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Review

Amyloid-β Pathology Is the Common Nominator Proteinopathy of the Primate Brain Aging

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Abstract. Senile plaques, mainly diffuse, and cerebral amyloid-β (Aβ) angiopathy are prevalent in the aging brain of non-human primates, from lemurs to non-human Hominidae. Aβ but not hyper-phosphorylated tau (HPtau) pathology is the common nominator proteinopathy of non-human primate brain aging. The abundance of Aβ in the aging primate brain is well tolerated, and the impact on cognitive functions is usually limited to particular tasks. In contrast, human brain aging is characterized by the early appearance of HPtau pathology, mainly forming neurofibrillary tangles, dystrophic neurites of neuritic plaques, and neuropil threads, preceding Aβ deposits by several decades and by its severity progressing from selected nuclei of the brain stem, entorhinal cortex, and hippocampus to the limbic system, neocortex, and other brain regions. Neurofibrillary tangles correlate with cognitive impairment and dementia in advanced cases. Aβ pathology is linked in humans to altered membrane protein and lipid composition, particularly involving lipid rafts. Although similar membrane alterations are unknown in non-human primates, membrane senescence is postulated to cause the activated β-amyloidogenic pathway, and Aβ pathology is the prevailing signature of non-human and human primate brain aging.

Keywords: Alzheimer's disease, amyloid-β, brain aging, primates, tau

INTRODUCTION

Senile plaques (SPs) were first described by P. Blocq and G. Marinesco as 'amas ronds',[1] and E. Redlich as 'miliare Sklerose' in the neuropil, interpreted at that time as nodules of glial sclerosis.[2] Later, using Bielchowsky's silver method allowed O. Fischer the identification of 'Drusen' or 'drusige Nekrosen' in sixteen cases of senile dementia.[3] Subsequent studies by Fischer detailed the morphology of abnormal fibrils and abnormal neurites surrounding central cores and their stages of formation in an extensive series of older individuals.[4,5] The term 'senile plaque' for these structures was proposed by T. Simchowitz.[6] Fischer also described 'drusige Entartung der Gefässe,' which corresponds to cerebral amyloid angiopathy. He also reported and illustrated the presence of abnormal fibrils in neurons, consistent with neurofibrillary tangles (NFTs), in the same cases with dementia.[7] At the same time, A.

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Alzheimer communicated the presence of NFTs and dystrophic neurites in the brain of a 51-year-old woman who had suffered from progressive dementia and hallucinations.[8] The term Alzheimer's pre-senile dementia was introduced by E. Kraepelin.[9] Hundreds of papers appeared in the following years, revealing the presence of large numbers of NFTs and SPs in patients with cognitive impairment and dementia and less numbers of NFTs and SPs (if present) in individuals with no cognitive impairment. In the earlier 1990 s, the term Alzheimer's disease (AD) was used to cover cases who had suffered pre-senile or senile dementia in which the neuropathological study revealed large numbers of SPs and NFTs.[10,11] Cases without neurological deficits and fewer NFTs and SPs were defined as 'normal for age'.[12]

In the middle 1980 s and early 1990 s, amyloid-β (Aβ) was identified as the primary component of SPs and cerebral amyloid angiopathy (Aβ-CAA).[13–16] Aβ may be modified by N-terminal truncation of soluble and insoluble peptide species, truncation at the C-terminal, pyroglutamate modifications, isomerization/racemization, glycosylation, phosphorylation, fibrilization. SPs can be categorized as diffuse plaques without dystrophic neurites, and neuritic plaques characterized by a core of Aβ surrounded by dystrophic neurites. At the same time, abnormal tau protein was identified as the main component of NFTs.[17–23] NFTs are composed of paired helical filaments. Tau deposits in human brain aging and AD manifest as granular cytoplasmic inclusions, pre-tangles, NFTs, neuropil threads, neurite clusters, and dystrophic neurites around Aβ cores in SPs. Tau deposits comprise 3Rtau and 4Rtau isoforms generated by alternative splicing of the microtubule-associated protein tau gene (*MAPT*). Tau in brain aging and AD is progressively altered by post-translational modifications, principally hyperphosphorylation at many phosphorylation sites (HPtau), acetylation, abnormal conformation, truncation at the C-terminal and N-terminal regions, oligomerization, fibrillization, and aggregation.[24]

Mutations in amyloid-β protein precursor (AβPP), increased AβPP dosage, PSEN1 (presenilin1), and PSEN2 (presenilin2) are causative of early-onset familial AD and Aβ angiopathy. All of them are involved in producing Aβ through the cleavage of AβPP by the combined action of β- and γ-secretases (amyloidogenic pathway of AβPP cleavage).[25–30] These discoveries led to the amyloid cascade hypothesis, which agrees with the idea that the production of Aβ fibrils and Aβ oligomers is the primary factor triggering NFT formation and AD progression.[31–33]

TIMING AND DISTRIBUTION OF Aβ AND TAU PATHOLOGY IN HUMAN BRAIN AGING

The systematic study of hundreds of human brains of different ages has permitted the evaluation of HPtau and Aβ pathology categorization and HPtau and Aβ progression.

Tau pathology increases following a typical gradient categorized as NFT Braak a-c subcortical and Braak I-VI stages. Braak a-c subcortical stages delineate NFTs in selected brain stem nuclei, including the raphe nuclei and locus coeruleus. Braak stages I-VI define the progression of NFTs from the entorhinal and transentorhinal cortices (stages I-II) to the hippocampus, amygdala, inferior part of the temporal lobe, and limbic system (stages III-IV), and finally to the diencephalon and most parts of the telencephalon (stages V-VI). The transit from one stage to the next is continuous and is accompanied by increased NFT density.[34–39] NFT Braak stages were formerly identified with silver stains; HPtau immunohistochemistry is currently used instead.[40]

In contrast, the regional distribution of SPs is categorized into stages A, B, and C, indicating the progressive involvement of cortical regions.[34] More recently, SP progression is classified according to consecutive phases encompassing the neocortex (phase 1), allocortex and limbic system (phase 2), diencephalon and basal ganglia (phase 3), brain stem (phase 4), and cerebellum (phase 5).[41]

Therefore, NFTs and SPs have different distributions in human brain aging. Moreover, HPtau pathology in human brain aging precedes by several decades or years the appearance of Aβ deposits. NFTs increase with age and affect about 85% of humans at age 65, involving the entorhinal and transentorhinal cortex, hippocampus, and the inner region of the temporal cortex. About 98% of individuals have NFTs in the telencephalon at 80 at least involving the same areas or more.[24,34–39,42,43] However, only 30% of people have SPs at age 65, and around 60% over 80. NFTs without SPs are detected in about 35% of individuals older than 90.[24,39,42,43]

Tau-PET studies confirm that HPtau pathology precedes by several decades the appearance of Aβ in brain aging without cognitive impairment; HPtau pathology may be found in some individuals suffering

from cognitive impairment without concomitant Aβ deposition, and HPtau pathology, rather than Aβ correlates with progressive cognitive decline in AD.[44–48]

Therefore, the Aβ cascade hypothesis does not apply to changes in human brain aging, as NFTs precede the appearance of Aβ for decades, and the distribution of NFTs does not match the distribution of Aβ deposits.[24,39,49–51]

DEFINITIONS OF ALZHEIMER'S DISEASE

The definition of AD by the National Institute on Aging-Alzheimer's Association (NIA-AA) is based on the creed of the Aβ cascade hypothesis. It assumes that the abundance of SPs, diffuse and neuritic, is the sine-qua-non condition for the neuropathological diagnosis of sporadic AD. The sole presence of NFTs is not considered a prime manifestation of sporadic AD.[52,53] Clinically, AD is categorized as preclinical AD, mild cognitive impairment due to AD, and mild, moderate, and severe AD dementia.[54–60] Preclinical AD is considered in individuals without apparent cognitive impairment but with positive neuroimaging and biological markers showing Aβ and HPtau pathology.[55,61,62] Cognitive changes correlate better with HPtau pathology than Aβ pathology.[63]

Due to the constraints of the NIA-AA definition of AD, the term Primary age-related tauopathy (PART) was conceived to include the majority of aged individuals in their sixties and seventies at NFT Braak stages I-IV and a percentage of older individuals without SPs.[64,65] The rate of PART decreases at the time that Aβ pathology develops, and AD is diagnosed following the NIA-AA guidelines. Notwithstanding, alternative scenarios have been proposed; one of them suggests that PART is a part of AD;[66] another, that PART is ordinary in human brain aging, and Aβ is later added in a time-, rate-, and region-dependent manner to produce AD.[67]

AD overture proposes that human brain aging with NFTs and SPs is a continuum with AD.[24,39,51] AD is a progressive neurodegenerative biological process prevalent in human brain aging, characterized by the early appearance of 3R+4Rtau NFTs that progresses following established Braak stages and followed decades later by Aβ pathology forming SPs and CAA. The process manifests as preclinical AD (covering early NFT stages). It progresses not universally to mild cognitive impairment due to AD and mild, moderate, and severe AD dementia.[24,51]

PHYLOGENY OF PRIMATES

Earliest-known primates called plesiadapiforms were living 65.9 million years ago, about 105,000 to 139,000 years after the Cretaceous-Paleogene extinction. Ancestors of lemurs appeared about 50 million years ago, and New World monkeys about 45 million years ago; extant New World monkeys are squirrel monkeys, marmosets, and cotton-top tamarins. Ancestors of the Old World monkeys (family *Cercopithecidae*) appeared about 25 million years ago. *Cercopithecidae* includes two subfamilies, *Cercopithecinae* (including the genera *Papio*, *Macaca*, and *Chlorocebus*) and *Colobinae*. Old World monkeys came from the same branch that later spliced into gibbons (superfamily *Hominoidea*, family *Hylobatidae*) and the family *Hominidae*, which expanded between 12 and 6 million years ago. The extant *Hominidae* include four genera *Pongo*, *Gorilla*, *Pan*, and *Homo*. Several species of *Homo* populated different territories (one or two million years ago), and they became extinct. One of the most recent species, *Homo neanderthaliensis* appeared about 430,000 years ago and lived in Eurasia until about 40,000 years. *Homo sapiens* appeared in Europe about 47,000 years ago, was contemporary with the Neanderthals for several thousand years, and is the only living species of *Homo*.[68–71]

The following species have been recorded in the present review: lemurs (*Microcebus murinus*), squirrel monkeys (*Saimiri sciureus*), marmoset (*Callithrix jacchus*), cotton-top tamarins (*Saguinus oedipus*), cynomolgus monkeys (*Macaca fascicularis*), rhesus monkeys (*Macaca mulatta*), stump-tailed macaques (*Macaca arctoides*), lion-tailed macaques (*Macaca silenius*), african green monkeys, vervets (*Chlorocebus aethiops sabaeus*), baboons (*Papio*), chimpanzees (*Pan troglodytes*), orangutan (Pongo), and gorillas (*Gorilla gorilla gorilla* and *Gorilla beringei beringei*).

The lifespan of these species in the wild and in captivity is shown in Table 1.

More than 6 million years elapsed from pre-hominids to *Homo sapiens*; various species of pre-hominids and *Homo*, some of them lasting on Earth for hundreds of thousands of years, were extinct. *Homo sapiens* have only 300,000 years, modern sapiens about 130,000, and Neolithic humans less than 12,000.

The lifespan of *Homo sapiens* has changed dramatically over time. In the Paleolithic era, about 200,000 BCE and 8,000 generations ago, the estimated lifes-

Table 1
Lifespan of primates assessed in this review

Species	Life span (y)	Life span in captivity (y)
Grey mouse lemurs		18
Squirrel monkeys		30
Marmosets	5–7	16.5
Cotton-top tamarins	13.4	24
Cynomolgus monkeys	25–30	
Rhesus monkeys	25–30	36–40
Stump-tailed macaque	30	
African green monkeys	30	
Baboons	20–30	40
Chimpanzees	15 (maximum age 53)	30–35 (oldest 78)
Orangutans	30	30–40 (oldest 60)
Gorillas	35–40	50 (up to 67)
Ancient *Homo sapiens*	35–40	
Modern *Homo sapiens*		65–85 (oldest 120)

pan was about 38–40 years. The estimated lifespan in the Industrial era, about 150 years and seven generations ago, was 43–65 years. By the end of the 20th Century and the beginning of the 21st, the human lifespan in developed countries reaches more than 80 years in only three generations.[72]

Aβ DEPOSITS AND HPTAU IN NON-HUMAN PRIMATES

The terminology used to designate SPs and tau pathology is heterogeneous in the different studies. Early descriptions of SPs were based on silver stains; however, SPs are now best recognized with isoform-specific anti-Aβ antibodies. Silver methods, such as Bielchowsky's method, are helpful in staining NFTs and dystrophic neurites of neuritic plaques. These structures are stained with anti-HPtau antibodies. Yet, HPtau deposits are not restricted to NFTs and dystrophic neurites, as HPtau-immunoreactive granular and diffuse cytoplasmic deposits are observed in the brains of aged primates. To normalize the vocabulary, we have used diffuse plaques to designate loose extracellular Aβ deposits without dystrophic neurites and neuritic plaques to designate structures composed of a core of Aβ surrounded by dystrophic neurites. The terms compact and mature plaques used in some papers have been here named neuritic plaques. HPtau deposits include granular cytoplasmic deposits, pre-tangles, threads, neurite clusters, and NFTs. It is worth pointing out that the term NFT is used in some papers to designate diffuse HPtau deposits and pre-tangles. The revision of the images used to illustrate representative HPtau inclusions in every paper has actualized the name of the different types of HPtau inclusions in the brains of aged primates, following the terminology currently used in human neuropathology.

SPs and CAA

SPs are not found in most middle-aged monkeys and apes, but their number and density increase with age. Aβ plaques and CAA are frequent in all species examined, including lemurs,[73–78] squirrel monkeys,[79–82] marmosets,[83,84] cotton tamarins,[85] cynomolgus monkeys,[86–93] rhesus monkeys,[94–106] stump-tailed macaques,[107] lion-tailed macaques,[108] Japanese macaques,[109] African green monkeys,[110–113] baboons,[114–116] chimpanzees,[99,100,117] orangutans,[118,119] and gorillas.[120–123] Diffuse plaques are predominant, whereas neuritic plaques are less abundant or absent. Moreover, neuritic plaques have altered neurites with neurofilaments, but dystrophic neurites containing HPtau are rare. $A\beta_{42}$ is predominant in plaques in lemurs.[77] The two primary isoforms $A\beta_{40}$ and $A\beta_{42}$ are expressed in SPs, but $A\beta_{40}$ predominates in arterioles in squirrel monkeys.[81,124] Yet, a predominance of $A\beta_{42}$ was reported in another study.[125] A predominance of $A\beta_{40}$ over $A\beta_{42}$ in plaques is identified in rhesus macaques,[97,100,102] stump-tailed macaques,[107] chimpanzees,[99,100] and orangutans.[118] However, another study reported that amyloid deposits in rhesus monkeys were composed of $A\beta_{40}$, $A\beta_{42}$, $A\beta_{43}$, AβN1, and 4 AβpN3.[126] Regarding SPs in gorillas, one study showed $A\beta_{42}$ positivity but the absence of $A\beta_{40}$ immunostaining;[120] another identified $A\beta_{42}$, $A\beta_{40}$, and Aβ oligomers.[121,122] Yet, diffuse plaques in baboons are primarily composed of $A\beta_{42}$ over $A\beta_{40}$.[116] In contrast with SPs, $A\beta_{42}$ and $A\beta_{40}$ are found in CAA.[87,88,116,117,126]

Differences in the antibodies used may account for the observed discrepancies. Phosphorylated Aβ (P-Ser8Aβ) in SPs and CAA has been identified in African green monkeys.[112]

SPs, mostly diffuse, predominate in the frontal cortex, parietal and temporal cortices, and amygdala; the hippocampal complex has lesser numbers of plaques. The distribution of SPs in aged rhesus monkeys is similar to that seen in human brain aging at early phases of neocortical plaque distribution.[34,41] However, the categorization of SPs localization and distribution following Thal phases applied to humans[41] is not feasible in monkeys and apes because lesions in the diencephalon are usually unavailable, and the cerebellum and brainstem are not assessed. Aβ deposits have exceptionally been reported in the brain of young common marmosets.[127]

CAA may affect meningeal and parenchymal blood vessels in monkeys; CAA is more abundant than plaques in some species, such as squirrel monkeys.[81,124] However, it is difficult in most cases to classify the CAA pathology into one of the two proposed types of sporadic amyloid angiopathy in humans[128] due to a lack of specific information regarding cortical capillaries in most species except in some small series of squirrel monkeys and gorillas.

The neocortex is the most vulnerable region to Aβ deposition in aged non-human primates and humans. This region is phylogenetically new regarding the evolution of species to mammals.[129,130]

HPtau pathology

In contrast with SPs and CAA, HPtau pathology is remarkably scarce in the brains of aged primates, including non-human *Hominidae.*

HPtau deposits are found in aged lemurs,[75,131,132] some of them composed of bundles of argyrophilic filaments,[73] but NFTs are absent. HPtau has been detected in marmosets.[133,134] However, HPtau deposits do not resemble common pre-tangles and tangles in aged human brains but granular cytoplasmic deposits.

NFTs with a distribution following Braak stages I-IV have been recognized in rhesus monkeys aged 24–26 years,[135] NFTs in the entorhinal cortex, hippocampus, and frontal cortex were found in a 43-year-old female rhesus monkey born and dead in captivity.[126] NFTs in the entorhinal cortex and hippocampus in two African green monkeys older than 20,[110] and scarce NFTs and pre-tangles in the cerebral cortex of various primates.[136]

A complex neuronal and glial tauopathy with HPtau-positive straight filaments consistent with pre-tangles, was identified in aged baboons: neuronal tauopathy involved the hippocampus and the dentate gyrus; thorn-shaped astrocytes were distributed in periventricular, subpial, and perivascular regions of limbic brain areas; and coiled bodies were abundant in the limbic tracts.[114,115]

In chimpanzees, HPtau-immunoreactive pre-tangles and neuritic clusters were more abundant with age and predominated in the neocortex over the hippocampal region; only five chimpanzees had NFTs, four in the CA1 region of the hippocampus.[117] A unique tauopathy was reported in a 41-year-old female chimpanzee; HPtau-positive pre-tangles, NFTs (with paired helical filaments), neuropil threads, and neuritic clusters were seen in the prefrontal cortex, temporal cortex, and occipital cortex over the hippocampus; HPtau-immunoractive thread-like processes in the basal ganglia and lower brainstem.[137]

Finally, a few astrocytes, coiled bodies, and plaque-like clusters of neurites containing HPtau, but not pre-tangles and NFTs, were reported in the neocortex and hippocampus of very old gorillas.[122]

In summary, no HPtau pathology has been identified in aged squirrel monkeys, lion-tailed macaques, Japanese macaques, and orangutans; mild to severe combined neuronal and glial tauopathies may occur in aged cynomolgus monkeys, baboons, and gorillas. HPtau pathology in these species has a difficult categorization.[138] Only a few old rhesus monkey[126,135] and chimpanzees[117,137] have HPtau pathology similar to that seen in human brain aging and AD at early Braak stages.

A rare neuronal and glial tauopathy with pre-tangles, HPtau inclusions in astrocytes, and coiled bodies involving the basal ganglia and neocortex was reported in cynomolgus monkeys; this 4R-tauopathy is reminiscent of progressive supranuclear palsy in humans.[139,140]

Table 2 summarizes the principal types of Aβ and HPtau deposits in different primates.

COGNITION IN AGED NON-HUMAN PRIMATES

Cognitive changes in aged primates are mild or moderate, and usually not global but limited to specific tasks in the species assessed, including lemurs,[141,142] squirrel monkeys,[143]

Table 2
Summary of principal amyloid-β and HPtau deposits in the brain of aged primates

Species	DP	NP	CAA	HPtau	NFT	Comments
Grey mouse lemurs	++	–	+	+	–	
Squirrel monkeys	++		++	–	–	
Marmosets	++	–	+	+	–	
Cotton-top tamarins	+	–	+	–	–	
Cynomolgus monkeys	++	+	+++	+	– (+)	Other series: PSP
Rhesus monkeys	++	+	++	++	+	
Lion-tailed macaque	+	–	NA	NA	NA	
African green monkeys	++	+	+	+	– (+)	
Baboons	+		+	++	–	TSA, coiled bodies
Chimpanzees	++	–	+	++	+	Rare tauopathy in one case
Orangutans	+	–	+	–	–	
Gorillas	+	+		+	–	
Humans						
	+++	+++	++	+++	+++	Aβ: Thal phases 1–5 NFT: Braak stages a-c; I-VI

DP, diffuse plaques; NP, neuritic plaques; CAA, cerebral amyloid angiopathy; HPtau, hyperphosphorylated tau; NFT, neurofibrillary tangles; PSP, progressive supranuclear palsy; TSA, thorn-shaped astrocytes. Signs are approximate as no quantitative data are available and the criteria to consider mild, moderate, and large numbers of determinate deposit depend on the choice of the investigator.

capuchin monkeys,[144] marmosets,[145] cynomolgus monkeys,[146–148] rhesus monkeys,[149–157] baboons,[158] chimpanzees,[159–162] and gorillas.[163] Severe cognitive impairment and dementia have never been observed in non-human primates, with exceptions.[126]

No correlation was found between Aβ burden and altered cognition in most species including lemurs,[131] marmosets,[145] cynomolgus monkeys,[93] and rhesus monkeys.[101] Exceptionally, a direct relation between the cortical Aβ burden and cognition was reported in one series of aged lemurs.[78]

Aβ PATHOLOGY IS THE PREVALENT PROTEINOPATHY IN THE PRIMATE BRAIN AGING

In non-human primates, Aβ deposition is the first or only proteinopathy in brain aging. HPtau inclusions, if present, correspond in most cases to unclassified HPtau pathology,[138] unrelated to Aβ. Only HPtau pathology, reminiscent of early NFT Braak stages, is found in rhesus monkeys and chimpanzees, but again with a distribution separate from Aβ pathology. The Aβ cascade hypothesis does not match the neuropathological changes observed in non-human primate brain aging. Conversely, considering that HPtau pathology is the initiating factor of Aβ pathology is not supported in non-human primates.

The presence of Aβ pathology in the aged primate brain suggests altered AβPP metabolism at the cell membranes. Cleavage of AβPP through α- and γ-secretase leads to the non-amyloidogenic pathway of AβPP degradation; cleavage of AβPP through β- and γ-secretase generates $A\beta_{42}$, $A\beta_{40}$, and other small peptides.[164–167] β-secretase (BACE) is a GPI-anchored aspartyl protease.[168] γ-secretase complex is composed of presenilin 1, presenilin 2, aph-1 homolog A, γ-secretase subunit APH1A, APH1B, nicastrin, presenilin enhancer γ-secretase subunit PEN2/PSENEN, neprilysin, and insulin-degrading enzyme. The γ-secretase complex acts as a proteolytic enzyme on more than 90 substrates and is considered the proteasome of the membrane.[169–171] The membrane's lipid content and, mainly, cholesterol modulate secretase activity.[172,173]

There is growing evidence that cell membranes are altered and dysfunctional in the old.[174–178] Proteomics studies have shown altered proteostasis and deregulated phosphorylation in human brain aging involving cell membrane components and cytoskeleton, among other proteins.[179,180] Altered membrane protein composition increases at middle and advanced stages of AD.[179] The lipid composition of brain lipid rafts is also altered in human brain aging and neurodegenerative diseases.[181–183] Human cortical lipid rafts are modified by aging in a gender-dependently way, being more pronounced in women than in men. Main changes involve plasmalogens,

polyunsaturated fatty acids (especially docosahexaenoic acid and arachidonic acid), total polar lipids (mainly phosphatidylinositol, sphingomyelin, sulfatides, and cerebrosides), and total neutral lipids (particularly cholesterol and sterol esters).[184] Lipid alterations increase at early stages of AD and increase with disease progression.[185,186] Biophysical alterations in lipid rafts augment β-secretase in lipid rafts and increase BACE/AβPP interactions,[186,187] thus modulating the convergence of the amyloidogenic pathway toward lipid rafts and pointing to a critical role of polyunsaturated fatty acids in the amyloidogenic processing of AβPP.[187] Unfortunately, similar studies are not available in non-human primates. Thus, Aβ deposition is probably linked to age-related altered protein and lipid composition of membranes.

Conclusion

Previous studies have suggested that AD is a disease unique to humans,[24,51,117,122,188,189] and it is. However, the point is that brain aging differs between non-human primates and humans.[51,188,190] HPtau pathology is the initial proteinopathy in human brain aging; NFTs, pre-tangles, dystrophic neurites of neuritic plaques, and neuropil threads are the primary type of intraneuronal HPtau deposits; and its progression is overwhelming in the aging of the human brain.[39] However, HPtau pathology is late and reduced if present in non-human primates compared to humans; HPtau deposits are mainly granular or diffuse conforming pre-tangles, whereas NFTs are extremely rare. NFTs first appear in selected nuclei of the brain stem and paleocortical regions, and later progress to the entire brain. This vulnerability is unique to the aged human brain.[191]

In contrast, Aβ deposits complying with SPs and CAA are common in the brain of aged primates, including *Homo sapiens*. The predominant types of SP in non-human primates are diffuse plaques, and their distribution is mainly in the convexity of the cerebral hemispheres. SPs in humans are categorized as diffuse at early stages and mainly neuritic at advanced stages. The density of SPs is higher, and their distribution is much more extensive in humans involving from the cerebral neocortex (as in all primates) to the diencephalon, brain stem, and cerebellum at later phases.

Albeit with species differences in severity, Aβ deposition in primates is brain aging.

AUTHOR CONTRIBUTIONS

Isidro Ferrer (Conceptualization; Data curation; Writing – review & editing)/

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REFERENCES

1. Blocq P and Marinesco G. Sur les lésions et la pathogénie de l'épilepsie dite essentielle. *Sem Méd* 1892; 12: 445–446.
2. Redlich E. Uber miliare Sklerose der Hirnrinde bei seniler Atrophie. *Jahrb Psychiat Neurol* 1898; 17: 208–216.
3. Fischer O. Miliare Nekrosen mit drusigen Wucherungen der Neurofibrillen, eine regelmässige Veränderung der Hirnrinde bei seniler Demenz. *Monatsschr Psychiat Neurol* 1907; 22: 361–372.
4. Fischer O. Die presbyophrene Demenz, deren anatomische Grundlage und klinische Abgrenzung. *Z Ges Neurol Psychiatr* 1910; 3: 371–471.
5. Fischer O. Ein weiterer Beitrag zur Klinik und Pathologie der presbyophrenen Demenz. *Z Ges Neurol Psychiatr* 1912; 12: 99–135.
6. Simchowitz T. Histologische Studien uber die senile demenz. In: Nissl F, Alzheimer A (eds) *Histologische und Histopathologische Arbeiten* ü*ber die Grosshirnrindem*, Vol. 4. Fischer, Jena, 1911, pp. 267–444.
7. Goedert M. Oskar Fischer and the study of dementia. *Brain* 2009; 132: 1102–1111.
8. Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. *Allg Z Psychiat* 1907; 64: 146–148.
9. Kraepelin E. *Psychiatrie: ein Lehrbuch f*ür *Studierende und* Ärzte. *II. Band, Klinische Psychiatrie.* Verlag Johann Ambrosius Barth, Leipzig, vol. II, 1910.
10. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* 1991; 41: 479–486.
11. Mirra SS, Hart MN and Terry RD. Making the diagnosis of Alzheimer's disease. A primer for practicing pathologists. *Arch Pathol Lab Med* 1993; 117: 132–144.
12. Knopman DS, Parisi JE, Salviati A, et al. Neuropathology of cognitively normal elderly. *J Neuropathol Exp Neurol* 2003; 62: 1087–1095.
13. Glenner GG and Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun* 1984; 120: 885–890.

14. Glenner GG, Wong CW, Quaranta V, et al. The amyloid deposits in Alzheimer's disease: their nature and pathogenesis. *Appl Pathol* 1984; 12: 357–369.
15. Masters CL, Simms G, Weinman NA, et al. Amyloid plaque core protein in Alzheimer disease and Down syndrome. *Proc Natl Acad Sci U S A* 1985; 82: 4245–4249.
16. Iwatsubo T, Odaka A, Suzuki N, et al. Visualization of a beta 42(43) and a beta 40 in senile plaques with end-specific a beta monoclonals: evidence that an initially deposited species is a beta 42(43). *Neuron* 1994; 13: 45–53.
17. Delacourte A and Defossez A. Alzheimer's disease: tau proteins, the promoting factors of microtubule assembly, are major components of paired helical filaments. *J Neurol Sci* 1986; 76: 173–186.
18. Kosik KS, Joachim CL and Selkoe DJ. Microtubule-associated protein tau (tau) is a major antigenic component of paired helical filaments in Alzheimer disease. *Proc Natl Acad Sci U S A* 1986; 83: 4044–4048.
19. Wood JG, Mirra SS, Pollock NJ and Binder LI. Neurofibrillary tangles of Alzheimer disease share antigenic determinants with the axonal microtubule-associated protein tau (tau). *Proc Natl Acad Sci U S A* 1986; 83: 4040–4043.
20. Grundke-Iqbal I, Iqbal K, Quinlan M, et al. Microtubule-associated protein tau. A component of Alzheimer paired helical filaments. *J Biol Chem* 1986; 261: 6084–6089.
21. Goedert M, Wischik CM, Crowther RA, et al. Cloning and sequencing of the cDNA encoding a core protein of the paired helical filament of Alzheimer disease: identification as microtubule-associated protein tau. *Proc Natl Acad Sci U S A* 1988; 85: 4051–4055.
22. Goedert M, Spillantini MG, Cairns NJ, et al. Tau proteins in Alzheimer paired helical filaments: abnormal phosphorylation of all six brain isoforms. *Neuron* 1992; 8: 159–168.
23. Buée L, Bussière T, Buée-Scherrer V, et al. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Res Brain Res Rev* 2000; 33: 95–130.
24. Ferrer I. Alzheimer's disease is an inherent, natural part of human brain aging: an integrated perspective. *Free Neuropathol* 2022; 3: 17.
25. Goate A, Chartier-Harlin MC, Mullan M, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 1991; 349: 704–706.
26. Chartier-Harlin MC, Crawford F, Houlden H, et al. Early-onset Alzheimer's disease caused by mutations at codon 717 of the β-amyloid precursor protein gene. *Nature* 1991; 353: 844–846.
27. Murrell J, Farlow M, Ghetti B, et al. A mutation in the amyloid precursor protein associated with hereditary Alzheimer's disease. *Science* 1991; 254: 97–99.
28. Levy-Lahad E, Wasco W, Poorkaj P, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science* 1995; 18: 973–977.
29. Sherrington R, Rogaev EI, Liang Y, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature* 1995; 375: 754–760.
30. Rogaev EI, Sherrington R, Rogaeva EA, et al. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. *Nature* 1995; 376: 775–778.
31. Hardy JA and Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science* 1992; 256: 184–185.
32. Selkoe DJ and Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med* 2016; 8: 595–608.
33. Cline EN, Bicca MA, Viola KL, et al. The amyloid-β oligomer hypothesis: beginning of the third decade. *J Alzheimers Dis* 2018; 64: S567–S610.
34. Braak H and Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol* 1991; 82: 239–259.
35. Braak H and Braak E. Staging of Alzheimer's disease-related neurofibrillary tangles. *Neurobiol Aging* 1995; 16: 271–278.
36. Braak H and Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging* 1997; 18: 351–357.
37. Braak H and Del Tredici K. The pathological process underlying Alzheimer's disease in individuals under thirty. *Acta Neuropathol* 2011; 121: 171–181.
38. Braak H and Del Tredici K. The preclinical phase of the pathological process underlying sporadic Alzheimer's disease. *Brain* 2015; 138: 2814–2833.
39. Arnsten AFT, Datta D, Del Tredici K, et al. Hypothesis: Tau pathology is an initiating factor in sporadic Alzheimer's disease. *Alzheimers Dement* 2021; 17: 115–124.
40. Braak H, Alafuzoff I, Arzberger T, et al. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol* 2006; 112: 389–404.
41. Thal RD, Rub U, Orantes M, et al. Phases of Aβ-deposition in the human brain and its relevance for the development of Alzheimer's disease. *Neurology* 2002; 58: 1791–1800.
42. Braak H, Thal DR, Ghebremedhin E, et al. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol* 2011; 70: 960–969.
43. Ferrer I. Defining Alzheimer as a common age-related neurodegenerative process not inevitably leading to dementia. *Prog Neurobiol* 2012; 97: 38–51.
44. Lowe VJ, Wiste HJ, Senjem ML, et al. Widespread brain tau and its association with ageing, Braak stage and Alzheimer's dementia. *Brain* 2018; 141: 271–287.
45. Berron D, Vogel JW, Insel PS, et al. Early stages of tau pathology and its associations with functional connectivity, atrophy and memory. *Brain* 2021; 144: 2771–2783.
46. Sanchez JS, Becker JA, Jacobs HIL, et al. The cortical origin and initial spread of medial temporal tauopathy in Alzheimer's disease assessed with positron emission tomography. *Sci Transl Med* 2021; 13: eabc0655.
47. Yoon B, Guo T, Provost K, et al. Abnormal tau in amyloid PET negative individuals. *Neurobiol Aging* 2022; 109: 125–134.
48. Wisse LEM, Xie L, Das SR, et al. Tau pathology mediates age effects on medial temporal lobe structure. *Neurobiol Aging* 2022; 109: 135–144.
49. Armstrong RA, Myers D and Smith CU. The spatial patterns of plaques and tangles in Alzheimer's disease do not support the 'Cascade Hypothesis'. *Dementia* 1993; 4: 16–20.
50. Herrup K. The case for rejecting the amyloid cascade hypothesis. *Nat Neurosci* 2015; 18: 794–799.
51. Ferrer I. Hypothesis review: Alzheimer's overture guidelines. *Brain Pathol* 2023; 33: 13122.
52. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association disease guidelines for

the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement* 2012; 8: 1–13.
53. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol* 2012; 123: 1–11.
54. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol* 2010; 9: 1118–1127.
55. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7: 280–292.
56. Albert MS, Dekosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7: 270–279.
57. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7: 263–269.
58. Ward A, Tardiff S, Dye C, et al. Rate of conversion from prodromal Alzheimer's disease to Alzheimer's dementia: a systematic review of the literature. *Dement Geriatr Cogn Disord Extra* 2013; 3: 320–332.
59. Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: mild cognitive impairment. *Neurology* 2018; 90: 126–135.
60. Jack CR, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018; 14: 535–562.
61. Knopman D. Clinical aspects of Alzheimer's disease. In: Dickson DW and Weller RO (eds) *Neurodegeneration, the molecular pathology of dementia and movement disorders*. Wiley- Blackwell, 2011, pp. 39–50.
62. Knopman DS, Jack CR, Wiste HJ, et al. Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease. *Neurology* 2012; 78: 1576–1582.
63. Nelson PT, Alafuzoff I, Bigio EH, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *J Neuropathol Exp Neurol* 2012; 71: 362–381.
64. Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol* 2014; 128: 755–766.
65. Jellinger KA, Alafuzoff I, Attems J, et al. PART, a distinct tauopathy, different from classical sporadic Alzheimer disease. *Acta Neuropathol* 2015; 129: 757–762.
66. Duyckaerts C, Braak H, Brion JP, et al. PART is part of Alzheimer disease. *Acta Neuropathol* 2015; 129: 749–756.
67. Spires-Jones TL, Attems J and Thal DR. Interactions of pathological proteins in neurodegenerative diseases. *Acta Neuropathol* 2017; 134: 187–205.
68. Hartwig W. *The primate fossil record*, Cambridge Studies in Biological and Evolutionary Anthropology, vol. 33, Cambridge, Cambridge University Press, 2002.
69. Benton MJ. *Vertebrate Palaeontology*, 4th Edition, John Wiley & Sons, 2014.
70. Gee H. *A short history of life on Earth*, McMillan Publishers, 2021.
71. Brussate SL. *The rise and reign of the mammals: A new history, from the shadow of the dinosaurs to us,* Mariner Books, 2022.
72. Goldman L. Tree stages of health encounters over 8000 human generations and how they inform future public health. *Am J Public Health* 2018; 108: 60–62.
73. Bons N, Mestre N and Petter A. Senile plaques and neurofibrillary changes in the brain of an aged lemurian primate *Microcebus murinus*. *Neurobiol Aging* 1992; 13: 99–105.
74. Bons N, Mestre N, Ritchie K, et al. Identification of amyloid beta protein in the brain of the small, short-lived lemurian primate Microcebus murinus. *Neurobiol Aging* 1994; 15: 215–220.
75. Giannakopoulos P, Silhol S, Jallageas V, et al. Quantitative analysis of tau protein-immunoreactive accumulations and beta amyloid protein deposits in the cerebral cortex of the mouse lemur, *Microcebus murinus*. *Acta Neuropathol* 1997; 94: 131–139.
76. Silhol S, Calenda A, Jallageas V, et al. β-amyloid protein precursor in Microcebus murinus: genotyping and brain localization. *Neurobiol Dis* 1996; 3: 169–182.
77. Mestre-Frances N, Keller E, Calenda A, et al. Immunohistochemical analysis of cerebral cortical and vascular lesions in the primate Microcebus murinus reveal distinct amyloid beta1-42 and beta1-40 immunoreactivity profiles. *Neurobiol Dis* 2000; 7: 1–8.
78. Schmidtke D, Zimmermann E, Trouche SG, et al. Linking cognition to age and amyloid-β burden in the brain of a nonhuman primate (*Microcebus murinus*). *Neurobiol Aging* 2020; 94: 207–216.
79. Walker LC, Kitt CA, Schwam E, et al. Senile plaques in aged squirrel monkeys. *Neurobiol Aging* 1987; 8: 291–296.
80. Walker LC, Masters C, Beyreuther K, et al. Amyloid in the brains of aged squirrel monkeys. *Acta Neuropathol* 1990; 80: 381–387.
81. Elfenbein HA, Rosen RF, Stephens SL, et al. Cerebral beta-amyloid angiopathy in aged squirrel monkeys. *Histol Histopathol* 2007; 22: 155–167.
82. Rosen RF, Tomidokoro Y, Farberg AS, et al. Comparative pathobiology of β-amyloid and the unique susceptibility of humans to Alzheimer's disease. *Neurobiol Aging* 2016; 44: 185–196.
83. Maclean CJ, Baker HF, Ridley RM, et al. Naturally occurring and experimentally induced beta-amyloid deposits in the brains of marmosets (*Callithrix jacchus*). *J Neural Transm (Vienna)* 2000; 107: 799–814.
84. Geula C, Nagykery N and Wu CK. Amyloid-beta deposits in the cerebral cortex of the aged common marmoset (*Callithrix jacchus*): incidence and chemical composition. *Acta Neuropathol* 2002; 103: 48–58.
85. Lemere CA, Oh J, Stanish HA, et al. Cerebral amyloid-beta protein accumulation with aging in cotton-top tamarins: a model of early Alzheimer's disease? *Rejuvenation Res* 2008; 11: 321–332.
86. Podlisny MB, Tolan DR and Selkoe DJ. Homology of the amyloid beta protein precursor in monkey and human supports a primate model for beta amyloidosis in Alzheimer's disease. *Am J Pathol* 1991; 138: 1423–1435.
87. Nakamura S, Tamaoka A, Sawamura N, et al. Carboxyl end-specific monoclonal antibodies to amyloid β protein (Aβ) subtypes (Aβ40 and Aβ42(43)) differentiate Aβ in

senile plaques and amyloid angiopathy in brains of aged cynomolgus monkeys. *Neurosci Lett* 1995; 201: 151–154.
88. Nakamura S, Kiatipattanasakul W, Nakayama H, et al. Immunohistochemical characteristics of the constituents of senile plaques and amyloid angiopathy in aged cynomolgus monkeys. *J Med Primatol* 1996; 25: 294–300.
89. Nakamura S, Nakayama H, Goto N, et al. Histopathological studies of senile plaques and cerebral amyloidosis in cynomolgus monkeys. *J Med Primatol* 1998; 27: 244–252.
90. Kimura N, Tanemura K, Nakamura S, et al. Age-related changes of Alzheimer's disease-associated proteins in cynomolgus monkey brains. *Biochem Biophys Res Commun* 2003; 310: 303–311.
91. Oikawa N, Kimura N and Yanagisawa K. Alzheimer-type tau pathology in advanced aged nonhuman primate brains harboring substantial amyloid deposition. *Brain Res* 2010; 1315: 137–149.
92. Kodama R, Yang X, Saski Y, et al. Age-related lesions in the cerebrum in middle-aged female cynomolgus monkeys. *Toxicol Pathol* 2010; 38: 303–311.
93. Darusman HS, Gjedde A, Sajuthi D, et al. Amyloid β1-42 and the phoshorylated tau threonine 231 in brains of aged cynomolgus monkeys (*Macaca fascicularis*). *Front Aging Neurosci* 2014; 6: 313.
94. Wisniewski HM, Ghetti B and Terry RD. Neuritic (senile) plaques and filamentous changes in aged rhesus monkeys. *J Neuropathol Exp Neurol* 1973; 32: 566–584.
95. Cork LC, Masters C, Beyreuther K, et al. Development of senile plaques: relationships of neuronal abnormalities and amyloid deposits. *Am J Pathol* 1990; 8137: 1383–1392.
96. Heilbroner PL and Kemper TL. The cytoarchitectonic distribution of senile plaques in three aged monkeys. *Acta Neuropathol* 1990; 81: 60–65.
97. Poduri A, Gearing M, Rebeck GW, et al. Apolipoprotein E4 and beta amyloid in senile plaques and cerebral blood vessels of aged rhesus monkeys. *Am J Pathol* 1994; 144: 1183–1187.
98. Mufson EJ, Benzing WC, Cole GM, et al. Apolipoprotein E-immunoreactivity in aged rhesus monkey cortex: colocalization with amyloid plaques. *Neurobiol Aging* 1994; 15: 621–627.
99. Gearing M, Rebeck GW, Hyman BT, et al. Neuropathology and apolipoprotein E profile of aged chimpanzees: implications for Alzheimer's disease. *Proc Natl Acad Sci U S A* 1994; 91: 9382–9386.
100. Gearing M, Tigges J, Mori H, et al. Aβ40 is a major form of β-amyloid in nonhuman primates. *Neurobiol Aging* 1996; 17: 903–908.
101. Sloane JA, Pietropaolo MF, Rosene DL, et al. Lack of correlation between plaque burden and cognition in the aged monkey. *Acta Neuropathol* 1997; 94: 471–478.
102. Sani S, Klink A, Traul D, et al. Distribution, progression and chemical composition of cortical amyloid-beta deposits in aged rhesus monkeys: similarities to the human. *Acta Neuropathol* 2003; 105: 145–156.
103. Uno H and Walker LC. The age of biosenescence and the incidence of cerebral beta-amyloidosis in aged captive rhesus monkeys. *Ann N Y Acad Sci* 1993; 695: 232–235.
104. Uno H, Alsum PB, Dong S, et al. Cerebral amyloid angiopathy and plaques, and visceral amyloidosis in aged macaques. *Neurobiol Aging* 1996; 17: 275–281.
105. Shah P, Lal N, Leung E, et al. Neuronal and axonal loss are selectively linked to fibrillar amyloid-β within plaques of the aged primate cerebral cortex. *Am J Pathol* 2010; 177: 325–333.
106. Zhang J, Chen B, Lu J, et al. Brains of rhesus monkeys display Aβ deposits and glial pathology while lacking Aβ dimers and other Alzheimer's pathologies. *Aging Cell* 2019; 18: e12978.
107. Toledano A, Alvarez MI, Lopez-Rodriguez AB, et al. ¿Existe la enfermedad de Alzheimer en todos los primates? Patología Alzheimer en primates no humanos y sus implicaciones fisiopatológicas. *Neurologia* 2014; 29: 42–55.
108. Martin LJ, Sisodia SS, Koo EH, et al. Amyloid precursor protein in aged nonhuman primates. *Proc Natl Acad Sci U S A* 1991; 88: 1461–1465.
109. Ichinohe N, Hayashi M, Wakabayashi K, et al. Distribution and progression of amyloid-beta deposits in the amygdala of the aged macaque monkey, and parallels with zinc distribution. *Neuroscience* 2009; 159: 1374–1383.
110. Cramer PE, Gentzel RC, Tanis KQ, et al. Aging African green monkeys manifest transcriptional, pathological, and cognitive hallmarks of human Alzheimer's disease. *Neurobiol Aging* 2018; 64: 92–106.
111. Latimer CS, Shively CA, Keene CD, et al. A nonhuman primate model of early Alzheimer's disease pathologic change: Implications for disease pathogenesis. *Alzheimers Dement* 2019; 5: 93–105.
112. Kumar S, Frost JL, Cotman CW, et al. Deposition of phosphorylated amyloid-β in brains of aged nonhuman primates and canines. *Brain Pathol* 2018; 28: 427–430.
113. Frye BM, Craft S, Latimer CS, et al. Aging-related Alzheimer's disease-like neuropathology and functional decline in captive vervet monkeys *(Chlorocebus aethiops sabaeus*). *Am J Primatol* 2021; 83: e23260.
114. Schultz C, Dehghani F, Hubbard GB, et al. Filamentous tau pathology in nerve cells, astrocytes, and oligodendrocytes of aged baboons. *J Neuropathol Exp Neurol* 2000; 59: 39–52.
115. Schultz C, Hubbard GB, Rüb U, et al. Age-related progression of tau pathology in brains of baboons. *Neurobiol Aging* 2000; 21: 905–912.
116. Ndung'u M, Härtig W, Wegner F, et al. Cerebral amyloid β(42) deposits and microvascular pathology in ageing baboons. *Neuropathol Appl Neurobiol* 2012; 38: 487–499.
117. Edler MK, Sherwood CC, Meindl RS, et al. Chimpanzees exhibit pathologic hallmarks of Alzheimer's disease. *Neurobiol Aging* 2017; 59: 107–120.
118. Gearing M, Tigges J, Mori H, et al. β-amyloid (Aβ) deposition in the brains of aged orangutans. *Neurobiol Aging* 1997; 18: 139–146.
119. Selkoe DJ, Bell DS, Podlisny MB, et al. Conservation of brain amyloid proteins in aged mammals and humans with Alzheimer's disease. *Science* 1987; 235: 873–877.
120. Kimura N, Nakamura S, Goto N, et al. Senile plaques in an aged western lowland gorilla. *Exp Anim* 2001; 50: 77–81.
121. Perez SE, Raghanti MA, Hof PR, et al. Alzheimer's disease pathology in the neocortex and hippocampus of the western lowland gorilla (*Gorilla gorilla gorilla*). *J Comp Neurol* 2013; 521: 4318–4338.
122. Perez SE, Sherwood CC, Cranfield MR, et al. Early Alzheimer's disease-type pathology in the frontal cortex of wild mountain gorillas (*Gorilla beringei beringei*). *Neurobiol Aging* 2016; 39: 195–201.
123. Marquez M, Serafin A, Fernandez-Bellon H, et al. Neuropathologic findings in an aged albino gorilla. *Vet Pathol* 2008; 45: 531–537.
124. Chambers JK, Kuribayashi H, Ikeda S, et al. Distribution of neprilysin and deposit patterns of Abeta subtypes in

the brains of aged squirrel monkeys (*Saimiri sciureus*). *Amyloid* 2010; 17: 75–82.
125. Sawamura N, Tamaoka A, Shoji S, et al. Characterization of amyloid beta protein species in cerebral amyloid angiopathy of a squirrel monkey by immunocytochemistry and enzyme-linked immunosorbent assay. *Brain Res* 1997; 764: 225–229.
126. Iwaide S, Nakayama Y, Chambers JK, et al. Senile plaques and phosphorylated tau deposition in a super-aged rhesus monkey (*Macaca mulatta*). *J Vet Med Sci* 2023; 85: 1296–1300.
127. Palazzi X, Switzer R and George C. Natural occurrence of amyloid-Aβ deposits in the brain of young common marmosets (Callithrix jacchus): a morphological and immunohistochemical evaluation. *Vet Pathol* 2006; 43: 777–779.
128. Thal DR, Ghebremedhin E, Rub U, et al. Two types of sporadic amyloid angiopathy. *J Neuropath Exp Neurol* 2002; 61: 282–293.
129. Roth G and Dicke U. Evolution of the brain and intelligence. *Trends Cogn Sci* 2005; 9: 250–257.
130. Pontarotti P. *Evolutionary Biology: Convergent Evolution, Evolution of Complex Traits*. Springer, 2016.
131. Kraska A, Dorieux O, Picq JL, et al. Age-associated cerebral atrophy in mouse lemur primates. *Neurobiol Aging* 2011; 32: 894–906.
132. Bons N, Jallageas V, Silhol S, et al. Immunocytochemical characterization of Tau proteins during cerebral aging of the lemurian primate *Microcebus murinus*. *C R Acad Sci III* 1995; 318: 77–83.
133. Rodriguez-Callejas JD, Fuchs E and Perez-Cruz C. Evidence of tau hyper-phosphorylation and dystrophic microglia in the common marmoset. *Front Aging Neurosci* 2016; 8: 315.
134. Sharma G, Huo A, Kimura T, et al. Tau isoform expression and phosphorylation in marmoset brains. *J Biol Chem* 2019; 294: 11433–11444.
135. Paspalas CD, Carlyle BC, Leslie S, et al. The aged rhesus macaque manifests Braak stage III/IV Alzheimer's-like pathology. *Alzheimers Dement* 2018; 14: 680–691.
136. Hartig W, Klein C, Brauer K, et al. Abnormally phosphorylated protein tau in the cortex of aged individuals of various mammalian orders. *Acta Neuropathol* 2000; 100: 305–312.
137. Rosen RF, Farberg AS, Gearing M, et al. Tauopathy with paired helical filaments in an aged chimpanzee. *J Comp Neurol* 2008; 509: 259–270.
138. Kovacs GG, Ghetti B and Goedert M. Classification of diseases with accumulation of Tau protein. *Neuropathol Appl Neurobiol* 2022; 48: e12792.
139. Kiatipattanasakul W, Nakayama H, Yongsiri S, et al. Abnormal neuronal and glial argyrophilic fibrillary structures in the brain of an aged albino cynomolgus monkey (Macaca fascicularis). *Acta Neuropathol* 2000; 100: 580–586.
140. Uchihara T, Endo K, Kondo H, et al. Tau pathology in aged cynomolgus monkeys is progressive supranuclear palsy/corticobasal degeneration- but not Alzheimer disease-like-Ultrastructural mapping of tau by EDX. *Acta Neuropathol Commun* 2016; 4: 118.
141. Picq JL. Aging affects executive functions and memory in mouse lemur primates. *Exp Gerontol* 2007; 42: 223–232.
142. Picq JL, Aujard F, Volk A, et al. Age-related cerebral atrophy in nonhuman primates predicts cognitive impairments. *Neurobiol Aging* 2012; 33: 1096–1109.
143. Lyons DM, Yang C, Eliez S, et al. Cognitive correlates of white matter growth and stress hormones in female squirrel monkey adults. *J Neurosci* 2004; 24: 3655–3662.
144. Bartus RT, Dean RL and Beer B. Memory deficits in aged cebus monkeys and facilitation with central cholinomimetics. *Neurobiol Aging* 1980; 1: 145–152.
145. Freire-Cobo C, Rothwell ES, Varghese M, et al. Neuronal vulnerability to brain aging and neurodegeneration in cognitively impaired marmoset monkeys (*Callithrix jacchus*). *Neurobiol Aging* 2023; 123: 49–62.
146. Darusman HS, Sajuthi D, Kalliokoski O, et al. Correlations between serum levels of β amyloid, cerebrospinal levels of tau, and phospho-tau and delayed response tasks in young and aged cynomolgus monkeys (Macaca fascicularis). *J Med Primatol* 2013; 42: 137–146.
147. Darusman HS, Call J, Sajuthi D, et al. Delayed response task performance as a function of age in cynomolgus monkeys (Macaca fascicularis). *Primates* 2014; 55: 259–267.
148. Darusman HS, Pandelaki J, Mulyadi R, et al. Poor memory performance in aged cynomolgus monkeys with hippocampal atrophy, depletion of amyloid β1-42 and accumulation of tau proteins in cerebrospinal fluid. *In Vivo* 2014; 28: 173–184.
149. Rapp PR and Amaral DG. Evidence for task-dependent memory dysfunction in the aged monkey. *J Neurosci* 1989; 9: 3568–3576.
150. Bachevalier J, Landis LS, Walker LC, et al. Aged monkeys exhibit behavioral deficits indicative of widespread cerebral dysfunction. *Neurobiol Aging* 1991; 12: 99–111.
151. Lai ZC, Moss MB, Killiany RJ, et al. Executive system dysfunction in the aged monkey: spatial and object reversal learning. *Neurobiol Aging* 1995; 16: 947–954.
152. Herndon JG, Moss MB, Rosene DL, et al. Patterns of cognitive decline in aged rhesus monkeys. *Behav Brain Res* 1997; 87: 25–34.
153. Moore TL, Killiany RJ, Herndon JG, et al. Impairment in abstraction and set shifting in aged rhesus monkeys. *Neurobiol Aging* 2003; 24: 125–134.
154. Moore TL, Killiany RJ, Herndon JG, et al. Executive system dysfunction occurs as early as middle-age in the rhesus monkey. *Neurobiol Aging* 2006; 27: 1484–1493.
155. Hara Y, Rapp PR and Morrison JH. Neuronal and morphological bases of cognitive decline in aged rhesus monkeys. *Age* 2012; 34: 1051–1073.
156. Harada CN, Natelson Love MC, et al. Normal cognitive aging. *Clin Geriatr Med* 2013; 29: 737–752.
157. Stonebarger GA, Bimonte-Nelson HA and Urbanski HF. The Rhesus macaque as a translational model for neurodegeneration and Alzheimer's disease. *Front Aging Neurosci* 2021; 13: 734173.
158. Lizarraga S, Daadi EW, Roy-Choudhury G, et al. Age-related cognitive decline in baboons: modeling the prodromal phase of Alzheimer's disease and related dementias. *Aging (Albany NY)* 2020; 12: 10099–10116.
159. Riopelle AJ and Rogers CM. *Age changes in chimpanzees*. New York: Academic Press, 1965.
160. Lacreuse A, Parr L, Chennareddi L, et al. Age-related decline in cognitive flexibility in female chimpanzees. *Neurobiol Aging* 2018; 72: 83–88.
161. Lacreuse A, Russell JL, Hopkins WD, et al. Cognitive and motor aging in female chimpanzees. *Neurobiol Aging* 2014; 35: 623–632.
162. Hopkins WD, Mareno MC, Neal Webb SJ, et al. Age-related changes in chimpanzee (*Pan troglodytes*) cog-

nition: Cross-sectional and longitudinal analyses. *Am J Primatol* 2021; 83: e23214.
163. Kuhar C. Factors affecting spatial ability of Lowland Gorillas: age, gender and experience. Atlanta, GA: Georgia Institute of Technology, 2004.
164. Beyreuther K and Masters CL. Amyloid precursor protein (APP) and beta A4 amyloid in the etiology of Alzheimer's disease: precursor-product relationships in the derangement of neuronal function. *Brain Pathol* 1991; 1: 241–251.
165. Masters CL and Beyreuther K. Alzheimer's centennial legacy: prospects for rational therapeutic intervention targeting the Abeta amyloid pathway. *Brain* 2006; 129: 2823–2839.
166. Masters CL and Selkoe DJ. Biochemistry of amyloid β-protein and amyloid deposits in Alzheimer disease. *Cold Spring Harb Perspect Med* 2012; 2: a006262.
167. Chen GF, Xu TH, Yan Y, et al. Amyloid beta: structure, biology and structure-based therapeutic treatment. *Acta Pharmacol Sin* 2017; 38: 1205-1235.
168. Vassar R, Kovacs DM, Yan R, et al. The β-secretase enzyme BACE in health and Alzheimer's disease: regulation, cell biology, function, and therapeutic potential. *J Neurosci* 2009; 29: 12787–12794.
169. Barthet G, Georgakopoulos A and Robakis NK. Cellular mechanisms of γ-secretase substrate selection, processing and toxicity. *Prog Neurobiol* 2012; 98: 166–175.
170. Zhang X, Li Y, Xu H, et al. The γ-secretase complex: from structure to function. *Front Cell Neurosci* 2014; 8: 427.
171. Wolfe MS. Structure and function of the γ-secretase complex. *Biochemistry* 2019; 58: 2953–2966.
172. Fassbender K, Simons M, Bergmann C, et al. Simvastatin strongly reduces levels of Alzheimer's disease β-amyloid peptides Aβ42 and Aβ40 *in vitro* and *in vivo*. *Proc Natl Acad Sci U S A* 2001; 98: 5856–5861.
173. Wood WG, Schroeder F, Igbavboa U, et al. Brain membrane cholesterol domains, aging and amyloid-beta peptides. *Neurobiol Aging* 2002; 23: 685–694.
174. Zs-Nagy I. Aging of cell membranes: facts and theories. *Interdiscip Top Gerontol* 2014; 39: 62–85.
175. Skowronska-Krawczyk D and Budin I. Aging membranes: Unexplored functions for lipids in the lifespan of the central nervous system. *Exp Gerontol* 2020; 131: 110817.
176. Das UN. "Cell membrane theory of senescence" and the role of bioactive lipids in aging, and associated diseases and their therapeutic implications. *Biomolecules* 2021; 11: 241.
177. Ziegler DV, Martin N and Bernard D. Cellular senescence links mitochondria-ER contacts and aging. *Commun Biol* 2021; 4: 1323.
178. Martín MG and Dotti CG. Plasma membrane and brain dysfunction of the old: Do we age from our membranes? *Front Cell Dev Biol* 2022; 10: 1031007.
179. Ferrer I, Andrés-Benito P, Ausín K, et al. Dysregulated protein phosphorylation: A determining condition in the continuum of brain aging and Alzheimer's disease. *Brain Pathol* 2021; 31: e12996.
180. Andrés-Benito P, Íñigo-Marco I, Brullas M, et al. Proteostatic modulation in brain aging without associated Alzheimer's disease-and age-related neuropathological changes. *Aging (Albany NY)* 2023; 15: 3295–3330.
181. Egawa J, Pearn ML, Lemkuil BP, et al. Membrane lipid rafts and neurobiology: age-related changes in membrane lipids and loss of neuronal function. *J Physiol* 2016; 594: 4565–4579.
182. Mesa-Herrera F, Taoro-González L, Valdés-Baizabal C, et al. Lipid and lipid raft alteration in aging and neurodegenerative diseases: A window for the development of new biomarkers. *Int J Mol Sci* 2019; 20: 3810.
183. Grassi S, Giussani P, Mauri L, et al. Lipid rafts and neurodegeneration: structural and functional roles in physiologic aging and neurodegenerative diseases. *J Lipid Res* 2020; 61: 636–654.
184. Díaz M, Fabelo N, Ferrer I, et al. "Lipid raft aging" in the human frontal cortex during nonpathological aging: gender influences and potential implications in Alzheimer's disease. *Neurobiol Aging* 2018; 67: 42–52.
185. Martín V, Fabelo N, Santpere G, et al. Lipid alterations in lipid rafts from Alzheimer's disease human brain cortex. *J Alzheimers Dis* 2010; 19: 489–502.
186. Fabelo N, Martín V, Marín R, et al. Altered lipid composition in cortical lipid rafts occurs at early stages of sporadic Alzheimer's disease and facilitates APP/BACE1 interactions. *Neurobiol Aging* 2014; 35: 1801–1812.
187. Díaz M, Fabelo N, Martín V, et al. Biophysical alterations in lipid rafts from human cerebral cortex associate with increased BACE1/AbetaPP interaction in early stages of Alzheimer's disease. *J Alzheimers Dis* 2015; 43: 1185–1198.
188. Heuer E, Rosen RF, Cintron A, et al. Nonhuman primate models of Alzheimer-like cerebral proteopathy. *Curr Pharm Des* 2012; 18: 1159–1169.
189. Walker LC and Jucker M. The exceptional vulnerability of humans to Alzheimer's disease. *Trends Mol Med* 2017; 23: 534–545.
190. Freire-Cobo C, Edler MK, Varghese M, et al. Comparative neuropathology in aging primates: A perspective. *Am J Primatol* 2021; 83: e23299.
191. Ferrer I. The unique neuropathological vulnerability of the human brain to aging. *Ageing Res Rev* 2023; 87: 101916.