Published in final edited form as:
Curr Pharm Des. 2012 March ; 18(8): 1159–1169.

Nonhuman Primate Models of Alzheimer-Like Cerebral Proteopathy

Eric Heuer[1,3], **Rebecca F. Rosen**[1], **Amarallys Cintron**[1], and **Lary C. Walker**[1,2]

[1]Yerkes National Primate Research Center, Emory University, Atlanta, GA 30329

[2]Department of Neurology, Emory University, Atlanta, GA 30329

[3]Psychology Department, University of Hawaii at Hilo, Hilo, HI 96720 USA

Abstract

Nonhuman primates are useful for the study of age-associated changes in the brain and behavior in a model that is biologically proximal to humans. The Aβ and tau proteins, two key players in the pathogenesis of Alzheimer's disease (AD), are highly homologous among primates. With age, all nonhuman primates analyzed to date develop senile (Aβ) plaques and cerebral β-amyloid angiopathy. In contrast, significant tauopathy is unusual in simians, and only humans manifest the profound tauopathy, neuronal degeneration and cognitive impairment that characterize Alzheimer's disease. Primates thus are somewhat paradoxical models of AD-like pathology; on the one hand, they are excellent models of normal aging and naturally occurring Aβ lesions, and they can be useful for testing diagnostic and therapeutic agents targeting aggregated forms of Aβ. On the other hand, the resistance of monkeys and apes to tauopathy and AD-related neurodegeneration, in the presence of substantial cerebral Aβ deposition, suggests that a comparative analysis of human and nonhuman primates could yield informative clues to the uniquely human predisposition to Alzheimer's disease.

Keywords

Aging; Alzheimer's disease; amyloid; cerebral amyloid angiopathy; monkeys; neurodegeneration; senile plaques; tauopathy

Introduction

Alzheimer's disease (AD) and other age associated neurodegenerative diseases present a significant challenge to the biomedical community and society at large, and effective, disease-modifying therapies remain elusive [1, 2]. One impediment to studying these disorders is that the field is still endeavoring to understand the fundamental pathogenic mechanisms underlying neurodegeneration, and to differentiate *disease* from *normal aging*. AD is typified pathologically by the presence of extracellular senile plaques (SP) and intracellular neurofibrillary tangles (NFT) [3–5], the primary molecular substrates of which are the β-amyloid (Aβ) and tau proteins, respectively. The assumption has been that these pathological hallmarks are linked to the dysfunction and eventual death of neurons, thus causing the cognitive and behavioral impairments characteristic of AD. However, the precise role that these lesions play in the pathogenesis of AD remains uncertain.

Address correspondence to: Lary C. Walker, Yerkes National Primate Center, Emory University, 954 Gatewood Rd, Atlanta, GA 30329. Phone: 404.727.7779, lary.walker@emory.edu.

Genetic, biochemical, and pathological evidence strongly supports the Aβ cascade hypothesis of AD, which holds that the aggregation of Aβ peptides is a critical early event in disease pathogenesis [6, 7]. The Aβ peptide most commonly exists as a 40–42 amino acid cleavage product of the β-Amyloid Precursor Protein (APP) [2, 5, 8]. Aβ has a proclivity to misfold and self-aggregate, subsequently forming the fibrillar, congophilic material (β-amyloid) that characterizes classical senile plaques [9]. Aβ also aggregates into pre-fibrillar (or non-fibrillar) oligomers and protofibrils, which are increasingly thought to mediate the cytopathic effects of the multimeric peptide [5, 10–12].

Neurofibrillary tangles consist mainly of intracellular tau protein, a microtubule-binding protein that, in AD, misfolds, becomes abnormally phosphorylated, and aggregates into skeins of filamentous material consisting ultrastructurally of paired helical or straight filaments [3, 13, 14]. Although the number of NFTs correlates significantly with the degree of dementia [15–17], genetic evidence in particular indicates that tauopathy is downstream of Aβ aggregation in the Aβ cascade [18]. The primacy of Aβ aggregation in AD pathogenesis is further underscored by the experimental demonstration that tau abnormalities can be induced or exacerbated by aggregated Aβ [19–23], but not vice-versa [19]. Furthermore, every known familial, autosomal dominant variety of AD results in the increased production or aggregation of Aβ [6, 7]. Thus, although tauopathy is a defining element of the AD phenotype, the seminal occurrence in the pathogenesis of AD appears to involve the misfolding and accumulation of Aβ [18, 24].

To promote a greater understanding of the neurobiological substrates of AD, and to investigate the role of senescence in the pathogenic process, many investigators have employed nonhuman primates as a comparator. Nonhuman primates have the advantages of biological proximity to humans, behavioral complexity, and relatively large brains that are favorable for *in vivo* imaging. In addition, nonhuman primates naturally generate human-sequence Aβ that, with age, deposits prodigiously in parenchymal senile plaques and within the cerebral vasculature (below). Simians thus can be useful for testing diagnostic and therapeutic approaches in a biologically optimal model of naturally occurring, age-associated pathology.

Despite their similarities to humans, it is surprising that nonhuman primates do not succumb to the profound dementia and neurodegenerative changes that typify AD [25, 26]. As such, long-lived nonhuman primates present a unique opportunity to examine complex brain aging in a context that is free of AD *per se*. In addition, nonhuman primates may help us to understand why, in the primate order, humans are uniquely vulnerable to AD. The present review summarizes current knowledge of AD-related neuropathology and behavior in apes, monkeys and prosimians, focusing in particular on β-amyloid lesions (senile plaques and cerebral Aβ-amyloid angiopathy [CAA]), tauopathy, and cognitive decline associated with normal aging.

Alzheimer's Disease and Related Neuropathology

β-Amyloid Precursor Protein (APP) and β-Amyloid (Aβ)

Aβ is a normal cleavage product of the β-Amyloid Precursor Protein (APP) [27], a single-spanning transmembrane protein expressed as several isoforms in cells throughout the body. In neurons, the predominantly expressed isoform is 695 amino acids long, whereas APP in non-neuronal cells is mainly 751 or 770 amino acids in length [8]. APP is highly conserved among extant mammals, suggesting an important (but still uncertain) biological function.

Senile Plaques (β-Amyloid)

Senile plaques are extracellular, parenchymal deposits of aggregated Aβ in the brain (Figure 1). Aβ deposits can assume a variety of morphotypes ranging from small, diffuse aggregates to large, diffuse or dense deposits [28, 29]. While there is no standard plaque type, so-called 'classical' senile plaques usually consist of a dense core of fibrillar Aβ (β-amyloid) that is associated with an array of secondary proteins [30], activated microglia and astrocytes, and dysmorphic neuronal processes (abnormal neurites) [3] arising from various transmitter-specific systems [31, 32]. 'Amyloid' is a generic term for aberrant deposits of any of a number of proteins in various organs. The definition of amyloid has evolved over the years as our understanding of the substance has grown. The Nomenclature Committee of the International Society of Amyloidosis defines amyloid as "an *in vivo* deposited material, which can be distinguished from non-amyloid deposits by characteristic fibrillar electron microscopic appearance, typical X-ray diffraction pattern and histological staining reactions, particularly affinity for the dye Congo red with resulting green birefringence" [33] (see also Chiti and Dobson [34] and Fandrich [35] for discussions of the definition of amyloid). Some proteinaceous deposits, however, are not birefringent after staining with Congo red; in this review, we use the term 'senile plaques' to designate histologically identifiable deposits of Aβ, regardless of whether they fully conform to the current definition of 'amyloid'.

Congophilic (fibrillar) β-amyloid in cortical senile plaques was long thought to be the injurious form of Aβ in AD, and its presence still is a diagnostic criterion for the post-mortem confirmation of AD [9]. Accordingly, much research has examined the deposition of the Aβ peptide and coincident features of senile plaques in animal models such as nonhuman primates; indeed, some of the earliest, high-quality ultrastructural analyses of senile plaques were conducted on aged rhesus monkeys [36]. However, Aβ aggregation is a highly dynamic process. Prefibrillar Aβ multimers (oligomers and protofibrils) occur throughout affected brain regions in AD, and mounting evidence points to these prefibrillar Aβ species as important mediators of cytotoxicity [10, 11, 37]. Furthermore, recent evidence suggests that the folded structure of Aβ (and other pathogenic proteins) can vary at the molecular level, forming variant 'strains' [38], although it is not yet clear if such structural variations influence the pathogenicity of Aβ.

Cerebral β-Amyloid Angiopathy (CAA)

Cerebral β-amyloid angiopathy (CAA) refers to the accumulation of Aβ in the walls of cerebral blood vessels (Figure 2) [39–42]. Some CAA is present, to varying degrees, in virtually all AD cases; however, CAA may develop independently of the more common hallmarks of Alzheimer's disease (plaques and tangles) [43, 44]. In humans, CAA affects mainly the leptomeningeal arteries and arterioles, the penetrating arterioles, and, less frequently, veins and capillaries [45, 46]. Capillary CAA appears to correlate particularly strongly with AD pathology [47] and cognitive impairment [48]. A rather low correlation between the amount of capillary CAA and larger vessel CAA suggests that the two lesions may be etiologically independent [47].

Neurofibrillary Tangles (Tau Protein)

In addition to senile plaques, the second major pathological hallmark of AD is the intraneuronal aggregation of abnormally phosphorylated tau protein (Figure 3), histopathologically described as neurofibrillary tangles (NFT). 'Neurofibrillary tangles' are flame-shaped or roundish bundles of tau filaments in cell somata, whereas 'neuropil threads' are bunches of tau filaments within neuronal processes (Hauw and Duyckaerts, 2001). Although contemporary evidence indicates that tauopathy is downstream of Aβ proteopathy in the pathogenesis of AD [18], NFTs are an important correlate of neuronal dysfunction and dementia in the disease [15–17, 49]. Tauopathy is a primary or secondary lesion in a number

of neurodegenerative disorders besides AD, including fronto-temporal dementia, progressive supranuclear palsy, and corticobasal degeneration [14, 50]. (Interestingly, head injury can induce the phosphorylation and aggregation of tau and the accumulation of Aβ in humans [51, 52]). A substantial effort has been put forth to generate therapeutics that target the aggregation of tau protein [53], as well as unwanted protein-protein interactions in general [54].

Cognitive Decline and Neurodegeneration

The primary clinical manifestation of AD is severe and progressive cognitive decline [55]. To a much more limited degree, cognitive decline also is a feature of normal human aging, and can be difficult to differentiate from mild cognitive impairment (MCI) or prodromal AD [56, 57]. Currently, AD can only be diagnosed with reasonable certainty via the postmortem examination of the brain for the characteristic lesions in patients with dementia [58]. For effective disease treatment, it will be important to identify, as early as possible, the clinical manifestations of both natural and pathological cognitive deterioration in the aging process. A thorough examination of cognitive decline in nonhuman primates will optimize the utilization of these animals as models of human aging and disease.

Aβ and Tau Pathology in Nonhuman Primates

Primate Phylogeny and Age-Related Proteopathy

Molecular evidence supports the estimate that the primate lineage emerged in the late Cretaceous period, possibly as long as 85 million years ago (although the fossil record currently suggests an earlier date) [59, 60]. Thereafter, the primates diverged into various lines, such that the biological relatedness of the extant primates is considered to be greatest in species that most recently separated [60, 61]. Accordingly, with regard to divergence distance from humans, the approximate order of relatedness (from closest to most distant) is: Great Apes (Family Hominidae), Old World monkeys (Family Cercopithecidae), New World monkeys (Parvorder Platyrrhini) and Prosimians (Suborder Strepsirrhini and Infraorder Tarsiiformes). {Tree shrews (Order Scandentia), once considered the most primitive form of extant primate, are no longer considered to be members of the Primate order; although tree shrews generate human type-sequence Aβ, they have not yet been found to develop senile plaques with age [62]}.

Despite their biological closeness to humans, no nonhuman primate species has yet been shown to develop Alzheimer's disease [25, 26]. Hence, nonhuman primates are a good model of brain aging and Aβ-amyloidosis *in the absence of neurodegenerative disease*. At the same time, the incomplete manifestation of AD-like changes in simians may provide clues to the unique susceptibility of the human brain to Alzheimer's disease [25, 26, 63].

It is important to note that the amount of existing information on the aging nervous system in different primate species varies widely, so in some instances, certain data may not be available. In addition, a prominent feature of aging and age-related protein aggregation in nonhuman primates is the high degree of variability, both in the age of onset of the process, and in the amount, distribution, and appearance of lesions at any given age. With these caveats in mind, the organization of the following discussion of each nonhuman primate group will follow that of the preceding paragraphs, i.e.: Neuropathology (β-Amyloid Precursor Protein and β-Amyloid, Cerebral Amyloid Angiopathy, Tau Protein) and Behavior (Cognitive Decline).

Great Apes

Neuropathology—Relatively few studies have characterized the neuropathology of aging in great ape species, in part because of their long lifespan (up to 60 years for chimpanzees) and small numbers in research facilities. There is a high degree of homology in APP, as well as in the promoters and regulators of its production, in chimpanzees (*Pan troglodytes*), gorillas (*Gorilla gorilla gorilla*) and orangutans (*Pongo pygmaeus*) [64]. Histological studies have confirmed the presence of senile plaques that are immunopositive for Aβ in aged great apes [65–68]. Biochemical quantification of Aβ 40 and Aβ 42 isoforms in a small sample of chimpanzees indicates that very old chimpanzees can accumulate levels of total Aβ close to those seen in the AD brain, and that the Aβ isoform ratio varies substantially among subjects [63]. Other histopathological studies of the three great ape species have revealed swollen neurites and glial activation in close proximity to senile plaques, similar to plaques in the AD brain. To date, too few individuals have been analyzed to establish the rate of Aβ deposition and the time-course of this process in the great apes, as well as potential differences between males and females. Studies in our laboratory indicate that Aβ plaque pathology is focal and relatively sparse in both male and female aged chimpanzees (unpublished data).

The limitedstudies of CAAin great apes have demonstrated that vascular Aβ amyloidosis is fairly prevalent in aged chimpanzees [65, 66]and orangutans [68, 69], and predominates over parenchymal plaque accumulation [70]. One analysis of anaged gorilla found senile plaques, but did not reportcerebral amyloid angiopathy [67]; a recent case report, however, diddemonstrate CAA in a 40 year-old albino gorilla [71].

Genetic studies in great apes have found that tau in chimpanzees and gorillas shares 100% and 99.5% sequence homology, respectively, with human tau [72]. The incidence of tauopathy in great apes cannot yet be determined with certainty due to the paucity of histopathologic analyses in aged animals. Nonetheless, in one study, tauopathy with human-like paired helical filaments was reported in a 41 year-old female chimpanzee who had suffered a stroke prior to death [73] (Figures 3B, 4). Like other aged chimpanzees, this animal had a moderate degree of CAA, but very few senile plaques. In addition, the NFTs were mainly in cortical neurons, whereas (unlike in AD) the hippocampus was largely free of tauopathy or obvious neuronal loss.

Behavior—Aged chimpanzees are impaired on the delayed response task, a measure of frontal cortical function [74], but they perform normally on associative memory tasks that are relatively non-dependent on the frontal cortex [75]. Similarly, associative memory in gorillas appears to be intact in old age [76]. Though limited, these data suggest that there may be a pattern of modest cognitive decline in great apes, akin to normal human aging.

Old World Monkeys

Neuropathology—The bulk of published data on age-associated neuropathology in nonhuman primates comes from studies of rhesus monkeys (*Macaca mulatta*) and a few other Old World species. The rhesus monkey and its close relative the cynomolgus monkey (*Macaca fascicularis*) are widely used in behavioral and biomedical research, and much is known about the physiology and pathology of aging in these species. The maximum lifespan of rhesus monkeys is currently thought to be approximately 40 years [61].

APP is ubiquitously expressed in neurons of all macaque species examined, including rhesus, cynomolgus, and lion-tailed macaques (*Macaca silenus*) [77, 78]. The 695 amino acid isoform of APP (APP_{695}) is completely homologous between humans and both rhesus and cynomolgus monkeys, whereas the common longer isoforms have either one (APP_{751})

or four (APP_{770}) amino acid differences [79]. The activity of the β-amyloid cleaving enzyme-1 (β-secretase, or BACE-1), which contributes to the liberation of Aβ from APP, increases with age in rhesus monkeys and humans [80]. A BACE-1 inhibitor recently was shown to lower Aβ levels in the cerebrospinal fluid and plasma of rhesus monkeys [81].

Early neuropathological studies of aged Old World monkeys demonstrated that animals above the age of 30 exhibit well-formed (‘mature’) senile plaques [69, 82], although plaque formation can begin much earlier. Aβ deposits are commonly found in rhesus monkeys after the age of 25 years [30, 82, 83]. Interestingly, 25 years marks the onset of significant biosenescence in rhesus monkeys [83], and is also the average age at which menopause becomes apparent in this species [84, 85]. The relationship of menopause to cerebral Aβ accumulation, and whether there are male-female differences in β-amyloidogenesis among primates, remain to be explored. Because recent data in Alzheimer patients suggest that estrogen may be neuroprotective, an investigation into sex differences in Aβ accumulation in nonhuman primates may prove informative [86, 87].

Total Aβ in the temporal and occipital cortices of aged rhesus macaques reaches levels comparable to cortical Aβ levels in Alzheimer subjects; biochemical analysis further reveals that the longer Aβ 42 isoform often predominates over Aβ 40 [63]. The highest plaque densities in rhesus monkeys are in the frontal and temporal cortices, with fewer plaques in the hippocampal formation [30, 88, 89]. This neocortical-to-allocortical pattern of expansion is somewhat akin to the progression of Aβ plaque formation in the AD brain [90]. Some senile plaques are surrounded by swollen, dystrophic neurites and activated astrocytes and microglia (Figures 5, 6) [77, 91]. However, there have been no reports of significant neuronal loss in areas of high plaque density.

Large-scale, cross-sectional studies have characterized the time-course, rate, and degree of plaque formation in aged rhesus and cynomolgus macaques [78, 83, 89, 92–95]. Confirming earlier studies, Aβ plaque formation was not seen in any macaques under the age of 15, and the accumulation of Aβ deposits was infrequent and highly variable within and among animals in their late teens and early twenties. The majority of plaques in animals under the age of 29 were of the diffuse or primitive type, with dense-core plaques most commonly occurring in animals older than 29 years. The relative paucity of mature plaques in any subjects other than the oldest macaques (over 30 years) supports the early report of Struble and colleagues [82], who showed a strong correlation between overall plaque density and the existence of mature (amyloid) plaques. Together, these studies identify a timeline for the progressive accumulation of Aβ peptides in the aging macaque brain [96] that is somewhat similar to the steady buildup of Aβ plaque pathology in the brains of nondemented humans [97, 98]. In addition to macaques, another Old World monkey, the vervet (*Chlorocebus aethiops*), also shows an age-related increase in Aβ plaque formation [99, 100]. As in macaques, there is no direct evidence linking the presence of amyloid plaques with neuronal loss in vervet monkeys.

Some degree of CAA has been reported in most aged macaques examined in these studies [65, 66, 69, 77, 82, 83, 88, 93, 96, 101]. In a well-powered, cross-sectional study of aging in rhesus monkeys, CAA was not detectable in any animal under the age of 20 years, and it was present in about 38% of animals near the end of the maximum lifespan [94]. Interestingly, this study showed that CAA develops at approximately the same age as do parenchymal Aβ deposits, albeit with a reduced frequency. Similar to rhesus monkeys, cynomolgus monkeys manifest CAA after ~20 years of age, and there is a positive correlation between parenchymal plaques and CAA [25] [93]. CAA also has been immunohistochemically detected in at least two non-macaque Old World monkey species, the aged baboon [102] and vervet monkey [100].

The amino acid sequence of the tau protein in rhesus monkeys differs from that in humans by only four residues, suggesting that Old World monkeys might be capable of producing NFTs [103]. Abnormally phosphorylated tau protein has been identified in rhesus [104] and cynomolgus macaques [96], although bona fide neurofibrillary tangles have not been confirmed ultrastructurally in these species. In our experience, it is not unusual to encounter occasional neurons and processes that are immunoreactive with antibodies to abnormally phosphorylated tau in aged macaques, but no study has yet shown widespread, AD-like tauopathy in these monkeys [65, 77]. One potential explanation for the lack of NFT in macaques is that the protein contains the product of exon 8 of the tau gene, which does not exist in humans and may prohibit the abnormal phosphorylation of tau [103].

Baboons manifest an unusual form of heavy, though highly localized, tauopathy. In the first of a series of studies, two aged baboons (aged 26 and 30 years) exhibited tau pathology in neurons and glial cells that was associated with hippocampal neuropil changes [102]. In a more exhaustive, cross-sectional study, the researchers showed that the abnormal tau develops as a function of age: 0% of animals aged 1–10 years, 31% of animals aged 11–20 years, 71% of animals aged 21–25 years and 91% of animals aged 26–30 years exhibited abnormal tau accumulation [105].

Behavior—Recognition memory is dependent on the medial temporal lobe, one of the earliest brain regions affected in the pathogenesis of AD [106]. Deficits in recognition memory are an indicator of mild cognitive impairment and AD in humans [107]. Old World monkeys manifest age-related decrements in recognition memory that begin in the late teens and become more salient in the mid-twenties [108–111]. In contrast, cognitive processes such as reversal learning, working memory and set-shifting, which are dependent on the frontal cortex [74, 112], are stable until the twenties in these animals [113–117]. These data suggest that declines in cognitive function begin with the temporal lobe in the late teenage years, but that frontal dysfunction is delayed until the twenties in macaques. However, plaque density has not been found to correlate significantly with cognitive decline in rhesus monkeys [110]. The progression of cognitive impairment from the temporal cortical areas to the frontal cortex mirrors what is seen in the development of tau pathology in AD [118], and opens the door to the possibility that non-fibrillar, oligomeric Aβ or tau may be responsible for the observed dysfunction in simians [2]. Studies aimed at examining whether oligomeric Aβ is related to cognitive decline in nonhuman primates would be particularly informative.

New World Monkeys

Neuropathology—The β-amyloid precursor protein is highly conserved between humans and squirrel monkeys (*Saimiri sciureus*) [89], the most thoroughly examined New World species in aging studies [119–121]. Squirrel monkeys have a known maximum lifespan of approximately 30 years [61], with menopause in females probably occurring in the mid-teens [119]. Aβ-immunopositive senile plaques are present in the brains of aged squirrel monkeys [69, 122], but not in those of younger conspecifics [123]. Subsequent studies of squirrel monkeys extended these early findings by localizing plaque-like deposits predominantly to the neocortex and amygdala, with relatively little deposition in the hippocampal formation proper [122]. Furthermore, Aβ accumulation in the squirrel monkey brain is mainly within the brain vasculature rather than in parenchymal plaques [120, 124, 125] (below). By enzyme-linked immunosorbent assay (ELISA), total cortical Aβ levels were substantially higher in a group of senescent squirrel monkeys than in a cohort of end-stage Alzheimer's subjects [63]. Total Aβ42 levels were comparable between the two groups, and Aβ42 levels were higher than Aβ40 levels in the cortices of both squirrel monkey and human subjects [63], replicating an earlier report [126]. In general, there is a decreasing rostral-caudal gradient in the density of both plaques and amyloid angiopathy in

squirrel monkeys [92], but there is also variability in the number, type and localization of Aβ lesions, both between and within animals [91, 92]. Senile plaques in squirrel monkeys are mostly smaller than those in macaques and humans [90, 91]. A comparable pattern of age-related amyloid pathology, including CAA, is observed in other New World monkeys such as the marmoset (*Callithrix jacchus*) [127, 128] and the cotton-top tamarin (*Saguinus oedipus*) [129]. In these species, Aβ deposition begins sometime in the teens, with high variability, and mature plaques do not emerge until the late teen years.

The development of age-related CAA has been particularly well studied in the squirrel monkey [69, 123, 124]. CAA is the predominant form of β-amyloid in the aged squirrel monkey brain [120, 122] (Figure 2), although the pattern and distribution of lesions vary [130]. CAA affects arteries and arterioles in *Saimiri*, but, unlike in humans [32; 33], capillaries also are heavily affected [124].

In rare familial human cases, CAA has been linked to specific mutations in the gene for APP [39, 131]; no such mutations have been discovered in squirrel monkeys [120]. In humans, apolipoprotein E (ApoE) polymorphisms influence both the risk of AD and the susceptibility to CAA. Specifically, compared to the ApoE3 or ApoE2 allelotypes, ApoE4 is associated with an enhanced tendency to develop CAA [132]. Interestingly, all nonhuman primates tested to date are homozygous for ApoE4 according to the human nomenclature [133]. However, an amino acid substitution at position 61 distinguishes simian ApoE from human ApoE, causing nonhuman primate ApoE4 to interact with lipoproteins similarly to ApoE3 in humans [133].

A rare form of familial cerebral amyloid angiopathy in Iceland involves a mutation in the gene for cystatin-C, which results in the deposition of cystatin C in the brain vasculature [40]. Interestingly, squirrel monkeys have an amino acid difference at the ‘Icelandic’ locus on this gene [134], but the amyloid in the vasculature of the monkeys is primarily Aβ, and not cystatin C. Whether the polymorphism in cystatin-C influences the deposition of Aβ in the vasculature in squirrel monkeys remains unknown, but it is worth noting that a human case of cerebral Aβ-amyloid angiopathy has been reported that had an Icelandic-like mutation in cystatin-C [135].

Other New World monkeys such as marmosets [127, 128] and cotton-topped tamarins [129] also develop significant CAA with age. The pattern of deposition appears to be similar to that in squirrel monkeys, in that CAA is an early and prominent lesion in both marmosets and tamarins [128, 129]. One study found rare β-amyloid plaques in very young marmosets [136], although the significance of this singular finding remains unclear.

As in Old World monkeys, significant tauopathy has not been reported in any New World primate. However, investigators have described occasional, abnormal tau-immunoreactive neurites and neurons in aged squirrel monkeys [69, 124], but not in marmosets [128] or cotton-topped tamarins [129] .

Behavior—Little information is available on cognitive aging in New World monkeys, with the exception of one study on the squirrel monkey and one on the marmoset. Aged squirrel monkeys were impaired on a motor inhibition task [137], suggesting a dysfunctional prefrontal cortex as it pertains to flexible decision making. The study of marmosets found an age-related impairment on a delayed-response task [138], also suggesting dysfunction of the prefrontal cortex. Taken together, these findings mirror the mild, age-related cognitive impairments seen in Great Apes and Old World monkeys.

Prosimians

Neuropathology—Among the prosimians, the bulk of aging research has focused on the grey mouse lemur (*Microcebus murinus*), small primates with a maximum lifespan in captivity of approximately 18 years [139]. The substantial conservation of APP in monkeys and apes also is observed in the mouse lemur [140]. Mouse lemurs develop senile plaques as young as 8 years of age, with consistent plaque formation in individuals 10 years and older [141–143]. Approximately 60% of aged individuals show severe β-amyloid deposition [140, 144, 145]. A recent study reported age-associated cerebral atrophy in microcebes that appeared to be linked to intracellular Aβ immunoreactivity, but not to plaque burden or tau immunoreactivity [146].

CAA has been consistently observed in mouse lemurs over 10 years of age [140, 142–144]. There is some uncertainty as to whether parenchymal plaques or CAA comprise the dominant form of β-amyloid in microcebes, although one study noted a preponderance of CAA [143].

Several reports have presented light microscopic evidence that mouse lemurs manifest neurofibrillary pathology/tauopathy with age [142, 143, 146]. The comparability of these anomalies to human neurofibrillary tangles has not yet been established ultrastructurally.

Behavior—One experiment compared young (2–4yrs) and aged (7–11yrs) mouse lemurs and found impairments in frontal lobe functions such as generalization, set-shifting and reversal learning [147]. A follow-up study confirmed these findings, and also detected a deficit in spatial memory in older animals [148]. Because these studies lacked a longitudinal or multi-age cross-sectional design, the age of onset of cognitive decline in the mouse lemur has not been determined. However, their small size, human-type Aβ sequence and relatively early age of lesion formation make these prosimians potentially useful models of naturally occurring, age related cerebral proteopathy.

Conclusions

Nearly half a century of neuropathological studies have confirmed that, like humans, nonhuman primates exhibit age- related deposition of Aβ in the brain parenchyma and vasculature (Figure 7). Conversely, tau pathology appears to be relatively rare in nonhuman primates, and, when present, it is generally focal and often mild. Furthermore, nonhuman primates do not develop the widespread neuronal degeneration and profound cognitive impairments that characterize AD. However, the variations in cerebral Aβ amyloidosis among primate species can provide clues to the origins of different types of lesions, and perhaps also to the human-specific predisposition to AD. For example, by comparing gene expression in closely related species, it may be possible to determine why Aβ-proteopathy in monkeys is relatively benign compared to that in humans with AD.

Most studies of nonhuman primates have relied on histochemical methods to characterize the age-associated lesions in the brain. New and emerging technologies will open avenues for investigators to perform enhanced biochemical, physicochemical, and high resolution neuroimaging studies of the Aβ and tau proteins at various points throughout the lifespans of primates, and to correlate these findings with longitudinal behavioral data. Quantitative ELISAs show that the levels of cerebral Aβ are comparable in humans with AD and aged chimpanzees, rhesus macaques, and squirrel monkeys [63]. Surprisingly, however, binding assays with radiolabeled Pittsburgh Compound B (PIB) have revealed striking disparities in the affinity of the ligand for Aβ deposits between simians and humans, suggesting potentially important differences in the architecture and/or endogenous binding partners of Aβ aggregates that govern their neurotoxicity.

Recent research suggests that oligomeric Aβ may be a key source of neuronal dysfunction in AD [149]. No studies of nonhuman primates have yet systematically measured oligomeric forms of Aβ (or tau). Thus, while previous studies have failed to find a correlation between plaque burden and cognitive dysfunction [110], future investigations should examine non-fibrillar Aβ load for its potential relation to cognitive deficits. Additional studies that may further clarify the relative resistance of apes and monkeys to AD include an investigation of intracellular Aβ, a detailed analysis of the intracellular binding partners of Aβ and tau, a characterization of species-specific ApoE functionality, and the detection of neuroinflammatory components in and around brain lesions.

While each nonhuman primate model has advantages and disadvantages for these studies (lifespan, size, biological relatedness to humans, safety, status in the wild, etc), the rhesus macaque, because it has been well-studied, currently is the most accessible and practical nonhuman primate model in which to study AD-like proteopathic processes. Rhesus monkeys have a fairly long lifespan (up to 40 years), and large, neuroanatomically sophisticated brains; they show substantial Aβ deposition, and can be assessed for complex cognitive functions using tasks that, in many instances, are translatable to humans. On the other hand, the squirrel monkey is perhaps the most suitable nonhuman primate model of CAA and age-related microvascular disease, as this animal has a predilection to develop considerable vascular amyloid. Additional advantages are its small size and large brain-to-body weight ratio, although a disadvantage is that it is more distantly related to humans than are macaques. As noted above, prosimians also have advantages for certain analyses, owing to their small size and relatively short lifespan, and baboons may be the best natural animal model of tauopathy, although the relatively small amount of data on the prevalence of tauopathy in baboons underscores the need for further investigation.

Aged nonhuman primates are valuable models of normal human brain aging, and they also are biologically relevant research models for the development of diagnostics and therapeutics for AD and CAA. As we expand our understanding of conserved and divergent properties of cerebral proteopathies in the various primate species, we may begin to shed light on why the uniquely capable human brain is particularly sensitive to age-related neurodegenerative disorders such as Alzheimer’s disease.

Acknowledgments

We thank Jeromy Dooyema and Carolyn Suwyn for excellent technical assistance, and Drs. Todd Preuss, Harry LeVine and James Herndon for advice and helpful discussions. This work was supported by NIH RR-00165, PO1AG026423, P50AG025688, and the Woodruff Foundation.

References

1. Carter MD, Simms GA, Weaver DF. The development of new therapeutics for Alzheimer's disease. Clin Pharmacol Ther. 2010; 88:475–86. [PubMed: 20811351]
2. Holtzman DM, Morris JC, Goate AM. Alzheimer's disease: the challenge of the second century. Sci Transl Med. 2011; 3:77sr1. [PubMed: 21471435]
3. Hauw, JJ.; Duyckaerts, C. Alzheimer's Disease. Oxford University Press; New York: 2001.
4. Alzheimer A. A characteristic disease of the cerebralcortex. Allegemeine Zeitschrift fur Psychiatrie und Psychisch-Gerichtliche Medizin. 1907; LXIV:146.
5. Querfurth HW, LaFerla FM. Alzheimer's disease. N Engl J Med. 2010; 362:329–44. [PubMed: 20107219]
6. Bekris LM, Yu CE, Bird TD, Tsuang DW. Genetics of Alzheimer disease. J Geriatr Psychiatry Neurol. 2010; 23:213–27. [PubMed: 21045163]
7. Bertram L, Lill CM, Tanzi RE. The genetics of Alzheimer disease: back to the future. Neuron. 2010; 68:270–81. [PubMed: 20955934]

8. Selkoe, DJ. Biology of β-Amyloid Precursor Protein and the Mechanism of Alzheimer Disease. In: Terry, RD.; Katzman, R.; Bick, KL.; Sisodia, SS., editors. Alzheimer Disease. Lippincott Williams & Wilkins; Philadelphia, PA: 1999. p. 293-310.
9. Murphy MP, LeVine H 3rd. Alzheimer's disease and the amyloid-beta peptide. J Alzheimers Dis. 2010; 19:311–23. [PubMed: 20061647]
10. Nimmrich V, Ebert U. Is Alzheimer's disease a result of presynaptic failure? Synaptic dysfunctions induced by oligomeric beta-amyloid. Rev Neurosci. 2009; 20:1–12. [PubMed: 19526730]
11. Kawahara M. Neurotoxicity of beta-amyloid protein: oligomerization, channel formation, and calcium dyshomeostasis. Curr Pharm Des. 2010; 16:2779–89. [PubMed: 20698821]
12. Jin M, Shepardson N, Yang T, Chen G, Walsh D, Selkoe DJ. Soluble amyloid {beta}-protein dimers isolated from Alzheimer cortex directly induce Tau hyperphosphorylation and neuritic degeneration. Proc Natl Acad Sci U S A. 2011; 108:5819–24. [PubMed: 21421841]
13. Goedert M, Klug A, Crowther RA. Tau protein, the paired helical filament and Alzheimer's disease. J Alzheimers Dis. 2006; 9:195–207. [PubMed: 16914859]
14. Lee VM, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. Annu Rev Neurosci. 2001; 24:1121–59. [PubMed: 11520930]
15. Crystal H, Dickson D, Fuld P, Masur D, Scott R, Mehler M, Masdeu J, Kawas C, Aronson M, Wolfson L. Clinico-pathologic studies in dementia: nondemented subjects with pathologically confirmed Alzheimer's disease. Neurology. 1988; 38:1682–7. [PubMed: 3185902]
16. Giannakopoulos P, Gold G, Kovari E, von Gunten A, Imhof A, Bouras C, Hof PR. Assessing the cognitive impact of Alzheimer disease pathology and vascular burden in the aging brain: the Geneva experience. ActaNeuropathol (Berl). 2007; 113:1–12.
17. Wilcock GK, Esiri MM. Plaques, tangles and dementia. A quantitative study. J Neurol Sci. 1982; 56:343–56. [PubMed: 7175555]
18. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002; 297:353–6. [PubMed: 12130773]
19. Bolmont T, Clavaguera F, Meyer-Luehmann M, Herzig MC, Radde R, Staufenbiel M, Lewis J, Hutton M, Tolnay M, Jucker M. Induction of tau pathology by intracerebral infusion of amyloid-beta -containing brain extract and by amyloid-beta deposition in APP x Tau transgenic mice. Am J Pathol. 2007; 171:2012–20. [PubMed: 18055549]
20. Clavaguera F, Bolmont T, Crowther RA, Abramowski D, Frank S, Probst A, Fraser G, Stalder AK, Beibel M, Staufenbiel M, Jucker M, Goedert M, Tolnay M. Transmission and spreading of tauopathy in transgenic mouse brain. Nat Cell Biol. 2009; 11:909–13. [PubMed: 19503072]
21. Gotz J, Chen F, van Dorpe J, Nitsch RM. Formation of neurofibrillary tangles in P301l tau transgenic mice induced by Abeta 42 fibrils. Science. 2001; 293:1491–5. [PubMed: 11520988]
22. Oddo S, Caccamo A, Tseng B, Cheng D, Vasilevko V, Cribbs DH, LaFerla FM. Blocking Abeta42 accumulation delays the onset and progression of tau pathology via the C terminus of heat shock protein70-interacting protein: a mechanistic link between Abeta and tau pathology. J Neurosci. 2008; 28:12163–75. [PubMed: 19020010]
23. Walker LC, Callahan MJ, Bian F, Durham RA, Roher AE, Lipinski WJ. Exogenous induction of cerebral beta-amyloidosis in betaAPP-transgenic mice. Peptides. 2002; 23:1241–7. [PubMed: 12128081]
24. Walker LC, LeVine H 3rd. The cerebral proteopathies. Neurobiol Aging. 2000; 21:559–61. [PubMed: 10924770]
25. Levine, H.; Walker, LC. Models of Alzheimer's disease. Michael Conn, P., editor. Academic Press, Elsevier; New York: 2006. p. 121-134.
26. Jucker M. The benefits and limitations of animal models for translational research in neurodegenerative diseases. Nat Med. 2010; 16:1210–4. [PubMed: 21052075]
27. Chow VW, Mattson MP, Wong PC, Gleichmann M. An overview of APP processing enzymes and products. Neuromolecular Med. 2010; 12:1–12. [PubMed: 20232515]
28. Fiala JC. Mechanisms of amyloid plaque pathogenesis. Acta Neuropathol. 2007; 114:551–71. [PubMed: 17805553]
29. Walker LC, Rosen RF, Levine H 3rd. Diversity of Abeta deposits in the aged brain: a window on molecular heterogeneity? Rom J Morphol Embryol. 2008; 49:5–11. [PubMed: 18273496]

30. Sani S, Traul D, Klink A, Niaraki N, Gonzalo-Ruiz A, Wu CK, Geula C. Distribution, progression and chemical composition of cortical amyloid-beta deposits in aged rhesus monkeys: similarities to the human. Acta Neuropathol. 2003; 105:145–56. [PubMed: 12536225]
31. Walker LC, Kitt CA, Cork LC, Struble RG, Dellovade TL, Price DL. Multiple transmitter systems contribute neurites to individual senile plaques. J Neuropathol Exp Neurol. 1988; 47:138–44. [PubMed: 2828554]
32. Benzing WC, Brady DR, Mufson EJ, Armstrong DM. Evidence that transmitter-containing dystrophic neurites precede those containing paired helical filaments within senile plaques in the entorhinal cortex of nondemented elderly and Alzheimer's disease patients. Brain Res. 1993; 619:55–68. [PubMed: 7690677]
33. Westermark P, Benson MD, Buxbaum JN, Cohen AS, Frangione B, Ikeda S, Masters CL, Merlini G, Saraiva MJ, Sipe JD. A primer of amyloid nomenclature. Amyloid. 2007; 14:179–83. [PubMed: 17701465]
34. Chiti F, Dobson CM. Protein misfolding, functional amyloid, and human disease. Annu Rev Biochem. 2006; 75:333–66. [PubMed: 16756495]
35. Fandrich M. On the structural definition of amyloid fibrils and other polypeptide aggregates. Cell Mol Life Sci. 2007; 64:2066–78. [PubMed: 17530168]
36. Wisniewski HM, Ghetti B, Terry RD. Neuritic (senile) plaques and filamentous changes in aged rhesus monkeys. J Neuropathol Exp Neurol. 1973; 32:566–84. [PubMed: 4202280]
37. Sakono M, Zako T. Amyloid oligomers: formation and toxicity of Abeta oligomers. FEBS J. 2010; 277:1348–58. [PubMed: 20148964]
38. Levine H 3rd, Walker LC. Molecular polymorphism of Abeta in Alzheimer's disease. Neurobiol Aging. 2010; 31:542–8. [PubMed: 18619711]
39. Revesz T, Ghiso J, Lashley T, Plant G, Rostagno A, Frangione B, Holton JL. Cerebral amyloid angiopathies: a pathologic, biochemical, and genetic view. J Neuropathol Exp Neurol. 2003; 62:885–98. [PubMed: 14533778]
40. Revesz T, Holton JL, Lashley T, Plant G, Frangione B, Rostagno A, Ghiso J. Genetics and molecular pathogenesis of sporadic and hereditary cerebral amyloid angiopathies. Acta Neuropathol. 2009; 118:115–30. [PubMed: 19225789]
41. Rensink AA, de Waal RM, Kremer B, Verbeek MM. Pathogenesis of cerebral amyloid angiopathy. Brain Res Brain Res Rev. 2003; 43:207–23. [PubMed: 14572915]
42. Greenberg SM, Gurol ME, Rosand J, Smith EE. Amyloid angiopathy-related vascular cognitive impairment. Stroke. 2004; 35:2616–9. [PubMed: 15459438]
43. Okamoto, Y.; Ihara, M.; Ito, H.; Yamamoto, T.; Tomimoto, H.; Takashima, R. Cortical microinfarcts are related to cerebral amyloid angiopathy rather than to senile plaques or neurofibrillary tangles. Society for Neuroscience, Online; Neuroscience Meeting Planner; San Diego, CA. 2010. Program Number 56.2
44. Ellis RJ, Olichney JM, Thal LJ, Mirra SS, Morris JC, Beekly D, Heyman A. Cerebral amyloid angiopathy in the brains of patients with Alzheimer's disease: the CERAD experience, Part XV. Neurology. 1996; 46:1592–6. [PubMed: 8649554]
45. Vinters HV. Cerebral amyloid angiopathy. A critical review Stroke. 1987; 18:311–24.
46. Preston SD, Steart PV, Wilkinson A, Nicoll JA, Weller RO. Capillary and arterial cerebral amyloid angiopathy in Alzheimer's disease: defining the perivascular route for the elimination of amyloid beta from the human brain. Neuropathol Appl Neurobiol. 2003; 29:106–17. [PubMed: 12662319]
47. Attems J, Jellinger KA. Only cerebral capillary amyloid angiopathy correlates with Alzheimer pathology--a pilot study. Acta Neuropathol. 2004; 107:83–90. [PubMed: 14655019]
48. Eurelings LS, Richard E, Carrano A, Eikelenboom P, van Gool WA, Rozemuller AJ. Dyshoric capillary cerebral amyloid angiopathy mimicking Creutzfeldt-Jakob disease. J Neurol Sci. 2010; 295:131–4. [PubMed: 20537354]
49. Maccioni RB, Farias G, Morales I, Navarrete L. The revitalized tau hypothesis on Alzheimer's disease. ArchMed Res. 2010; 41:226–31.
50. Ballatore C, Lee VM, Trojanowski JQ. Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. Nat Rev Neurosci. 2007; 8:663–72. [PubMed: 17684513]

51. McKee AC, Cantu RC, Nowinski CJ, Hedley-Whyte ET, Gavett BE, Budson AE, Santini VE, Lee HS, Kubilus CA, Stern RA. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. J Neuropathol Exp Neurol. 2009; 68:709–35. [PubMed: 19535999]
52. Ikonomovic MD, Uryu K, Abrahamson EE, Ciallella JR, Trojanowski JQ, Lee VM, Clark RS, Marion DW, Wisniewski SR, DeKosky ST. Alzheimer's pathology in human temporal cortex surgically excised after severe brain injury. Exp Neurol. 2004; 190:192–203. [PubMed: 15473992]
53. Gong CX, Grundke-Iqbal I, Iqbal K. Targeting tau protein in Alzheimer's disease. Drugs Aging. 2010; 27:351–65. [PubMed: 20450234]
54. Ballatore C, Brunden KR, Trojanowski JQ, Lee VM, Smith AB 3rd, Huryn D. Modulation of Protein-Protein Interactions as a Therapeutic Strategy for the Treatment of Neurodegenerative Tauopathies. Curr Top Med Chem. 2010
55. Daviglus ML, Bell CC, Berrettini W, Bowen PE, Connolly ES Jr, Cox NJ, Dunbar-Jacob JM, Granieri EC, Hunt G, McGarry K, Patel D, Potosky AL, Sanders-Bush E, Silberberg D, Trevisan M. National Institutes of Health State-of-the-Science Conference statement: preventing alzheimer disease and cognitive decline. Ann Intern Med. 2010; 153:176–81. [PubMed: 20547888]
56. Werner P, Korczyn AD. Mild cognitive impairment: conceptual, assessment, ethical, and social issues. Clin Interv Aging. 2008; 3:413–20. [PubMed: 18982912]
57. Warsch JR, Wright CB. The aging mind: vascular health in normal cognitive aging. J Am Geriatr Soc. 2010; 58 (Suppl 2):S319–24. [PubMed: 21029061]
58. Murayama S, Saito Y. Neuropathological diagnostic criteria for Alzheimer's disease. Neuropathology. 2004; 24:254–60. [PubMed: 15484705]
59. Williams BA, Kay RF, Kirk EC. New perspectives on anthropoid origins. Proc Natl Acad Sci U S A. 2010; 107:4797–804. [PubMed: 20212104]
60. Wilkinson RD, Steiper ME, Soligo C, Martin RD, Yang Z, Tavare S. Dating primate divergences through an integrated analysis of palaeontological and molecular data. Syst Biol. 2011; 60:16–31. [PubMed: 21051775]
61. Finch CE, Sapolsky RM. The evolution of Alzheimer disease, the reproductive schedule, and apoE isoforms. Neurobiol Aging. 1999; 20:407–28. [PubMed: 10604433]
62. Pawlik M, Fuchs E, Walker LC, Levy E. Primate-like amyloid-beta sequence but no cerebral amyloidosis in aged tree shrews. Neurobiol Aging. 1999; 20:47–51. [PubMed: 10466892]
63. Rosen RF, Walker LC, Levine H 3rd. PIB binding in aged primate brain: enrichment of high-affinity sites in humans with Alzheimer's disease. Neurobiol Aging. 2011; 32:223–34. [PubMed: 19329226]
64. Adroer R, Lopez-Acedo C, Oliva R. Conserved elements in the 5' regulatory region of the amyloid precursor protein gene in primates. Neurosci Lett. 1997; 226:203–6. [PubMed: 9175602]
65. Gearing M, Rebeck GW, Hyman BT, Tigges J, Mirra SS. Neuropathology and apolipoprotein E profile of aged chimpanzees: implications for Alzheimer disease. Proc Natl Acad Sci U S A. 1994; 91:9382–6. [PubMed: 7937774]
66. Gearing M, Tigges J, Mori H, Mirra SS. A beta40 is a major form of beta-amyloid in nonhuman primates. Neurobiol Aging. 1996; 17:903–8. [PubMed: 9363802]
67. Kimura N, Nakamura S, Goto N, Narushima E, Hara I, Shichiri S, Saitou K, Nose M, Hayashi T, Kawamura S, Yoshikawa Y. Senile plaques in an aged western lowland gorilla. Exp Anim. 2001; 50:77–81. [PubMed: 11326427]
68. Gearing M, Tigges J, Mori H, Mirra SS. beta-Amyloid (A beta) deposition in the brains of aged orangutans. Neurobiol Aging. 1997; 18:139–46. [PubMed: 9258890]
69. Selkoe DJ, Bell DS, Podlisny MB, Price DL, Cork LC. Conservation of brain amyloid proteins in aged mammals and humans with Alzheimer's disease. Science. 1987; 235:873–7. [PubMed: 3544219]
70. Rosen RF, Farberg AS, Hof PR, Sherwood J, Dooyema J, Walker LC, Preuss TM. The hippocampus of aged chimpanzees: regional neuron numbers, regional proportions and amyloid and tau pathology. In Preperation.
71. Marquez M, Serafin A, Fernandez-Bellon H, Serrat S, Ferrer-Admetlla A, Bertranpetit J, Ferrer I, Pumarola M. Neuropathologic findings in an aged albino gorilla. Vet Pathol. 2008; 45:531–7. [PubMed: 18587101]

72. Holzer M, Craxton M, Jakes R, Arendt T, Goedert M. Tau gene (MAPT) sequence variation among primates. Gene. 2004; 341:313–22. [PubMed: 15474313]
73. Rosen RF, Farberg AS, Gearing M, Dooyema J, Long PM, Anderson DC, Davis-Turak J, Coppola G, Geschwind DH, Pare JF, Duong TQ, Hopkins WD, Preuss TM, Walker LC. Tauopathy with paired helical filaments in an aged chimpanzee. J Comp Neurol. 2008; 509:259–70. [PubMed: 18481275]
74. Mishkin M. Effects of small frontal lesions on delayed alternation in monkeys. Journal of Neurophysiology. 1957; 20:615–22. [PubMed: 13476217]
75. Riopelle, AJ.; Rogers, CM. Age changes in chimpanzees. Academic Press; New York: 1965.
76. Kuhar, C. Factors Affecting Spatial Ability of Lowland Gorillas: Age, Gender and Experience. Georgia Institute of Technology; Atlanta, GA: 2004.
77. Martin LJ, Sisodia SS, Koo EH, Cork LC, Dellovade TL, Weidemann A, Beyreuther K, Masters C, Price DL. Amyloid precursor protein in aged nonhuman primates. Proc Natl Acad Sci U S A. 1991; 88:1461–5. [PubMed: 1899927]
78. Martin LJ, Pardo CA, Cork LC, Price DL. Synaptic pathology and glial responses to neuronal injury precede the formation of senile plaques and amyloid deposits in the aging cerebral cortex. Am J Pathol. 1994; 145:1358–81. [PubMed: 7992840]
79. Podlisny MB, Tolan DR, 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; 138:1423–35. [PubMed: 1905108]
80. Fukumoto H, Rosene DL, Moss MB, Raju S, Hyman BT, Irizarry MC. β-Secretasee Activity Increases with Aging in Human, Monkey and Mouse Brain. American Journal of Pathology. 2004; 164:719–25. [PubMed: 14742275]
81. Sankaranarayanan S, Holahan MA, Colussi D, Crouthamel MC, Devanarayan V, Ellis J, Espeseth A, Gates AT, Graham SL, Gregro AR, Hazuda D, Hochman JH, Holloway K, Jin L, Kahana J, Lai MT, Lineberger J, McGaughey G, Moore KP, Nantermet P, Pietrak B, Price EA, Rajapakse H, Stauffer S, Steinbeiser MA, Seabrook G, Selnick HG, Shi XP, Stanton MG, Swestock J, Tugusheva K, Tyler KX, Vacca JP, Wong J, Wu G, Xu M, Cook JJ, Simon AJ. First demonstration of cerebrospinal fluid and plasma A beta lowering with oral administration of a beta-site amyloid precursor protein-cleaving enzyme 1 inhibitor in nonhuman primates. J Pharmacol Exp Ther. 2009; 328:131–40. [PubMed: 18854490]
82. Struble RG, Price DL Jr, Cork LC, Price DL. Senile plaques in cortex of aged normal monkeys. Brain Res. 1985; 361:267–75. [PubMed: 4084799]
83. Uno H, Walker LC. The age of biosenescence and the incidence of cerebral beta-amyloidosis in aged captive rhesus monkeys. Ann N Y Acad Sci. 1993; 695:232–5. [PubMed: 8239288]
84. Walker ML. Menopause in female rhesus monkeys. American Journal of Primatology. 1995; 35:59–71.
85. Walker ML, Herndon JG. Menopause in nonhuman primates? Biol Reprod. 2008; 79:398–406. [PubMed: 18495681]
86. Correia SC, Santos RX, Cardoso S, Carvalho C, Santos MS, Oliveira CR, Moreira PI. Effects of estrogen in the brain: is it a neuroprotective agent in Alzheimer's disease? Curr Aging Sci. 2010; 3:113–26. [PubMed: 20167003]
87. Simpkins JW, Yi KD, Yang SH, Dykens JA. Mitochondrial mechanisms of estrogen neuroprotection. Biochim Biophys Acta. 2010; 1800:1113–20. [PubMed: 19931595]
88. Heilbroner PL, Kemper TL. The cytoarchitectonic distribution of senile plaques in three aged monkeys. Acta Neuropathol. 1990; 81:60–5. [PubMed: 1707575]
89. Mufson EJ, Benzing WC, Cole GM, Wang H, Emerich DF, Sladek JR Jr, Morrison JH, Kordower JH. Apolipoprotein E-immunoreactivity in aged rhesus monkey cortex: colocalization with amyloid plaques. Neurobiol Aging. 1994; 15:621–7. [PubMed: 7824054]
90. Thal DR, Capetillo-Zarate E, Del Tredici K, Braak H. The development of amyloid beta protein deposits in the aged brain. Sci Aging Knowledge Environ. 2006:re1. [PubMed: 16525193]
91. Poduri A, Gearing M, Rebeck GW, Mirra SS, Tigges J, Hyman BT. Apolipoprotein E4 and beta amyloid in senile plaques and cerebral blood vessels of aged rhesus monkeys. Am J Pathol. 1994; 144:1183–7. [PubMed: 8203459]

92. Cork LC, Masters C, Beyreuther K, Price DL. Development of senile plaques. Relationships of neuronal abnormalities and amyloid deposits. Am J Pathol. 1990; 137:1383–92. [PubMed: 1701963]

93. Nakamura S, Nakayama H, Goto N, Ono F, Sakakibara I, Yoshikawa Y. Histopathological studies of senile plaques and cerebral amyloidosis in cynomolgus monkeys. J Med Primatol. 1998; 27:244–52. [PubMed: 9926980]

94. Uno H, Alsum PB, Dong S, Richardson R, Zimbric ML, Thieme CS, Houser WD. Cerebral amyloid angiopathy and plaques, and visceral amyloidosis in aged macaques. Neurobiol Aging. 1996; 17:275–81. [PubMed: 8744409]

95. Nakamura S, Kiatipattanasakul W, Nakayama H, Ono F, Sakakibara I, Yoshikawa Y, Goto N, Doi K. Immunohistochemical characteristics of the constituents of senile plaques and amyloid angiopathy in aged cynomolgus monkeys. J Med Primatol. 1996; 25:294–300. [PubMed: 8906609]

96. Oikawa N, Kimura N, Yanagisawa K. Alzheimer-type tau pathology in advanced aged nonhuman primate brains harboring substantial amyloid deposition. Brain Res. 2010; 1315:137–49. [PubMed: 20004650]

97. Warzok RW, Kessler C, Apel G, Schwarz A, Egensperger R, Schreiber D, Herbst EW, Wolf E, Walther R, Walker LC. Apolipoprotein E4 promotes incipient Alzheimer pathology in the elderly. Alzheimer Dis Assoc Disord. 1998; 12:33–9. [PubMed: 9539408]

98. Walker LC, Pahnke J, Madauss M, Vogelgesang S, Pahnke A, Herbst EW, Stausske D, Walther R, Kessler C, Warzok RW. Apolipoprotein E4 promotes the early deposition of Abeta42 and then Abeta40 in the elderly. Acta Neuropathol. 2000; 100:36–42. [PubMed: 10912918]

99. Lemere CA, Beierschmitt A, Iglesias M, Spooner ET, Bloom JK, Leverone JF, Zheng JB, Seabrook TJ, Louard D, Li D, Selkoe DJ, Palmour RM, Ervin FR. Alzheimer's disease abeta vaccine reduces central nervous system abeta levels in a non-human primate, the Caribbean vervet. Am J Pathol. 2004; 165:283–97. [PubMed: 15215183]

100. Nakamura S, Okabayashi S, Ageyama N, Koie H, Sankai T, Ono F, Fujimoto K, Terao K. Transthyretin amyloidosis and two other aging-related amyloidoses in an aged vervet monkey. Vet Pathol. 2008; 45:67–72. [PubMed: 18192580]

101. Nakamura S, Tamaoka A, Sawamura N, Shoji S, Nakayama H, Ono F, Sakakibara I, Yoshikawa Y, Mori H, Goto N, et al. Carboxyl end-specific monoclonal antibodies to amyloid beta protein (A beta) subtypes (A beta 40 and A beta 42(43)) differentiate A beta in senile plaques and amyloid angiopathy in brains of aged cynomolgus monkeys. Neurosci Lett. 1995; 201:151–4. [PubMed: 8848240]

102. Schultz C, Dehghani F, Hubbard GB, Thal DR, Struckhoff G, Braak E, Braak H. Filamentous tau pathology in nerve cells, astrocytes, and oligodendrocytes of aged baboons. J Neuropathol Exp Neurol. 2000; 59:39–52. [PubMed: 10744034]

103. Nelson PT, Stefansson K, Gulcher J, Saper CB. Molecular evolution of tau protein: implications for Alzheimer's disease. J Neurochem. 1996; 67:1622–32. [PubMed: 8858947]

104. Hartig W, Klein C, Brauer K, Schuppel KF, Arendt T, Bruckner G, Bigl V. Abnormally phosphorylated protein tau in the cortex of aged individuals of various mammalian orders. Acta Neuropathol. 2000; 100:305–12. [PubMed: 10965801]

105. Schultz C, Hubbard GB, Rub U, Braak E, Braak H. Age-related progression of tau pathology in brains of baboons. Neurobiol Aging. 2000; 21:905–12. [PubMed: 11124441]

106. Braak H, Braak E, Bohl J, Bratzke H. Evolution of Alzheimer's disease related cortical lesions. J Neural Transm Suppl. 1998; 54:97–106. [PubMed: 9850918]

107. Belleville S, Sylvain-Roy S, de Boysson C, Menard MC. Characterizing the memory changes in persons with mild cognitive impairment. Prog Brain Res. 2008; 169:365–75. [PubMed: 18394487]

108. Presty SK, Bachevalier J, Walker LC, Struble RG, Price DL, Mishkin M, Cork LC. Age differences in recognition memory of the rhesus monkey (Macaca mulatta). Neurobiol Aging. 1987; 8:435–40. [PubMed: 3683724]

109. Moss MB, Rosene DL, Peters A. Effects of aging on visual recognition memory in the rhesus monkey. Neurobiol Aging. 1988; 9:495–502. [PubMed: 3062461]

110. Sloane JA, Pietropaolo MF, Rosene DL, Moss MB, Peters A, Kemper T, Abraham CR. Lack of correlation between plaque burden and cognition in the aged monkey. Acta Neuropathol. 1997; 94:471–8. [PubMed: 9386780]
111. Herndon JG, Moss MB, Rosene DL, Killiany RJ. Patterns of cognitive decline in aged rhesus monkeys. Behav Brain Res. 1997; 87:25–34. [PubMed: 9331471]
112. Jones B, Mishkin M. Limbic lesions and the problem of stimulus--reinforcement associations. Experimental Neurology. 1972; 36:362–77. [PubMed: 4626489]
113. Rapp PR, Amaral DG. Evidence for task-dependent memory dysfunction in the aged monkey. J Neurosci. 1989; 9:3568–76. [PubMed: 2795141]
114. Bachevalier J, Landis LS, Walker LC, Brickson M, Mishkin M, Price DL, Cork LC. Aged monkeys exhibit behavioral deficits indicative of widespread cerebral dysfunction. Neurobiol Aging. 1991; 12:99–111. [PubMed: 2052134]
115. Lai ZC, Moss MB, Killiany RJ, Rosene DL, Herndon JG. Executive system dysfunction in the aged monkey: spatial and object reversal learning. Neurobiol Aging. 1995; 16:947–54. [PubMed: 8622786]
116. Moore TL, Killiany RJ, Herndon JG, Rosene DL, Moss MB. Impairment in abstraction and set shifting in aged rhesus monkeys. Neurobiol Aging. 2003; 24:125–34. [PubMed: 12493558]
117. Moore TL, Killiany RJ, Herndon JG, Rosene DL, Moss MB. Executive system dysfunction occurs as early as middle-age in the rhesus monkey. Neurobiol Aging. 2006; 27:1484–93. [PubMed: 16183172]
118. Braak H, Braak E. Diagnostic criteria for neuropathologic assessment of Alzheimer's disease. Neurobiol Aging. 1997; 18:S85–8. [PubMed: 9330992]
119. Walker ML, Anderson DC, Herndon JG, Walker LC. Ovarian aging in squirrel monkeys (Saimiri sciureus). Reproduction. 2009; 138:793–9. [PubMed: 19656956]
120. Levy E, Amorim A, Frangione B, Walker LC. beta-Amyloidprecursor protein gene in squirrel monkeys with cerebral amyloid angiopathy. Neurobiol Aging. 1995; 16:805–8. [PubMed: 8532114]
121. Williams, L. Aging Cebidae. Karger: Basel; 2008.
122. Walker LC, Masters C, Beyreuther K, Price DL. Amyloid in the brains of aged squirrel monkeys. Acta Neuropathol. 1990; 80:381–7. [PubMed: 2239150]
123. Walker LC, Kitt CA, Schwam E, Buckwald B, Garcia F, Sepinwall J, Price DL. Senile plaques in aged squirrel monkeys. Neurobiol Aging. 1987; 8:291–6. [PubMed: 3306432]
124. Elfenbein HA, Rosen RF, Stephens SL, Switzer RC, Smith Y, Pare J, Mehta PD, Warzok R, Walker LC. Cerebral beta-amyloid angiopathy in aged squirrel monkeys. Histol Histopathol. 2007; 22:155–67. [PubMed: 17149688]
125. Chambers JK, Kuribayashi H, Ikeda S, Une Y. Distribution of neprilysin and deposit patterns of Abeta subtypes in the brains of aged squirrel monkeys (Saimiri sciureus). Amyloid. 2010; 17:75–82. [PubMed: 20462366]
126. Sawamura N, Tamaoka A, Shoji S, Koo EH, Walker LC, Mori H. Characterization of amyloid beta protein species in cerebral amyloid angiopathy of a squirrel monkey byimmunocytochemistry and enzyme-linked immunosorbent assay. Brain Res. 1997; 764:225–9. [PubMed: 9295214]
127. Maclean CJ, Baker HF, Ridley RM, Mori H. Naturally occurring and experimentally induced beta-amyloid deposits in the brains of marmosets (Callithrix jacchus). J Neural Transm. 2000; 107:799–814. [PubMed: 11005545]
128. Geula C, Nagykery N, 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. [PubMed: 11837747]
129. Lemere CA, Oh J, Stanish HA, Peng Y, Pepivani I, Fagan AM, Yamaguchi H, Westmoreland SV, Mansfield KG. Cerebral amyloid-beta protein accumulation with aging in cotton-top tamarins: a model of early Alzheimer's disease? Rejuvenation Res. 2008; 11:321–32. [PubMed: 18341428]
130. Walker LC. Animal models of cerebral beta-amyloid angiopathy. Brain Res Brain Res Rev. 1997; 25:70–84. [PubMed: 9370051]

131. Levy E, Carman MD, Fernandez-Madrid IJ, Power MD, Lieberburg I, van Duinen SG, Bots GT, Luyendijk W, Frangione B. Mutation of the Alzheimer's disease amyloid gene in hereditary cerebral hemorrhage, Dutch type. Science. 1990; 248:1124–6. [PubMed: 2111584]

132. Bell RD, Zlokovic BV. Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. Acta Neuropathol. 2009; 118:103–13. [PubMed: 19319544]

133. Morelli L, Wei L, Amorim A, McDermid J, Abee CR, Frangione B, Walker LC, Levy E. Cerebrovascular amyloidosis in squirrel monkeys and rhesus monkeys: apolipoprotein E genotype. FEBS Lett. 1996; 379:132–4. [PubMed: 8635577]

134. Wei LH, Walker LC, Levy E. Cystatin C. Icelandic-like mutation inan animal model of cerebrovascular beta-amyloidosis. Stroke. 1996; 27:2080–5. [PubMed: 8898820]

135. Graffagnino C, Herbstreith MH, Schmechel DE, Levy E, Roses AD, Alberts MJ. Cystatin C mutation in an elderly man with sporadic amyloid angiopathy and intracerebral hemorrhage. Stroke. 1995; 26:2190–3. [PubMed: 7482672]

136. Palazzi X, Switzer R, George C. Natural occurrence of amyloid-Abeta deposits in the brain of young common marmosets (Callithrix jacchus): a morphological and immunohistochemical evaluation. Vet Pathol. 2006; 43:777–9. [PubMed: 16966460]

137. Lyons DM, Yang C, Eliez S, Reiss AL, Schatzberg AF. Cognitive correlates of white matter growth and stress hormones in female squirrel monkey adults. J Neurosci. 2004; 24:3655–62. [PubMed: 15071114]

138. Bartus RT, Dean RL, Beer B. Memory deficits in aged cebus monkeys and facilitation with central cholinomimetics. Neurobiology of Aging. 1980; 1:145–152.

139. Bons N, Rieger F, Prudhomme D, Fisher A, Krause KH. Microcebus murinus: a useful primate model for human cerebral aging and Alzheimer's disease? Genes Brain Behav. 2006; 5:120–30. [PubMed: 16507003]

140. Silhol S, Calenda A, Jallageas V, Mestre-Frances N, Bellis M, Bons N. beta-Amyloid protein precursor in Microcebus murinus: genotyping and brain localization. Neurobiol Dis. 1996; 3:169–82. [PubMed: 8980017]

141. Bons N, Jallageas V, Silhol S, Mestre-Frances N, Petter A, Delacourte A. Immunocytochemical characterization of Tau proteins during cerebral aging of the lemurian primate Microcebus murinus. C R Acad Sci III. 1995; 318:77–83. [PubMed: 7757807]

142. Bons N, Mestre N, Petter A. Senile plaques and neurofibrillary changes in the brain of an aged lemurian primate, Microcebus murinus. Neurobiol Aging. 1992; 13:99–105. [PubMed: 1542387]

143. Bons N, Mestre N, Ritchie K, Petter A, Podlisny M, Selkoe D. Identification of amyloid beta protein in the brain of the small, short-lived lemurian primate Microcebus murinus. Neurobiol Aging. 1994; 15:215–20. [PubMed: 7838294]

144. Dhenain M, Michot JL, Privat N, Picq JL, Boller F, Duyckaerts C, Volk A. MRI description of cerebral atrophy in mouse lemur primates. Neurobiol Aging. 2000; 21:81–8. [PubMed: 10794852]

145. Mestre-Frances N, Keller E, Calenda A, Barelli H, Checler F, Bons N. 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. [PubMed: 10671318]

146. Kraska A, Dorieux O, Picq JL, Petit F, Bourrin E, Chenu E, Volk A, Perret M, Hantraye P, Mestre-Frances N, Aujard F, Dhenain M. Age-associated cerebral atrophy in mouse lemur primates. Neurobiol Aging. 2009

147. Picq JL. Aging affects executive functions and memory in mouse lemur primates. Exp Gerontol. 2007; 42:223–32. [PubMed: 17084573]

148. Picq JL, Aujard F, Volk A, Dhenain M. Age-related cerebral atrophy in nonhuman primates predicts cognitive impairments. Neurobiol Aging. 2010

149. Palop JJ, Mucke L. Amyloid-beta-induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. Nat Neurosci. 2010; 13:812–8. [PubMed: 20581818]

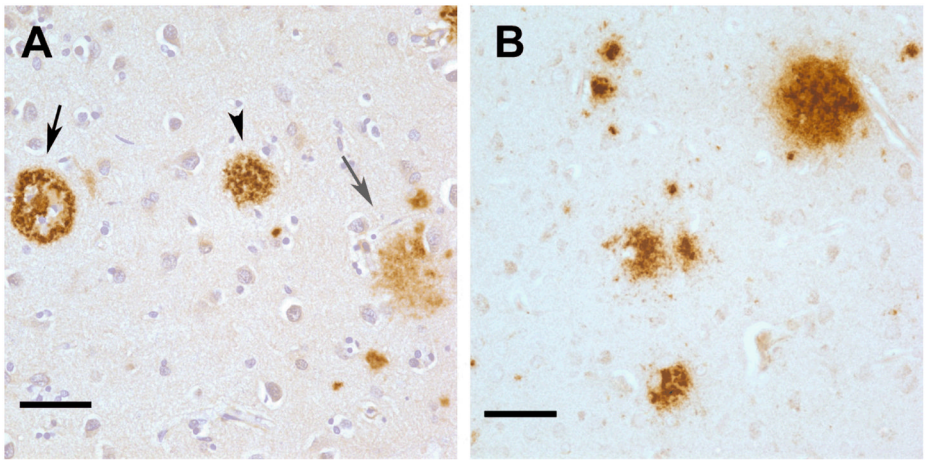

Figure 1.
Senile plaques in a human with AD (**A**) and in a 35 year old female rhesus macaque (**B**). (**A**) Dense core plaque (black arrow); 'primitive' plaque (arrowhead); diffuse plaque (gray arrow). Antibody 6E10 specific amino acids 1–17 of Aβ. Bars = 50μm.

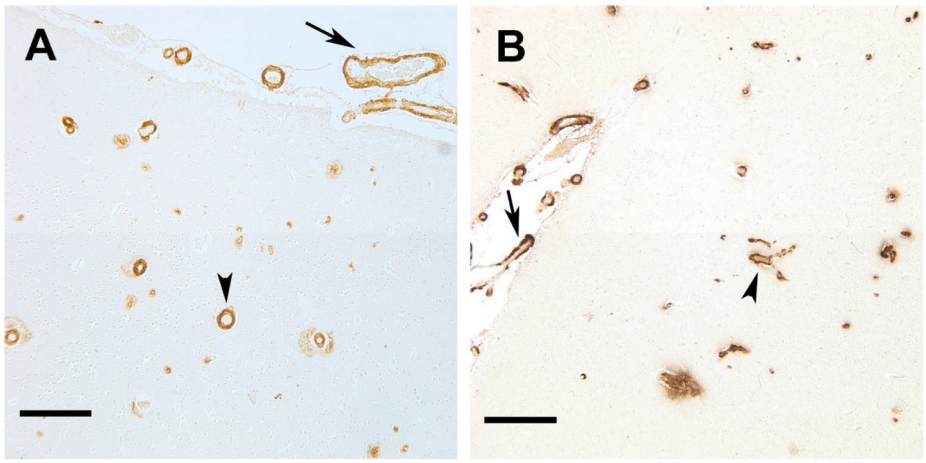

Figure 2.

Cerebral β-amyloid angiopathy immunostained with antibodies to Aβ in a human AD patient (**A**) and in a 27-year old female squirrel monkey (**B**). Superficial vessels are indicated by arrows, and parenchymal vessels by arrowheads. Antibody 10D5 specific to residues 3–6 of Aβ (A) and β/A4 specific to Aβ phosphorylated at threonine 743. (B), courtesy of Dale Schenk and Colin Masters, respectively. Bars = 50μm.

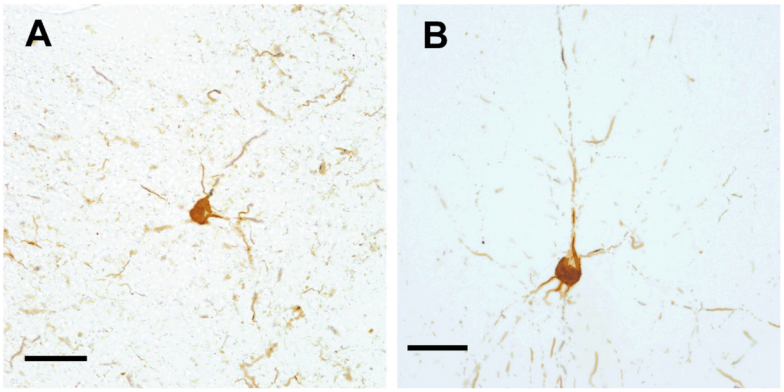

Figure 3.

Cortical neurons immunoreactive for abnormally phosphorylated tau in a human patient with AD (**A**) and in a 41 year-old female Chimpanzee (**B**). Note also the neuropil 'threads' surrounding the somata. Antibody AT8 specific for Tau doubly phosphorylated at Ser202/ Thr205. Bars = 50μm.

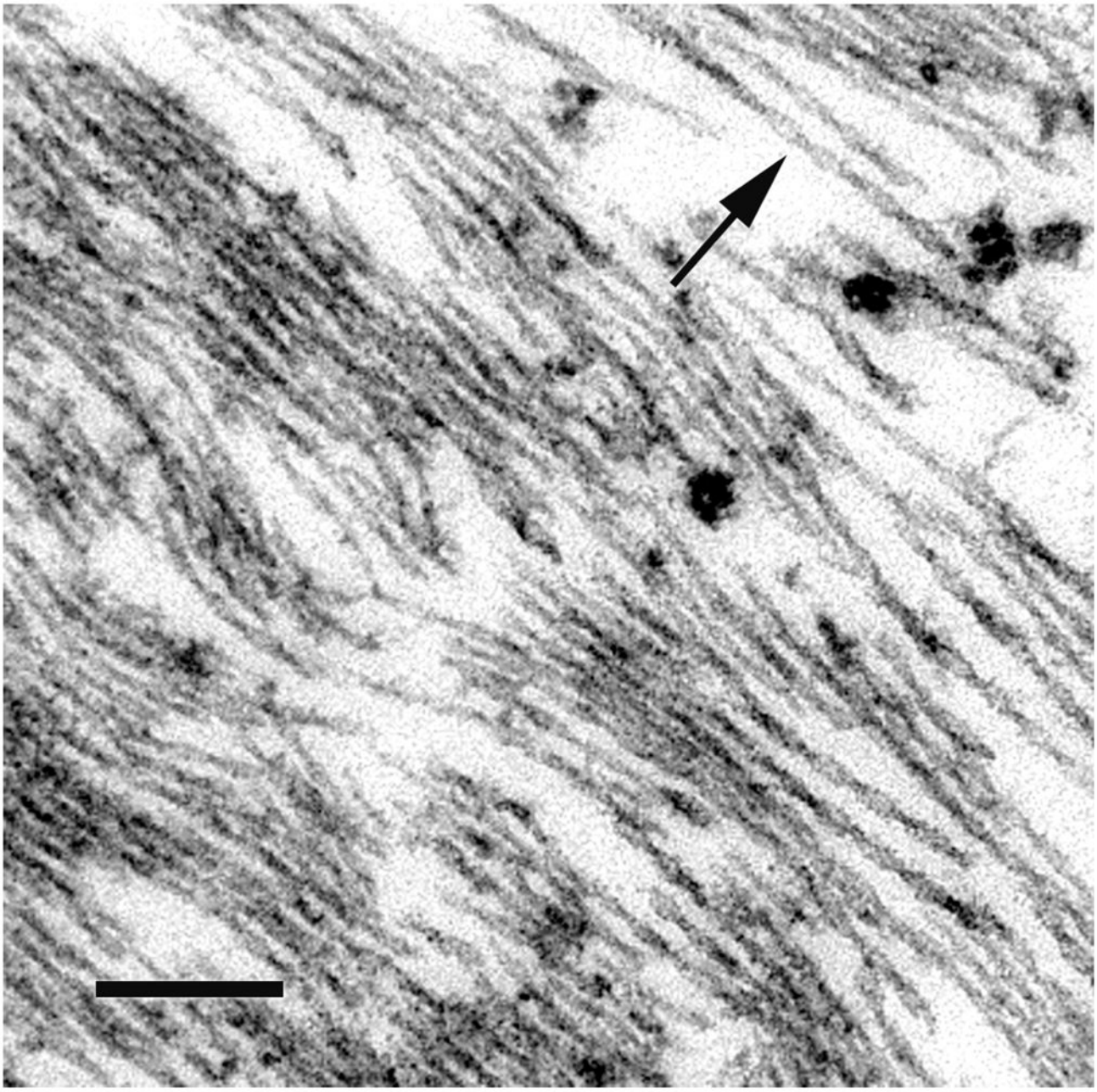

Figure 4.
Ultrastructure of a neurofibrillary tangle in a cortical neuron from a 41-year old female chimpanzee. The paired helical filaments (arrow marks an isolated PHF) are identical in size and periodicity to those in humans with AD. Bar = 200nm.

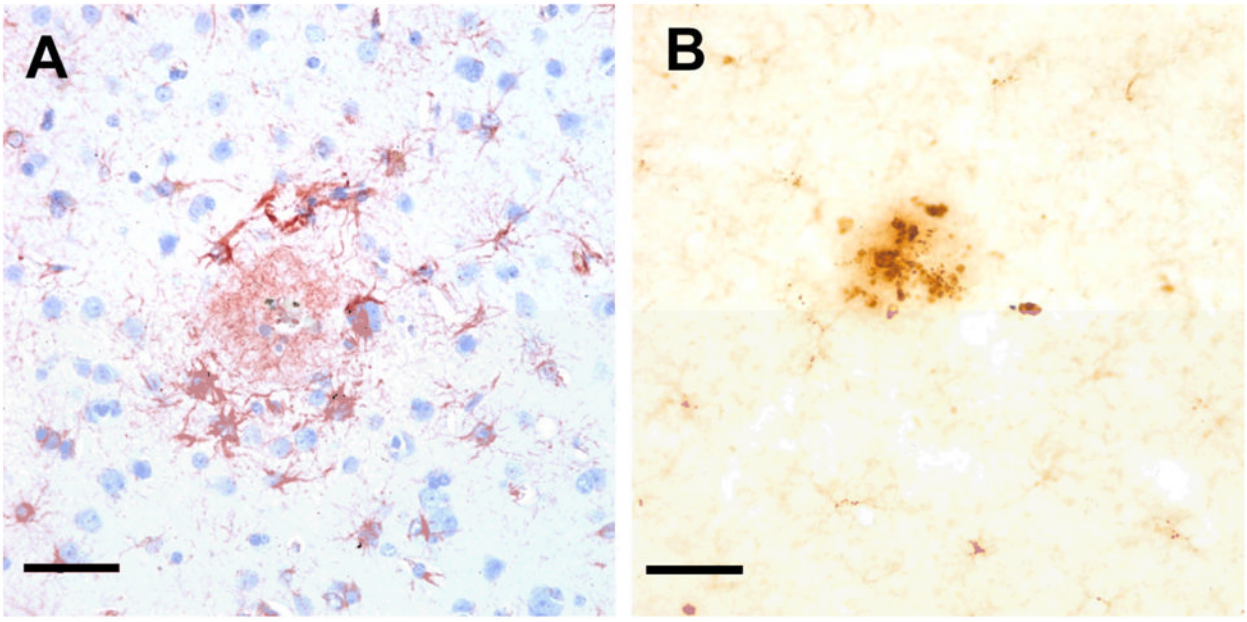

Figure 5.

Reactive gliosis associated with senile plaques in aged rhesus monkeys. **A**) Activated astrocytes (red) surrounding a cortical senile plaque in a 34 year old male rhesus monkey (antibody to GFAP). **B**) Activated microglia (brown) in a cortical senile plaque (antibody to CD68 epitope PG-M1, which is specific for macrophages and microglia) of a 30 year old male rhesus monkey. Note that microglia tend to be spatially more centrally located; note also the relatively quiescent glia more distant from the plaques. Bars = 50μm.

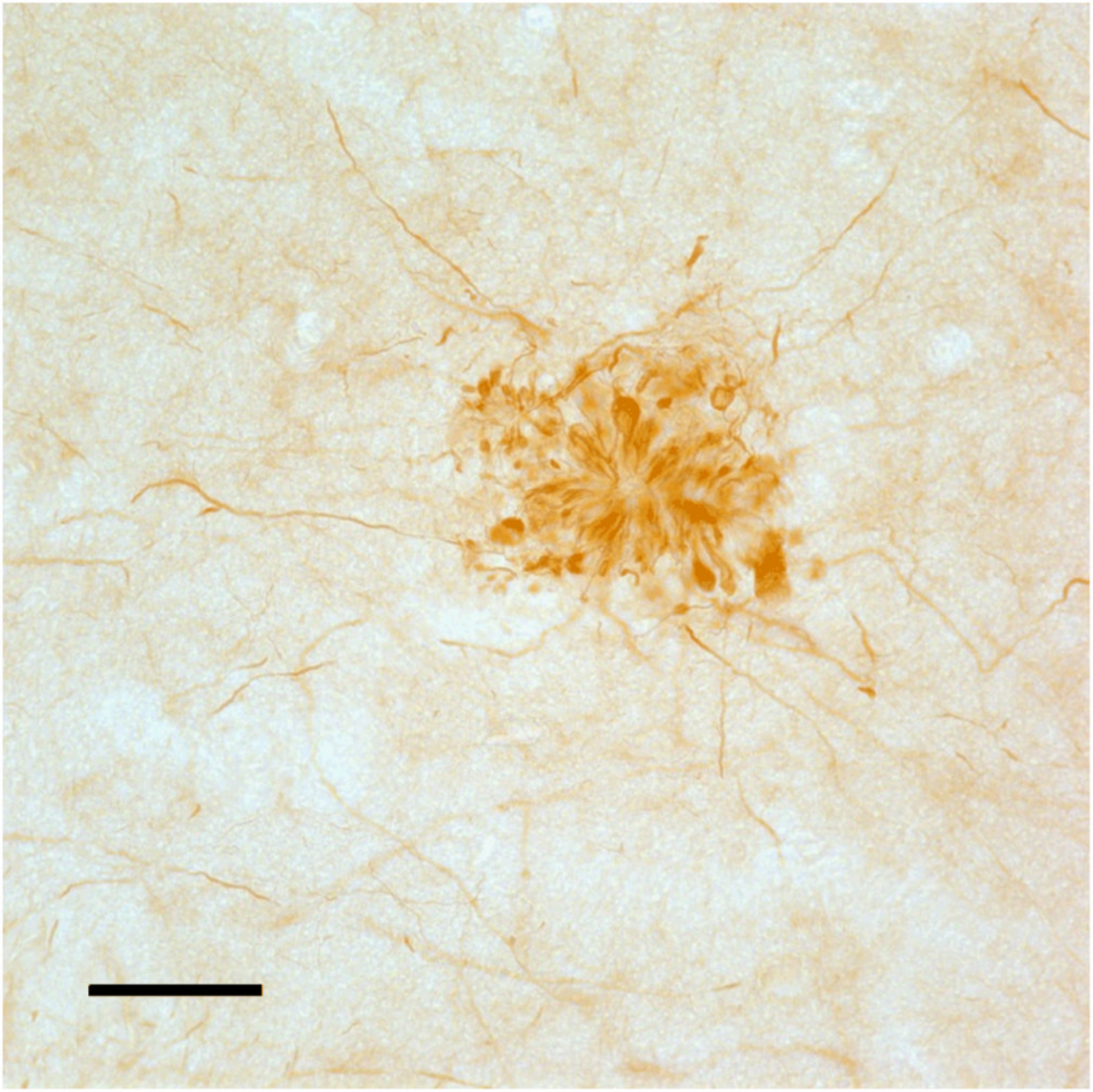

Figure 6.
Abnormally distended neurites in a senile plaque from the hippocampal formation of a ~30 year old male rhesus monkey. Note the normal-appearing neuronal processes distal to the plaque. Antibody 6–17 to phosphorylated neurofilaments recognizes NF-H in axons. Bar = 50μm.

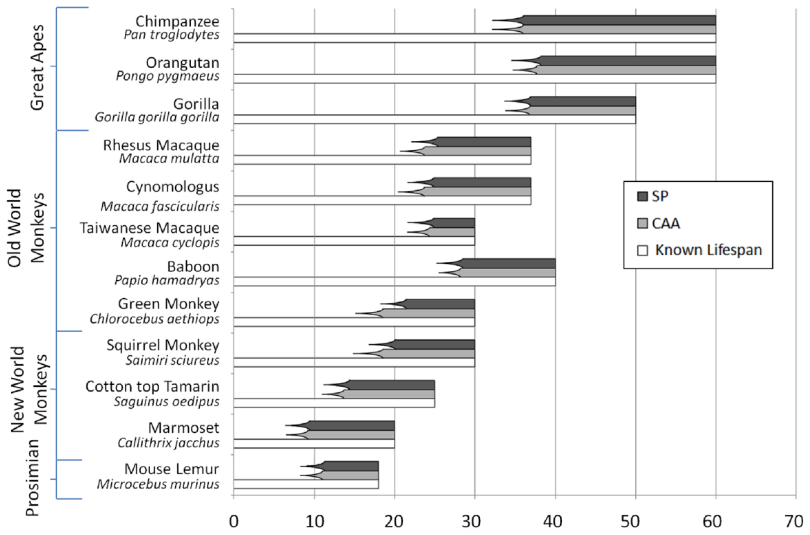

Figure 7.

Maximum known lifespans and approximate ages at which Aβ deposition is present [Senile Plaques (SP), and Cerebral Amyloid Angiopathy (CAA)] in some representative nonhuman primate species. Note that there is variability in age of lesion onset (indicated by the hatched bars) among members of the same species. Some estimates are approximate, due to the relatively small numbers of aged animals studied.