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Some evolutionary perspectives on Alzheimer's disease pathogenesis and pathology

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Abstract

There is increasing urgency to develop effective prevention and treatment for Alzheimer's disease (AD) as the aging population swells. Yet, our understanding remains limited for the elemental pathophysiological mechanisms of AD dementia that may be causal, compensatory, or epiphenomenal. To this end, we consider AD and why it exists from the perspectives of natural selection, adaptation, genetic drift, and other evolutionary forces. We discuss the connection between the apolipoprotein E (*APOE*) allele and AD, with special consideration to *APOE* ϵ 4 as the ancestral allele. The phylogeny of AD-like changes across species is also examined, and pathology and treatment implications of AD are discussed from the perspective of evolutionary medicine. In particular, amyloid- β (A β) neuritic plaques and paired helical filament tau (PHFtau) neurofibrillary tangles have been traditionally viewed as injurious pathologies to be targeted, but may be preservative or restorative processes that mitigate harmful neurodegenerative processes or may be epiphenomena of the essential processes that cause neurodegeneration. Thus, we raise fundamental questions about current strategies for AD prevention and therapeutics.

Keywords

Alzheimer's disease; Dementia; Evolutionary medicine; Amyloid- β plaques; Neurofibrillary tangles; *APOE*; Comparative biology

1. Introduction

As baby boomers enter the vulnerable ages for Alzheimer's disease (AD), biomedical research is in a race against time to prevent, stabilize, or cure the disease. Implicitly or explicitly, rational therapeutic discovery relies on understanding the root cause(s) as well as intermediate and proximate pathophysiological processes of disease. Basic research on AD has historically focused on characterizing the signature pathological lesions, that is, amyloid- β (A β) neuritic plaques and paired helical filament tau (PHFtau) neurofibrillary tangles, and the precedent and consequent molecular, biochemical, and physical mechanisms that most likely link these disease lesions to the neurodegeneration and cognitive decline caused by AD.

From a therapeutic standpoint, a major challenge is to discern where one should intervene in the mechanistic chain of events of AD so as to achieve the best and least toxic effect. The

body is an evolved, complex system that strives to maintain homeostasis and promote individual survival and genetic reproduction; thus, any particular stage of biochemical and pathological progression in a disease may be an adaptive homeostatic response to the upstream events that preceded it. Evolutionary biomedical approaches attempt to account for the initial abnormality or dysfunction before dealing with its downstream effects. Depending on its contextual function, intervening at a downstream stage could be helpful, unhelpful, or even harmful. Seeking evolution-based answers to questions about the cause of diseases like AD can provide important perspectives on downstream “pathological” processes that, in fact, may be preservative or restorative.

There has been relatively little attention to evolutionary aspects of AD. One hypothesis is that AD is simply an inevitable manifestation of senescence [1]. AD, with its neuropathological signatures, decline in function, and associated suffering, is considered a disease rather than a natural, “normal” phenomenon of aging. However, all body systems deteriorate with age; it would be surprising if the brain did not. The risk of developing AD may be as high as 50% by age 85 [2], and some have estimated that by age 130, everyone would have the “disease” [3].

Another major hypothesis that is not mutually exclusive involves “antagonistic pleiotropy,” in which genes that are beneficial in one respect are detrimental in another. It has been suggested that the robust neuroplasticity of the human brain, which is especially advantageous during developmental and reproductive years when learning and mental flexibility are at a premium, comes at a bioenergetic cost of higher risk of lesions in later life [4]. These perspectives are part of the more general evolutionary theories of biological aging. See Rose [5] for a full overview, and Martin [6] for a discussion specifically on brain aging.

2. Evolutionary perspectives on the genetics and origins of AD

2.1. APOE

AD exists in both familial early-onset forms, in which uncommon mutations in specific genes (i.e., *APP*, *PSEN1*, *PSEN2*) cause the disorder [7], and the much more common “sporadic” type, with a typically later onset, to which most of this review and commentary will be limited. A number of genes have been associated with sporadic AD such as *A2M*, *FE65*, *GLUR5*, and *SORL1*, among others [7–12]), but so far, the only unequivocal risk gene is apolipoprotein E (*APOE*) [13,14].

APOE resides on chromosome 19 and consists of four exons and three introns encoded in 3597 base pairs. There are three major alleles, *APOE* ε2, *APOE* ε3, and *APOE* ε4, which translate three isoforms of the protein: apoE-ε2, apoE-ε3, and apoE-ε4. Individuals heterozygous for the ε4 allele are at a 2- to 3-fold higher risk of developing AD, whereas homozygosity for ε4 confers a 10- to 30-fold risk [15,16]. In contrast, the presence of an ε2 allele may confer a 25% decreased risk of developing AD [17]. Thus, *APOE* ε4 has classically been seen as injurious; *APOE* ε2, as protective; and *APOE* ε3, as neutral.

The addition of a phylogenetic perspective, however, warrants a shift in the way the *APOE* alleles are conceptualized. Among all other primates besides humans, there is only one common *APOE*, which, like human ε4, has arginine codons at amino acid positions 112 and 158 (*APOE* ε3 has cysteine residues at position 112 and arginine at position 158, whereas *APOE* ε2 has cysteine at both positions) [18]. This suggests that *APOE* ε4 is the ancestral form of the gene [18,19], and *APOE* ε3 arose later with a single cytosine to thymidine substitution at position 112 after the human lineage diverged from that of chimpanzees and bonobos. Another such mutation at position 158 in the *APOE* ε3 allele later gave rise to the

APOE $\epsilon 2$ form of the gene [18,20]. Rather than *APOE* $\epsilon 4$ “cropping up” at some point in our recent evolutionary history, it appears that such a gene was present in our nonhuman ancestors and has only recently been joined in the gene pool by competing functional variants [21] that may confer evolutionary advantages. In light of this, it may be more accurate to describe the $\epsilon 4$ allele as the “neutral” form because it predates the others, and to describe both the $\epsilon 2$ and $\epsilon 3$ alleles as protective, acting to mitigate the risk of AD, with the $\epsilon 2$ conferring more cognitive protection than $\epsilon 3$.

Such a distinction may affect how we approach therapeutic interventions. Should we be attempting to inhibit the effects of *APOE* $\epsilon 4$, mimic the effects of *APOE* $\epsilon 2$ or $\epsilon 3$, or both [19]? Rebeck et al. propose that the apoE- $\epsilon 2$ and - $\epsilon 3$ isoforms might simply perform the same lipid transport, antioxidant, anti-inflammatory, metabolic, and/or neuroprotective functions as those performed by apoE- $\epsilon 4$, only more efficiently [16].

2.2. Prevalence of protective alleles

Researchers studying the evolutionary origins of AD have considered the question of why the “new” alleles, and especially *APOE* $\epsilon 3$, have become so prevalent; approximately 95% of humans on average are estimated to carry at least one copy of the *APOE* $\epsilon 3$ allele, with 55% of humans homozygous for the allele (by contrast, about 28% of humans carry at least one *APOE* $\epsilon 4$ allele, with only 1%–2% homozygous for *APOE* $\epsilon 4$) [22]. It is possible that the *APOE* $\epsilon 2$ and *APOE* $\epsilon 3$ alleles, after arising in local populations, were subject to genetic drift such as a population bottleneck or founder effect. Not all genotypic or phenotypic traits necessarily have adaptive explanations, and genetic drift, as opposed to natural selection, accounts for a great deal of nonadaptive phenotypic variation [23]. According to Keller and Miller [24], drift almost inevitably results in genotypic uniformity, as the neutral allele either arbitrarily becomes fixated in the population or disappears entirely. Thus, if the spread of *APOE* $\epsilon 3$ is due to drift, it will eventually fixate in the genome over the course of many more generations (while *APOE* $\epsilon 2$ and $\epsilon 4$ would seem destined to be lost due to drift, given their relatively rarer distributions).

Alternatively (or additionally), the *APOE* $\epsilon 2$ and $\epsilon 3$ alleles may have been favored by natural selection, despite the fact that AD, with its postreproductive onset, would not seem to be strongly selected against. Researchers attempting to reconcile this conundrum have found evidence that the *APOE* $\epsilon 3$ allele confers benefits beyond AD protection. *APOE* $\epsilon 4$ carriers are at higher risk for atherosclerotic cardiovascular disease, not just AD [25]. Indeed, the gene *APOE* and the protein it encodes are involved in lipid absorption, immunity, and nerve growth [21]. Perhaps selection pressure on one of these effects, not neuroprotective factors, has allowed the *APOE* $\epsilon 2$ and *APOE* $\epsilon 3$ genes to flourish.

On the other hand, *APOE* $\epsilon 4$ carriers have been reported to have, on average, decreased levels of intellectual functioning throughout life and an increased likelihood of dropping out of high school relative to age-matched peers [26]. It is unclear whether this is due to early, subclinical accumulations of AD neuropathology that are known to begin decades before the typical ages of sporadic AD [27], or due to other effects independent of AD pathology. Alternatively, *APOE* $\epsilon 2$ and *APOE* $\epsilon 3$ alleles might have other neurological benefits besides AD protection, including fewer tangles and plaques in young adults [28] and after head trauma [29].

Sapolsky and Finch discuss yet another way in which protective *APOE* alleles may be selected for: the human phenomenon of “grandmothering” [30]. Durable functioning in old age is selected for via *kin selection* [31]; that is, early humans who remained functionally able for longer were able to provide more care and food for their grandchildren, who in turn had a greater chance of survival and passing on those protective alleles to their own

offspring. Although motherly care is the norm in all mammal species, “grandmothering” in nonhuman primates is almost entirely unheard of. As Sapolsky and Finch note, this fits with the observation that dementia in nonhuman primates occurs shortly after reproductive senescence, whereas dementia in humans tends to occur around 20 years after menopause, allowing more time for postreproductive females to contribute to the care of their grandchildren [30].

2.3. Recent origins of *APOE* ϵ 3 and ϵ 2

Given its presence in species as distantly related to humans as rabbits [32], the ancestral *APOE* gene (comparable with human *APOE* ϵ 4) must have been present for millions of years in our nonhuman ancestors; yet the now-widespread protective alleles arose only recently, between 200,000 and 300,000 years ago [19], after the genus *Homo* diverged from *Pan* (chimpanzees and bonobos). The “grandmothering” theory ties in with evolutionary life history to provide a possible explanation for this.

As brain size in our ancestors increased relative to other apes, and bipedality resulted in smaller birth canals, babies had to be born relatively earlier in their development to allow passage of their larger heads during childbirth. This resulted in a longer period of helplessness and the need for more prolonged parental care, which in turn created a greater genetic opportunity for grandmothers to benefit by helping with childcare. Therefore, there would have been selection pressure for human grandmothers to stay functional after menopause. This may have led to the spread of the *APOE* ϵ 3 allele, which was now beneficial but which would have conferred little advantage before the increase in brain size.

A related hypothesis posits a connection to our changing diet; Finch and Stanford suggest that at some point, our ancestors began eating more meat than earlier primates used to eat [33]. The shift in dietary emphasis meant higher cholesterol intake, allowing the *APOE* ϵ 3 allele, with its lowered risk of atherosclerotic vascular disease, to confer a survival advantage to meat-eaters. AD protection would thus be incidental. Alternatively, it has been reported that the *APOE* ϵ 4 allele is associated with a younger age of menopause [34] (although others have not found this [35]). If true, then the *APOE* ϵ 3 or *APOE* ϵ 2 alleles would provide an obvious procreative advantage. None of these theories are mutually incompatible with the others. The *APOE* ϵ 2 allele later evolved from the *APOE* ϵ 3 form and may have spread relative to the other alleles by any combination of the above hypotheses, including neuroprotective function, cardiovascular effects, or random genetic drift.

2.4. Conservation of the ϵ 4 allele

Some researchers have attempted to explain why the *APOE* ϵ 4 allele has not been eliminated from the gene pool altogether, in favor of *APOE* ϵ 2 and *APOE* ϵ 3, if these more protective forms confer a survival advantage. The simplest answer is the force of natural selection decreases as organisms age. However, the *APOE* ϵ 2 and *APOE* ϵ 3 alleles, having arisen recently in evolutionary history, seem to be overrepresented in the gene pool, suggesting possible selection pressure for them (see section 2.2). If this is the case, why does *APOE* ϵ 4 persist? If a gene variant confers any net reproductive disadvantage, there is selection against it.

Some researchers have looked for potential counterbalancing benefits of the *apoE*- ϵ 4 isoform. Various studies have discovered possible protection against liver damage in patients with the hepatitis C virus [36], reduced cardiovascular response to mental stress [37], and decreased chance of spontaneous abortion in fetuses [38]. Also, although ϵ 2 carriers are at reduced risk for developing AD, they may be at higher risk for atherosclerotic disease, given the association of *APOE* ϵ 2 homozygosity with type III hyperlipoproteinemia

[39], giving the $\epsilon 4$ allele a relative advantage based on this disease association. These are all possible antagonistic pleiotropic mechanisms of maintaining harmful alleles.

Keller and Miller [24] believe that the *APOE* $\epsilon 4$ allele is indeed on its way to extinction, a process that began with the rise of the protective *APOE* $\epsilon 3$ allele. In their view, antagonistic pleiotropy is unlikely to result in generationally stable allelic variation; because it is highly improbable that multiple alleles would confer precisely the same reproductive value, one of the competing alleles is almost certain to eventually reach fixation. From this perspective, the only explanation for the continued existence of the ancestral allele is that we are viewing an “evolutionary snapshot” of a process that will, after many generations, drive *APOE* $\epsilon 4$ to extinction [24].

Reser [1] discusses the intriguing possibility that preclinical or prodromal AD itself is an adaptation, a kind of “rescue program” that allows the body to conserve resources in food-scarce environments. Many other body systems downregulate in response to low caloric intake, shunting precious calories from the least crucial areas to the most vital ones, and because the brain is a bioenergetically high-cost organ, it might be expected to do the same. Reser suggests that the parts of the brain involved in attending to and encoding new information are expendable in a natural environment once an animal reaches the age where it has learned all the skills it needs to survive. In such an environment, the loss of the least crucial brain areas in exchange for precious calories is a utilitarian trade. In modern human society, however, those brain regions (the hippocampus and higher-order association cortices) are involved in domains that we now highly value, such as higher-level executive functions, personality, working memory, and episodic memory. Also, contemporary civilization, public health initiatives, and medical advances, especially in infectious disease, cardiovascular disease, and cancer, have extended the life span far beyond what we would assume to be that of *Homo* in the wild, who generally would have died of predation, starvation, injury, or infectious disease. Therefore, clinical AD, in Reser's view, is “the unnatural progression of natural brain aging changes.” Circumstances notwithstanding, apoE influences the deposition, aggregation, activity, and neurotoxicity of A β , and *APOE* $\epsilon 4$ correlates with increased A β load in AD patients relative to the other alleles [16]. Next, we examine how A β and neurofibrillary tangles, the two signature pathologies of AD, fit into this integrated evolutionary picture and how evolutionarily informed research should approach them.

3. Evolutionary medicine and AD

3.1. AD pathology

One goal of evolutionary medicine is to determine the function of disease pathology, signs, and symptoms. It is important that adaptive defenses that the body has evolved in response to pathogens or adverse conditions are recognized as such [40]. Much of the recent and current drug therapy research for AD targets the processes of A β production, oligomerization, aggregation, and clearance. The rationale for this line of drug development derives from the predominant amyloid cascade hypothesis, which holds that A β , in either oligomeric or aggregated (plaque) forms, impairs neural transmission and is toxic to synapses and neurons, promoting their degeneration. Ultimately, this degeneration manifests in cognitive and functional decline [41]. Accordingly, A β lesions should be prevented from forming (e.g., with β - or γ -secretase inhibitors) or removed if present (e.g., with anti-A β immunotherapies); otherwise, their downstream effects will be harmful. However, despite more than two decades of research, uncertainties about the extent, mechanisms, and clinical relevance of A β in AD remain [42].

The proximate molecular and biochemical steps of processing amyloid precursor protein (APP) into A β and subsequent biophysical chemistry of A β oligomerization and aggregation have been studied in much detail [42]. A β production and plaque formation are most commonly viewed as abnormal biochemical and physical signs of disease, causing injury to healthy brain tissue. This notion is chiefly supported by the dominantly inherited early-onset AD caused by APP, presenilin 1 and presenilin 2 mutations, and the statistical associations between the presence of A β plaques and dementia in sporadic late-onset AD. Although the case for A β being at the core of the hereditary early-onset AD is compelling (but see Lee et al. [43,44]), the case for its role in late-onset AD is less so. Correlation does not necessarily signify causation, and it is possible that plaques are epiphenomena, reparative reactions, or compensatory phenomena stimulated by the same processes that cause neurodegeneration.

Neurofibrillary tangles (NFTs), composed of paired helical filament tau (PHFtau), are the other defining pathological lesions of AD. Tau is an important microtubule-associated protein that is abundant in neurons, promotes assembly of tubulins into microtubules, and stabilizes microtubules. Phosphorylation of tau by various kinases is an important posttranslational modification that serves to destabilize microtubules, allowing for growth and plastic remodeling. However, hyperphosphorylation of tau, presumably due to either hyperactive kinases or hypoactive phosphatases, is thought to promote the self-assembly of tau into straight and paired helical filaments and ultimately into NFTs [45]. The relationship between tau and A β remains unclear. Some have argued that A β is upstream to tau in the pathogenesis of AD based on genetic data related to APP and presenilin mutations [46], whereas pathological studies have indicated that in large population samples, tau lesions are observed earlier than A β lesions [27]. Neurofibrillary pathology is also more closely correlated with impaired cognition in AD than is A β [47]. Eckert et al. [48] propose a link between A β and tauopathy and describe a model in which both pathologies synergistically deregulate mitochondrial function, creating a “vicious cycle” that eventually leads to cell death.

3.2. An evolutionary perspective on plaques and tangles

A default evolutionary assumption is that plaques and tangles are biological “spandrels,” that is, by-products of the evolution of some other phenotypic trait, and are not adaptations in their own right (for a general discussion of spandrels, see Gould and Lewontin [23]). The term “spandrel” refers to the origination of the trait rather than its current function; that is, a trait that originally arose as a by-product may later, over the course of evolutionary time, come to serve an adaptive function via cooption [49]. Accordingly, A β plaques and PHFtau tangles might have initially arisen as spandrels, but may be currently harmful, neutral, or even beneficial.

The view of plaques and tangles as harmful spandrels, that is, injurious processes that humans happen to be susceptible to, has been implicit in the traditional view of AD pathology [50] (see Lee et al. [43,44]) for a brief summary of proposed toxic mechanisms). However, plaques and tangles may be merely epiphenomena, their presence signaling that neurodegeneration is taking place, rather than indicating a mechanistic role [51]. This possibility underscores the need for continued research into the chain of events that the brain undergoes in the degenerative dementia of AD, and aging in general.

If plaques and/or tangles are spandrels, then what processes might have given rise to them? Finch and Marchaloni posit that A β plaques are evolutionary holdovers of the ancient inflammatory immune system that preceded the more elaborate and effective immune system of jawed vertebrates [52]. Indeed, a recent report supports and extends this hypothesis in that A β was determined to have potent antimicrobial activity [50].

Additionally, and not mutually exclusive with Finch's hypothesis, it has been proposed that plaques, tangles, or both might be normal or even beneficial reactions to the primary process(es) that actually cause(s) the neurodegeneration [43,44,53]. In this case, plaques and tangles would be either spandrels, which later came to serve an adaptive purpose (known as "exaptation"), or naturally selected adaptations in their own right. In a body doing all it can to maintain homeostasis, it is conceivable that some of the hallmarks of AD pathology are evolved salutary processes working to protect the brain rather than damage it. Ideally, this possibility would be examined and incorporated into the assessment of new disease-modifying therapies, to ensure that treatments are not doing more harm than good [44]. Indeed, postmortem study of subjects from the clinical trial of AN1792, an experimental anti-A β agent, indicates that the immunotherapy was successful in disrupting A β plaques, but it was not effective at arresting the dementia or reducing other pathological features of the disease such as total and soluble A β concentrations, total tangles, or angiopathy [54–56]. In addition, recent trials of semagacestat, an inhibitor of γ -secretase, an enzyme that cleaves APP to form A β , were prematurely stopped when an interim analysis found that AD subjects on active medication were deteriorating at a faster rate than those on placebo. There are many possible reasons for this, most likely related to the nonspecificity of this particular drug's γ -secretase inhibition. However, one possibility that will have to be considered is that production of A β may be a compensatory or reparative response in idiopathic AD and that its inhibition accelerates neurodegeneration.

Although A β neurotoxicity has been clearly demonstrated in vitro [57], a mechanistic role of A β in neurodegeneration has still not been unequivocally shown in vivo [58]. The data in transgenic mice that overexpress human APP are complex. Like humans with these mutations, mice produce both soluble oligomeric A β protofibrils as well as aggregated A β plaques. They exhibit evidence of synaptic injury as well as progressive behavioral deficits [59], but little evidence, if any, of the neuron loss per se of the type that is seen in human AD. Anti-A β immunotherapies in these mice produce reductions in A β abundance, clearance of A β plaques, decreased interaction of soluble A β oligomers with synaptic constituents, and reversal of behavioral deficits [60]. An interesting study that monitored the temporal profiles of levels of insoluble A β and soluble A β oligomers in the Tg2576 mouse described a transient lowering of soluble A β oligomers that occurs during an initial phase of fibrillar A β plaque formation and coincides with improved memory functioning back to normal for that brief time period [61]. This suggests that it is the oligomeric A β , and not the insoluble A β plaques, that is responsible for memory dysfunction in this mouse model.

Transgenic organisms can be instructive in modeling the biology of a particular gene and gene products, but they are not natural, and lack an evolutionary or adaptive context in which to interpret any but the most flagrant effects of the genetic manipulation. In humans, the toxicity of A β , in either fibrillary plaque or oligomeric forms, is not clear. Although generally lower in density than in those with AD, A β plaques can be found in the brains of almost all older humans. However, epidemiological studies with pathology have shown that high densities of A β plaques are not rare among elders with normal cognition. This shows that abundant A β plaques alone are not sufficient to cause dementia [62–65]. Other aspects of A β plaques that support the argument against their being considered toxic are that their topographical distribution does not correlate well with that of NFTs, neuron or synaptic loss, or the neuropsychological profile of AD [66]. In fact, the density of plaques in the entorhinal cortex and hippocampal formation is among the lowest anywhere in the AD brain [66].

3.3. Potential benefits of A β and PHFtau

The cleavage of APP by β - and γ -secretases to form β may just be an evolutionary by-product, but there have also been attempts to find positive functions of β as well. Soscia et al. have shown that β functions as an antimicrobial peptide in vivo [50]. Kamenetz et al.

found that neural activity increases β production, which in turn decreases excitatory neurotransmission [67]. This suggests a role for β (and thus APP) as a negative-feedback regulator of synaptic activity [58]. The effect of β on neurotransmission seems to be concentration-dependent; at picomolar levels of β_{1-42} , synaptic transmission and memory are increased, whereas nanomolar concentrations show the opposite pattern [68,69]. Thus, β might have a normal, and perhaps even necessary, function at low levels, and may be disruptive only when its levels are increased due to mutations or other genetic vulnerabilities, or overstimulatory environmental factors. Yao and Papadopoulos suggest that APP and β have a function in controlling cholesterol transport and homeostasis, and that β overproduction leads to neuro-degeneration through a disruption of cholesterol trafficking [70]. APP knockout mice have been shown to display deficits in certain learning tasks, locomotor activity, and grip strength [71], indicating a role of APP in normal cognition. The cleavage of APP by β and γ -secretases to form β may actually be a crucial part of neuroplasticity that contributes to pruning of synapses that are no longer needed, counterbalancing the α -secretase pathway, which facilitates the creation of new connections [19]. Therefore, brain aging may also be an antagonistic pleiotropic effect of the synaptic pruning that is a normal part of brain development, a process in which APP plays a crucial role.

Regardless of whether monomeric β is functional or oligomeric β is harmful, the occurrence of plaques may be either functional, harmful, or both. Plaques have been hypothesized to act as “sinks” to immobilize harmful free oligomeric β in the brain [43,72]. It is conceivable that β 's tendency to aggregate, because of its fibril structure, is a design feature of the protein to ensure that neurons are not harmed by soluble oligomeric β , or to mitigate the effects of some harmful cellular process in AD [73]. The presence of APP and β deposits after brain trauma [74] suggests that these features can form in response to neuronal injury rather than, or in addition to, causing it.

An analogous account may be made for PHFtau and neurofibrillary pathology. Normal phosphorylation of tau and the resulting destabilization of microtubules are necessary for cytoskeletal rearrangement in the process of axonal and dendritic growth and plasticity [19]. Tau undergoes many other posttranslational modifications, including abnormal hyperphosphorylation, nitration, glycosylation, glycation, ubiquitination, cross-linking, oxidation, deamidation, and others (for review, see Meraz-Ríos et al. [75]). Each of these may promote or attenuate oligomerization and aggregation through various biophysical mechanisms. Like β , it is conceivable that hyperphosphorylated tau oligomers are the toxic species, or they may serve as the niduses for further filamentous aggregation. Tau oligomers have been reported to occur in vulnerable brain regions before observable NFTs in AD and tauopathies, and to occur in a time-dependent manner in tauopathy animal models in correlation with memory impairment [76]. Furthermore, although densities of tangles are highly correlated with neuron loss and cognitive decline in AD, it is also reported that most neurons that die in AD do not show tangles, indicating that tangles are neither sufficient nor necessary for cell death in AD [53,77]. Finally, like plaques, it may be that sequestration and aggregation of oligomerized PHFtau into NFTs is protective [53]. Indeed, some recent work has suggested a protective effect against activated caspase-induced apoptotic death in the neurons that bear NFTs in the *rTg4510* mouse model of tauopathy [78,79]. Antagonistic pleiotropy related to tau's role in synaptic pruning may suggest a “trade-off” hypothesis of brain aging similar to that mentioned for APP; this process, which is necessary for early development, becomes harmful when the organism reaches advanced age.

3.4. AD pathologies in nonhuman species and their significance for understanding human AD

Humans are not the only species to show age-related cognitive impairment or even AD-like pathology. Comparing the disease in humans with similar phenomena in other animals, especially from a phylogenetic perspective, provides insights into the evolution and function of AD pathology.

All examined nonhuman primate species have been shown to display either NFTs, A β plaques, or both [20,80]. (It has recently been suggested that chimpanzees and other non-human primates might not show age-related cognitive impairment or neurodegeneration at all, and that the structure of the A β found in these animals' brains may be different than that found in humans [81,82]; however, it is worth noting that Sherwood et al.'s analysis [82] did not include the long-lived chimpanzee individuals in which brain aging would be expected to appear.) Ungulates, whales, bears, dogs, and cats also have been found to display AD-like pathology [20,83], and A β deposits have even been found in birds [84] and fish [51], the latter possibly suggesting an ancient origin for plaques. Age-related cognitive impairment has been observed in primates [20], rodents [85], dogs, and cats [86] (see Fig. 1). As in humans, AD-like pathologies are more likely to be found in older specimens, especially domesticated or captive individuals, whose life spans are likely to be longer than their wild counterparts. As more species are found to be susceptible to the same triad of AD-like features (plaques, tangles, and age-related cognitive impairment) that humans display, the distinction between these syndromes in other animals and AD in humans may become less useful [20].

Presence of A β deposits and PHFtau NFTs in other animals suggests homology, that is, that the vulnerability to these pathologies existed before our ancestral split with those species. The preservation of these pathologies over millions of years would be due to one of two factors: (a) some constraint on the strength of natural selection (e.g., their late-life manifestation may result in a lack of selection pressure) or (b) a possible beneficial function for these traits (e.g., amyloid aggregations might serve to prevent harm by oligomeric A β). More research into possible health-promoting or survival benefits of plaques and tangles may eventually provide an answer to the question of why they persist among different species.

While of increasing use in disease genetics [87], studies incorporating phylogenetic approaches to understanding AD pathology have been rare. A survey of other species, including nonmammals and especially long-lived ones like certain tortoises and elephants, would yield more clues to the universality of AD pathological lesions. Elephants may be of particular interest because they are renowned for their intelligence, memory, and complex social structure as well as longevity. Indeed, elephant grandmothers, great-aunts, and other postreproductive females play a role in caring for young [88]. Although these mammals are phylogenetically distant from humans, the age-related cognitive impairment and neuropathological changes (e.g., A β and PHFtau) in elephants, if they occur, might be expected to be similar to that of humans.

4. Conclusion and therapeutic implications

Viewing AD from an evolutionary perspective prompts a rethinking of the way we describe the relationship between the clinical dementia and the neuropathology by which we define the disease. By integrating the fields of phylogeny, life history theory, genetics, biochemistry, and evolutionary medicine, a unified theory of AD can be developed. The precursor of *APOE* ϵ 4, universal in our ancestors, became a risk factor for dementia only after changing lifestyle and increased life span allowed alternative alleles (*APOE* ϵ 3 and

APOE ϵ 2) to provide reproductive benefits to their bearers. Perhaps partly because of its improved metabolism of A β , *APOE* ϵ 3 became ubiquitous, but *APOE* ϵ 4 remains in the gene pool, disposing its bearers to increased rates of A β deposits, neurofibrillary tangles, and age-related cognitive decline. Future integrated research into the pathology of AD will reveal whether these disease hallmarks are neutral spandrels, beneficial adaptations, or perhaps an inevitable downside of our complex and highly plastic brains.

Given the complex biology of A β and PHFtau monomers, oligomers, and fibrillar aggregates, and their polymorphously deleterious but also potentially beneficial effects for the person, prudence may be advised in attacking these lesions directly. Community-based epidemiological studies of cognition and AD pathology as well as other clinical and preclinical studies provide compelling evidence that although plaques and tangles are commonly associated with AD-type dementia, these lesions are neither necessary nor sufficient for cognitive decline. In fact, some people appear *resilient* in their cognitive function, despite abundant plaque and tangle pathology. Conversely, others exhibit *cognitive frailty*, exhibiting severe dementia with only minimal or no pathology.

Orthodox thinking about AD views the neuropathology as the cause of dementia, and the differing levels of impairment among the subjects as being due to multifactorial contributions of A β and PHFtau pathology-induced injury such as inflammation and synaptodendritic degeneration. In this formulation, the resilient and cognitive frailty groups are exceptional, and the classification, nomenclature, and framework fit. However, if it turns out that A β plaques and/or PHFtau NFTs are correlated spandrels rather than mechanistic intermediaries of neurodegeneration, or perhaps even health-promoting adaptive responses to the as-yet-uncertain causes of idiopathic late-onset AD, then an alternative theoretical framework can be considered wherein plaques/tangles help to mitigate neurodegeneration and cognitive decline, and it is because of these disease features, not in spite of them, that brains remain resilient. Thus, it would be the so-called “resilient” and “cognitive frailty” groups that fit the expected pattern. A β plaques protect against dementia in the former and fail to “deploy” in the latter, allowing neuron damage to take place. In patients with both pathology and dementia, harmful processes eventually overwhelm the defensive plaque and/or tangle system and begin to cause cell death. We would then ask why these people get AD despite their defense mechanisms when the “resilient” people's defenses work so well. Why do the “frail” patients' defenses fail to work at all? Research designed to address these questions is pressing, especially as more drug therapies based on classical models of AD pathology, such as the A β -cascade hypothesis, enter clinical trials.

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Fig. 1. Plaques, tangles, and age-related cognitive impairment in other species. The triad of AD hallmarks (plaques, tangle, and age-related cognitive impairment) as found in other species, underscoring the need for more research. For specificity and ease of reference, various taxonomic ranks, as well as paraphyletic groupings, have been used.