging approaches to report synapse pathology in living patients.

2. Microscopy studies of synapses in post-mortem AD tissue

The term "synapse pathology" encompasses a multitude of pathological changes at the synapse. These include synaptic loss, dysfunction, and toxic accumulation or aggregation of proteins within the synapse.

Below and in Table 1 we summarise observations of synapse pathology in AD made using electron microscopy (EM), diffraction-limited light microscopy and super-resolution nanoscopy (SRN), including abnormalities in synapse density, altered morphology of dendritic spines,

* Corresponding author.
E-mail address: seth.grant@ed.ac.uk (S.G.N. Grant).

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changes in synaptic protein levels and synaptic targets, and altered synaptic mitochondrial number.

2.1. Electron microscopy studies reveal synapse loss and altered morphology in AD

EM approaches have been at the forefront of studies showing a correlation between synapse loss and cognitive decline [125,122,29]. By studying mild cognitive impairment (MCI) – a presumed prodromal AD transitional state – Scheff and colleagues tracked synapse loss throughout the progression of clinical AD in many different brain regions, identifying some of the areas where synapse damage is first detected. In cases with MCI, synapse loss was first observed in the CA1 regions of the hippocampus [122], inferior temporal cortex [123] and posterior cingulate cortex [125]. In late-stage AD, synapse loss was further observed in the outer molecular layer of the dentate gyrus [122] and the precuneus cortex [124]. Interestingly, some studies also show regional and layer specificity. For example, while both posterior and anterior cingulate cortex showed reduced synapse density in layer III, only the posterior cingulate cortex had a reduction in layer V, possibly owing to its relation to motor connectivity [117]. Surprisingly, no differences were seen in synapse density in the entorhinal cortex (layer III and V), one of the most severely and earliest areas affected by neuronal degeneration in AD [119]. However, later studies have reported a reduction in the total number of synapses in the entorhinal cortex [33]. Consistent across studies and regions is the progression of synapse loss, with approximately 15–20% loss in the neocortex and limbic system in MCI and early AD, which later increases to 20–50% loss [121,147]. It is also interesting to note that although synaptic loss was observed, many of the studies above also documented a correlated increase in the size of synapses, with a maintained synaptic contact area, suggestive of a compensatory mechanism.

Focused ion beam milling and scanning EM (FIB/SEM) [88] has also been used to reveal region- and layer-specific changes in dendritic spine morphology in the transentorhinal cortex, entorhinal cortex and the CA1 region of the hippocampal formation [32,33,95]. In the entorhinal cortex, layer II spines were described as being larger and more complex, whereas layer III spines were smaller and "simple" when compared with controls [33].

2.2. Impact of AD on dendritic structure and insights at the molecular level revealed by diffraction-limited light microscopy

Although EM has regularly been used to study synapse morphology in post-mortem human AD brains, it lacks the molecular specificity and throughput that can be achieved by light microscopy. Light microscopy has been used with a range of tissue staining methods, including the classical Golgi method and antibody staining. Recently, Golgi-Cox staining and 3D modelling has been used to assess dendritic spine structure in AD [11,12]. Using this technique, thin and mushroom-shaped spine populations were reported to be lost in the dorsolateral prefrontal cortex, whereas these populations were maintained in non-demented AD pathology cases [12]. These selective structural alterations were also found to correlate with age [11].

Dendritic branching and spine structure have been examined using dye-filling approaches such as the intracellular injection of Lucifer Yellow (LY) and immunostaining for LY and phospho-tau (soma-specific phosphorylated tau). Using this approach, in the parahippocampal cortex and CA1, the presence of phospho-tau at a "pre-tangle" state was not associated with changes in dendritic spine structure or number [89]. However, once tau aggregates of neurofibrillary tangles (NFTs) formed, significant changes occurred in spine structure and number. Interestingly, when the authors combined these morphological studies with graph-theory approaches they found that phosphorylated tau-positive pyramidal neurons had communities of smaller and shorter spines and that tau-related synapse loss occurred in organised clusters rather than randomly along the dendrite [91].

The studies above provide evidence that AD is associated with changes in synapse morphology but lack information on the molecular composition of the synapses. Toward this issue, a number of studies have used immunolabelling methods with antibodies directed to synaptic proteins. Some of the earliest studies used densitometry of areas of tissue immunostained for synaptophysin, a protein found in presynaptic terminals. In early AD, a loss of synaptophysin immunoreactivity was detected specifically in the dentate gyrus oriens lacunosum-moleculare (OLM) but was maintained in neocortical and entorhinal regions until late AD [85]. Severe loss of synaptophysin was observed in all neocortical layers and in the limbic systems in advanced AD [78,84]. Reduced expression of other presynaptic proteins (complexin 1, syntaxin 1A, synaptotagmin 1 and synaptogyrin 1) has also been found in the OLM, but preserved in other layers of the hippocampus [50]. Moreover, the

Table 1
Synaptic changes observed in human post-mortem AD tissue by microscopy.

Brain Region	Density	Morphology		Synaptic Proteins Levels						Other	Ref.
		Size	Spine type	SYP	SYN	GAD	PSD95	GPHN	Other		
Frontal ctx	↓	↑, ↓ stubby	↓ thin & mushroom	↓						↓ presynaptic mitochondria	[12,78,84, 103,118]
Parietal ctx	↓			↓			NC in density, ↓ PSD95/GPHN IR ratio, ↑ peak PSD95/GPHN IR		↓ PAK3 + ACTR2		[124,72,73, 84]
Temporal ctx	↓	↑, ↓ volume if oAβ+	↑ large, ↓ small	↓	↓	↓	↓			↓ presynaptic mitochondria, ↑ clusterin in synapses	[59,64,69, 79,86,105, 121,123]
Cingulate ctx	↓										[117,125]
Entorhinal ctx	NC	NC overall	↑ complex in LI, ↑ simple in LII	NC						↓ synapses targeting spine heads	[32,33,85, 119]
Hippocampus - CA1	↓/ NC*	↑ PSD	↓ perforated and large AS synapses							SR: ↓ axodendritic S SP: ↓ axospinous AS & ↑ axodendritic	[50,95,122]
Hippocampus - DG	↓	↑		↓					↓ CPLX1, STXIA, SYTI & SYNGRI in OLM		[7,85,122, 120,116]

*Inconsistent result between studies. SYP, synaptophysin; SYN, synapsin; GAD, glutamic acid decarboxylase; PSD95, post-synaptic density 95; GPHN, gephyrin; ctx, cortex; IR, immunoreactivity; NC, no change; PAK3, p21 (RAC1) activated kinase 3; ACTR2 (Arp2), actin-related protein 2; oAβ, oligomeric amyloid beta; L, layer; CA1, cornu ammonis 1; SR, stratum radiatum; SP, stratum pyramidale; DG, dentate gyrus; CPLX1, complexin 1; STXIA, syntaxin Ia; SYTI, synaptotagmin 1; SYNGRI, synaptogyrin 1; S, symmetric; AS, asymmetric; OLM, outer molecular layer.

presynaptic vesicle proteins VAMP2 and SHANK2 were not altered, indicating that some proteins are affected more than others. With regards to inhibitory synapse loss, triple fluorescence confocal microscopy in APP/PS1 mice and AD patients revealed that membrane surfaces in contact with plaques lack GABAergic (VGAT- and GAT1-positive) peri-somatic synapses, potentially leading to hyperactivity of neurons in contact with plaques [40].

To go beyond the axial resolution of light microscopy (~70 nm), ultra-thin tissue sectioning and deconvolution methods have been used in array tomography and fluorescence deconvolution tomography. Combined with fluorescent antibody labelling of inhibitory and excitatory synaptic proteins, these methods have been used to study synapse numbers and their association with plaque location, oligomeric Aβ, genotype, and the ratio of excitatory and inhibitory synapses in AD post-mortem brain tissue [58,64,68,72,73]. Koffie and colleagues were the first to use array tomography to study synapse loss specific to the *APOE* ε4 genotype in human [64]. The authors also found that synapse density decreases closer to the plaques' halo of oligomeric Aβ, suggesting that pre- and postsynaptic terminals may have differential vulnerability dependent on plaque distance. This technique was also used to identify reduced levels of two actin regulatory proteins, the Rho GTPase effector p21-activated kinase (PAK) and Arp2 (ACTR2), which could indeed play a role in synaptic actin cytoskeleton destabilisation early in AD [72]. Most recently, it was found that the ratio of PSD95-positive excitatory and gephyrin-positive inhibitory synapses is significantly altered in AD, particularly in layer II of the inferior parietal cortex [73], highlighting a possible electrophysiological imbalance that could lead to altered network activity.

2.3. Super-resolution nanoscopy and AD impacts on subsynaptic nanoarchitecture

In contrast to conventional fluorescence light microscopy, which is constrained by light diffraction limitations, SRN can resolve the subsynaptic localisation of labelled proteins, revealing their differential distribution within and between synapses. To date, few SRN studies have been directed at synaptic pathology in human AD, although mouse models and cell cultures have been used. In APP/PS1 mice, stimulated emission depletion (STED) nanoscopy revealed changes in hippocampal spine head and neck morphology [145]. The morphology of a whole human amyloid plaque was reconstructed using STED and array tomography [107]. STED has also been used to resolve tau filament structures in AD cortical grey matter [6] and to validate potentially novel synaptic biomarkers from CSF in preclinical AD [79].

Both pre- and postsynaptic components are organised into dynamic, asymmetric, nanodomains or nanoclusters that are thought to regulate synaptic transmission and synaptic plasticity [52]. Given that NMDA, AMPA and PSD95 all form nanodomains [14,80,96] and all interact with Aβ and tau, it has been speculated that these nanodomains could become damaged and impair downstream signalling events [101]. These authors suggested that extracellular Aβ, via receptor binding and recruitment of signalling and scaffolding molecules, could generate neurotoxic nanodomains, or that intracellular tau could form its own neurotoxic domain, alongside altering synaptic stability and composition.

The current guidelines from the National Institute on Aging-Alzheimer's Association (NIA-AA) categorise three preclinical stages of AD (Phase 1 - cognitively normal subjects with signs of brain amyloidosis; Phase 2 – amyloidosis and neurodegeneration; Phase 3 – amyloidosis and neurodegeneration with subtle cognitive decline) [134]. Most of the microscopy studies detailed above compare synapse changes in individuals who are cognitively healthy with those with MCI or early/mild and late AD. These studies have not directly measured or clearly categorised synapse pathology in preclinical AD, not least because of the different criteria and interpretations of these stages in the literature [126,134,34,97]. The term "preclinical AD" has also been used to describe individuals who are resilient to dementia or ageing normally [12,34]. Proteomic studies of CSF from preclinical AD (NIA-AA categorised) have indeed shown changes in synapse protein levels that precede neurodegeneration [79], suggesting that synapse pathology is one of the earliest hallmarks of AD. It would be of great importance to thoroughly characterise synapse loss and damage at the preclinical stages of AD and understand whether there are differences between those individuals who do or do not develop clinical AD later in life.

3. Mechanisms of synapse pathology in AD

Pathogenic Aβ and tau species can drive synaptic deficits in AD via interactions with specific synaptic proteins as well as mitochondria. This can cause alterations in synaptic protein composition and lead to oxidative stress. Indirectly, they are also instrumental in instigating chronic inflammatory responses and overactivation of glial cells, leading to excessive synapse elimination. These events are followed by axonal degeneration and ultimately lead to neuronal loss.

Large-scale proteomic studies of post-mortem AD tissue have identified numerous changes in synaptic protein levels throughout the progression of the disease and in different brain regions. The identified proteins are involved in endosomal pathways, vesicular assembly, signal transduction, axonal transport, and mitochondrial function [152,16,18,147,53].

Studies are yet to understand what causes Aβ, tau and glial cells to target certain synapses in vulnerable brains and regions in AD; however, toxic species heterogeneity and specific molecular targets are starting to be unravelled. Below and in Fig. 1 we discuss and show some of the major synaptic targets of Aβ and tau.

3.1. Aβ species and synaptic targets

Synapse loss occurs at a greater rate closer to aggregated Aβ or amyloid plaques [64], indicating that Aβ could be playing a role in this selectivity. Heterogeneous distributions and mixtures of Aβ assemblies of both low and high molecular weight are generated in the brain [144,40]. Specific oligomers and soluble forms of Aβ have been located at the synapse [104,131,36,61] and shown to correlate with dementia progression, appearing before phosphorylated tau species [148,9]. Interestingly, rather than aggregated Aβ, oligomeric Aβ surrounding these aggregates is considered the synaptotoxic component [64] and is linked to AD-related cognitive decline [10]. It is thought that by acting at the postsynaptic density (PSD), soluble Aβ disrupts the induction of synaptic plasticity. Soluble Aβ species have also been identified at damaged synapses in AD [139] and associated with the PSD *in vivo* [63]. Additionally, subsynaptic localisation of soluble Aβ species has been confirmed using SRN [104]. Region-specific binding of oligomeric Aβ has also been identified, reminiscent of the brain regions vulnerable in AD [69]. It is possible that variability in the composition and regional distribution of Aβ assemblies or oligomers lead to differential impacts on synapses according to their molecular composition.

From *in vitro* studies, oligomeric Aβ applied to the extracellular medium appears to preferentially bind to excitatory compared with inhibitory synapses [69]. However, an accumulation of Aβ has been found in a small subset of inhibitory presynaptic terminals near Aβ aggregates in the visual and temporal cortex of human AD brains [68]. Moreover, both glutamate [48] and GABAergic [49] activity are defective in synaptosomes from AD brain, suggesting that Aβ may target both excitatory and inhibitory synapses.

It is possible that Aβ has alternative binding sites and affinities for different synaptic molecules at pre- and postsynaptic terminals. Aβ has been speculated to interact with numerous synaptic receptors (as shown in Fig. 1) leading to increased intracellular Ca^{2+} levels, impaired synaptic plasticity, proteasome degradation and, ultimately, synaptic deterioration. These include NMDA [111,128,27], mGluR5 [108], EphB2 [21], EphA4, α7 [146,77] and α4β2 [106] nicotinic acetylcholine receptors. Using unbiased far western ligand blots, α3 Na/K-ATPase,

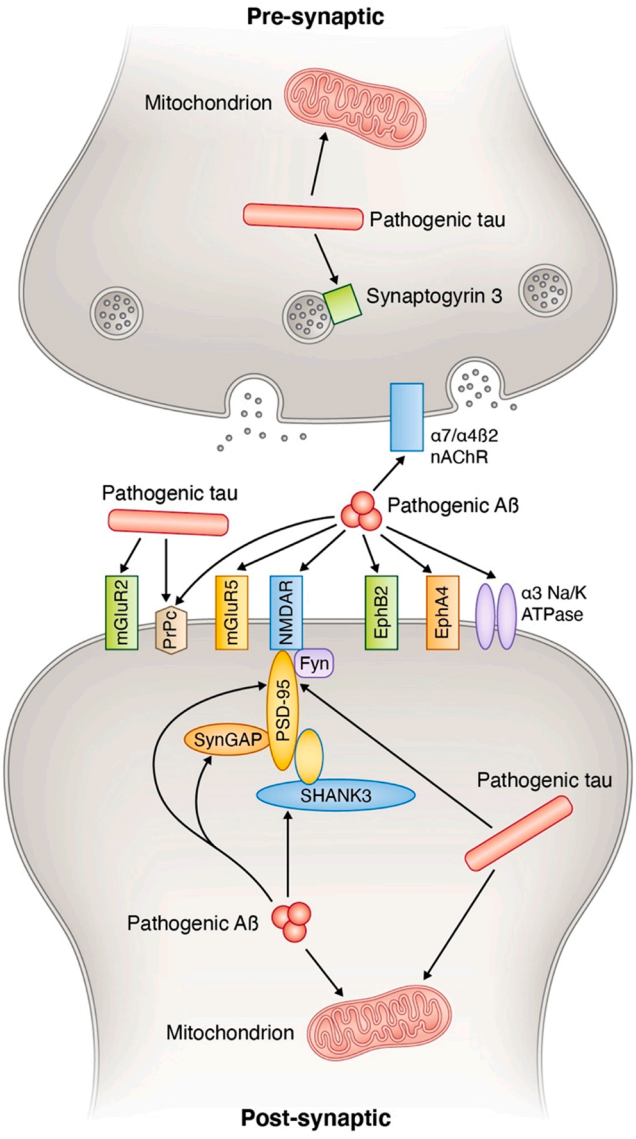

Fig. 1. Synaptic protein targets of pathological proteins in AD. Pathogenic Aβ and tau target presynaptic and postsynaptic proteins in the extracellular space and cytoplasm. Mitochondria are also targeted, interfering with energy metabolism.

PSD95, SynGAP and SHANK3 have also been identified as key binding partners and all show a loss at the PSD of human AD frontal cortices [31,44], revealing that there are intracellular as well as extracellular direct targets.

3.2. Tau species and synaptic targets

Normally, tau protein interacts with and stabilises axonal microtubules. Normal tau has also been localised and postulated to play a role in synaptic vesicle and receptor trafficking at the pre-synapse and PSD, respectively [110]. Hyperphosphorylated, misfolded, and oligomeric tau, accumulate at pre- and postsynaptic terminals in AD brains [130,132,138,36]. While tau phosphorylation has been found to drive mislocalisation to both synaptic terminals [55], tau misfolding has also been shown to occur locally at the synapse [138]. Moreover, some species of tau spread trans-synaptically [2,30,93], leading to perturbed pre- and postsynaptic function before NFT pathology in human AD [105,130,30,66].

Like Aβ oligomers, tau oligomers are considered the most synaptotoxic species of tau [70], with increased levels correlating with increased ubiquitylated substrate and proteasome components, possibly mediating proteotoxicity at the synapse [137]. Moreover, the presence of tau oligomers at synapses has been linked to the cognitive deficits in AD [130].

Tau has also been shown to interact with pre- and postsynaptic targets (Fig. 1). In the presynaptic terminal, tau interacts with synaptic vesicles, possibly mediated through an interaction with synaptogyrin 3, which could cause clustering of F-actin, affecting vesicle mobility and release [153,86]. In the postsynaptic terminal, phosphorylated tau physically interacts with FYN and the complex formed by PSD95 and NMDA receptors [94], likely disrupting glutamate receptor signalling, trafficking, and leading to reduced receptor surface expression [57]. Phosphorylated tau also appears to colocalise with mGluR2, with phosphorylated tau-mediated mGluR2 upregulation being reported in a subset of pyramidal neurons in the CA1 and NFT-containing CA3 neurons, but not dentate gyrus neurons [74].

Studies have reported colocalisation of Aβ and phosphorylated tau species in human AD synaptosomes, suggesting that there may also be synergistic mechanisms at play [36]. Interestingly, tau shares a synaptic target with Aβ, with both pathological species binding to the lipid-anchored cellular prion protein (PrP^c) [143,24,71]. While Aβ-bound PrP^c has been shown to drive mGluR5-dependent FYN kinase activation [143], this interplay between Aβ and phosphorylated tau possibly causes accelerated spread of tau pathology [42].

3.3. Mitochondrial dysfunction and synapse loss

Mitochondrial dysfunction is an early etiological event in AD, causing reduced ATP production, altered mitophagy, oxidative stress, and increased ROS production [5], leading to progresive synaptic loss, axonal alterations and eventually neuronal degeneration. It has even been suggested that altered mitophagy in the entorhinal cortex may be the initial hallmark of AD pathology [62]. In human AD post-mortem tissue, a selective reduction of mitochondria has been reported at the presynaptic terminal in the primary auditory cortex [103]. Proteomic studies have also highlighted a downregulation of proteins involved in oxidative phosphorylation in synaptoneurosomes isolated from the auditory cortex, and this downregulation was enhanced in *APOE* ε4 carriers [53].

In AD models and patients, both Aβ and pathogenic tau have been shown to directly interact with mitochondrial components, including Aβ with the mitochondrial fission protein Drp1 [83,82], and Aβ and pathogenic tau with complex IV and I of the electron transport chain, respectively [109,26]. Mutant tau can also disrupt microtubule-based cellular transport, affecting mitochondrial transport and possibly altering their recruitment and redistribution at the synapse [65]. Moreover, ROS-mediated redox modification of phosphorylated Akt1, a target for mTOR signalling, causes activity-dependent protein translation defects in AD [1], possibly leading to changes in synaptic protein composition.

Other organelles are also affected early in AD. For example, endosomes are significantly enlarged in AD patients [17]. Accumulating evidence has shown a link between early AD and alterations in autophagy and the endosomal-lysosomal system [98,99]. Functional autophagy has also been proposed to be required for neurotransmission and synaptic plasticity [76]. It is therefore possible that disrupted autophagy directly damages synapses through altered degradation of synaptic proteins and indirectly by hindering the degradation of Aβ and tau.

3.4. Glia-mediated synapse loss

Microglial cells have received considerable attention in recent years because of their postulated role in engulfing either the pre- or postsynaptic terminal [114,149] and because AD risk genes are enriched in microglial markers [59,67]. Because microglial cells are highly

influenced by their environmental context, their effects in AD are very complex. Initially, when an innate immune response is triggered by a build-up of toxic protein aggregates, microglia may be protective, as they can cluster and clear toxic protein via phagocytosis and release of proteases [60]. In later AD, further build-up of Aβ and tau causes a shift from a neuroprotective to a neurotoxic microglia state. This can lead to sustained release of pro-inflammatory cytokines such as IFN-γ, IL-1β and TNF-α, causing excessive complement-mediated synaptic elimination, inhibition of synaptic plasticity, and ultimately neurotoxicity [102,54]. *APOE* ε4 patients with AD also have an exacerbated increase in microglial activation [92], in line with exuberated synapse loss [64].

An overarching question remains: how do glia decide which synapses should be eliminated? Components of the complement pathway are enriched in human AD synaptoneurosomes [53], suggesting that they might be "eat me" signalling candidates for microglia synapse "ingestion". Genetic deletion of C3, CR3 and C1q reduces synapse loss and cognitive deficits in AD mouse models [129,150,28,54]. Also, overexpression of C1q at excitatory synapses has indeed led to aberrant synapse elimination, with C1q knockout mice preventing oligomeric Aβ-induced synaptotoxicity and synaptic plasticity impairments [37,54,8]. Conversely, CD47-Sirpa has been reported as a potential "don't eat me" signal in AD [75].

The role of astrocytes in synapse loss has been much less studied. Accumulation of Aβ, plus the upregulation of proinflammatory cytokines via microglia, leads to astrogliosis [35]. Moreover, reactive astrocytes appear to engulf presynaptic terminals from dystrophic neurites in late AD [43]. Whether this mechanism is impaired and leads to excessive synapse elimination in AD remains to be investigated.

While many studies have examined glia-mediated synapse loss in mouse models, one-third of AD risk genes lack mouse orthologues and human microglia have heterogeneous transcriptional profiles compared with mouse microglia [41], suggesting that species differences will be important in interpreting the results of studies in mouse models. Efforts are currently being put forward to transplant stem cell-derived human microglia into the mouse brain to study AD [81].

4. A link between AD risk genes and synapse pathology

APOE ε4 is a strong risk variant for AD, and in patients carrying this allele oligomeric Aβ has enhanced synaptic localisation alongside higher oligomeric Aβ burden and synapse loss [64]. APOEε4 has also been shown to selectively impair glutamate activity and NMDA receptor phosphorylation via reelin, reducing low-density lipoprotein, NMDA, and AMPA receptor surface expression [20], a mechanism that may be specific to *APOE* ε4 patients [135]. Moreover, with APOEε4 being a cholesterol transport protein and a primary risk factor in AD, studies have emphasised a dysregulation in membrane lipids as an important pathological mechanism in AD. Flow cytometry analysis of Aβ-positive AD synaptosomes has shown elevated levels of cholesterol and GM1 ganglioside, alongside an increase in SNAP25 and reduced levels of PSD95 [46,47]. It is unknown whether molecularly distinct synapses are altered due to APOEε4.

A mutant variant of the triggering receptor expressed on myeloid cells 2 (*TREM2*) gene is also strongly associated with an elevated risk of developing AD [59]. *TREM2* encodes a microglia-specific innate immune receptor and plays a role in microglial phagocytosis and synapse elimination. It has been reported that the AD-linked R47H-TREM2 mutation may induce disease-associated microglia (DAM) and hyperactivation of AKT [113], possibly leading to excessive synaptic pruning in AD.

5. The role of synapse diversity in AD

The substantial literature on synapse pathology of AD described above has clearly demonstrated synapse loss, changes in synapse morphology and differential interactions of synapse proteins with pathogenic mechanisms. Advances in our understanding of the fundamental organisation of the postsynaptic proteome of excitatory synapses has uncovered two general principles that are of importance to this literature. The first principle is that the overall population of excitatory synapses (the synaptome) is highly heterogeneous with respect to their protein composition and their protein turnover rates; these diverse synapses are spatially distributed across the brain (the synaptome architecture) and this spatial distribution changes with age (the lifespan synaptome architecture) (Fig. 2) [100,14,15,154,22,90]. It therefore follows that pathogenic proteins will target particular excitatory synapse subtypes, which will be vulnerable to the toxic effects of these proteins. By contrast, there will be subtypes of synapses that do not express targets of pathogenic proteins and these will be resistant to their toxic effects (Fig. 3). The second principle is that there is a molecular logic that explains why certain proteins are found in particular synapses (Fig. 2) [154,38,39]. This logic links a hierarchy of gene expression, protein expression and protein assembly into complexes and supercomplexes with the synapse nanoarchitecture and, ultimately, synapse molecular diversity and the brain synaptome architecture (Fig. 2). As discussed below, pathogenic mechanisms that interfere with this hierarchical framework at any of its levels can result in alterations in the synaptome.

5.1. Synaptome mapping as a tool to uncover disease impacts

The recent development of 'synaptome mapping' methods that enable protein composition and lifetime to be systematically measured at single-synapse resolution has provided the first insight into how the synaptome and synaptome architecture are altered by disease processes. Initial studies encompassing *Psd93*, *Sap102* and *Pax6*, which are mutated in cognitive disorders including autism, intellectual disability and schizophrenia, have shown that these mutations indeed alter synapse diversity in the mouse brain and that impacts may be targeted to particular age-windows [142,154]. There are hundreds of genes encoding synapse proteins that are mutated in human brain diseases and it is likely that they will each have a synaptomic disease signature [45]. A key advantage of synaptome mapping technology is that it can be systematically applied on a whole-brain scale in mouse disease models and detect pathology wherever it may occur, obviating the limitations that arise from microscopy studies that are restricted to small brain regions.

5.2. The human brain synaptome and prospects for AD research

Little is known about the human brain synaptome. A recent pioneering study of PSD95-labelled excitatory synapses confirmed different populations of synapses in human brain regions [25]. Moreover, correlations revealed conservation of synaptome architecture in homologous regions of human and mouse brain. In a preliminary study of the synaptome of excitatory synapses in the human hippocampal formation, we have identified excitatory synapse subtypes that are affected at different stages of AD progression (O. Curran, Z. Qiu, B. Notman, C. Smith, S.G.N. Grant, unpublished). Application of synaptome mapping approaches to human AD post-mortem tissue will be crucial for comprehensively describing the synapse types affected in AD. Synaptome mapping can be integrated with other forms of synaptic, cellular and anatomical analysis, such as quantitative imaging of Aβ and tau, spatial transcriptomics and proteomic methods, an objective of the UK Dementia Research Institute Multi-'omics Atlas Project.

The scalability of synaptome mapping could be applied to study the anatomical spread of AD. The timing, route and spread of Aβ plaques and tau aggregates differ, with amyloid deposition occurring before the onset of tau, starting in the neocortex, progressing to the allocortex, subcortical nuclei, and eventually reaching the brainstem and cerebellum [141]. Conversely, NFTs stereotypically first appear in layer II of the entorhinal cortex and accumulate in the transentorhinal region in

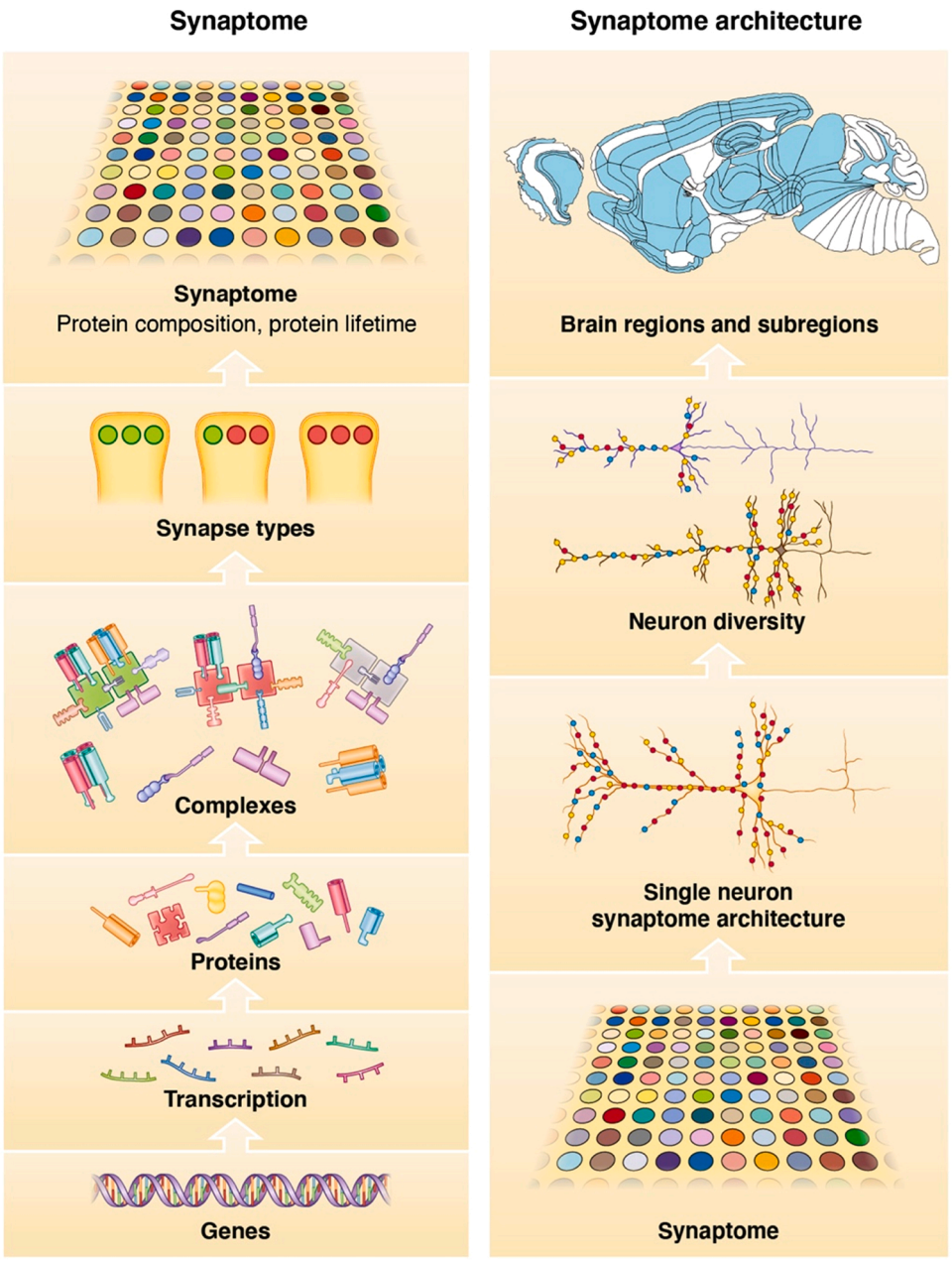

Fig. 2. The molecular logic linking the genome to synaptome architecture. The left panel shows how gene expression produces proteins that are physically assembled into complexes and supercomplexes, which are then differentially distributed into individual synapse types, which together comprise the synaptome. The right panel shows how the synaptome is spatially distributed on neurons and ultimately in brain regions producing the synaptome architecture of the brain.

the medial temporal lobar structures, progressing to the neo- and allocortex [13]. Moreover, we know that pathological tau can spread trans-synaptically early in AD [30]. It is possible that this spread could progressively modify the synaptome architecture. Conversely, synaptic composition may also be important in determining the rate/pattern of the spread of tau pathology, offering the possibility that certain synaptome architectures may be vulnerable to AD.

Old age is another major risk factor for AD. We know from studies of the mouse brain lifespan synaptome architecture that although there is an overall loss of excitatory synapses in ageing mice, there are subsets of synapses that are preferentially preserved and, conversely, others that are lost at a higher rate [22]. The age-resilient synapses are those with the longest PSD95 protein lifetimes [15], suggesting that their slow rate of protein turnover may influence their susceptibility to pathogenic mechanisms. It will be important to establish whether synapse subtypes that are affected by natural ageing are those that are vulnerable or resilient to AD. This will be a stepping-stone toward identifying the molecular composition of those synapse subtypes and hence the molecular mechanism that renders them selectively vulnerable to AD. Fig. 3 shows how loss of synapse subtypes at stages of AD progression could have selective effects on neuronal circuitry. The identification of biomarkers of these synapse subtypes could contribute to the development of cell-based screening assays for compounds that stabilise these synapses or promote their formation, potentially leading to pro-synaptic therapeutic approaches.

Monitoring synapse pathology in living patients will be necessary for evaluation of pro-synaptic therapeutics. Currently, there is considerable interest in the positron emission tomography (PET) tracers that bind to the presynaptic vesicle protein SV2A, which has been proposed as a ubiquitous synaptic marker. Studies in AD patients have shown

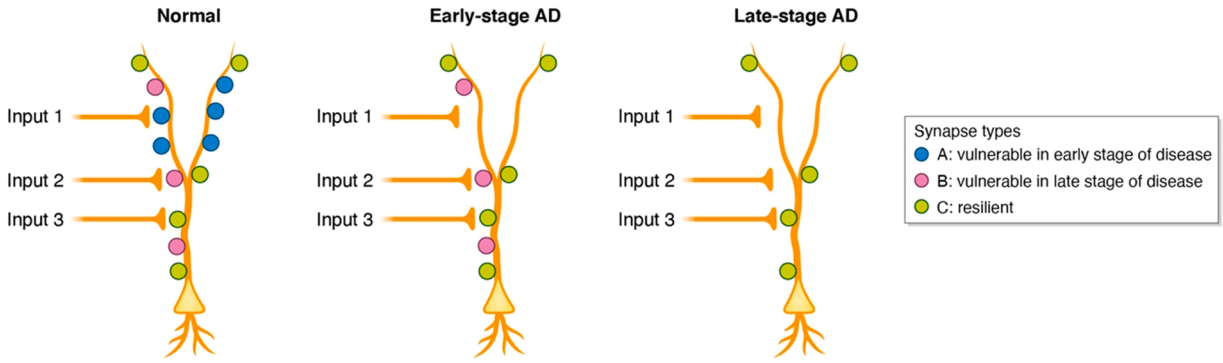

Fig. 3. How synapse diversity could impact on AD progression. A neuron decorated with three synapse types (A,B,C) that each contain different proteins that make them vulnerable at early or late stages of AD or resilient (key). Type C proteins may be resilient because they do not contain targets for pathogenic proteins (Aβ and tau). The differential loss of synapse types with disease progression may impact on connectivity, as shown by the inputs (1−3).

alterations in the distribution of SV2A labelling [19,87]. Little is in fact known about the synaptome of SV2A-positive synapses, and in order to understand what these clinical impacts mean it will be crucial to establish whether it is subsets of synapses, rather than all synapses, that express SV2A and to what extent these synapses are damaged in AD.

6. Conclusions

It is evident that synaptic dysfunction and loss orchestrated by exposure to pathological Aβ and tau are mechanisms of AD. However, our knowledge of how these mechanisms disrupt the highly complex synapse proteome is still in its early phases. The recognition that synapses are highly diverse has opened up a new front in AD research aimed at identifying and characterising synapses that are affected at different stages of AD progression. Addressing these issues may lead to new diagnostic and therapeutic avenues focussed on preserving vulnerable synapses or replacing those that are lost and thereby slow or reverse the progression of dementia.

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Conflict of Interest

We declare there is no conflict of interest in the preparation of submission of this manuscript.

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