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Review

Recent Progress in Alzheimer's Disease Research, Part 1: Pathology

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Abstract. The field of Alzheimer's disease (AD) research has grown exponentially over the past few decades, especially since the isolation and identification of amyloid-β from postmortem examination of the brains of AD patients. Recently, the *Journal of Alzheimer's Disease* (JAD) put forth approximately 300 research reports which were deemed to be the most influential research reports in the field of AD since 2010. JAD readers were asked to vote on these most influential reports. In this 3-part review, we review the results of the 300 most influential AD research reports to provide JAD readers with a readily accessible, yet comprehensive review of the state of contemporary research. Notably, this multi-part review identifies the "hottest" fields of AD research providing guidance for both senior investigators as well as investigators new to the field on what is the most pressing fields within AD research. Part 1 of this review covers pathogenesis, both on a molecular and macro scale. Part 2 review genetics and epidemiology, and part 3 covers diagnosis and treatment. This part of the review, pathology, reviews amyloid-β, tau, prions, brain structure, and functional changes with AD and the neuroimmune response of AD.

Keywords: Aggregation, Alzheimer's disease, amyloid, brain structure, connectome, neuroinflammation, pathology, prion, signaling, tau

INTRODUCTION

Following a long period of mystery since Alois Alzheimer first described a patient suffering from dementia over 100 years ago [1], the field of Alzheimer's disease (AD) research has grown exponentially since Glenner and Wong's initial report identifying the purification of an amyloid protein in the brains of demented patients [2] and the positing of the amyloid cascade hypothesis [3, 4] in the early 1990s. Within the past 5 years, over 20,000 papers have been published on the subject of AD according to our search of PubMed "Alzheimers disease". These advances have tremendously increased our understanding of this disease and reinforced just how complex AD is. This complexity and multifactorial nature of AD has led some leading AD researchers to hypothesize that AD is not a disease in the technical sense, but more like a syndrome, a collection of pathologies which manifest themselves as common symptoms classically described as age-related memory loss and personality changes [5]. Regardless of whether or not this hypothesis is true, it has become readily apparent that AD is a complex disease and the pathophysiology of AD cannot be explained by solely the abnormal metabolism of amyloid-β (Aβ) [6].

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Recently, the *Journal of Alzheimer's Disease* presented their readership with approximately 300 of the most significant reports in the field of AD research within the last five years, and solicited their membership to vote to select the top 50 impactful reports. (These papers and comments can be found at http://www.j-alz.com/top50). This exercise inspired us to write a multipart review reviewing the most significant contributions in the field in the last five years, a so-called "Greatest Hits" of the field of AD. Due to the diversity of the field of AD research, we felt that this review would be best presented as a multi-part review, with each review uniting a broad spectrum of subjects tied together under a unifying theme. Part one, *Pathology*, covers the pathophysiology of AD on a molecular, cellular, and organ level. On a molecular basis, a contemporary treatment of our understanding of Aβ and the microtubule tau protein is provided. On a cellular level, mitochondrial dysfunction has been observed in AD providing yet another effect (or cause) of AD pathology. Furthermore, cell signaling and inflammatory and immunological responses have also been demonstrated to either exacerbate the symptoms, or be the result of, AD. Despite the reductionist tendencies of biophysicists and biochemists, the molecular and cellular effects of AD should not be seen in isolation; rather they should be viewed as a complex and interdependent system in which macroscopic effects will alter brain structure and therefore the psychology and well-being of the AD patient. How these various factors affect this system is a burgeoning, and very important, aspect of contemporary AD research. Research into the brain "connectome", the network of synaptic connections in the brain, is one aspect of this systems research. The increase in modern computing power and "big data" may allow further insights into how the multitude of factors affects the cognitive capacity of AD patients.

Part two, *Genetics and Epidemiology*, provides a broad treatment of the genetic basis of AD, and especially the *APOE* gene, of which the ε4 allele is strongly correlated with the early onset and prevalence of AD. Additionally, numerous other loci have been demonstrated to be associated with AD onset. Because of the wide prevalence of AD, especially with the aging population in North America, the epidemiology and risk factors of AD have been extensively studied. The second part of this review covers these risk and public health factors.

The third, and final part, *Diagnosis and Treatment*, draws together the knowledge gained on AD etiology to address the diagnosis, imaging, and treatment of AD. Whereas the conclusive pathological diagnosis of AD was previously only possible postmortem, the advent of modern imaging techniques such as positron emission tomography (PET) together with novel molecular probes, has allowed clinicians and researchers the ability to localize molecular process in the brain while the subject is still alive. These techniques have opened up an entirely new way of studying AD and other dementias. Despite a much greater understanding of AD, an efficacious treatment of AD is still elusive. The third part of this review concludes with a discussion of pharmaceutical and non-pharmaceutical treatment strategies of AD and a discussion of the failures of the clinical trials within the last five years.

Despite the diversity of the research contained within this part, there are two topics which appear to be the "hottest" in the AD pathology field: 1) the concept of amyloid as a prion-like disease, which perhaps explains why so many clinical trials relying on Aβ vaccines have failed, and 2) how the brain's "connectome", the network of neurons, is affected by AD. The AD-connectome subject is particularly fascinating because it attempts to harness the true complexity of AD pathology and how molecular variations result in changes to how neurons interact with one another on a grander scale. We are of the opinion that in the past, AD researchers took an overly reductionist view of AD. This point is perhaps captured best by the somewhat humorous "religious" wars of the past between the βAptists versus the Tauists, neither side initially realizing that neither Aβ nor tau were solely capable of explaining the diversity of pathologies in the brains of AD patients.

In its entirety, we hope that this multi-part review can serve as a starting point to chronicle the knowledge gain in the AD field over the last five years and serve as a primer of the direction the most relevant and exciting AD research is heading.

METHODS

All 300 reports identified by JAD (http://www.j-alz.com/top50) were downloaded and sorted into the appropriate categories (Part 1: Amyloid, Tau, Prions, Brain Structure and Functions, and Neuroimmune Response; Part 2: Epidemiology, Factors, and Genetics; Part 3: Diagnosis, Biomarkers, Imaging, and Treatment). The results of these reports were summarized and discussed. Additional reports sourced from within the citations of the 300 "top

reports" were included in some cases to provide additional background for the readership.

AMYLOID-β

Aβ was first identified in 1984 as the principal component of amyloid deposits [2]. Amyloid fibril, or amyloid, is classically defined as an extracellular proteinaceous deposit which displays apple-green birefringence when stained with Congo Red and viewed under circularly polarized light. This pattern is attributed to the cross β-sheet secondary structure associated with amyloid fibrils [7]. However this definition has recently been put under some scrutiny as there are many other proteins which form fibrils that do not meet the classical definition [8]. In more contemporary definitions, amyloid is defined as "any polypeptide aggregate with a cross β-sheet structure" regardless of whether or not birefringence is observed [8]. The preference of which amyloid definition is more correct is likely largely dependent on the field of study. For a biophysicist or molecular biologist, the more contemporary definition of amyloid is more representative of the large advances that have been made in studying synthetic (i.e., custom peptide section created *in vitro*). On the contrary, for a physician, concerned merely with pathological amyloid deposits, the classical definition of amyloid may be more appropriate.

The discovery of amyloid in AD led to the proposal of the amyloid cascade hypothesis which posits that the presence of these amyloid plaques, leading to a postmortem diagnosis of AD, or later proposed, their oligomers, resulting in synaptic failure and neurodegeneration [3, 4]. Aβ is a disordered peptide with a peptide length of 39–43, the most abundant being $Aβ_{40}$ [9] with $Aβ_{42}$ being the predominant isoform in senile plaques [10].

In aqueous solution, Aβ occurs predominantly in a random coil conformation. When integrated within a membrane, amyloid-β consists of a hydrophilic, extracellular region located at residues 1–28, and a hydrophobic, α-helical coil at residues 29–42 [11].

The amyloid-β protein precursor (AβPP) encoding gene is located within chromosome 21 and is expressed in a variety of glial, endothelial, epithelial, and spleen cells. The function of AβPP is still unclear, but research has suggested that AβPP may have a role as an autocrine factor to stimulate the proliferation of fibroblasts [12] and as a modulator of cell adhesion. In addition, AβPP is implicated in the regulation of intracellular calcium [13], metal ion homeostasis [14], cholesterol binding [15], and cell growth [12].

Once Aβ is cleaved from AβPP by the β- and γ-secretase enzymes, it is secreted into the interstitial fluid (ISF) [16]. In healthy persons, excess Aβ is cleared from the brain whereas in pathological cases, Aβ misfolds, aggregates, and becomes neurotoxic [17] with intermediate oligomers likely being the most neurotoxic species [18]. Aβ has been shown to form a variety of quaternary structures including amyloid fibrils [19], and a broad class of possibly intermediate structures termed "amyloid oligomers", which include a variety of structures such as prefibrillar oligomers [20] and annular protofibrils [21], among others.

Perhaps the most frightening insight into Aβ pathology is the recent work by Jaunmuktane et al. who recently showed that Aβ is transmissible between humans (though thankfully not infectious) [22]. It is possible, though rare, that toxic Aβ and eventually AD symptoms can be transmitted from dura mater donors to recipients. Because of the prion-like properties of insoluble toxic Aβ structures which may be resistant to destruction by autoclaving, it is theoretically possible that AD could be transmitted via neurosurgical instruments.

Amyloid structure

The molecular structure of Aβ structures including monomers, fibrils, and oligomers were long unresolvable because of their inability to crystallize and the monomers' inherent random structure. However, recent advances in x-ray diffraction have provided atomic details into small segments of amyloid structure, while solution NMR has provided insight into the overall structure of complete amyloid peptides and evidence of variations of Aβ structures (Fig. 1) [23–31]. The most common amyloid aggregate isolated from the brains of AD patients is the fibril [9]. The amyloid fibril is comprised of a series of Aβ peptides, which fold back on themselves, arranged in a parallel or anti-parallel manner to form a slender protofilament. A number of these protofilaments wrap around one another to form a mature amyloid fibril [23, 32].

Plaque density has been demonstrated to be a poor correlate of cognitive impairment in AD patients [44]; however, amyloid deposition has been shown to correlate with the probability of mild cognitive impairment (MCI) progression to AD [45]. The poor

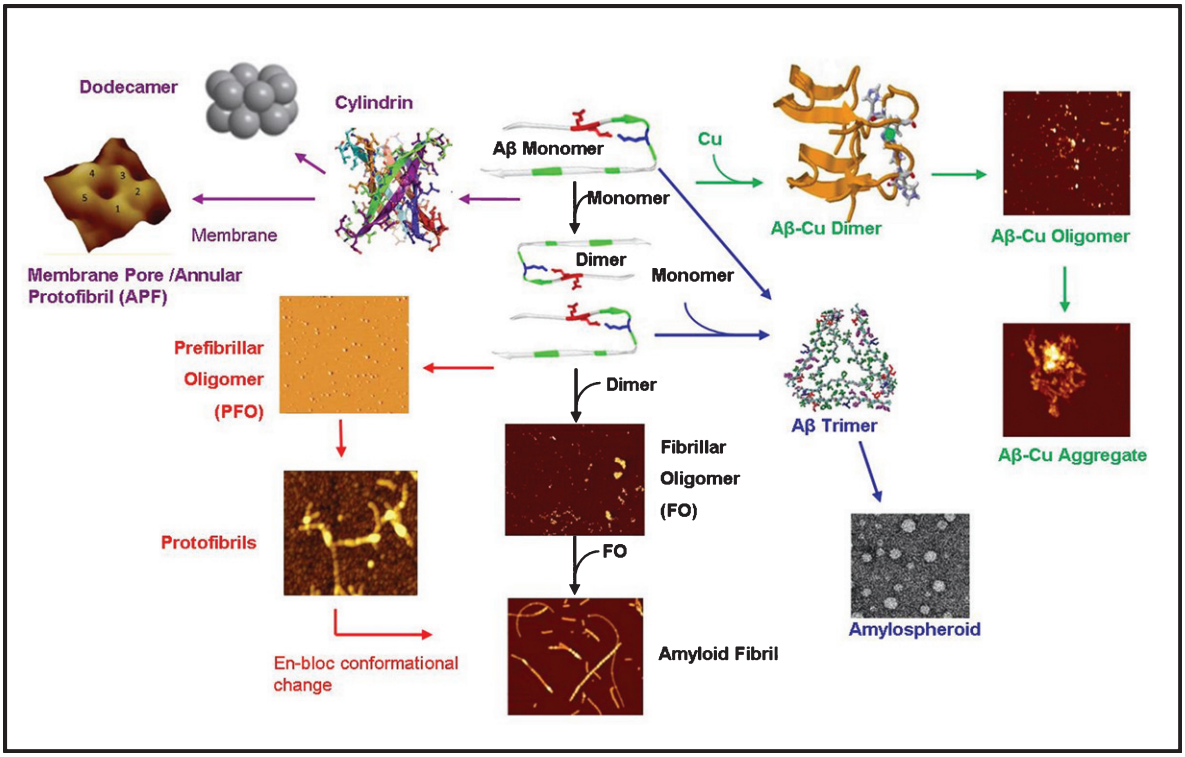

Fig. 1. Diagram summarizing known amyloid-β (Aβ) aggregation pathways. The aggregation cascade is initiated with an Aβ monomer which dimerizes, forming OC+ fibrillar oligomers (black pathway) [33]. Fibrillar oligomers polymerize to form mature amyloid fibrils [34]. Along another reaction pathway, the amyloid dimer can form A11+ prefibrillar oligomers forming protofibrils (red pathway) [35, 36]. These protofibrils may undergo an en-bloc conformational change to form amyloid fibrils [35]. The monomer may also travel along a pathway ending in amylospheriods (blue pathways) [37, 38]. The pathways have a trimeric intermediate [39]. Amyloid dimerization may be mediated by a copper ion forming small amyloid-copper oligomers [39] eventually leading to larger amyloid-copper aggregates [34]. In the pathway mediated by lipid membranes (purple pathway), the amyloid dimer forms a hexameric ion pore [40] which may be identical to the annular protofibrils identified by the Glabe group [21] or the recent atomic structure of the amyloid oligomer [31]. These hexameric ion pores may stack to form deeper dodecameric structures [21]. This diagram reprinted in accordance with a Creative Commons License [41] and was created using images from [18, 20, 31, 34, 35, 38, 39, 42, 43].

correlation between plaque deposition and AD cognitive impairment could be attributed to differing molecular structures making up the plaque. For example, fibrillar oligomers have been demonstrated to be elevated in AD patients, but not non-fibrillar oligomers [46], suggesting that some amyloid structures, although of similar appearance, but with different molecular structure, may be responsible for the differing reports of neurotoxicity.

What is interesting about the diversity of these structural data is the diversity of molecular conformations possible in an amyloid fibril and the number of different off-pathway oligomeric structures. Originally researchers believed that the path to the final fibrillary structure was a linear one transitioning through oligomeric intermediates. However, a body of research has shown that some oligomers are "off-pathway" and occur at the end of their own reaction pathway, in other words, they will never become amyloid fibrils [41]. These divergent pathways were highlighted by Sandberg et al., who showed that by genetically engineering Aβ to have two cysteine residues ($A\beta_{CC}$) stabilizing the beta-hairpin structure, two divergent pathways are formed: one forming in low molecular weight oligomers which result in large non-fibrillar aggregates which are A11 reactive, and the other pathway forming toxic aggregates which are the precursors to protofibrils [47]. These $A\beta_{CC}$ aggregates were 50 times more toxic than wild type Aβ aggregates given their structural stability. A variety of Aβ structural mutations have been shown to either increase or decrease Aβ toxicity. This work highlights how potential genetic mutations in the *APP* gene can result in aggregates with different toxicities.

Previous structural work on Aβ was based solely on fibrils aggregated under artificial conditions. In a

particularly novel approach, Lu et al. were able to obtain an NMR structure of Aβ fibrils from plaques obtained from a couple of deceased AD suffers despite an inadequate amount of tissue harvested [9]. Their approach relied on the assumption that the molecular structure of a large quantity of amyloid fibrils is identical to the structure of the initial amyloid nucleation "seed" previously reported [43, 48]. Lu et al. showed that the fibrillary structure differed between the two samples despite the fact that both patients had AD, albeit, with differing clinical histories. They were able to make an NMR structural determination for one of the samples. ssNMR revealed a trimeric structure similar to the structure determined from synthetic fibrils determined earlier [43]. Their work suggests that AD pathology may spread from an initial site in the brain, with variations in AD causing structural variations in Aβ. This highlights the importance of elucidating the initial single molecule events initiating the amyloid cascade which culminates in macroscale neurologic structural variation and AD symptoms.

Other recent works by the Eisenberg group have used x-ray crystallography to further elucidate the structure of a novel amyloid fibrillary structures [49, 50]. Liu et al. reported the x-ray structure of a unique amyloid fibril, one with out of register sheets, whereby the β-sheets are sheared relative to one another eventually forming cytotoxic cylindrical oligomers and fibrils ("cylindrins"), possibly explaining the porous nature of amyloid laden lipid membranes [49, 51, 52]. These cylindrins have been proposed to lie along a more toxic amyloid aggregation pathway, distinct from the "normal" in-register pathway which has been shown to be less toxic [49]. This hypothesis is supported by the lack of in- and off-register "hybrid" fibrils that would be energetically unfavorable.

While the molecular structure of amyloid fibrils has now been well documented, work continues to be done characterizing structures with different toxicities which may explain the diversity of manifestations, symptoms and nanoscale observations of the AD brain.

Amyloid aggregation

The functional structure of a protein is generally assumed to be solely a function of its primary amino acid sequence; however, the correct folding of the protein, from a 1-dimensional amino acid sequence to a 3-dimensional physiological functional protein is not a sure thing: proteins may misfold and aggregate into a non-functional or even a toxic structure [53–55]. Often α-helical domains will misfold into a β-sheet structure which is referred to as the toxic amyloid fold which is responsible for amyloid aggregation and toxicity [18]. This misfolding process, referred to as amyloidosis [56], is responsible for at least 50 different pathologies including AD [57] and a variety of other diseases in which misfolded proteins accumulate in various organs destroying surrounding cells through apoptosis [58]. No clear reasons have emerged why these proteins misfold and aggregate, but recent research has shown that this aggregation process is a function of the polypeptide backbone, rather than the sidechains. This suggests that any protein has the potential to aggregate and form a fibrillary structure [59]. Furthermore, the fibrillary structure occupies the global free energy minimum of the protein folding energy landscape [60]. Considering Gould's seminal and highly cited "spandrel's" hypothesis [61], this has led to thought-provoking hypothesis questions of how the amyloid fibril and functional amyloid has evolved [62, 63] and re-consideration of how the scientific community ought to approach the theory of the evolution of proteins [64].

The initial aggregation step of Aβ is believed to occur with the 16–23 and 28–35 α-helical regions forming β strands and folding back on one another to "self-dimerize" into a double layer hairpin-like monomeric structure stabilized by hydrophobic interactions and a salt-bridge on residues D23–K28 [65, 66]. However, given the multitude of amyloid structures, not all amyloid aggregates may begin their aggregation in this manner. Following the initial misfold, the next step in the aggregation process is the dimerization of two monomers, the initial process resulting in neurotoxicity [67]. Aβ may dimerize in different conformations leading to a divergence in the aggregation pathway leading to either amyloid fibrils or some other non-structured amyloid structure [34, 41]. Amyloid fibrils may form via a "Dock and Lock" mechanism of fibril elongation. This hypothesis attempts to explain how monomers are added to a growing amyloid fibril. This mechanism posits that elongation is mediated by two distinct kinetic processes. In the first conformational selection phase (dock), there is a reversible process in which monomers are added to the amyloid seeds. During the second (induced fit optimization (lock)) phase, additional monomers are added irreversibly in a time-dependent manner [68, 69].

Despite a considerable wealth of evidence demonstrating the divergence of aggregation pathways, some recent reports have demonstrated that some oligomers still lie on the fibrillary pathway. Bleiholder et al. demonstrated that some oligomers can in fact alter their conformations from oligomeric to fibrillar [70]. These data just reinforce the question of what exactly an "oligomer" is and the need to further characterize the multitude of amyloidogenic structures including amylospheroids, pre-fibrillar oligomers, fibrillar oligomers, protofibrils, and annular protofibrils.

As Aβ aggregates, its deposition begins in the default mode network (DMN), comprised of the medial and lateral parietal, posterior cingulate, retrosplenial and medial prefrontal areas, as well as the hippocampal formation [71]. Despite cleavage of Aβ throughout the brain region, this observation suggests that synaptic activity in these regions regulates Aβ cleavage or clearance. Alternatively, it is possible that other factors, such as interactions with metals could affect this Aβ deposition.

As discussed above, Aβ aggregates in templating method with additional monomers binding to the amyloid seed consistent with the molecular conformation of the amyloid seed. Likewise, intraperitoneal and intracranial injections of minute quantities of Aβ rich inoculates induced cerebral amyloid plaque deposition [72]. These results make Aβ a kind of "anti-vaccine", the injection of which results not in the production of specific antibodies and its increased clearance, but a further aggregation of the toxic species. Interestingly, intravenous, intraocular, and intranasal inoculations did not result in the deposition of amyloid plaques. While the intracranial injection results seem intuitive, the intraperitoneal injection results seem somewhat counterintuitive, considering the role of the blood-brain barrier and absence of positive results from intravenous and intranasal injections. It is possible, although speculative at this point, that the gut-brain axis [73, 74] may be involved in this mechanism and provide a potential explanation how intraperitoneal injections of Aβ result in increased amyloid deposition in the brain.

Imaging studies by Villemagne et al. suggest a long preclinical phase of AD in which Aβ deposition reaches a threshold [75]. Amyloid deposition exceeding this threshold is associated with hippocampal atrophy and the onset of dementia. Using an ^{11}C-PiB (Pittsburgh Compound B) magnetic resonance imaging (MRI) molecular probe, Villemagne et al. demonstrated that human subjects with high rates of probe retention (and therefore higher rates of Aβ deposition) had higher rates of memory loss, cortical gray matter loss, and hippocampal atrophy than those subjects with low probe retention. Subjects with an *APOE* ε4 genotype displayed higher rates of Aβ deposition and memory decline than subjects without any *APOE* ε4 alleles. The long period of Aβ deposition likely extends for over 20 years. It is thus possible that this extended preclinical phase of AD can be detected and future interventions started prior to the onset of AD symptoms when treatments may be more likely to be effective [75].

Amyloid metabolism

The complexity of AD has resulted in a myriad of hypothesized mechanisms attempting to explain the symptoms and pathological changes in the AD brain. Even within individual hypothesis, possible mechanisms continue to branch out. For example, the Aβ hypothesis posits that the dysregulation and metabolism of Aβ is responsible for AD symptoms. However, it is not just the overproduction or abnormal cleavage of AβPP as occurs in familial AD. Recent research has shown that the ineffective clearance of Aβ, in any of its structures, may be responsible for AD [76, 77]. This abnormal clearance may result in the generation of toxic amyloid species [76]. These reports, combined with studies that Aβ is cleared from the ISF during sleep [78], could provide a potential mechanism for how a lack of sleep could be a risk factor for AD.

Recent data suggest that areas of the brain with higher aerobic glycolysis correlate with the areas of the brain commonly associated with Aβ deposition. Work by Bero et al. indicates that the manipulation of neuronal activity regulates lactate levels. Given that increased Aβ production is partially a function of neuronal activity, spatial differences in neuronal activity may underlie the regional inhomogeneities of Aβ deposition [71]. These results suggest that areas of elevated neuronal activity over long periods of time result in increased Aβ deposition.

Work by Hong et al. used microdialysis to study the presence of amyloid species from the brains of transgenic AD mice [79]. They report that the most diffusible brain pool, in the ISF pool, contains almost solely dissolved monomers as opposed to insoluble oligomers which may distribute to more hydrophobic surfaces such as the cell membrane or especially cell membranes with existing amyloid deposits.

As more amyloid deposited in the parenchyma, the concentration of dissolved Aβ dropped significantly. Furthermore, Aβ dissolved in the ISF cleared more rapidly in plaque-rich mice than plaque-free mice [79].

Amyloid cleavage

Aβ is cleaved from AβPP by the α-, β-, or γ-secretase complexes which are made up of the intramembrane presenilin proteins. Familial mutations in the presenilin genes (*PSEN1* and *PSEN2*), along with an overproduction of AβPP, are a leading cause of familial (early onset) AD [80]. The abnormal cleavage of Aβ from its more abundant $A\beta_{40}$ isoform to the more toxic $A\beta_{42}$, and therefore a higher than normal $A\beta_{42}$:$A\beta_{40}$ ratio, has been linked to late-onset AD [81].

Knockout studies of the presenilin gene showed that the presenilins play a role in autophagy-mediated degradation of protein aggregates [80]. Further to these studies, pharmacological studies show that the application of γ-secretase inhibitors reduce Aβ peptides whereas γ-secretase modulators reduce $A\beta_{42}$ concentration [82].

While $A\beta_{42}$ is more toxic than $A\beta_{40}$, $A\beta_{43}$ is more toxic than $A\beta_{42}$ [83]. $A\beta_{43}$ is further cleaved and converted to $A\beta_{40}$ whereas $A\beta_{42}$ is cleaved independently from $A\beta_{48}$. This difference provides a possible explanation with how a mutation in a *PSEN* gene, such as the PS1–R278I, can cause AD: by producing more $A\beta_{43}$ instead of $A\beta_{40}$ leading to an acceleration of Aβ deposition. In fact, the PS1–R278I mutation leads to synaptic dysfunction and cognitive impairment even before the onset of amyloid plaque formation [83].

Amyloid toxicity

A variety of possible mechanisms of amyloid neurotoxicity have been identified including amyloid causing an inflammatory reaction with the cell membrane [84], oxidative stress caused by reactive oxidative species [85], oxidative stress caused by Aβ-metal coordination [86–90], competitive binding of membrane receptors [91], formation of ion channels [18, 92], increased permeability and thinning of the cell membrane [93, 94], over excitation of the NMDA receptor [95], and modification of DNA structure by amyloid attachment [96]. Furthermore, different receptors appear to mediate different aspects of Aβ toxicity [97]. These cell-Aβ interactions also result in Aβ being toxic to bacteria making Aβ by definition an antimicrobial peptide [98].

Originally, amyloid plaques comprised of amyloid fibrils were implicated as the toxic species in AD. Recent research has shown that oligomers, more so than fibrils, are the toxic amyloid species leading to synaptic collapse and dendritic spine loss [99]. These reports some researchers to hypothesize that amyloid plaques (made of mature fibrils) are a "last ditch cellular attempt to wall off potentially toxic Aβ oligomers" [88]. While the misfolding of $A\beta_{42}$ has been shown to be causal to the pathogenesis of AD, attributing AD pathology strictly to the presence of $A\beta_{42}$ is problematic. Firstly, it is unknown why amyloid deposits are focused on the synapse and are not uniform in the cerebral parenchyma, especially because Aβ is uniformly expressed and $A\beta_{42}$ is a normal constituent of all cerebrospinal fluid. Secondly, amyloid deposition increases with age, yet amyloid production does not. It appears that processes which clear amyloid deposits are diminished with age as are mechanisms to protect against redox effects [81]. A difference between Aβ production and Aβ clearance is likely an underlying factor in the AD disease process [88].

Aβ can aggregate into different oligomeric structures, each with varying levels of toxicities [100, 101]. Trimers have a toxicity three times higher than that of monomers, where tetramers have a toxicity 13 times greater than monomers. Unfractionated cross-linked oligomers have a toxicity three times greater than that of monomers [102]. The order of toxicity related to structure is tetramers > trimers > dimmers > fibrils > monomers [102]. The exposure of hydrophobic motifs in oligomers, rather than their size and secondary structure is the primary determinant of neurotoxicity [103].

Amyloid toxicity may be directly related to interaction of various amyloid species with the surfaces of neuronal cellular membrane [104]. Peroxidation of lipids is also a major sign of elevated levels of oxidative stress in the brain which has been found in the brains of AD patients. This phenomenon is likely caused by reactive oxidative species such as free radicals resulting in increased apoptosis [105]. Oxidative stress may also lead to abnormal protein structure and function leading to pathological symptoms [106].

Within the last five years, a number of additional mechanisms have been identified which implicate Aβ in AD pathology. Recently, Ohnishi et al. showed that amylospheroid oligomer targets the Na+/K+-ATPase α3 subunit with nanomolar affinity [107]. Amylospheroid are especially toxic and are structurally

distinct from Aβ dimers, amyloid diffusible ligands, and dodecamers [37, 108]. This results in activated N-type voltage-gated calcium channels causing mitochondrial calcium dyshomeostasis, tau abnormalities which lead to neurodegeneration. Yao et al. provided additional evidence of the role of Aβ in mitochondrial dysfunction demonstrating that Aβ binds to the mitochondria resulting in a lack of cellular energy production leading to cell death [109]. However, a molecular mechanism for how Aβ interferes with the mitochondria has yet to be determined but work by Roberson et al. implicates reduced enzyme activity associated with complex IV in the respiratory chain, a reduction in oxygen consumption, decreased brain glucose metabolism, and decreased ATP as possible mechanisms of Aβ induced mitochondrial dysfunction [110].

TAU

Tau is a soluble microtubule-associated protein responsible for stabilizing neuronal microtubules promoting stability of the cytoskeleton. Tau was originally believed to a defined secondary structure in solution [111]. However, recent work has demonstrated that tau adopts a structure which resembles a "paperclip" [112]. Tau is mainly present in the axons of neurons [113]. Tau is expressed by the microtubule-associated protein-tau (MAPT) in six isoforms. Together with Aβ, tau deposition is implicated in AD and correlates well with disease progression [114]. Beyond AD, tau is implicated in a variety of other diseases including chronic traumatic encephalopathy, progressive supranuclear palsy, corticobasal degeneration, argyrophilic grain disease, and frontotemporal dementia (Pick's disease) and parkinsonism linked to chromosome 17. All of these diseases result in, among other pathological features, neuronal tau inclusions [115]. However in some cases, tau inclusions are also found in the glia [116] or in some rare cases, in the extracellular space [113]. In some patients, tau aggregates are found in the brain yet no cognitive decline is observed. This condition is known as primary age-related tauopathy [117]. Mutations in the tau encoding gene MAPT results in abnormal folding of the tau protein resulting in dominantly inherited frontotemporal dementia (Pick's disease). Pathologically, Pick's is differentiated from AD because of the absence of Aβ plaques [116]. Similar to Aβ, the tau pathological pathway passes through a number of intermediate structures before reaching their final structure as paired helical fragments [118] or neurofibrillary tangles (NFT) [113].

Tau aggregation

Tau has a propensity to misfold resulting in paired helical fragments (PHF) and NFTs. Aβ lesions begin in the neocortex and appear later in the hippocampus (Fig. 2). By contrast, tau lesions in the brain first appear in the locus coeruleus and entorhinal cortex before spreading to the hippocampus and the neocortex [116]. AD symptoms generally appear once tau inclusions and Aβ deposits are found in the neocortex [119]. Tau inclusions located in the hippocampus and entorhinal cortex are possibly necessary,

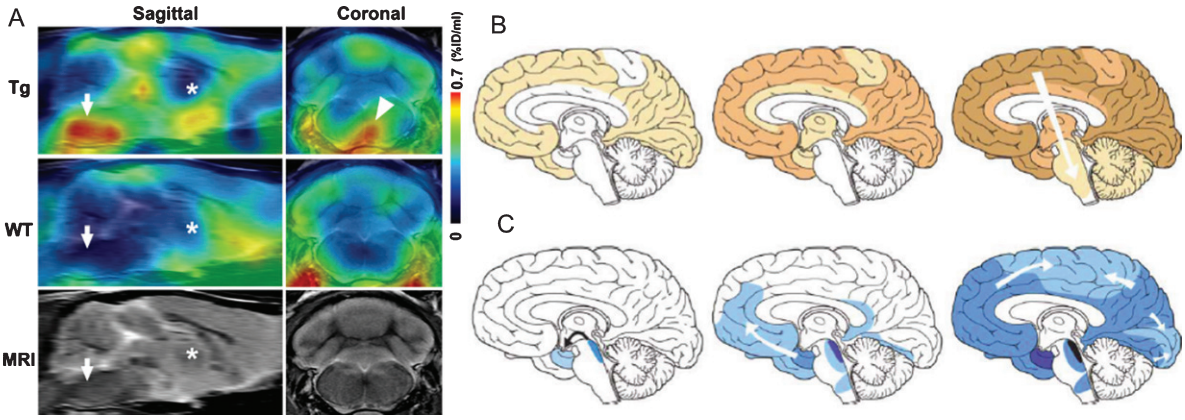

Fig. 2. A) Sagittal and coronal PET images of transgenic and wild-type mice following intravenous administration of [^{11}C]PBB3 which is a probe for tau deposition. Arrows and asterisks denote the brain stem and striatum, respectively [121]. B) Spread of Aβ pathology starts in the neocortex to the allocortex and eventually to the subcortical regions of the brain. C) Tau pathology spreads in reverse, beginning in the locus coeruleus and transenterorhinal areas and then spreading to the amygdala and neocortex [122]. Images reprinted with permission.

but unlikely to be sufficient for AD progression [120].

As tau begins to aggregate, it sources its material from tau expressed into the ISF resulting in decreased levels of ISF tau [123]. Similar to Aβ, tau "seeds" can act as a template to promote tau aggregation in neurons [124] recruiting soluble tau in a highly efficient nucleation dependent mechanism [125]. This seeding results in a bypass of the rate limiting "lag-phase" associated with the nucleation dependent mechanism when a critical nucleus is formed, accelerating the fibrillization of tau monomers [125].

Liu et al. demonstrated that tau pathology spreads, neuron-by-neuron, along synaptically connected circuits starting at the entorhinal cortex, along the perforant pathway, to the hippocampus and eventually reaching the dentate gyrus and granule cells [126] despite regional and cellular restrictions in the entorhinal cortex [127]. Tau is transported through the axons to their terminals in the middle molecular layer of the dentate gyrus [127]. A large quantity of this aggregated tau is acetylated raising the question of what causes what: does acetylation accelerate aggregation or does aggregation induce acetylation? The work by Irwin et al. supports the hypothesis that once tau fibrillizes, it undergoes post-translational acetylation [128].

The hyperphosphorylation of tau in AD has been well documented [97, 113]. Hyperphosphorylation of tau has been demonstrated to increase tau aggregation [129], however tau hyperphosphorylation on its own is insufficient to induce tau aggregate [113]. Prior to any tau aggregation, tau hyperphosphorylation may result in cytotoxic process such as impairment of mitochondria and axonal transport [130, 131]. When combined with increased aggregation, tau hyperphosphorylation may work "synergistically" to reduce microtubule stability [125].

The pathway nature of tau aggregation throughout the brain raises some interesting unresolved questions: 1) why are some neurons in the regions of the tau aggregation pathway immune from tau aggregation? 2) Can potential immunotherapies reach intracellular tau? 3) Can tau, on its own, begin its aggregation cascade or must it be initiated or signaled by another molecule such as Aβ?

Tau-mediated amyloid toxicity

Tau toxicity and its role in AD seems to be inextricably linked to its relationship with Aβ. The extent of contemporary research studying the Aβ-tau relationship seems to have put the βAptist versus Tauist religious wars to rest. While it is now understood that other forms of amyloid, such as α-synuclein and CLAC collagen, are also present in the AD brain, early work focusing on Aβ and tau dominated research and provided conflicting reports leading to the illusory "religious wars". It is perhaps little more than empirical evidence that has allowed for the mutual conciliations of these two hypotheses and has allowed the biophysical and biochemical aspects of AD research to progress beyond the simple biophysical explanations of the past.

A number of mechanisms have been put forth in the literature to explain how tau results in neurotoxicity. These mechanisms include altered microtubule stability [132], regulation of neuronal activity [95], and interference with the Fyn pathway [110].

The toxic structure of tau is still unclear; however, recent research suggests that similar to Aβ, the oligomeric structure of tau is the most neurotoxic [133–135] while NFTs are largely inert. The difficulty in confirming the toxicity of oligomers is partially because of the difficulty in making consistent preparations of oligomers and the diversity of known oligomeric structures. Research suggests that the brain contains a significant compensatory mechanism to protect against the toxicity of tau. Neurons appear to function normally for years despite tau inclusions [136]. This compensatory mechanism hypothesis is supported by research showing that older mice, but not young have symptoms associated with neurodegenerative disease suggesting that these compensatory mechanisms fail with age [137]. Though tau is primarily found in the axons, it does appear to have a function in the dendrites suggesting that tau disruptions may lead to dendritic dysfunction [97]. Synaptic loss has been shown to cause a partial deafferentation of granule cells of the dentate gyrus [138, 139] and that synaptic density is strongly correlated with cognitive impairment [140] suggesting that a loss of the synaptic network is associated with disease progression [127].

In one notable report, Sydow et al. genetically engineered transgenic mice to be able to regulate the expression of tau protein between two different forms of tau with differing propensities for aggregation [141]. In their work, Sydow et al. demonstrated that only the pro-aggregate form of tau caused synaptic loss and hyperphosphorylation. Interestingly, Sydow et al. showed that synaptic loss caused by tau toxicity appears to be reversible. When the pro-aggregate form of tau was "switched off" after ten months in

favor of the anti-aggregate form, histopathological changes associated with AD were reversed after a four-month period [141].

Recently, Kanaan et al. demonstrated that axonal protein phosphatase 1 and glycogen synthase kinase 3 (GSK3) is activated by kinesin based fast axonal transport pathway independent of microtubule binding and therefore does not required aggregated tau [112]. A phosphatase activating domain consisting of amino acids 2–18 of tau activate this pathway and results in axonal transport disruption suggesting a link between tau deposition, axonal dysfunction and neurodegenerative symptoms [112].

On its own, tau has been shown to be neurotoxic as is seen in frontotemporal dementia; however, its synergistic and positive feedback relationship with Aβ has been increasingly seen as a likely mechanism to explain the histopathological and symptomatic observations associated with AD. It is this tau-Aβ relationship which has been increasingly been elucidated by contemporary AD research.

An increasing body of evidence supports the hypothesis that tau mediates, or may even be necessary for, the toxic effects of Aβ [95, 110, 142–144]. On one hand, *APP* mutations, responsible for Aβ production, leads to early onset AD, yet MAPT, responsible for tau production does not. On the other hand, NFTs are likely required for the development of AD: people with no NFTs regardless of Aβ plaque deposition do not appear to have AD [116, 145]. However, similar to Aβ plaques, the presence of NFTs may be a symptom of the disease rather than a cause. Morris et al. showed that that preclinical AD is initiated by Aβ abnormalities, but not tau abnormalities [6].

The use of tau-knockout mice has allowed researchers to compare Aβ toxicity in mice with and without tau expression. The tau-Aβ toxicity relationship is supported by the observation that tau -/- neurons are protected by Aβ induced cell death [132]. These observations raise the question how tau fits into the amyloid cascade hypothesis. Aβ and tau each use different mechanisms to exert their toxicity [146], yet it is still unclear whether tau is a mediator or co-factor of Aβ toxicity [97]. However, amyloid-β derived diffusible ligands (ADDLs) appear to induce tau hyperphosphorylation and disruptions of microtubules impairing the cytoskeleton [147].

Ittner et al. suggested three different mechanisms of tau-Aβ toxicity: the first is that tau hyperphosphorylation is signaled by tau which mediates neurotoxicity as was demonstrated by [148]. The second proposed mechanism is that Aβ toxicity is mediated by tau, somewhat analogous to a co-factor, in which presence of tau in the dendrite is a requirement for Aβ to exert its toxicity at the synapse. Lastly, Aβ and tau may target organelles, providing a positive feedback mechanism for one another's toxic effects [97].

Jin et al. subnanomolar concentrations of Aβ dimers, the smallest neurotoxic species of Aβ, induced tau hyperphosphorylation in the hippocampus disrupting the cytoskeleton causing neurotic degeneration [149]. However, knocking out tau prevented neuronal degeneration whereas overexpressing tau accelerated these changes.

Work by Roberson et al. suggests that tau may modulate the tyrosine kinase Fyn pathway mediating Aβ toxicity by jointly impairing network and synaptic function [95, 110]. A reduction of tau expression reduces cognitive deficits in mice that overexpress Fyn which sensitizes them to Aβ toxicity. This resulted in a reduced interaction with the NMDA receptors. Roberson et al. concluded that a reduction of tau is not neuroprotective but may impair a mechanism shared by Aβ and the Fyn pathway.

Ittner et al. have postulated a "tau axis hypothesis" that links Aβ and tau neurotoxicity. Tau increases targeting of Fyn to the postsynaptic compartment linking NMDA receptors to downstream signaling pathways sensitizing NMDARs to Aβ toxicity by excitotoxic signaling. Positive feedback is provided by Aβ which triggers tau hyperphosphorylation compromising the cytoskeleton accelerating the pace of dendritic deposition. This hyperphosphorylated tau has a higher affinity for Fyn further sensitizing NMDARs making them more susceptible to Aβ toxicity [97]. The tau axis hypothesis may be linked to other previously reported AD hypothesis, namely the axonal transport hypothesis which posits that tau impairs axonal transport [150] and oxidative stress hypothesis in which mitochondria are functionally impaired by reactive oxygen species [151].

Other groups have reported on physical aggregation relationships between Aβ and tau. Do et al. reported on the interaction between tau and Aβ fragments [152]. The incorporation of tau within Aβ leads to a reduction in fibrils formation. This could result in more toxic oligomeric aggregates- a secondary toxic mechanism of tau-Aβ interaction. Secondly, tau aggregates form larger globular oligomers when Aβ fragments are incorporated. In human brain studies, Aβ-ptau interaction has been correlated with AD progression [153]. Additional information on tau-Aβ interactions is reviewed in [154].

PRIONS

The relationship between amyloid and prions is presently one of the most active areas of AD research. While it has been known for a considerable length of time that amyloids and prions have similar propensities to misfold, their relationship has only recently been studied within the past 5 to 10 years. Prions (a portmanteau of protein and infectious) were first proposed by Prusiner [155, 156]. The concept of an infectious protein lacking any DNA was initially dismissed by the scientific community, but as evidence mounted, prions became an increasingly accepted pathology. Stanley Prusiner was eventually awarded a Nobel prize in 1997 for his work on the discovery of prions [156].

The prion pathology is implicated in a number of disease including bovine spongiform encephalopathy in bovine, Cruetzfeldt-Jakobs Disease (CJD), scrapie in sheep, and kuru, a disease of the indigenous people of New Guinea likely caused by their cannibalistic rituals [156]. What makes prion diseases unique is that they can be of genetic, infectious, or idiopathic etiology [157]; however, only 1% of prion infections are acquired with the remainder being genetic or idiopathic [116]. The prion pathology is caused by an infectious misfolding of PrP^{c} into the toxic PrP^{sc} β-sheet conformation [158]. A PrP^{sc} conformed protein recruits other PrP^{c} to aggregate into the toxic conformation causing further pathology, neurodegeneration, and quite quickly, death. It is this "corruptive protein templating" that suggests a common molecular mechanism with AD [122]. Cells continually express PrP^{c} sustaining the aggregation of the PrP^{sc} form [157]. The mechanism of how PrP^{sc} spreads is believed to be via trans-synaptic transport [159]. Obviously intracranial injection of PrP^{sc} is the most efficient route of prion transmission [72]. However, evidence of transmission of PrP^{sc} from the peripheries into the central nervous system is conflicting [72, 116].

A number of lines of investigation into prions are interesting to AD researchers. Firstly, the Aβ protein misfolds and aggregates in a method similar to PrP^{c}, albeit at a much slower rate. This similarity led researchers to hypothesize that Aβ pathology is transmissible and reports are frequently naming the Aβ *prion* as the pathological species in AD [160, 161]. The concept of prion-like behavior now includes tau, α-synuclein, huntingtin, and superoxide dismutase 1 which are implicated in frontotemporal dementia, Parkinson's/Lewy body disease, Huntington's disease, and amyotrophic lateral sclerosis, respectively [122].

The first evidence of the transmissibility of Aβ was reported by Ridley et al. who inoculated marmosets with homogenized brain tissue from the brains of AD patients and observed the development of AD in these marmosets [162]. Epidemiological evidence has shown that over two hundred individuals have contracted CJD as a result of being treated with pituitary-derived growth hormone from human cadavers that were contaminated with prions [163]. Additionally, CJD has been acquired from dura mater grafts following neurosurgical transplant [164].

A recent remarkable report by Jaunmakthane et al. showed that in a small sample of brains autopsied from patients who died of iatrogenic CJD at a young age (36–51 years of age), half of them had evidence of moderate to severe Aβ pathology [22]. Their work suggests that AD is, similar to CJD, a transmissible disease, albeit not contagious. However, their report opens the door for future research ensuring that known iatrogenic routes of prion transmission, such as neurosurgery and blood products, are precluded from transmitting AD.

Secondly, contemporary research has shown that the PrP^{c} protein has an Aβ binding site further intertwining AD and prion pathology. ADDLs, but not Aβ monomers, were shown to bind PrP^{c} with high affinity [165]. Over 50% of the high affinity binding sites on hippocampal neurons are PrP^{c} binding sites functioning as a receptor modulating Aβ toxicity. Lipid rafts have been implicated in Aβ aggregation and are believed to serve as aggregation templates [166]. It is perhaps no small coincidence that PrP^{c} is also found in high concentration in the lipid rafts further implicating lipid rafts and PrP^{c} in AD pathology [167, 168]. Blocking the PrP^{c} with an antibody prevents ADDLs from binding to PrP inhibiting long-term potentiation in neurons [169, 170]. Transgenic mice lacking PrP^{c} accumulate amyloid plaques, but the mice have no memory loss and have no increased mortality providing strong evidence that PrP^{c} is a co-factor in Aβ toxicity [171]. Um et al. showed that this synergistic effect between Aβ and PrP^{c} may lead through the Fyn signaling pathway to alter synaptic function and destroy dendritic spines and loss of surface NMDA receptors [172]. The short-term activation of Fyn by Aβ and PrP^{c} results in increased NMDA receptor phosphorylation and excitotoxicity. This convergence of Aβ, PrP^{c}, and Fyn may occur within lipid rafts adding more evidence of the role of lipid rafts in the pathogenesis of AD. Furthermore,

Fyn is also known to associate with tau which sensitize neuronal synapsis to glutamate excitotoxicity [173]. Increasing evidence is emerging that the confluence of these factors, Aβ, tau, PrP^c, and Fyn are responsible for the complexity of AD. Further work studying the synergistic effects of these factors will continue to shed light on the pathology of AD.

BRAIN STRUCTURE AND FUNCTION IN RELATION TO AD

The human brain is a very complicated yet elegant piece of biological machinery. This organ not only serves as the "command center" of our nervous system, but is also responsible for storing our memories, our thought processes, and most importantly, our personalities. In a typical person, there are approximately 86 billion neurons and 85 billion non-neuronal glial cells [174]. These neurons are all interconnected through their axon terminals and nearby dendrites via neuronal synapses, allowing for electrical signals and action potentials to be passed on from one neuron to another. This biological neural network, or neural pathway, can form a cohesive and comprehensive map known as the "connectome", which can help scientists and AD researchers understand the organization of neural interactions within the human brain.

Due to the complexity of the brain and intricacies of neuronal interactions, any changes or alterations made to the neural network and connectome can result in catastrophic consequences to both brain function and our personalities. AD is one such neurodegenerative disease that can cause synaptic damage and memory deficits in patients suffering from this illness.

Neuropathology

The neuropathological hallmarks of AD are manifold and can be divided into two categories: "positive" features such as amyloid plaques, NFTs, cerebral amyloid angiopathy, and astrogliosis, while "negative" features involve the loss of neurons, neuropil, and synaptic elements [175]. As mentioned previously, Aβ and tau protein play a large role in the pathogenesis of AD. In fact, AD is primarily driven by the extracellular deposition of Aβ and the intracellular accumulation of tau, which has led to the development of the revised guidelines for neuropathological evaluation of AD from the National Institute on Aging [176]. This tiered evaluation classifies AD neuropathologic change using three parameters involving Aβ plaques, NFTs, or phospho-tau immunohistochemistry, and neuritic plaques [176]. Visual scoring scales have also been used to measure the volume of the hippocampus or entorhinal cortex to predict the development of MCI patients to AD (Fig. 3) [177]. Although there is a guideline to diagnose AD, there is a continuing and pressing interest for AD researchers and scientists to further investigate the condition and nature of the pathological processes that take place in the diseased brain.

Choi et al. developed a three-dimensional neural cell culture model of AD, marking the first single disease model that has linked both Aβ plaques and NFTs

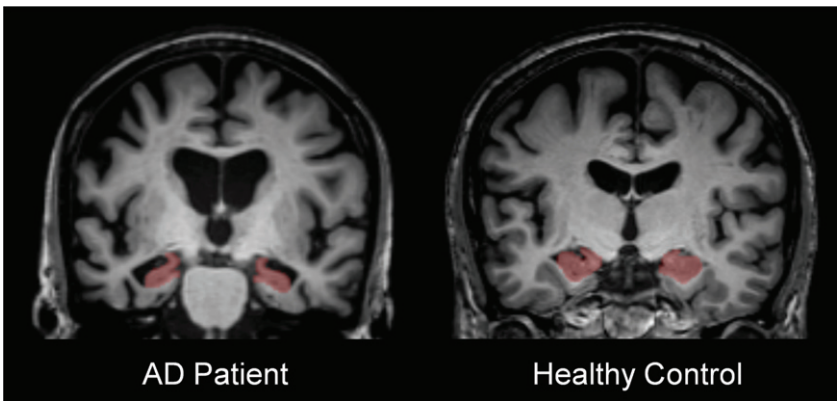

Fig. 3. High-resolution structural MRI scans that show the head of the hippocampus, in red, are presented between a healthy individual and a patient with AD. The patient with AD (A) suffers from atrophy of the hippocampus as compared to the healthy individual (B), which allows for the use of high-resolution structural MRI scans as a visual scoring scale for AD progression [177]. Reprinted with permission from *The Lancet Neurology*.

together under one roof [178]. Using this model, the group observed that tauopathy was driven by the accumulation of Aβ peptides, therefore validating the amyloid hypothesis of AD [178]. In an attempt to obtain a greater insight into the pathological process of sporadic AD, over 2,000 brains from all age groups were examined for tau lesions from a study in 2011 [179]. Gallyas silver staining was used to detect abnormal tau while both Campbell-Switzer staining and immunocytochemistry (4G8) was used to detect Aβ in the brain samples. The results showed that over 44% of the brains had Aβ plaques, with these plaques first occurring in the neocortex after the onset of tauopathy and generally starting to develop in age groups around 40 years of age and gradually increasing by the decade [179]. These results, along with another study by the same group, strongly suggest that tauopathy in sporadic AD may begin during early adulthood instead of later adulthood, and that the development of tau lesions and subsequent pathology start in the lower part of the brainstem [179, 180]. It was also suggested that AD may be the result of two main stages of pathology, the first being a form of tauopathy occurring in pre-tangle stages and the second being a form of Aβ aggregation that exacerbates the underlying tauopathy to spark the progression of the disease [179].

There are also amyloid-independent mechanisms in AD pathogenesis, primarily involving defective endo-lysosomal trafficking, modified intracellular signaling cascades, and impaired neurotransmitter release which can ultimately lead to AD symptoms and dementia [181]. One study suggested that age, *APOE* status, and various comorbidities could lead to differences in clinical presentations of AD [182]. A study has also shown that there are different AD subtypes with distinct clinical presentations, with hippocampal sparing and limbic-predominant AD subtypes accounting for about 25% of the cases in that study [183]. Therefore, a stronger understanding of both types of mechanisms dependent and independent of amyloid will be required to describe and clarify the findings that cannot be explained by just one mechanism alone.

Apart from being able to further understand and identify the molecular mechanisms and neuropathological processes of AD, there is a strong desire to develop therapeutic and pharmaceutical approaches to treat this neurodegenerative disease. One study found a strong correlation between atrophic symptoms of the brain and Aβ deposition load in very early and minimally symptomatic stages of AD, but not in later stages of cognitive impairment, suggesting that anti-amyloid treatments should be administered very early in the disease to minimize neuron damage and synaptic loss [184]. Through functional MRI (fMRI), it has been observed that numerous conditions which confer risk for AD involve elevated hippocampal activation [185, 186]. This increased hippocampal activation has been tied to memory impairment and widespread neurodegeneration in prodromal AD [187]. In a study by Bakker et al., the anti-epileptic drug levetriacetam was used to successfully reduce the excess hippocampal activity in patients with amnestic MCI. These findings suggest that regulating neural activity can be a possible therapeutic method in modifying and disrupting the progression of AD pathology [188]. Meanwhile, another group observed that neuronal death was promoted when astrocyte, microglia, and neuron hemichannels were activated by the presence of Aβ, paving the way for alternative therapeutic methods that target these hemichannels to reduce the progression of neurodegeneration in AD [189].

Another marker of AD is the change in volume and absolute volume of the hippocampus. One group used an improved technique called multiple-atlas propagation and segmentation to detect the volume difference and atrophy rate in groups of patients with AD and MCI [190]. A high level of accuracy was reported and expected patterns were observed, with atrophy rates increasing with disease progression and hippocampal volume decreasing with disease progression [190]. As a result, this technique may prove useful in larger trials to assess disease progression and baseline characteristics of all patients. A study was also performed using blood-oxygen level dependent (BOLD) fMRI to characterize local and global connectivity changes of the functional neural network in AD patients. The results suggest that individuals with AD experience a loss of global information integration, and that there are functional differences between the frontal, parietal and occipital lobes which affect long-distance connectivity (Fig. 4) [191].

Induced pluripotent stem cells have also been demonstrated to be useful in observing phenotypes and treatments involving AD, where primary cells are reprogrammed in order to model the sporadic or familial form of AD [192, 193]. One study found that the certain sporadic AD patients will have genomes that generate strong neuronal phenotypes [192], and another study showed that patient-specific induced pluripotent stem cells can help with analyzing AD pathology and drug evaluation [193].

Neurogenesis

Neurogenesis, the regeneration or birth of neurons, is a process by which neural stem cells can generate new neurons. Aging is strongly correlated with a gradual decline of adult stem cells and therefore neurogenesis, resulting in cognitive impairments in geriatric populations [194]. What is not well known is that neurogenesis continues throughout life. Although primarily evident in pre-natal brain development, it has been shown that the human hippocampus and olfactory bulb still have the ability to generate neurons throughout life [195, 196]. New neurons can incorporate into the granular cell layer of the dentate gyrus and there is a continuous generation of striatal interneurons within adult human brains, which defines a unique pattern of neurogenesis [196, 197].

In early developmental stages, there is a rapid production of neurons that form the brain and peripheral nervous system. Once this has occurred, neurogenesis plays a stronger role in brain plasticity instead of brain development, taking place in specific locations in the adult brain like the sub-granular zone of the dentate gyrus in the hippocampus [198]. One study estimated that approximately 700 new neurons were generated per day in the dentate gyrus throughout adulthood, which corresponds to an annual turnover of 1.75% of renewing neurons [199]. Larger posterior hippocampi have also been associated with greater recollection and memory abilities [200]. It is believed that the generation of new neurons and their subsequent integration into the brain's neural network directly contributes to different cognitive processes such as learning and memory. These areas of neural regeneration are in close proximity to blood vessels, so it is also hypothesized that while aging, diminished neurogenesis could be modulated by two independent forces: intrinsic forces derived from the central nervous system itself or extrinsic forces derived from blood-born factors affecting the central nervous system [194].

Considering hippocampal neurogenesis in relation to AD leads to some interesting observations. Although numerous investigations of AD in transgenic mouse models report a reduction in hippocampal neurogenesis, some studies show that amyloid depositions can increase neurogenesis [201]. Decreased and impaired neurogenesis are typically due to the presence of toxic amyloid depositions [202, 203], while enhanced neurogenesis is speculated to be a compensatory response to progression and burden of AD [204–206].

In a study by Haughey et al., transgenic mice (with a mutated form of *APP* that causes early onset AD) were used to observe the proliferation, survival, and neuronal differentiation of neural progenitor cells and to determine the effects of pathogenic Aβ on these cells [202]. It was shown that Aβ was able to alter the proliferation and differentiation of neural progenitor cells while inhibitors of calpains and caspases were able to protect these cells from Aβ-induced death [202]. Meanwhile, another study by Jin et al. showed that enhanced neurogenesis is observed in AD-transgenic mice. They postulated that this phenomenon could be explained by the disease itself and therefore not a result of medication or pharmaceutics, and that synaptic abnormalities and impaired neural transmission is the main culprit behind induced neurogenesis instead of neuronal loss [204]. Although these two studies differ in their observations and conclusions, it further exemplifies the complexity of AD, and that more studies will need to be performed in order to determine which factors and triggers will affect neurogenesis in AD patients.

Looking back, it is apparent that many studies focus separately on either adult neurogenesis or AD neurogenesis. Stepping forward, it is crucial that we begin to consider the interplay between both regular and diseased neurogenesis in order to make meaningful conclusions on how it affects AD or how we can possibly enhance adult neurogenesis in AD patients.

Connectome

The human brain is a highly complex network of neurons and synapses that form a connectome. This human connectome actually consists of numerous highly connected neocortical hub regions, each of which plays a crucial role in integrating global information between different parts of the neural network. In fact, it was demonstrated that these brain hubs form a so-called "rich club", a phenomenon in which these hubs connect among themselves more densely and strongly than areas of a lower degree [207, 208]. Any alterations to this "rich club" from the onset of AD could pose serious consequences to neural connectivity and functionality.

To determine how AD could affect the brain's functional connectome, studies must first be done to determine how a healthy neural network acts. Task-free functional MRI was used by a group to derive healthy intrinsic connectivity patterns in regions of the brain that were vulnerable to neurodegenerative disease, with the angular gyrus and posterior elements

serving as the key neural hub behind AD and amyloid/tau pathological processes [209]. Disruption of the functional brain connectome in those at risk for AD, led to the observation that multiple connections linking functional modules within the brain's network were disrupted, resulting in decreased functional integration throughout the brain on connectional, nodal, and global levels [210].

Neural network disruptions are an important neuroimaging parameter that can help identify subjects with AD [211]. The DMN is one of the resting state networks in the brain that undergo changes through age and is affected by the progression of AD [212]. The brain regions within the DMN are the hippocampus, posterior cingulate, lateral parietal and medial frontal cortices, which are also areas that undergo Aβ plaque formation in AD [213]. It was previously shown that functional connections in the DMN were disrupted using PiB PET imaging of patients with Aβ plaques [214], and that *APOE* ε4 carriers can alter the resting state functional connectivity of the brain [215]. In fact, the functional connectivity in the posterior DMN is reduced in *APOE* ε4 carriers and can potentially be used as a biomarker and early detector of AD [216].

One group investigated the diffusion behavior in AD to see whether it would be associated with the degeneration of a particular neural network. Diffusion tensor imaging was used to find compelling evidence that the limbic-diencephalic network was selectively vulnerable to neurodegeneration [217]. Another study used the same technique to demonstrate that white matter was vulnerable to AD pathology and that the deterioration of neuronal connections in the hippocampal formation are associated with the degeneration of the medial temporal lobe and relevant pathways [218]. Meanwhile, the reduction of working memory and therefore memory-related firing as we age could make higher cortical circuits even more vulnerable to AD [219]. A mathematical network diffusion model of disease progression in dementia was also created to mimic the synaptic transmission of disease agents like Aβ and tau, allowing for the prediction of future directions of atrophy from baseline scans taken from patients [220].

Intracellular processes

It is very true that the onset of AD is due to Aβ and tau pathologies, but AD is also associated by a progressive dysfunction of various cellular components. Specifically, AD is associated with several neuronal dysfunctions such as the impairment of information processing and loss of neuronal activity in the brain [221]. Busche et al. demonstrated that hippocampal hyperactivity is present very early in the brains of transgenic AD mice independent of the level of amyloid plaque formation whereas wild-type mice did not have any brain hyperactivity [221]. These results showcase the significant role of soluble Aβ in the impairment of functional neuronal activity.

In AD patients, there is a dysregulation of excitatory and inhibitory synaptic signaling [222]. Since the majority of energy goes to synaptic signaling in neurons [223], it can be concluded that neuronal energetics is very closely associated with neurotransmission, and any imbalances to regional excitatory or inhibitory signals can cause complex and disruptive microcircuit alternations in the neural network. Inhibitory imbalances can be induced by GABA receptor agonists and impair synaptic plasticity [224], while excitatory imbalances can be induced by converse agents (such as reduced GABAergic signaling) and degenerate both synapses and neurons [225]. Synaptic plasticity is the ability of neurons to establish new contacts and strengthen the existing ones. Synaptic plasticity is involved in memory formation and is largely disrupted in AD patients [226].

Other molecular alternations in individuals with AD can also disrupt the metabolism of neuronal energy. The formation of Aβ oligomers can generate hydrogen peroxide and hydroxyl radicals, which impair the function of calcium, sodium, and potassium ATPases and glucose transporters due to lipid peroxidation neuronal and glial plasma membranes [227]. This results in an imbalance of cellular calcium and energy homeostasis, causing impairment of synaptic function [227]. These disrupted cellular processes and associated oxidative stress also play a role in tauopathy, where increased GSK3β activity can cause hyperphosphorylation and self-aggregation of tau [228]. *APOE* ε4 can also contribute to the development and progression of AD pathology by disrupting neurogenesis, cholesterol metabolism, and other cellular processes or pathways [229].

Apart from neurogenesis, mitochondrial biogenesis (an important player in maintaining physiological homeostasis) is also affected in AD patients [230]. One study demonstrated mitochondrial biogenesis signaling was reduced in AD brains and cell models, and that the induction of mitochondrial biogenesis helped to improve mitochondrial dysfunction [231], while intraneuronal accumulations of oligomeric

Aβ led to mitochondrial and synaptic deficiencies [232]. It was suggested that different therapeutic or pharmacological approaches which could enhance mitochondrial biogenesis may be useful in the treatment of AD [231]. In fact, the findings from Manczak et al. suggest that the mitochondria-targeted antioxidants, MitoQ and SS31, can be used as potential treatments to prevent Aβ toxicity as they were able to increase the synaptic connectivity between neurons affected by AD [233].

Cell signaling

Cell signaling is an important aspect of AD disease pathology, because alternations to communications between cells, whether mechanical or biochemical, can result in severe consequences. Synaptic loss is the main culprit behind cognitive decline in AD, but there are multiple cellular pathways involving cell signaling and the interplay of Aβ and tau pathologies that lead to synaptic failure and neuron dysfunction [97]. Understanding the cause of such cell signaling dysfunctions can allow us to identify potential targets and ultimately pharmacological treatments or therapies during early stages of AD.

Several studies have focused on the signaling pathways of caspase. One study found a caspase-3-dependent mechanism for dendritic spine loss, in which the activation of calcineurin by caspase-3 triggered the dephosphorylation and removal of the GluR1 subunit of an AMPA-type receptor from postsynaptic sites, subsequently impairing glutamatergic synaptic transmission and plasticity and therefore directly stimulating spine degeneration and memory loss [234]. A different signaling pathway was found to help mediate the inhibition of hippocampal long-term potentiation due to Aβ deposition. This pathway involved caspase-3, Akt1, and GSK3β, and a GSK3 inhibitor was found to ameliorate the long-term potentiation deficit caused by Aβ, marking another potential target for therapeutic approaches in the future [235]. Kanaan et al. posited that reducing GSK3 activity could be a strategy to reduce the pathogenic and neurotoxic forms of tau protein [112]. Apart from dendritic loss and impaired neuronal transmissions, caspase signaling has also been found to regulate microglia activation, where caspase-8 and caspase-3/7 are involved in executing apoptotic cell death due to the activation of microglia through a protein kinase C-δ-dependent pathway [236]. It can be hypothesized that inhibiting these caspases, and therefore microglia activation and associated neurotoxicity, could be a future approach to neuroprotection.

Various other studies have been performed to elucidate the effect of different mechanisms of AD pathology and whether they could act as potential therapeutic targets. In a normal brain, cyclin-dependent kinase (Cdk5) and its regulatory subunit (p35) are thought to play a role in brain function and therefore be involved with neuropathology [237]. *S*-nitrosylation or a reaction of nitric oxide related species forms SNO-Cdk5, which contributes to Aβ-induced dendritic spine loss [238]. Enhanced levels of SNO-Cdk5 were observed in postmortem AD brains but not in human brains, suggesting that Cdk5's *S*-nitrosylation is an abnormal regulatory mechanism that could contribute to AD pathology [239]. In an aging brain, decreases in the expression of DNA methyltransferase Dnmt3a2 in the hippocampus were found to be associated with cognitive decline [240]. The group suggested that a gating function for DNA methylation was involved in cognition and that Dnmt3a2 could be a potential drug target for the restoration of cognitive abilities in aged or diseased individuals [240]. The depletion of receptor tyrosine kinase EphB2 has also been found to play a crucial role in Aβ-induced neuronal dysfunction, where it impaired long-term potentiation in the dentate gyrus of transgenic AD mice [241]. Increased levels or enhanced activity of EphB2 could help confer neuroprotective qualities.

NEUROIMMUNE RESPONSE

Unlike the peripheral immune system, the neuroimmune system consists of processes that involve numerous interactions between the nervous system and the immune system, primarily interactions that are biochemical or electrophysiological. These interactions help to protect neurons from disease and illness by conferring host defense against pathogens, maintaining the balance in the blood-brain barrier, and facilitating neuroinflammation as a response to damaged neurons [242]. The cellular components that play a key role in the neuroimmine system include glial cells (astrocytes, microglia and oligodendrocytes), which make up the majority of the cells within a human brain [243], and cytokines that regulate neuroinflammation and cell signaling [244].

Dysfunctions within the neuroimmune system are strongly correlated with the progression of AD. Since microglia are the primary immune effector cells

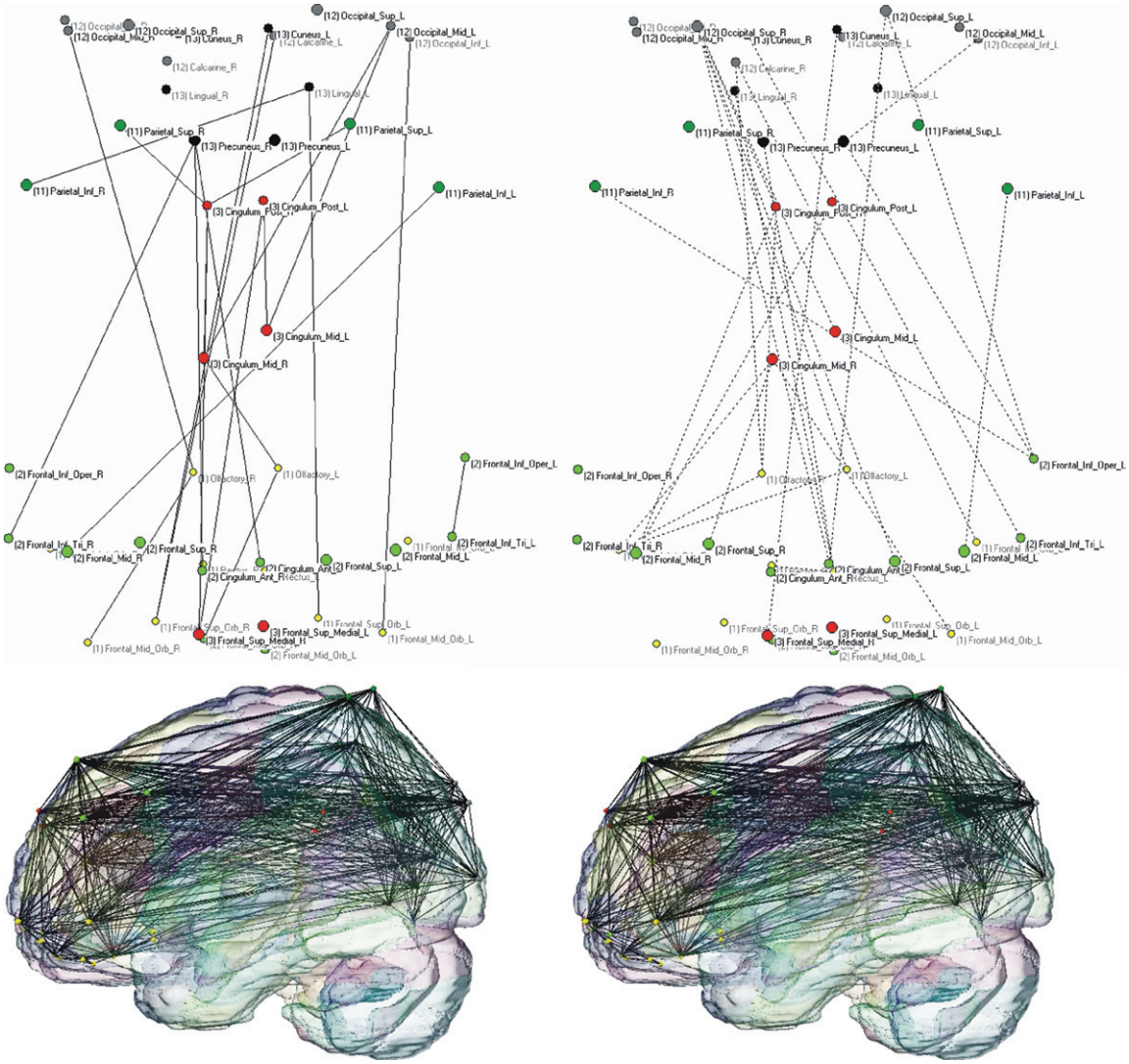

Fig. 4. Comparison of long-distance functional connections between an AD patient's brain (left) and a healthy individual's brain (right). The connectivity pattern of these two networks show a net loss of front-parietal and front-occipital functional connections in the AD patient, signifying abnormal global connectivity patterns [191]. Reprinted in accordance with a Creative Commons License.

within the brain, their regulation is important to AD pathology and a primary focus for research to further elucidate its effect on neuroimmunity [245]. One group found that CX3CL1-CX3CR1 (microglial chemokine fractalkine and its cognate receptor, respectively) signaling can reduce the phagocytic abilities of microglia, suggesting that reduced levels of this signaling pathway can lead to enhanced Aβ clearance [245]. Heneka et al. showed that deficient levels of NLRP3 inflammasome in microglia resulted in lower levels of Aβ deposition in AD mouse brains, revealing an important role of the NLRP3 and caspase-1 axis in AD pathology [246].

The dysfunction of the endosomal-lysosomal pathway has also been tied to neuronal pathology in early AD, where endosomes enlarge and lysosomes proliferate in affected neurons, resulting in the impairment of autolysosomal proteolysis [247, 248]. Yang et al. provided evidence that enhancing the function of lysosomes in AD models improves the clearance of autophagy substrates and reduces intracellular and extracellular Aβ levels, suggesting the ameliorating of neurodegenerative effects of AD [249]. However, another group's findings led them to hypothesize that although the upregulation of autophagy may be beneficial in normal aging or early stages of AD,

lysosomal blockage and the downregulation of autophagy would be more beneficial in later stages of AD to reduce the stress on the system [250].

Critical contributors to an aging brain's susceptibility to neurodegeneration involved systemic immune-related factors [194]. Specific age-related chemokines (CCL2, CCL11, and CCL12) were tested to determine their effect on neurogenesis, learning, and memory in the brains of young adult mice. Specifically, CCL11 was injected into the dentate gyrus of these brains, and it was observed that mice with this injection exhibited impaired learning and memory as well as inhibited adult neurogenesis [194]. Another study showed that chemokine receptor 2 (CCR2) mononuclear cells were the source of immigrating phagocytes in transgenic mice brains, cells that were capable of Aβ clearance in a CCR2-dependent manner [251]. It was shown that a CCR2 deficiency impaired Aβ clearance and amplified Aβ deposition vascularly [251].

Neuroinflammation

Apart from the two pathological hallmarks of AD, it is now believed that neuroinflammation plays a key role in AD pathogenesis due to the increased activation of microglia in postmortem AD brains and the presence of inflammatory cytokines, complement components, and toxic free radicals that contribute to Aβ accumulation in the diseased brain [252–255]. Cytokines take part in inflammatory and anti-inflammatory mechanisms in AD, specifically with the overexpression of interleukin-1 (IL-1) which causes neuronal dysfunction and neuron loss [256]. IL-6 and tumor necrosis factor α also play roles in AD neuroinflammation, while other cytokines like IL-4, IL-10, and transforming growth factor β helps to suppress proinflammatory cytokine production and prevent neurodegeneration [256]. Modifications to the mechanisms of these cellular components may help provide additional therapeutic options to treating AD.

Various studies have also been conducted to elucidate the different mechanisms of these cellular components in relation to AD. Microglia are strongly tied to Aβ clearance as they phagocytose Aβ fibrils in response to receptor ligation [257]. Compromised microglial function and therefore insufficient microglial phagocytic capacity results in increased Aβ deposition and neuroinflammation [258]. Similar to microglia, astrocytes can also release cytotoxic molecules such as cytokines and interleukins which aggravate neuroinflammatory responses [257]. Interference with the calcineurin/NFAT signaling pathway can reduce Aβ concentrations [259], while astrocytes can enhance the expression of Aβ-degrading proteases such as neprilysin [260, 261] and help to internalize Aβ *in vivo* [262].

Lewis et al. showed that the overexpression of the human apolipoprotein A-I can reduce neuroinflammation and cerebral amyloid angiopathy, thus preserving learning and memory capabilities within the brain [263]. Oxidative stress has also been established as one of the earliest markers of AD pathology, specifically MCI, which is a precursor to AD [264]. The findings from Smith et al. show that iron dyshomeostasis and redox activity result in oxidative stress and that this generation of free radicals contribute to impaired cognition [265].

Other factors that drive neuroinflammation include preventable, non-communicable diseases such as obesity, diabetes, and traumatic brain injury. Obese individuals have greater levels of white fat tissue that contain a lot of activated macrophages, which secrete proinflammatory cytokines on a continuing basis [266]. Type 2 diabetic mice have been observed to experience greater neuroinflammation and higher memory dysfunction [267]. Finally, traumatic brain injury results in sustained cerebral inflammation, which promotes the persistent release of cytokines and subsequent dysfunction of microglial phagocytosis and neuronal functionality [268, 269].

CONCLUSIONS

In this part, we reviewed the most notable advances in AD pathology research that have occurred since 2010. Modern x-ray diffraction and NMR studies have yielded impressive insights into the atomic and molecular structure of amyloid. The accumulation of evidence associating Aβ deposition with prion like pathologies is interesting albeit somewhat frightening. Advancements in MRI have allowed researchers to further differentiate minute changes in brain structure. "Big Data" approaches, utilizing graph theory and network theory, combined with high computing power have allowed mathematicians and physicists to make large contributions in the AD research field by demonstrating how the "connectome", or the network of neuronal connections, is altered by AD pathology. Although the molecular mechanism behind amyloid and tau pathologies have been studied in detail, there is a greater need to

conduct research on the interplay between these two pathologies as well as different factors that affect the development and progression of these pathological mechanisms. Whether it be neuroinflammation or the presence of pre-existing conditions, all factors will need to be taken into account in order to derive cohesive therapeutic approaches to preventing or treating AD. We are hopeful that the next five years of AD research will yield clarification on the pathology of AD and greater insights into the relationship between Aβ and tau. Additionally, we anticipate mechanisms obtained *in vitro* to be confirmed in *in vivo* studies.

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