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# Evolution of Human Susceptibility to Alzheimer's Disease: A Review of Hypotheses and Comparative Evidence

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## ABSTRACT

Primates rely on memory to navigate both physical and social environments and in humans, loss of memory function leads to devastating consequences. Alzheimer's disease (AD) is a neurodegenerative disease which begins by impacting memory functioning and is ultimately fatal. AD is common across human populations and its prevalence is predicted to rise with increases in the aging population. Despite this, the full AD phenotype has not been observed in any other nonhuman primate species. While a significant amount of research has been devoted to understanding the immediate mechanisms involved in AD pathogenesis in humans, less research has focused on why humans are particularly vulnerable to neurodegenerative diseases like AD. Here we explore hypotheses on the evolution of distinct human susceptibility to AD and place these in the context of findings from comparative neuroanatomical and molecular studies and discuss recent evidence for evolutionary changes protective against AD in the primate lineage.

## 1 | Introduction

Primates rely on memory and cognitive flexibility to navigate both their physical and social environments and loss of memory function can lead to devastating consequences. Alzheimer's disease (AD) is a neurodegenerative disease characterized, at first, by memory loss and language problems and progressing until basic bodily functions, such as walking or swallowing, become impaired and patients become bed-bound. Eventually, AD is fatal. In 2019, there were approximately 50 million individuals living with AD globally and this number is projected to increase to approximately 150 million by 2050 due to increases in aging populations [1]. AD is the most common form of age-dependent dementia, but the causes and mechanisms of the disease remain incompletely understood.

Interestingly, despite the prevalence of AD in human populations, the full AD phenotype has not been observed in any nonhuman primate (NHP) species. This is remarkable given that organisms which are more genetically similar to one another are more likely to experience the same or similar diseases [2]. It is unclear exactly how conserved patterns of brain aging are among primates, although typical brain aging in both humans and NHPs studied is characterized by a number of similar structural and neuropathological changes. These include reduced brain volume, neuroinflammation, synaptic loss, and dysfunction, as well as amyloid-beta (Aβ) deposition and, in some cases, the appearance of various tau pathologies (reviewed in Freire-Cobo et al. [3] and August et al. [4]). In a biomedical context, brain aging and neurodegeneration are often studied using animal models, particularly mice. While mouse models are a practical research choice and their use has

increased our understanding of AD pathogenesis, recent work has drawn attention to the fact that mice are not the most evolutionarily relevant models of aging [5, 6]. Indeed, genome-scale comparative analyses of gene expression changes in mice, macaques, and humans reveal that, while a small subset of age-related gene expression changes are conserved between species, major changes have occurred in macaques and humans which may be related to age-related changes in cognition and susceptibility to neurodegeneration [7]. It is also notable that wild-type mice do not develop Aβ plaques or neurofibrillary tangles (NFTs) with age [8]. Comparative primate research affords us the opportunity to identify ancestral elements of aging neurobiology and increase our understanding of how unique features of brain aging may have increased human susceptibility to neurodegenerative diseases.

Evolutionary perspectives suggest a number of possibilities for the evolution of human susceptibility to AD. Hypotheses related to antagonistic pleiotropy and age-related selection bias suggest that AD is the result of pleiotropic effects of genes beneficial to an individual earlier in the lifespan and weak selection later in life. Other hypotheses point out that humans have large brains which are slow to develop and metabolically expensive and that these features may play a significant role in the evolution of AD. Finally, some propose that AD is an artifact of modern life. They suggest that the recent extension of the human lifespan may play a role in the development of AD or that modern environment cause AD risk factors to function differently than they did in the past.

Here we briefly review age-related structural and neuropathological changes in humans and other primate species as well as the brain changes characteristic of AD in humans. We then explore the hypotheses mentioned above related to the evolution of human susceptibility to AD and place these in the context of findings from comparative neuroanatomical and molecular studies before finally discussing recent evidence for evolutionary changes protective against AD in the human lineage.

## 2 | Brain Aging, Cognitive Decline, and AD in Primates

### 2.1 | Brain Aging and Cognitive Decline in Primates

Humans, as well as many other primate species, experience a number of age-related structural and pathological brain changes (Figure 1). In humans, typical brain aging is characterized by a decline in total brain volume and an increase in ventricle size and cerebrospinal fluid volume [9, 10]. The decrease in total brain volume involves both gray and white matter; however, white matter volume may decline at a slightly slower rate than grey matter [11]. The decline of grey matter volume is related to cortical thinning which occurs throughout the brain with age [12]. However, numerous studies have shown that declines in grey matter volume do not impact all brain regions equally [13–15]. Brain regions which are particularly vulnerable to

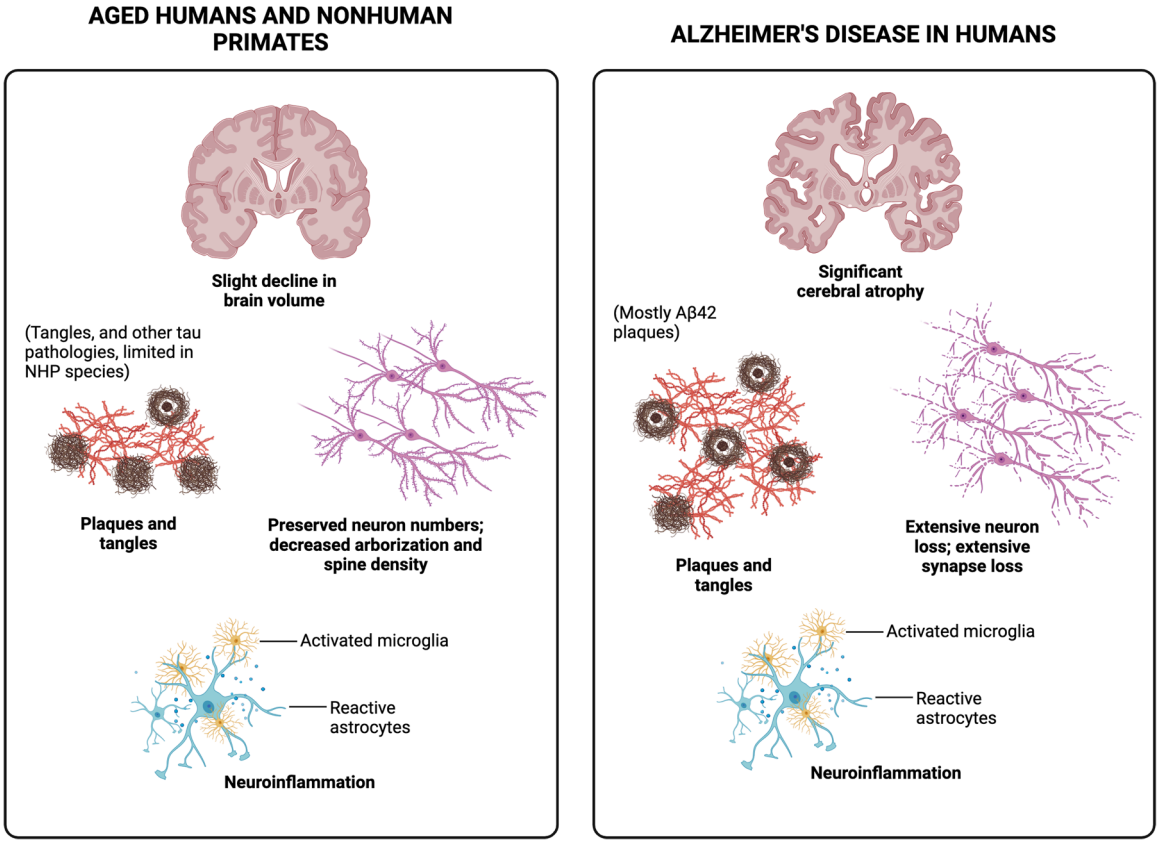


**FIGURE 1** | Side-by-side comparison of the structural and neuropathological changes identified in typically aging humans/select aged nonhuman primates and humans with AD. Image created with BioRender.

age-related volumetric decline include the superior parietal lobule, inferior temporal cortex, hippocampus, and prefrontal cortex. Areas which are relatively spared during typical aging include the occipital cortex and parahippocampal gyrus. These age-related decreases in grey matter volume are likely related to changes in dendritic arborization and decreased dendritic spine density and synaptic changes, rather than loss of neurons (reviewed in Freire-Cobo et al. [3] and August et al. [4]). Evidence also suggests that a decrease in brain volume, particularly grey matter volume, is characteristic of brain aging in those NHP species studied, namely, mouse lemurs, macaques, and chimpanzees [16–22]. However, Sherwood et al. [23] report no significant age-related volumetric changes in chimpanzees compared to humans and suggest that age effects on brain volume in humans may be evolutionarily novel. More recent research has identified a positive relationship between cortical expansion and age-related decline in grey matter volume in humans compared to chimpanzees suggesting a relationship between evolutionary expansion of particular brain regions and vulnerability to degeneration in humans [22]. As in humans, decreases in brain volume with age in those NHP species studied is likely related to changes in dendritic arborization and spine density rather than loss of neurons (reviewed in Freire-Cobo et al. [3] and August et al. [4]).

Neuropathological changes with age in humans include neuroinflammatory changes as well as Aβ and tau (glycoproteins that accumulate abnormally in the extracellular and intracellular space, respectively in AD pathology. Transcriptional analyses of age-related changes in gene expression reveal that glial cells display the majority of differential gene expression with age [24]. Microglia, the resident immune cells in the brain, exhibit a number of age-related changes. These include morphological changes indicative of activation, increased number and density, and decreased regularity of distribution [25]. In astrocytes, there is an age-related increase in cytoskeletal glial fibrillary acidic protein (GFAP) expression, indicating increased activation of astrocytes with age [26]. Many studies have also documented Aβ plaques, NFTs composed of abnormally hyperphosphorylated tau [27–31], and vascular Aβ in cognitively intact older adults [32, 33]. Indeed, by age 80–85, many nondemented older adults have substantial plaque and NFT pathologies. However, Aβ plaques seen in typical aging are more commonly of the diffuse Aβ40 subtype (rather than the compact Aβ42 subtype more typical of AD) and NFT pathology is milder than what is seen in AD.

Aβ deposition appears to be a common feature of aging in many mammal species, including primates [34]. Several studies have identified Aβ plaques and vasculature Aβ in aged chimpanzees [35–37]. An early study of Aβ plaques in chimpanzees found they are most commonly diffuse Aβ40 plaques and that there is a higher ratio of Aβ40 to Aβ42 in the brains of aged chimpanzees [38]. However, more recent research suggest Aβ42 is more common in aged chimpanzees and that regional distribution of plaques matches that seen in AD [35]. Aβ plaques and vasculature Aβ has also been described in aged gorillas and this is true for both captive (*Gorilla gorilla gorilla*) and wild (*Gorilla beringei beringei*) gorillas [39, 40]. Finally, Aβ is also present in diffuse plaques and cerebral vasculature in aged orangutans. This study also identified a higher ratio of Aβ40 to Aβ42 in aged orangutans [41]. Aβ plaques and vascular Aβ are also quite common in many aged monkey and lemur species (for a thorough review, see Freire-Cobo et al. [3]). Among nonhuman apes, tau pathology has been identified in chimpanzees and gorillas. Pretangles, NFTs, and neuritic clusters have been described in aged chimpanzees that also exhibited Aβ plaques and significant Aβ vascular pathology [35]. Tau-like lesions and tau-positive astrocyte and oligodendrocyte coiled bodies have been observed in both captive and wild gorillas although tau pathology is less extensive in wild gorillas [39, 40]. Various tau pathologies have also been observed in several monkey and lemur species (for a thorough review see Freire-Cobo et al. [3]). Finally, neuroinflammatory responses to AD-like pathologies have also been described in several NHP species (reviewed in Freire-Cobo et al. [3]).

Understanding neuropathological changes that occur with age in other highly intelligent, nonprimate species (such as cetaceans and corvids) could shed light on evolutionary changes that have increased human susceptibility to AD. However, much less is known about the neuropathology of aging in these species. A few studies investigating the neuropathological hallmarks of AD in cetaceans have identified aβ plaques and limited tau pathology in several species of toothed whale [42–44]. However, some of these pathological changes may be related to hypoxia from diving [42]. Interestingly, a few studies suggest AD-like pathology in dolphins may be related to exposure to certain toxins [45, 46].

Age-related changes in cognition are also a part of typical aging in humans and other primate species studied. Executive functions are a collection of top-down mental process necessary for concentration and attention. The generally agreed-upon core executive functions are inhibition and interference control, working memory, and cognitive flexibility [47]. A decline in executive functions and reduced processing speed are hallmarks of typical cognitive aging in humans [48]. However, semantic and verbal abilities generally remain intact. While cognitive changes can be difficult to assess in NHPs, a number of tests have been devised to assess those cognitive domains most often studied in human neuropsychological research. A recent review of findings from these NHP studies, as well as human neuropsychological research, indicates that a decline in executive functions is part of typical aging in several NHP species including rhesus macaques, mouse lemurs, marmosets, and chimpanzees. The authors further suggest that the presence of these cognitive changes across species with differing lifespans, life histories, and brain architectures may indicate that age-related decline in executive functions is a hallmark of cognitive aging in primates generally [49]. However, it remains unclear whether similar neuroanatomical changes underlie this age-related cognitive decline across primate species.

### 2.2 | AD in Humans

AD is the most common neurodegenerative disorder seen in age-dependent dementia and it is characterized by a number of neuropathological changes and severe cognitive impairment (Figure 1). The hallmark pathologies of AD at the cellular level are Aβ plaques and NFTs. Aβ is a normal byproduct of amyloid

precursor protein (APP) cleavage by β- and γ-secretases in neurons and the term amyloid refers to the starch-like appearance of these molecular complexes. In AD, abnormal accumulation of Aβ with either 40 or 42 amino acids results in the formation of extracellular plaques. However, Aβ42 plaques are more common in AD due to the higher rate of fibrilization and insolubility of Aβ42. Morphologically, plaques can also be divided into diffuse and compact subtypes, with compact plaques more commonly identified in AD patients [50]. While the spatiotemporal progression of Aβ plaques is less predictable than NFTs, two staging systems have been proposed. Braak and Braak [51] identified three stages of plaque deposition: in Stage A plaques are found in basal portions of the frontal, temporal, and occipital lobes, in Stage B neocortical association areas are affected, the hippocampal formation is minimally involved and the primary sensory, motor, and visual areas are unaffected, in Stage C plaques are found in these primary areas as well as subcortical nuclei and the molecular layer of the cerebellar cortex. Another staging scheme proposed by Thal et al. Thal et al. [52] describe five phases of plaque deposition: in Phase 1 isocortical regions are affected, in Phase 2 plaques spread to allocortical regions, subcortical nuclei begin to be affected in Phase 3, Phase 4 is characterized by the involvement of a number of brainstem regions, and finally, Phase 5 involves further brainstem regions as well as the molecular layer of the cerebellar cortex (see also [53]). Notably, total number of plaques is not associated with disease severity and the spatiotemporal distribution of Aβ plaques does not match the neuropsychological profile typical of the disease [50]. Accumulation of the more soluble form of Aβ (Aβ40) also occurs in the endothelia of cerebral blood vessels, and while this can occur in isolation, it is commonly identified in AD patients.

Intracellular NFTs are composed of misfolded and abnormally hyperphosphorylated microtubule-associated protein tau [50] which is also hypoglycosylated with the intracellular O-GlcNAc modification [54–56]. The spatiotemporal progression of NFTs occurs in six stages: Stages I and II are often referred to as the "transentorhinal stages" and NFTs are present in transentorhinal and entorhinal regions, Stages III and IV are referred to as the "limbic stages" and involves regions of the hippocampal formation, amygdala and thalamus, finally Stages V and VI are known as the "isocortical stages" during which isocortical areas are profoundly impacted by NFTs [57]. Unlike Aβ plaques amount of NFTs does correlate with disease severity and their distribution matches the neuropsychological profile typical of the disease [58]. Additionally, a correlation exists between neuron and synapse loss and NFTs [50].

Neuron loss is central to the pathogenesis of AD and related to the significant atrophy characteristic of the disease. Neuron loss matches the distribution of NFTs, but neuron loss exceeds number of NFTs in these regions. Neuron loss is also correlated with the cognitive decline typical of AD [50]. Interestingly, certain classes of neurons are particularly vulnerable to degeneration in AD, while others appear more resistant [59]. Extensive loss of synapses is also characteristic of AD and correlates most strongly with cognitive decline [50]. This association was first observed using electron microscopy [60] and measures of synaptic protein concentrations [61]. Since then, these findings have been replicated a number of times and a recent meta-analysis confirms that synapse loss in selected brain regions is an early event in the pathogenesis of AD [62]. Recent research has also highlighted the significant role of inflammation in AD. Toxic Aβ and tau in the brain can trigger an immune response which is carried out by microglia and astrocytes. In the healthy brain, these cells are primarily involved in providing metabolic and structural support to neurons and they are fundamental in the pathogenesis of AD because of both their neuroprotective and neurotoxic capabilities. When functioning in a neuroprotective capacity, microglia and astrocytes can act as effector cells and release neuroprotective cytokines. However, failure to perform their neuroprotective functions can result in neurons being exposed to excitotoxicity and oxidative stress. Moreover, chronic inflammation and accelerated AD progression can result if these cells fail to remove toxic Aβ [63].

The main consequence of these brain changes is severe cognitive impairment and, while there is some overlap between cognitive changes characteristic of typical aging and AD, there are also notable differences. Both typical aging and AD involve decline in executive functions and processing speed, however, cognitive decline in AD is marked by significant impairments in memory functioning. Declarative memory, involving information that can be consciously evoked, can be divided into two types: episodic and semantic memory, both of which are impacted in AD. Episodic memory is involved in storing personal experiences [64] and deficits in episodic memory are an early symptom of AD. Difficulty encoding new information prevents the consolidation of new information into long-term memory and impaired retrieval and recognition are often regarded as hallmark symptoms of AD-related cognitive decline [48]. Semantic memory involves storing information about facts [64] and is also affected early in disease progression. These semantic memory deficits are often reflected in word-finding difficulties. Finally, orientation difficulties and deficits in executive functions arise later in the progression of AD [48].

## 3 | Evolutionary Perspectives on AD

It is intriguing that, despite its prevalence in human populations, the full AD phenotype has not been observed in any other primate species and it has been proposed that humans are uniquely susceptible to neurodegenerative diseases like AD [2]. Additionally, while a significant amount of research has been directed toward understanding the immediate mechanisms involved in AD pathogenesis in humans, much less has been aimed at understanding why humans may be uniquely susceptible to the disease. However, evolutionary perspectives propose several hypotheses to account for the prevalence of AD in human populations.

### 3.1 | Antagonistic Pleiotropy and Age-Related Selection Bias

Antagonistic pleiotropy has long been proposed as a mechanism for the evolution of senescence [65]. Pleiotropy refers to the phenomenon in which single genes affect two or more

apparently unrelated traits. Antagonistic pleiotropy as a mechanism of senescence rests on the idea that certain genes which are beneficial earlier in life (i.e., genes that increase reproduction and survival to reproductive age) may have deleterious effects in later life and suggests a kind of evolutionary "trade off." That is, genes favorable to reproductive success would be selected over genes which increase longevity but are less favorable to reproductive success [66]. Indeed, there is evidence that antagonistic pleiotropy may play a role in several non-communicable chronic diseases in humans. For instance, certain cancer and coronary artery-related genes are positively associated with fertility [67, 68].

Antagonistic pleiotropy has also been proposed as an explanation for the evolution of AD (Figure 2). This hypothesis suggests that AD exists in human populations because genes which increased susceptibility to AD later in an individual's life also have adaptive benefits earlier in the lifespan. A notable example of this is the E4 allele of the apolipoprotein E (ApoE) gene. The ApoE4 allele is the most common genetic risk factor for sporadic AD but has also been shown to be beneficial in other contexts by providing, protection against hepatitis-C-associated liver damage, cardiovascular stress, miscarriage, age-related macular degeneration, and malaria [69–73]. However, it should be noted that the ApoE4 allele is also involved in susceptibility to other diseases such as cardiovascular disease [74]. ApoE4 is the ancestral allele, showing closer similarity to the chimpanzee ApoE sequence, but two derived alleles (ApoE2 and ApoE3) have reached high frequency in modern human populations [75]. It has also been suggested that selection for genes involved in neuroplasticity may be related to the development of AD [76, 77]. Many genes whose expression has increased in the human brain, particularly the association cortex, allow for increased synaptic activity and plasticity throughout life. This increase in plasticity is beneficial for learning in complex social and physical environments but may also be related to increased susceptibility to AD [76, 78].

Others have proposed that AD may persist in human populations because of age-related selection bias [79]. That is, the notion that selection is weak or absent in later life because what occurs during this period does not, or only minimally, impacts an individual's reproductive success. According to this hypothesis, AD persist in humans because it typically does not appear until after reproductive senescence and is, therefore, not subject to selection. However, this hypothesis does not account for evolution of human susceptibility to AD in the first place, nor for the notion of inclusive fitness and the significant role played by older adults in human groups, as discussed in more detail below.

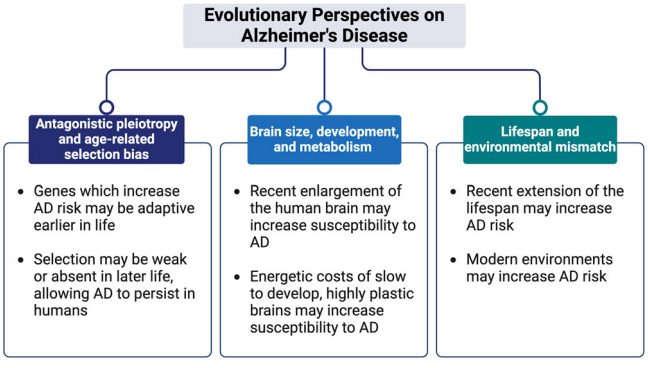


**FIGURE 2** | Summary of hypotheses related to the evolution of human susceptibility to AD. Image created with BioRender.

## 3.2 | Brain Size, Development, and Metabolism

The human brain has increased in both absolute size and relative to body size over the course of our evolution and it is approximately three times the size of that of our closest living relatives the chimpanzees and bonobos. Moreover, it has been suggested that this increase in size may play a significant role in the evolution of AD (Figure 2). However, increase in size alone is not sufficient to explain AD in humans as there are several species with larger brains that are not subject to AD-like degeneration. Rather, enlargement of particular brain regions is likely more significant to the evolution of AD and it has been claimed that regions subject to some of the most extreme enlargement over the course of our evolution (areas of frontal, temporal, parietal, and hippocampal cortex) are also particularly vulnerable to degeneration in AD [80, 81]. Indeed, a recent MRI study examining grey matter changes with age in humans and chimpanzees identified a positive relationship between cortical expansion, particularly in the ventral prefrontal cortex, and age-related decline in grey matter volume in humans [22]. This relationship suggests a link between more recent evolutionary expansion of particular brain regions and vulnerability to degeneration in later life that is present in humans but not chimpanzees.

The human brain is also very slow to develop and neurons in phylogenetically younger areas remain incompletely myelinated with increased synaptic activity and plasticity well into adulthood. All of which results in the human brain using a higher proportion of metabolic energy. Indeed, the human brain consumes about 20% of the total energy consumption at rest, about twice that used by other ape brains. This increased metabolic expenditure by the human brain, particularly as it is sustained over a long period of time, is proposed to increase susceptibility to degeneration via oxidative stress which is known to play a role in AD [82].

## 3.3 | Lifespan and Environmental Mismatch

The evolution of a long lifespan in humans has also been considered as a significant factor in the development of AD. Indeed, it is a widely held belief that extension of the lifespan beyond the fourth decade is a recent trend in humans and it has been suggested that many diseases which impact older adults are a modern phenomenon resulting from this extended lifespan [83]. According to this hypothesis, AD persists in human populations, despite it deleterious effects, because enough time has not yet passed to allow selection to impact the frequency of disease-associated alleles (Figure 2). However, this explanation is challenged by the notion that, while life expectancy at birth has increased dramatically, adult mortality rates have likely remained the same across human history [84] with a modal age at death of 70 or more years in hunter-gathering societies [85].

Others have proposed that a mismatch between modern life and our evolutionary history may drive AD prevalence in human populations. That is, modern environments may cause certain AD risk factors (including insulin resistance, estrogenic neuroprotection, inflammation, and ApoE) to function differently than they did in the environments in which these risk factors evolved. These differences in functioning may have resulted in lower age-matched AD risk during the vast majority of human (pre)history [83]. It is also notable that environmental pollutants, arising from industry, coal ignition, mining, pesticides, and millions of anthropogenic synthetic compounds, are a major risk factor for AD. These pollutants can induce toxicity in the brain and ultimately lead to neurodegeneration through a variety of mechanisms [86]. Briefly, major pollutants found in the air include lead, ozone, and particulate matter. Lead can cause hyperphosphorylation of tau and increased apoptotic cell death. Exposure to ozone can lead to neuroinflammation and increased production of reactive oxygen species (ROS), which are known to play a significant role in AD [87]. Fine particulate matter in the air can also promote chronic inflammation and has been associated with AD in the United States [88]. Major pollutants found in the soil include pesticides and cadmium. Pesticides can cause oxidative stress, apoptosis, and excitotoxicity through a variety of molecular pathways. Cadmium also triggers several inflammatory, oxidative stress, and cellular death pathways. Major pollutants found in the water include aluminum, arsenic, and mercury and exposure to these toxins can lead to neuroinflammation and increased ROS production as well as abnormal APP processing or aβ clearance leading to accumulation of aβ in the brain [86].

Studies investigating brain aging and neurodegeneration in small-scale subsistence populations can also shed light on the role of environmental mismatch in AD. While it is important to note that small-scale subsistence populations cannot be considered untouched by industrialized environments, the environment and lifestyles of these communities can shed light on certain selective pressures that may have shaped our evolution. The Tsimane are an indigenous population of forager-horticulturalists living in the Bolivian Amazon and the Moseten are another indigenous population that are genetically and linguistically related to the Tsimane. While the Moseten generally engage in high levels of physically intensive subsistence work, they are more acculturated into Bolivian society than the Tsimane. Recent research demonstrates a significantly slower decrease in brain volume with age among the Tsimane, despite high systemic inflammation associated with a high infectious disease burden in this population [89]. Additionally, dementia prevalence in the Tsimane and the Moseten is among the lowest in the world [90]. Notably, these populations lead physically active lifestyles and experience low rates of cardiovascular disease, diabetes, and obesity which may contribute to reduced AD risk in these populations [90, 91]. Other environmental factors may also play a role in reduced AD prevalence in the Tsimane. Interestingly, while prevalence of AD and cardiovascular disease is low in Tsimane, prevalence of the ApoE4 allele is high among this population. However, a recent study found that cognitive performance in older adults with the E4 allele and high parasite burden remained the same or slightly improved. In contrast, cognitive performance declined in older adults with a high parasite burden who were not E4 carriers, suggesting that, under certain environmental conditions, the E4 allele may be advantageous [92].

Finally, it is worth noting that the hypotheses reviewed in this section are not mutually exclusive and, given the heterogeneity and multifactorial nature of AD, monocausal explanations are likely to be incorrect. While the above hypotheses are compelling, comparative neuroanatomical and molecular studies are necessary to truly understand the evolution of human susceptibility to AD.

## 4 | Human Brain Evolution and AD Susceptibility

Primates in general, and humans in particular, are heavily dependent upon memory and cognitive flexibility to navigate complex ecological and social environments and this dependence may have been a driving force in human brain evolution and may also impact AD risk in humans. While large-scale shifts in brain size over the course of human evolution can be reconstructed based on fossil evidence [93], this cannot be said of finer-resolution brain changes because such changes are not preserved in the fossil record. However, studies employing comparative neuroanatomical and molecular methods can be used to identify human-specific differences in the brain.

### 4.1 | Changes in Brain Structure and Gene Expression

The frontal and temporal lobes are critical for cognition and are both critically impacted in the progression of AD. These brain regions have also been frequently studied in a comparative context. A disproportionate increase in overall frontal lobe volume was once thought to characterize human brain evolution [94]. However, further research has since shown that neither the frontal lobe nor the frontal cortex as a whole is larger than expected in humans [95], although gyral white matter (white matter immediately underlying the cortex) is enlarged in the human frontal and temporal lobes [96]. In contrast to findings in the frontal lobe, neuroimaging studies have demonstrated that the temporal lobe is larger than predicted for an ape with a human-sized brain [97, 98] (Figure 3).

Many comparative histological studies have also identified species-specific differences in prefrontal association areas and areas related to language processing in the frontal and temporal lobes, including a relatively enlarged orbitofrontal cortex and frontal pole in humans (Figure 3) [99]. Brodmann area 10, which forms the frontal pole in humans and is involved in a number of cognitive functions including memory, is twice as large as expected. There is also a decrease in neuron density and increase in neuropil space in BA 10 in humans [100, 101]. Studies of dendritic morphology show that humans have more branched neurons with an increased number of dendritic spines in BA 10 compared to chimpanzees [102]. In Broca's (BAs 44 and 45) and Wernicke's (area Tpt) areas, minicolumns are larger in humans than great apes [103, 104]. Notably, Vickery et al. [22] suggest that the expansion-aging relationship they identified in humans may be

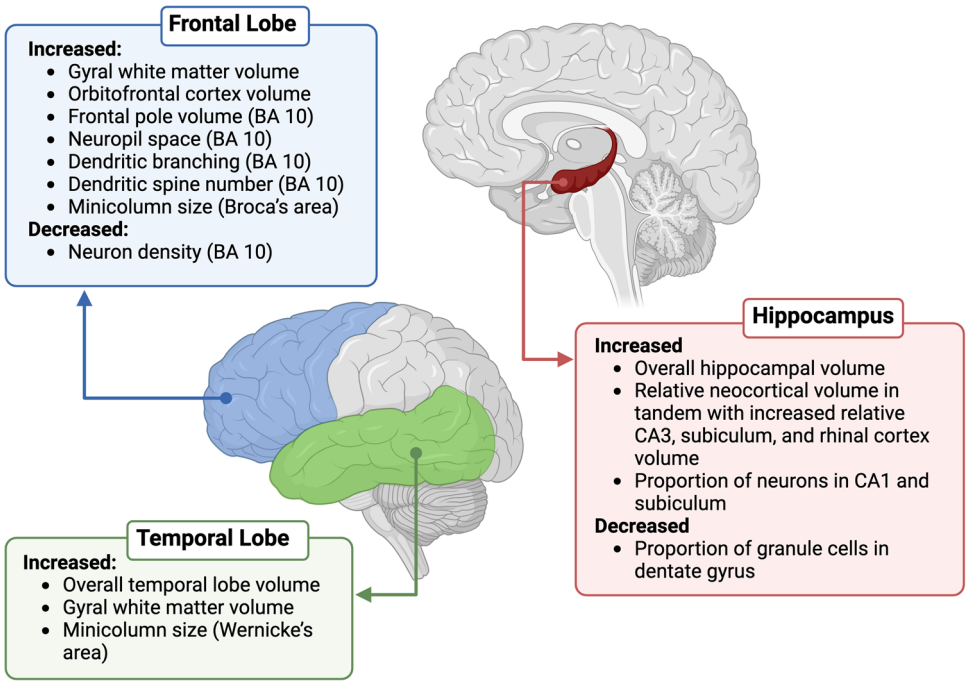


**FIGURE 3** | Brain regions which have been frequently studied in a comparative context, play a role in memory and language functions, and are significantly impacted in the progression of AD. Callouts highlight human-specific changes identified in select areas of these brain regions. BA, Brodmann area; CA, cornu ammonis. Image created with BioRender.

related, at least in part, to increased neuropil space given that reduction of dendritic spines and synapse loss are characteristics of normal age-related changes in the brain. A number of differences in neocortical innervation by various neurotransmitters have also been observed in humans and chimpanzees compared to macaques. In humans and chimpanzees BA 9, in the dorsolateral prefrontal cortex, and BA 32, in the anterior cingulate cortex, have a higher number of dopaminergic afferents in layers III, V, and VI [105] and a greater density of serotonin transporter (SERT) immunoreactive axons in layers V and VI [106]. Additionally, there is an increase in neuropeptide Y (NPY) innervation in neocortical areas in humans and great apes compared to select monkey species [107]. Notably, decreases in dopamine, SERT density, and NPY have been associated with AD in humans [108–110].

Comparative molecular analyses between humans and mice have shown increased diversity in glutamatergic cell types in humans, particularly in the supragranular layers of the cortex [111]. Moreover, deep layer III in humans contains highly distinctive cell types which also express a neurofilament protein (SMI-32) that labels long-range projection neurons in primates [111, 112]. SMI-32 immunoreactive neurons have previously been shown to be selectively vulnerable to degeneration in AD [113, 114]. While relatively few studies have analyzed differences in SMI-32 neuron distribution between primate species, there are a few studies which suggest that there is an increase in the number and size of SMI-32 neurons with decreasing phylogenetic distance to humans [112, 115, 116] and that these differences are more prominent in neocortical association areas [112].

The hippocampus, located deep in the temporal lobe, is critical to the storage and retrieval of memories as well as spatial navigation and it is severely impacted in AD. The hippocampus can be divided into the dentate gyrus, hippocampus proper, and subiculum. This basic structure is conserved across mammals [117]. The entorhinal cortex, part of the adjacent parahippocampal cortex, serves as the primary interface between the hippocampus and the neocortex [118]. While the overall structure of the hippocampus is conserved, changes in size and cytoarchitecture have been observed over the course of primate evolution, particularly in humans (Figure 3). Indeed, a recent analysis of 12 subregions in the hippocampal complex (hippocampus and related allocortical structures) of 44 primate species revealed that shifts in size and subregional organization were largest in the human lineage [119]. Moreover, a comparison of volumetric changes in the hippocampal complex compared to the neocortex indicates that a decrease in relative CA3, fascia dentata, subiculum, and rhinal cortex volume occurs in tandem with an increase in relative neocortical volume in anthropoid primates. However, in humans, increased relative neocortical volume is combined with increased relative CA3, subiculum, and rhinal cortex volume [120]. The human hippocampus is also 50% larger than predicted for an ape of human hemisphere volume, with the greatest increase observed in the CA1 region [99]. The proportions of neurons in the CA1 region, as well as the subiculum, also increases from rhesus monkeys to chimpanzees to humans, while the proportion of dentate gyrus granule cells decreases [121]. Notably, the CA1 region is particularly vulnerable to neuron loss in AD and the subicular region is one of the earliest brain regions to be impacted by tauopathy in AD [122, 123].

Synaptic plasticity is thought to play a significant role in memory and learning and it has been suggested that higher striatal dopamine and lower acetylcholine in humans may reflect an evolutionary shift in basal ganglia neurotransmission that favors synaptic plasticity [124]. Moreover, comparative

molecular analyses reveal an increase in the expression of genes involved in synaptic plasticity in the human association cortex compared to other primate species [76, 125]. Humans also have the highest number of synapses per neuron compared to other primate species [126] as well as the largest numbers of cortical–cortical glutamatergic NMDAR2B synapses [127]. Notably, synaptic dysfunction and loss is an early event in the pathogenesis of AD [62] and NMDAR2B synapses are particularly vulnerable to calcium dysregulation which has been proposed to play a significant role in initiating tau pathology in AD [127, 128].

The extent to which human-specific genetic changes in genes involved in neurodevelopment potentially brought with them AD susceptibility as a liability remains an open question. These include genes such as SRGAP2 and ARHGAP11C that underlie increased synaptic density and prolonged cell division of basal neuronal progenitors, respectively [129, 130]. They also include the gene TKTL1, with a human-specific variant different from that seen in the Neanderthal genome, which causes greater neurogenesis in frontal neocortex [131]. It would be surprising if prolonged maturation and delayed development, as well as distinct developmental trajectories including proliferation patterns and differences in synaptic density do not alter neuropathological risks.

### 4.2 | Changes in Aβ and Tau

In addition to changes in brain structure and gene expression over the course of primate brain evolution, it is possible that changes in aβ and tau may be linked to the evolution of human susceptibility to AD. The amino acid sequence of aβ is the same in humans and all NHPs studied so far [132]. However, there is evidence of human-specific differences in Pittsburg compound B (PiB) between humans and NHPs. PiB is a synthetic, radiolabeled benzothiazole ligand which was developed to image aβ deposits in vivo using positron-emission tomography. Differences in PiB binding have also been used to probe aβ pathogenicity. In squirrel monkeys, rhesus monkeys, and chimpanzees, high-affinity PiB binding is reduced compared to humans with AD. Although, it is worth nothing that high-affinity PiB binding in cognitively intact aged humans is also reduced compared to humans with AD [133].

The amino acid sequence of the longest brain tau isoform (splice variant) is 98% identical between humans and macaques and 100% identical in humans and chimpanzees and the six tau isoforms found in the human brain have also been identified in all NHPs studied [134, 135]. However, there are some tau isoforms in macaques which contain exon 8 which is not expressed in humans (or other animals prone to tauopathy). Additionally, there are a several single amino acid differences between humans and macaques [135]. Differences in intronic tau sequences have also been identified between humans and NHPs studied [134]. While the findings discussed here suggest that there are slight differences in human Aβ and tau, more studies are needed to determine if human-specific changes in Aβ and tau give these proteins unique pathogenic properties making them more prone to aggregation.

## 5 | Compensatory Evolution

Further complicating our understandings of the evolution of human susceptibility to neurodegenerative diseases like AD is the apparent recent evolution of alleles protective against cognitive decline in postreproductive individuals. As discussed above, it is commonly assumed that selection is weak or absent in later life because what occurs during this stage does not impact an individual's reproductive success [79]. However, this may not be entirely true in humans given the significance of older adults in human groups. The “Grandmother Hypothesis” [136, 137], which has been proposed to explain the long post-reproductive lifespan of human females in particular, suggests that grandmothers can increase the fitness of their younger relatives by provisioning them with food, care, and important cultural knowledge. However, this is only possible if an individual maintains their cognitive health in later life.

The ApoE and CD33 genes are both involved in AD risk in humans, and both have derived alleles in humans which support cognitive health in later life. ApoE is a protein involved in regulating calcium, lipid metabolism, and cellular repair processes. The ApoE gene is polymorphic in humans and the three alleles differ with respect to disease risk. The E4 allele is the high-risk allele for sporadic AD, the E3 allele is neutral with respect to disease risk, and the E2 allele is associated with decreased risk of AD. ApoE4 is the ancestral allele and ApoE2 and E3 have evolved more recently in the human lineage [138]. However, differences between the human and chimpanzee E4 allele cause chimpanzee ApoE4 to function more similarly to human ApoE3 [139]. The immunoregulatory receptor CD33 (Siglec 3) is involved in microglia immune response in the brain and variations in CD33 have been implicated in AD risk. Human full-length CD33 specifically recognizes the sialic acid Neu5Ac, whereas chimpanzee CD33 specifically binds to Neu5Gc, a sialic acid absent in the mammalian brain and completely absent from the human body [140]. Studies of CD33 have revealed a human-specific CD33 allele, encoding a truncated isoform that lacks the sialic acid binding domains and leads to higher microglia activation, which is strongly protective against AD. Interestingly, the derived CD33 allele favors a functional molecular state more similar to that seen in chimpanzees. In both ApoE and CD33 the human-specific alleles appear to restore more ape-like functioning and it has been suggested that the derived alleles may be compensatory, restoring functions that were lost as a consequence of human brain evolution and reducing risk of AD degeneration [139, 140].

Other human-specific changes exist in the form of microglia-specific expression of inhibitory Siglec 11 in humans [141] as well as mutations in the otherwise highly conserved sialyl motif of several tranferase enzymes involved in sialylation of glycoproteins and glycolipids in the brain [142] and sialic acid binding domains of Complement Factor H [143].

Given that both Siglec 3 (CD33) and Siglec 11, as well as Complement Factor H, are involved in regulation of immune responses outside the brain as well, these human-specific changes may also reflect adaptations to past pathogen regimes (bacterial, viral, and protozoan), including human-specific ones,

that are secondarily associated with human-specific immune regulation and pathologies in the human brain [140]. These human-specific derived features in sialic acid biology, both synthesis of sialic acid containing glycoconjugates and recognition of such molecular patterns via endogenous lectins, warrant further investigation of their potential involvement in AD. APP beta is posttranslationally modified with N-Glycans that are sialylated and the degree of sialylation influences secretion of these glycoproteins [144] and elevated levels of sialic acid in serum are associated with AD [145].

## 6 | Conclusions

Primates in general, and humans in particular, are heavily dependent upon memory and cognitive flexibility to navigate complex physical and social environments, and this dependence may have been a driving force in human brain evolution, where language massively augments individual cognitive potential and cumulative culture at population levels. While humans appear to be the only primates to suffer from neurodegenerative diseases like AD, a number of age-related structural and neuropathological changes do appear to be shared between humans and other primate species. Most AD research, particularly in a biomedical context, has focused on understanding the immediate mechanisms of AD pathogenesis. Far less has focused on understanding why humans are particularly vulnerable to neurodegeneration. Comparative primate research has the potential to shed light on neurobiology underlying this increased vulnerability to neurodegenerative disease in humans and, while the research available on NHP brain aging is more limited than that available on human brain aging, it is still substantial. Much less is known about other highly intelligent nonprimate animals such as cetaceans and corvids. Although, a few studies have identified aβ plaques and limited tau pathology in several species of toothed whale. However, the causes of these neuropathological changes in cetaceans remains unclear. Ultimately, more comparative neuroanatomical and molecular studies, in NHPs and other nonprimate species, are necessary to understand how unique features of human brain aging may have increased our susceptibility to neurodegenerative diseases.


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### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The authors have nothing to report.

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