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Nonhuman primates at the intersection of aging biology, chronic disease, and health: An introduction to the American Journal of Primatology Special Issue on aging, cognitive decline, and neuropathology in nonhuman primates

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Abstract

Aging across the Primate Order is poorly understood because ages of individuals are often unknown, there is a dearth of aged animals available for study, and because aging is best characterized by longitudinal studies which are difficult to carry out in long-lived species. The human population is aging rapidly, and advanced age is a primary risk factor for several chronic diseases and conditions that impact healthspan. As lifespan has increased, diseases and disorders of the central nervous system (CNS) have become more prevalent, and Alzheimer's disease and related dementias have become epidemic. Non-human primate (NHP) models are key to understanding the aging primate CNS. This Special Issue presents a review of current knowledge about NHP CNS aging across the Primate Order. Similarities and differences to human aging, and their implications for the validity of NHP models of aging are considered. Topics include aging-related brain structure and function, neuropathologies, cognitive performance, social behavior and social network characteristics, and physical, sensory, and motor function. Challenges to primate CNS aging research are discussed. Together, this collection of articles demonstrates the value

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

of studying aging in a breadth of NHP models to advance our understanding of human and nonhuman primate aging and healthspan.

Keywords

aging; Alzheimer's disease; cognitive decline; gait speed; nonhuman primate

1 | INTRODUCTION

The human population is aging. By 2050, the United Nations Department of Economic and Social Affairs predicts that 1 in 6 people will be over the age of 65 (United Nations, 2019). Aging is accompanied by a suite of physiologic changes, not all of which are detrimental to health. However, advancing age represents a key risk factor for several chronic diseases and conditions, including neurodegenerative disorders such as Alzheimer's disease (AD) (Hou et al, 2019). The purpose of this Special Issue is to present a review of current knowledge about nonhuman primate (NHP) aging, with a focus on the central nervous system (CNS), and to examine similarities and differences to human aging and their implications for the validity of NHP models of human aging. This Special Issue examines aging-related changes across the Primate Order, from prosimians to hominids, in multiple domains including cognitive performance, brain structure and function, neuropathologies, social behavior and social network characteristics, and physical, sensory, and motor function.

1.1 | Animal models

Animal models of human health are important for several reasons. Human studies enroll individuals that vary in many ways that can affect outcome variables, and many of these variables cannot be controlled or accounted for in statistical analyses. For example, differences in social status in humans are accompanied by disparities in education, health care, living conditions, access to food, clean water, and green spaces, all confounding factors that are known to affect a myriad of health outcomes. Long-term clinical trials also suffer from selection bias (Abdelnour et al, 2020) or cohort effects (Dodge et al, 2014), reducing the reproducibility of results. In contrast to human studies, captive animals can be housed under controlled conditions in which light/dark cycles, diet composition, water availability, physical and social characteristics of housing, and health care are uniform across all individuals in a study. Studies of free-ranging animals may provide opportunities to study age-related processes independent of the effects of modern sociocultural practices. Longer term human studies also rely largely on self-report of characteristics that may impact health outcomes such as diet, use of alcohol or other drugs, or exposure to psychological stressors. The accuracy of self-report of many of these variables has been shown to be poor. Such variables can either be excluded, controlled or accurately measured in animal studies. Further, many outcomes cannot be directly measured in humans for logistic or ethical reasons; in these cases, studies rely on indirect measures of biomarkers, which less accurately reflect experimental effects. For all of these reasons determination of causal relationships relies on animal models (Verdier et al, 2015).

1.2 | Nonhuman primate models of aging

NHPs have played a critical role in medical science and health because of their close phylogenetic relatedness and similarity to humans in structure and function of multiple systems (Phillips et al., 2014). NHPs are useful models for investigations involving the reproductive system, bioenergetics, diet, obesity, diabetes, cardiovascular health, the musculoskeletal system, CNS structure and function, cognitive and social behavior, and diseases of aging. Studies on prospective (birth-to-death) NHP wild populations have provided unique opportunities to assess variables which drive maturation, rates of aging, and lifespan (Bjork et al., 2019; Campos et al., 2021; Sapolsky & Altmann, 1991; Snyder-Mackler et al., 2020). NHPs also have been critical models to understand women's health, in particular the role sex hormones in disease susceptibility and resistance (Shively & Clarkson, 2009). NHP research was instrumental in stemming the rate and impact of HIV infection (Friedman et al., 2017; Veazey & Lackner, 2017), and NHPs provided the foundation for the rapid development of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines (Lu et al., 2020). The Office of Research Infrastructure Programs of the National Institutes of Health (ORIP, NIH) listed well over 150 coronavirus SARS-CoV-2 studies and reviews using NHPs just 9 months after the COVID-19 epidemic was first identified (https://orip.nih.gov/Nonhuman-primate-models).

NHPs are particularly valuable to understanding human aging because they appear to age like humans (Verdier et al., 2015). Humans experience a relatively long, slow degradation of motor, sensory, and cognitive function and accumulate chronic diseases of aging such as sarcopenia, arthritis, hypertension, chronic kidney disease, diabetes, cardiovascular disease, and AD (Jaul & Barron, 2017). This is due in part to the aging of a population supported by good health care and nutrition (Chetty et al., 2016; Hao et al., 2020). However, with advancing age has come an increase in aging-related diseases. A primary goal of geroscience is to understand how aging enables diseases and use that knowledge to slow the rate and progression of disease and disability, thus extending the healthspan (Olshansky, 2018; Seals et al., 2016; Sierra, 2016). NHPs also experience aging-related declines in sensory, motor, and cognitive function, and social interaction (Verdier et al., 2015), accumulate many similar disabilities and diseases with age, and thus may be used to understand the basic biology of aging and how aging enables disease (Mattison & Vaughan, 2017).

This Special Issue explores aging in detail in seven NHP species. Table 1 presents approximate developmental time points and approximate lifespan parameters drawn from captive data for these NHP species, and these are graphically compared in Figure 1. Table 1 also shows that all seven NHP species naturally develop neuropathology similar to two major types found in human neurodegenerative disorders: β-amyloid (Aβ) and tau-related pathologies. Likewise, Table 1 identifies the NHP species in which Aβ and tau-pathologies have been experimentally induced to manipulate and study disease progression, a valuable approach that is not possible in human participants. Freire-Cobo et al. (2021) in this issue provides a comprehensive review of age-related brain changes in NHPs and details on exact neuropathological findings, beyond the seven species summarized here.

1.3 | Alzheimer's disease

Neurocognitive decline, and AD and related dementias (ADRD) have become epidemic in the US and around the world causing a public health crisis. Ninety-five percent of cases are diagnosed after 65 years of age, and are referred to as late-onset AD. AD is the sixth leading cause of death, and the only one in the top 10 with no known treatment or cure ("2020 Alzheimer's Disease Facts and Figures," 2020). AD also is one of the most expensive disease in the world, costing societies trillions of dollars in the forms of direct medical, social, and informal care (Wimo et al., 2017). In the US alone, over five million adults have AD, and that figure is expected to grow to 13.8 million by 2050 ("2020 Alzheimer's Disease Facts and Figures," 2020). Moreover, AD disproportionately affects women and people of color; two-thirds of cases are women, and Hispanics and African-Americans have 1.5 and 2 times higher rates of AD than do the rest of the population, respectively (https://www.cdc.gov/aging/aginginfo/pdfs/Module1-Alzheimers-Disease-Public-Health-Crisis.pdf).

Longitudinal studies of cognitive function, neuroimaging (positron emission tomography [PET] and magnetic resonance imaging [MRI], and cerebrospinal fluid (CSF) biomarkers have characterized a long preclinical phase of accumulating pathophysiology that precedes the onset of clinical AD symptoms by 1–2 decades (Sperling et al., 2011; Vermunt et al., 2019) (Figure 2). The course of disease is characterized by early (β-amyloid (Aβ) accumulation in the precuneus and other cortical regions, followed by neuroinflammation indicated by microglia and astrocyte activation (PET) (Jack et al., 2019); (Gordon et al., 2016; Gordon et al., 2018). Cortical hypometabolism manifests after Aβ accumulation, indicating the onset of synaptic dysfunction (fluorodeoxyglucose PET) (Mosconi et al., 2008). Synaptic dysfunction gives way to tau phosphorylation, detected via changes in the CSF (Karikari et al., 2020), neurofibrillary tangle tau pathology (PET), hippocampal atrophy (structural MRI), and finally cognitive impairment (Bateman et al., 2012; T. Fagan et al., 2006; Gordon et al., 2016); (A. M. Fagan et al., 2007; A. M. Fagan et al., 2014; Gordon et al., 2018; Hanseeuw et al., 2019; Jack & Holtzman, 2013; Long & Holtzman, 2019; Morris et al., 2009; Vos et al., 2013).

The accumulation of Aβ results in extracellular amyloid plaque deposition which impairs intercellular communication (Hughes et al., 2020). Amyloid may also be deposited in the cerebrovasculature resulting in cerebral amyloid angiopathy (Greenberg et al., 2020). The ensuing vascular dysfunction reduces perivascular amyloid clearance, thereby promoting amyloid deposition in the brain (Greenberg et al., 2020). The lack of clearance of amyloid is thought to promote tau phosphorylation, and accumulation of these pathological tau proteins disrupts intracellular function, and results in intracellular neurofibrillary tangles that interrupt processes associated with intracellular transport (Long & Holtzman, 2019). Thus, the available data strongly support the central role of pathologic Aβ accumulation in mediating AD pathogenesis and that aggregated, hyperphosphorylated forms of tau may be a primary driver of neurodegeneration and cognitive decline (Hanseeuw et al., 2019; Long & Holtzman, 2019).

The earliest cognitive changes typically include impairments in learning, memory, attention, and executive function (Guarino et al., 2019, 2020; Kirova et al., 2015; McKhann et al., 2011). Impairments in hearing, vision, olfaction, physical function, and sleep may precede

or accompany cognitive decline (Brzecka et al., 2018; Bubu et al., 2017; Chen et al., 2016; Ju et al., 2013; Lim et al., 2013; Lloret et al., 2020; Murphy, 2019; Spira et al., 2012, 2014; Vanderheyden et al., 2018). Importantly, heterogeneity is characteristic of the underlying neuropathology and clinical presentation. AD overlaps clinical presentation and neuropathology with a number of other dementias which together are considered ADRD (https://www.ninds.nih.gov/Current-Research/Focus-Disorders/Alzheimers-Related-Dementias).

Given the long preclinical period and heterogeneous presentation of pathologies, and role(s) of comorbidities, the study of AD etiology faces considerable challenges. Moreover, by the time of diagnosis, neuropathology is extensive, defying intervention (Long & Holtzman, 2019). While late-onset AD may have a heritable component (Gispert et al., 2017), risk factors amenable to modification have been identified and include many of the most common chronic diseases and disorders of aging mentioned above, as well as lifestyle factors (Askarova et al., 2020; Edwards et al., 2019). Notably, many of these are also cardiovascular risk factors including obesity, hypertension, diabetes, hypercholesterolemia, depression, psychological stress, social isolation, physical inactivity, and poor nutrition (Serrano-Pozo & Growdon, 2019).

1.4 | Aging-related neurocognitive decline and neuropathology in NHP models

NHPs have been valuable models for the study of most of these known risk factors for AD (Phillips et al., 2014). The current understanding of the basic biology of AD is largely dependent on rodent models, however, to date, the translation of novel therapeutics from rodent to humans has had little success (Drummond & Wisniewski, 2017). Rodents and humans diverged much earlier than humans and NHPs, and this may have led to fundamental differences in their aging processes (Messaoudi & Ingram, 2012). NHPs are particularly valuable to understanding aging effects on the CNS because of their long lifespan, and similarity to humans in the accrual of decrements in sensory, motor, social and cognitive function (Mattison & Vaughan, 2017). Unlike the rodent brain, many aging-related gene expression changes in the brain are conserved from NHPs to humans (Loerch et al., 2008). Thus, NHPs may fill the gap between rodent models and humans (Verdier et al., 2015).

Several NHP species develop aging-related neuropathologies that are reminiscent of preclinical and early changes observed in human AD (see (Bateman et al., 2012; Long & Holtzman, 2019; Sperling et al., 2011) for reviews). Table 1 summarizes naturally occurring age-related and induced neuropathologies of the species that are the focus of articles in this special issue, and a broader overview of NHP neuropathology is provided by Freire-Cobo et al. (2021). Taken together, these data demonstrate that several aging NHPs naturally display human AD-like amyloid plaques and aggregated hyperphosphorylated tau protein, but a relative lack of tangles.

1.4.1 | Induced models—The use of induced NHP models of AD complements studies of naturally occurring NHP models, thereby advancing our mechanistic understanding of the transitions from normal aging to AD. For example, induced cynomolgus macaque

(*Macaca fascicularis*) models, in which Aβ oligomers were injected directly into the brain, re-capitulated several signatures of human AD, including Aβ accumulation, tau hyperphosphorylation, microglial and astrocyte activation, cognitive impairment, and the formation of neurofibrillary tangles (Forny-Germano et al., 2014). Recent work in rhesus macaques (*M. mulatto*) supports these findings, showing that Aβ injection leads to dendritic spine loss reminiscent of normal aging, induces neuroinflammation, and increases AD biomarkers (Beckman et al., 2019b). Induced models of tau propagation (Beckman et al., 2021) may be critically important given that NHPs do not appear to develop the extensive neurofibrillary tangles due to tauopathies characteristic of human AD. Taken together with the ongoing work in naturally occurring NHP models of aging and NHPs, studies using induced models will support the development of therapeutic interventions to slow or even reverse AD progression.

1.5 | Current limitations of NHP models of aging and AD

There is a need to better understand CNS aging and factors that influence it across the primate Order. The following limit the understanding of aging in NHPs: (1) Currently, the field lacks critical data regarding the physiologic changes that accompany normal aging for many species of NHPs. These data are necessary to distinguish healthy from pathologic aging phenotypes. (2) There is limited availability of aged animals. Relatively long lifespans (compared to rodents) as well as the costs associated with maintaining aged populations of NHPs in captivity are primary factors contributing to the low availability of age-appropriate subjects (NIH, 2018). In addition, high demands for a particular species (e.g., rhesus monkeys for vaccine testing, marmosets for neuroscience studies), and lack of commercially available resources severely restrict the numbers of animals available for aging studies (Servick, 2018). Within the populations of NHPs that are available for study, the sex ratios of older-aged animals often are skewed. This situation arises because husbandry practices may aim to recapitulate the normal social structures of wild animals, in which there is a low male: female ratio. Thus, the availability of older-aged male monkeys is limited for many species of interest to aging and AD. Finally, due to the NIH chimpanzee breeding moratorium, retirement of NIH-owned animals to sanctuaries, and restrictions on the type of research that can be conducted, the population of chimpanzees available for aging research has been drastically reduced (Collins, 2015). (3) It is difficult to establish stable long-term funding for long-lived animals. While efforts to increase the availability of aged NHPs are currently underway (e.g., “Brain Initiative” NIH), many funding mechanisms are less than five years, and multiple successful renewals are necessary to reach natural end of life. As such, ongoing longitudinal studies of NHP aging may end prematurely due to financial constraints. These challenges emphasize the need for increased support for long-term studies of aging NHP cohorts.

1.6 | Contributions of the articles in this Special Issue

Within the comparative perspective of this Special Issue, the authors have addressed various aspects of the aging phenotype in well-characterized and emerging NHP models, ranging from prosimians to hominids, including: gray mouse lemurs (Chaudron et al. 2021), common marmosets (Rothwell et al., 2021), vervet/African green monkeys (Frye et al, 2021), three macaque species: rhesus (Arnsten et al, 2021; Beckman & Morrison, 2021;

Upright & Baxter, 2021), cynomolgus (Darusman et al, 2021), and Barbary (Rathke & Fischer, 2021); and chimpanzees (Mulholland et al, 2021). Four main themes emerge from this collection.

One theme highlights the diversity of NHP models suitable for aging research. The review by Chaudron et al. (2021) provides a detailed description of the aging phenotype in a well-characterized prosimian, the gray mouse lemur. The authors review the cognitive and psychomotor changes that develop with age in this species and summarize age-related cerebral, metabolic and cellular alterations that correlate with cognitive decline. They also discuss the effectiveness of nutritional interventions such as caloric restriction and diet supplementation in affecting aging trajectories in this species. Similarly, Frye et al. (2021) provide a comprehensive characterization of the aging phenotype in vervet/African green monkeys. Their review emphasizes the many similarities between humans and vervets in age-related decline in cognitive, physical, metabolic, and cerebral function. Rothwell et al. (2021) comment on the crucial importance of longitudinal assessments for understanding neurocognitive aging and discuss the value of the common marmoset, an NHP with a relatively short lifespan, to assess age-related change in cognition, behavior, and brain function. They point out that the heterogeneity of cognitive profiles identified in aging marmosets provides an opportunity to capture trajectories of healthy versus pathological aging and to identify predictors of cognitive decline. While the papers above highlight the advantages and limitations of NHP models of natural AD pathology, Beckman & Morrison (2021) underline the usefulness of an induced model of early AD, based on cerebral injection of Aβ soluble oligomers. Their paper summarizes the suite of neural alterations observed in Aβ-treated female rhesus monkeys and argue for the development of this model for a better understanding of sex-specific manifestations of AD.

The second theme of this volume addresses one aspect of aging that has received little attention until recently, social aging. Rathke & Fischer (2021) use social network analysis to assess age-related differences in social activity in semi-free barbary macaques. Interestingly, age-related reductions in social effort were found, and social aging was independent of sex. This work provides much needed comparative insights into patterns typifying social aging in both male and female primates.

The third theme highlighted in the Special Issue is brain aging and AD neuropathology. Based on cytoarchitectonie and structural similarities between the human and macaque prefrontal cortex, Upright & Baxter (2021) emphasize the value of cross-species comparisons and review the prefrontal-dependent cognitive changes observed in healthy aging in the rhesus monkey. Also focusing on healthy aging, Mulholland et al. (2021) illustrate how neuroimaging and cognitive data can be used in concert to characterize neurocognitive aging. Using Volumetric Based Morphometry in chimpanzees who were cognitively characterized, they show that successful agers have greater gray matter volume in many brain regions compared to apes who underperform for their age, and that these differences concern regions that typically decline with age. Frye et al. (2021) also provide evidence that vervet monkeys recapitulate many of the features of early AD pathophysiology. Finally, the review by Freire-Cobo et al. (2021) offers a much-needed

inventory of the age-related cellular changes that occur with normal and pathological aging across primate species.

The last theme of this volume focuses on potential mechanisms for age-related cognitive decline. Focusing on molecular mechanisms, Darusman et al. (2021) use qPCR to examine the expression of 6 APP-pathway related genes in blood samples from cognitively impaired versus unimpaired cynomolgus macaques. One gene (*GAPDPH*) involved in amyloidogenesis was upregulated in cognitively impaired monkeys versus control monkeys and correlated with the magnitude of cognitive impairment, providing a potential target for treatment. Based on extensive data collected in rhesus monkeys and other primate comparisons, Arnsten et al. (2021) propose that dysregulation of calcium signaling due to aging or inflammation is a key factor in initiating tau pathology. Framing this hypothesis in an evolutionary framework, the authors argue that the expansion of association cortices in the course of primate evolution led to an increase in synapses critical to calcium signaling, making the brain of humans and closely related species more vulnerable to calcium toxicity and tau pathology. This compelling hypothesis may lead to identifying key cortical circuits for early intervention.

2 | CONCLUSION

This Special Issue provides a comprehensive description of phenotypes that accompany aging in several species of NHPs that are valuable models for advancing our understanding of human aging. In addition to providing important comparative insights across the Primate Order, this body of work delivers important translational lessons about aging trajectories that may culminate in chronic diseases, including neurodegenerative disorders, such as Alzheimer's disease. Characterizing these patterns of aging in primates will promote understanding of the degree to which aging is malleable and identification of interventions that extend healthspan.

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DATA AVAILABILITY STATEMENT

This is an Introduction and thus exempt. Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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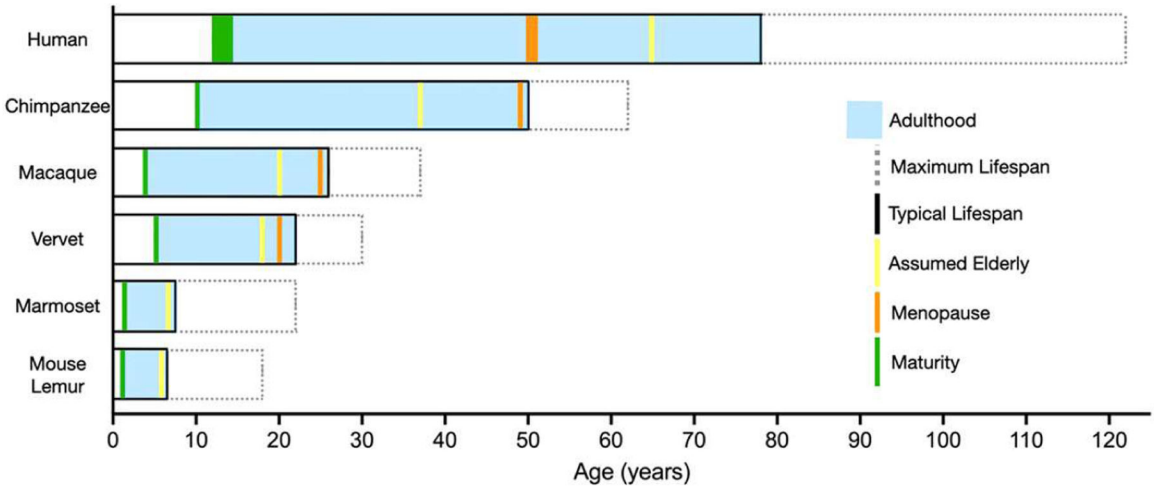

FIGURE 1.

Comparison of major developmental time points and approximate lifespan in species discussed in this Special Issue, drawn from captive NHP data. Definitions: (1) Maturity. Age of known sexual maturity or first successful conception; (2) Adulthood. Span between maturity and end of lifespan; (3) Assumed Elderly. Ages used to categorize old-age; (4) Menopause. Age at cessation of menstrual cycling for females; (5) Typical Lifespan. Typical age at death for captive individuals in this species, drawn from life expectancy and mean or median lifespan values; (6) Maximum Lifespan. Oldest documented age for an individual of this species. Reference values are drawn from Table 1. Vervet: aka African green monkey

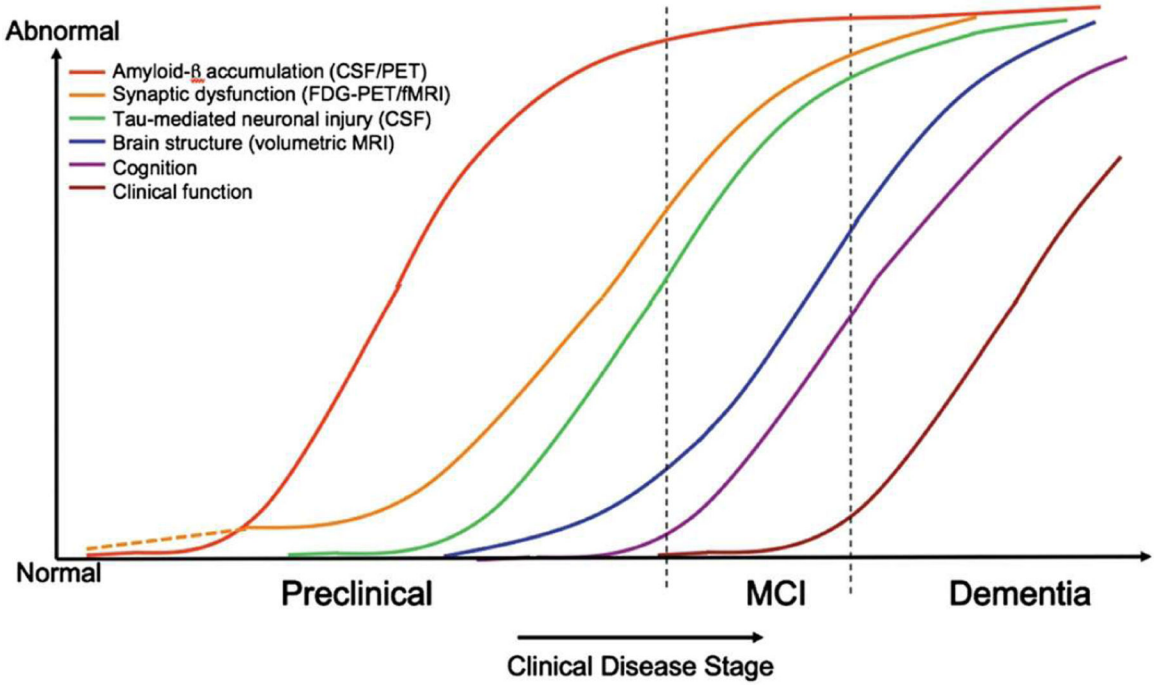

FIGURE 2.

Hypothetical model of accumulating late-onset Alzheimer's disease (AD) pathophysiology, including Aβ deposition, synaptic dysfunction, tauopathy-associated neuronal injury, volumetric reductions, and cognitive and functional declines. Dashed lines indicate that synaptic dysfunction may be detectable before Aβ accumulation in carriers of the ε4 allele of the apolipoprotein E. Figure is reprinted with permission from Sperling et al., 2011

TABLE 1

Approximate developmental milestones and neuropathology of nonhuman primates across the Primate Order

Species *(Scientific Name)*	Adult Weight (kg)	Age of maturity (years)	Lifespan (years)		Age (years) of menopause	Age assumed elderly (years)	Neuropathology	
			Typical	Maximum			Natural[a]	Induced
Gray mouse lemur *(Microcebus murinus)*	0.06–0.12[b]	1[c]	5–8[**d,e,f]	18[f]	Absent[d]	6[b]	Aβ, Tau	Aβ[g], Tau[g]
Common marmoset *(Callithrix jacchus)*	0.25–0.60[i]	1–1.5[h]	5–8[*,i]	22[f,j]	Absent[k]	7–8[k]	Aβ, Tau	Aβ[l,m,n]
Vervet/African green monkey *(Chlorocebus aethiops sabaeus)*	3–9[o]	4–6[p,q]	22[*o]	30[q,r]	20[p]	16–18[s,t]	Aβ, Tau	Not studied
Macaque species								
Rhesus macaque *(Macaco mulatto)*	5–10[u,v]	3–5[u,v]	25–27[*,w,x]	44[y]	25[z]	20[x]	Aβ, Tau	Aβ[aa], Tau[bb]
Cynomolgus macaque *(M. fascicularis)*	3–8[cc]	3_5[dd, ee]	25–30[**,ee]	37[g]	29[ff]	20[gg]	Aβ, Tau	Aβ[hh]
Barbary macaque *(M. sylvanus)*	8–18[ii]	4–5[jj]	25[kk]	29[f,jj]	25[jj]	20[kk]	Aβ, Tau	Not studied
Chimpanzee *(Pan troglodytes)*	35–60[ll]	10[mm]	35–50[**,nn]	62[oo]	50[oo]	37[pp]	Aβ, Tau	Not studied
Human *(Homo sapiens)*	60–80[qq]	12–16[rr]	yg[***,SS]	122[tt]	50–53[uu]	65[vv]	Aβ, Tau	Not studied

Note:

[*] Approximate median lifespan;

[**] Approximate mean lifespan;

[***] Life expectancy. Absent: does not exist; not studied: no published reports.

References:

[a] (Freire-Cobo et al., 2021),

[b] (Languille et al., 2012),

[c] (Chaudron, Pifferi, & Aujard, 2021),

[d] (Perret, 1997),

[e] (Hämäläinen et al., 2014),

[f] (Weigl, 2005),

[g](Gary et al., 2019),

[h](Abbott & Hearn, 1978),

[i](Ross, 2019),

[j](Nishijima et al., 2012; Weigl, 2005),

[k](Abbott et al., 2003),

[l](Maclean et al., 2000),

[m](Philippens et al., 2016),

[n](Ridley et al., 2006),

[o](Jorgensen, 2021) & Jorgensen pers. comm.,

[p](Atkins et al., 2014),

[q](Schmitt et al., 2018),

[r](Cramer et al., 2018),

[s](Kavanagh et al., 2019)

[t](Frye et al., 2021),

[u](van Wagenen, 1952),

[v](Plant, 2005),

[w](Tigges, Gordon, McClure, Hall, & Peters, 1988),

[x](Upright & Baxter, 2021),

[y](Stonebarger et al., 2020),

[z](Walker, 1995),

[aa](Beckman et al., 2019a),

[bb](Beckman et al., 2021),

[cc](Fa, 1989),

[dd](Luetjens & Weinbauer, 2012),

[ee](Van Esch et al., 2008),

[ff](Kavanagh et al., 2005),

[gg](Darusman et al., 2014),

[hh](Fomy-Germano et al., 2014),

[ii](Fooden, 2007),

[jj](Paul, Kuester, & Podzuweit, 1993; Weigl, 2005),

[kk](Rathke & Fischer, 2021),

[ll](Leigh & Shea, 1995),

[mm](Muller et al., 2020),

[nn](Dyke et al., 1995),

[oo](Lacreuse et al., 2008),

[pp](Hopkins et al., 2020),

[qq](Walpole et al., 2012),

[rr](Hochberg & Konner, 2020),

[ss](Arias et al., 2020),

[tt](Robine & Allard, 1999),

[uu](Gold, 2011),

[vv](Shoven, 2007).

Abbreviation: Aβ, amyloid-beta.