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Review

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

Isidro Ferrer*
*Department of Pathology and Experimental Therapeutics, University of Barcelona, Hospitalet de Llobregat, Barcelona, Spain*

**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.

*Correspondence to: Prof. Isidro Ferrer, Department of Pathology and Experimental Therapeutics, University of Barcelona, Feixa LLarga sn, 08907 Hospitalet de Llobregat, Barcelona, Spain. E-mail: 8082ifa@gmail.com; ORCID: 0000-0001-9888-8754

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 $\gamma$-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 pri-

mates, 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 $A\beta_{40}$, $A\beta_{42}$, $A\beta_{43}$, $A\beta N1$, and 4 $A\beta pN3$.[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<br>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 $\alpha$- and $\gamma$-secretase leads to the non-amyloidogenic pathway of AβPP degradation; cleavage of AβPP through β- and $\gamma$-secretase generates $A\beta_{42}$, $A\beta_{40}$, and other small peptides.[164–167] β-secretase (BACE) is a GPI-anchored aspartyl protease.[168] $\gamma$-secretase complex is composed of presenilin 1, presenilin 2, aph-1 homolog A, $\gamma$-secretase subunit APH1A, APH1B, nicastrin, presenilin enhancer $\gamma$-secretase subunit PEN2/PSENEN, neprilysin, and insulin-degrading enzyme. The $\gamma$-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 docosahex-aenoic acid and arachidonic acid), total polar lipids (mainly phosphatidylinositol, sphingomyelin, sul-fatides, 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 alter-ations in lipid rafts augment β-secretase in lipid rafts and increase BACE/AβPP interactions,[186,187] thus modulating the convergence of the amyloido-genic pathway toward lipid rafts and pointing to a critical role of polyunsaturated fatty acids in the amy-loidogenic processing of AβPP.[187] Unfortunately, similar studies are not available in non-human pri-mates. Thus, Aβ deposition is probably linked to age-related altered protein and lipid composition of membranes.

## CONCLUDING COMMENTS

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 pri-mary 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 catego-rized 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

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