

Nonhuman Primate Models of Cognitive Aging

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Abstract Nonhuman primates are indispensable for the study of aging processes. Like other animals, they permit us to observe the effects of age in the absence of the confounds inherent in studies of human beings. Additionally, because they are phylogenetically close to humans and possess certain uniquely primate morphological, endocrine, behavioral, and cognitive traits, they can provide data uniquely relevant to human aging. Among nonhuman primates, the rhesus monkey is by far the most widely studied in the context of aging, as verified in the large number of reviews that have summarized the studies on this species. To date, however, there is no published overview of the many other species of nonhuman primates in which age-related changes have been studied. This chapter is intended to fill that gap. Thus, we discuss results from a wide variety of prosimian, monkey, and ape species, ranging from the mouse lemur to the great apes. We include species about which a great deal is known as well as those, such as the gorilla and chimpanzee, on which only one or two studies have been conducted. For each species or group of species, we describe what is known about age-related changes in cognition, in the brain, and in patterns of reproductive senescence. We conclude that, although studies on the rhesus monkeys have provided the greatest depth of knowledge about cognitive aging processes, the many other primate species, with their wide variety of reproductive, morphological, and behavioral adaptations, can shed new light on the factors underlying age-related cognitive changes in our own species.

Keywords Brain aging • cognition • memory • estrogen • menopause

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Introduction

Preventing or slowing age-related cognitive decline remains one of the greatest challenges of our times. As this chapter is being written, people over 65 years make up about 13% of the US population. In this group, approximately 13% are estimated to suffer from mild to severe memory impairment, a percentage that increases to 32% in the 85+ population. The proportion of aged persons is expected to increase in the years ahead, with old people making up as much as 20% of the population in the 2050 projections and cognitive impairment reaching 16% of the 65+ group and 67% of the 85+ group (Federal Interagency Forum on Aging-Related Statistics. Older Americans Update 2006: Key Indicators of Well-Being). As our population ages, the undesirable effects, both societal and personal, of age-related decline in cognitive function can be expected to increase as well.

Thus, there is a pressing need to develop strategies aimed at promoting cognitive health in the later years of life. Animal models in which cognitive aging can be studied without confounds inherent in human studies are indispensable to accomplish this goal. As can be gleaned from several chapters of this book, a great deal of our knowledge concerning the mechanisms of cognitive and brain aging has been provided by rodent studies. Because of their phylogenetic proximity to humans, however, nonhuman primates offer some advantages over other species as models for human age-related cognitive decline.

In principle, species phylogenetically closest to humans, in particular the genus *Pan*, with which we shared a common ancestor about 6 million years ago, constitute the most relevant models for human cognitive aging. Yet, practical considerations have led to the selection of more distantly related primate species as primary models. Thus, species of the genus *Macaca*, with which we shared a common ancestor about 25 million years ago, have provided the bulk of the data concerning cognitive and brain aging in nonhuman primates. An overview of these findings will be presented in the first section of this chapter. The use of macaque species as models, however, presents a number of drawbacks. Alternative nonhuman primate models are being explored in an effort to circumvent some of these problems and/or to focus on one aspect of cognitive aging for which a particular species might be well suited.

Among these alternative models, a few medium- and small-sized (<500 g) primate species, which exhibit some features of human cognitive and brain senescence, have great potential. The advantages and disadvantages of using such primate models will be discussed in subsequent sections. Finally, the last part of this chapter presents findings related to cognitive aging in the great apes. We will argue that the comparison of cognitive and brain aging in apes and humans should elucidate unique characteristics of the aging phenotype of the human, and provide insight into the origins of human-specific neurodegenerative diseases such as Alzheimer's disease (AD).

Throughout this chapter, we will emphasize what can be gained from species with distinct life histories and adaptations. In addition, we will highlight one aspect of cognitive aging that has received intense scrutiny in recent decades concerning

possible interactions between age-related changes in the endocrine milieu and changes in cognitive functioning. In particular, the animal and human literature strongly suggest that sex and adrenal steroids are key modulators of cognitive and brain aging. Research on nonhuman primate models should help to elucidate the mechanisms by which these hormones influence age-related cognitive change. Thus, when possible, we will present data that reveal the effects of gonadal and adrenal steroids on patterns of cognitive and brain aging in each species of interest.

The Aged Macaque as a Model for Human Cognitive Aging

The macaque model of human cognitive aging has been described in many review articles (1–10). In this section, we provide a brief overview of the findings relevant to human cognitive aging, before focusing on some of the endocrine factors that modulate cognitive and brain aging in macaque species.

Cognitive Aging

Studies investigating cognitive aging in the genus *Macaca* have primarily used the species *Macaca mulatta* (rhesus monkey), to a lesser extent *M. fascicularis* (cynomolgus monkey), and more rarely *M. fuscata* (Japanese macaque; e.g. (11, 12)), *M. nemestrina* (pig-tailed macaque; e.g. (13)), and *M. radiata* (bonnet macaque; (14, 15)). Since the rhesus monkey is by far the most prominently used model for studying human cognitive aging, most of the data reported here concern this species.

Rhesus monkeys weigh from 5 to 10 kg in adulthood and have a life span that is about one third of that of humans. Their adult life extends from 4 to 40 years, with very few individuals surviving past 30 years (16). On this basis, monkeys over the age of 20 are generally considered aged, monkeys between 15 and 19 as middle-aged, and monkeys younger than 15 as young adults. One advantage of nonhuman primates like macaques is that they can be tested in settings and tasks that are very similar to those given to humans. One apparatus that has been used for several decades as a main tool to probe a variety of cognitive domains in monkeys is the Wisconsin General Testing Apparatus (WGTA; (17)), which allows the presentation of three-dimensional objects and their delayed recognition. In more recent years, computerized systems with either a joystick or touch screen allowing enhanced flexibility of stimuli presentation have also been developed. Using either the WGTA or computerized systems, several research groups have found striking similarities between the aging phenotype of macaques and humans, with most aged monkeys showing impairments in visual recognition memory, spatial memory, executive function, and attention (1–3, 6–8, 18–23). As in humans, some of these deficits develop during middle age, with impairments in spatial memory (21) and executive function (24) being the earliest cognitive domains affected. These cognitive deficits are not uniform, however, as some individuals demonstrate little cognitive impairment, while others are severely affected (21). One of

the challenges of cognitive aging research is to elucidate the neurobiological and physiological bases for these differences.

Changes in Brain Anatomy and Function

Rhesus monkeys do not develop AD, and, therefore, provide a model in which aging can be studied in the absence of concomitant age-related dementing illnesses. The recently completed sequence of the *M. mulatta* genome may help identify the molecular bases for the differential vulnerability to neuropathology in humans and other primates. Indeed, a unique characteristic of aged human brains is that they accumulate extracellular, aggregated β -amyloid peptide ($A\beta$) in the form of plaques (senile plaques), as well as neurofibrillary tangles, which consist of intracellular fibrils made of aberrantly polymerized, hyperphosphorylated tau, a microtubule protein. $A\beta$ and tau accumulation are greatly increased in AD and are a hallmark of this disease. Interestingly, in contrast to humans, rhesus monkeys do not develop neurofibrillary tangles (25); nor do they show significant declines in brain weight (26) or hippocampal atrophy with aging (27). Such findings suggest that age-related cognitive dysfunction is not dependent upon a shrinking brain and that age-related hippocampal atrophy might reflect pathology rather than normal aging. Indeed, normal aged humans show only small declines in hippocampal volume, while hippocampal regions are severely affected in pathological processes (28). On the other hand, many of the senescent changes that are typical of human aging populations are present in the rhesus monkey (for reviews see (25, 29)), including overall reduction of gray matter volume (30), decline in specific regions such as the striatum (31, 32), amyloid deposition in several brain structures (33, 34), myoinositol elevations suggestive of myelin alterations (35), increased activation of microglia (36), severe axonal pathology (37, 38), loss of cholinergic fibers in the hippocampus (39), alterations of all neurotransmitter systems (40–44), and minimal changes in total neuron numbers in the cerebral cortex (25).

Functional differences have also been noted between young and aged monkeys, such as reduction of presynaptic cholinergic function in the striatum (44), increased dopamine turnover and clearance in the striatum (45), and reduction of resting state cerebral metabolic rate for glucose (46–48) and cerebral blood flow (48) in several brain regions.

These marked structural and functional differences between young and old monkeys suggest possible bases for cognitive impairment, yet relatively few studies have been able to assess the relevance of these age-related brain changes for the development of cognitive impairment. Age-related brain changes that have been reported to correlate with specific cognitive deficits include thinning of layer I in area 46 of the prefrontal cortex and widespread disruption of myelinated axons (49), alterations of white matter integrity connecting frontal regions to other fore-brain regions (50), loss of neurons in specific subcortical regions (51, 52), and reduction of monoamine receptor binding in the prefrontal cortex (43). In contrast,

reduction in hippocampal cholinergic innervation, which has been proposed to play a major role in cognitive decline, was not related to performance on a task dependent on medial temporal structures (39). Similarly, no relationship could be found between amyloid plaque content and cognitive dysfunction in aged macaques (34), supporting the view that concomitant tau pathology is necessary for the development of the cognitive deficits characteristic of AD.

Importantly, most studies with aged monkeys reported large individual variations both at the neurobiological and cognitive levels. The source of this variability is not currently understood, but may be related to factors that have been largely ignored in nonhuman primate aging research, such as biological sex or endocrine influences. New evidence indicates that age-related changes in the endocrine milieu have important consequences for the aged brain. In the following sections, we examine how age-related alteration of sex steroids and adrenal steroids may modulate age-related cognitive decline in primates.

Endocrine Influences on Cognitive and Brain Aging

Gonadal Hormones

The brain is an important target organ for the action of ovarian hormones (53, 54). Estrogen receptors are present in areas crucial for cognition, such as the hippocampus, cortex, and amygdala (in humans (55, 56); in nonhuman primates (57, 58); and in rodents (59)). Estrogens exert a multitude of effects in these regions: they enhance neuronal connectivity in the hippocampus (60), provide neuroprotection against a variety of toxic stimuli (61), modulate all neurotransmitter systems (62–64), and affect brain activity patterns in women (65, 66). Less attention has been given to progestins, but it is clear that they also affect brain regions involved in cognition: progesterone decreases hippocampal dendritic spine density (67), interacts with several neurotransmitter systems (68, 69), and is neuroprotective (70).

Recent studies have reported similar effects of androgens. In both primates (71, 72) and rodents (73), androgen receptor mRNA is found in several brain regions typically not involved in reproduction, including the hippocampus. Testosterone increases spine density in CA1 of the hippocampus in both male and female rats (74, 75), and circulating levels of androgens are necessary for the maintenance of spine density in male nonhuman primates (76, 77). In humans, testosterone treatment has been shown to increase cerebral blood perfusion in hypogonadal aged men (78), and endogenous testosterone levels predict regional cerebral blood flow in regions critical for cognition (79).

Given the dramatic effects of sex steroids on neuronal morphology and brain activity in regions involved in cognition, one might expect age-related changes in the endocrine milieu to have important consequences for cognitive function. Indeed, sex steroids appear to be important modulators of cognitive aging. In women, estrogen deficiency associated with menopause may exacerbate age-related

cognitive decline (80), especially in the domain of verbal memory and verbal fluency; estrogen replacement therapy (ERT) may protect against these verbal deficits (81). ERT may also reduce a woman's risk of AD or delay the onset of the disease (82), perhaps through an inhibition of A β accumulation (83). The rationale for using estrogen as an agent against cognitive decline has been seriously challenged by the findings of the Women Health Initiative and Memory Study (WHIMS), which reported decreased cognitive performance (84) and a higher risk of dementia (85) in women over 65 years using a combination of Conjugated Equine Estrogen (CEE) and Medroxy Progesterone Acetate (MPA) for 5 years. However, caution must be taken when interpreting these results: The particular hormonal regimen used, the limited range of cognitive function assessed, and the characteristics of the population tested may explain this negative outcome (86–90). Given these limitations in the human studies conducted thus far, a final verdict on possible beneficial effects of estrogen treatment on cognition in aging women will have to await more exhaustive studies of combinations of hormone treatments and schedules. Such studies should first be carried out on nonhuman primates.

In men the steady decline of testosterone levels after 50 years of age (91) is associated with impairments in spatial cognition, spatial memory, and working memory that can be reversed by testosterone supplementation (for reviews see (92–96)). In addition, both cross-sectional (97) and longitudinal studies (98) have revealed positive correlations between bioavailable testosterone levels and cognitive function in older men. Interestingly, testosterone may also reduce the risk of AD in men (99), likely via protection against A β toxicity (100, 101). As in women studies, however, questions concerning the risks and benefits of testosterone treatment and its efficacy on different systems have been raised, and the Institute of Medicine recommended that future studies on testosterone treatment be limited to hypogonadal men (Liverman & Blazer, 2004). Studies on nonhuman primates will be needed to overcome some of these limitations.

Because of their similarity to humans in terms of reproductive endocrinology and cognitive ability, macaques are excellent models to study the effects of sex steroids on cognitive aging. Young female rhesus monkeys have a 28-day menstrual cycle that is almost identical to that of women (102), and aged females undergo menopause, although relatively late in life (~25 years old) compared to women (103, 104). Ovarian senescence (105) and reproductive hormone profiles of female rhesus monkeys during pre-, peri-, and postmenopause (106) are equivalent to those of women at the same stages. In males, patterns of androgen secretion resemble those of men (107), but it remains unclear whether aged rhesus monkeys experience a decline in serum testosterone levels with age, as occurs in humans (108). Several studies found differences in patterns of pulsatile testosterone secretion between young and old animals, but failed to find age differences in serum testosterone levels (109–111). In contrast, a recent study reported reduced testosterone levels in old versus young male rhesus monkeys (112). If confirmed, such a decrease in testosterone levels could account for the sex difference in age-related decline in rhesus monkeys performing a spatial working memory task, the spatial Delayed Recognition Span Test (DRST) (113). The study revealed that while young males

outperformed young females, the sex difference was no longer present among old individuals, apparently due to a greater decline in performance in aged males than in aged females. The low performance of aged males could be directly related to declining testosterone levels; studies are underway to test the validity of this hypothesis.

To our knowledge, the effects of androgen deficiency and replacement on cognition have not been investigated in nonhuman primates. Indeed, only a few studies have examined the activational effects of gonadal hormones on cognition in adult nonhuman primates and all have focused on the effects of estrogens in females. We and others have found that some aspects of learning and memory in aged female macaques are sensitive to estrogen deficiency after natural (114) or surgical menopause (115) and to estrogen treatment ((116–118) see for reviews (6, 119)). The effects appear to be task-specific and sensitive to the duration of estrogen deprivation prior to estrogen replacement. For example, in the delayed response (DR) task, a classic test of prefrontal function, performance was impaired in postmenopausal compared to age-matched premenopausal rhesus monkeys (114), suggesting that estrogen depletion associated with menopause was detrimental to prefrontal function. Congruent with this hypothesis, estradiol-replaced aged monkeys that had been ovariectomized for 7 months performed better than age-matched controls (118). In contrast, DR performance was *not* influenced by estradiol treatment in another study with aged monkeys that had been deprived of estrogens for a much longer period (about 12 years; (116)). Notwithstanding experimental differences among studies, this pattern of results supports the idea that the timing of estrogen replacement is crucial for estrogens to benefit cognitive function (120–122). However, our data suggest that “the window of opportunity hypothesis” may not apply to all cognitive domains studied. Indeed, while estradiol treatment had no influence on the DR in these long-term ovariectomized monkeys, it enhanced, in the same individuals, performance on the spatial-DRST, a task dependent on medial temporal lobe function (116).

A crucial question concerns the mechanisms by which estrogens may exert their influence on the aged primate brain. Recent neuromorphological studies indicate that, unlike the aged rat brain (123), the aged primate brain retains the plasticity of the young brain in its response to estradiol in regions important for cognitive processing, including the prefrontal cortex (124), the hippocampus (125), and the basal forebrain (126). Hormone-induced changes in dendritic spines have been largely assumed to underlie associated changes in cognition, yet evidence for such a relationship remains merely correlational (124, 127). Moreover, the increase in dendritic spine numbers in the young primate brain following estradiol treatment is not necessarily accompanied by changes in cognition (119). This suggests that the young brain may undergo a range of neuromorphological changes without measurable changes in cognitive processes, while similar changes in the aged brain may systematically affect cognition. Another important question is whether brain plasticity is maintained after a long period of estrogen deprivation. Based on our results in aged long-term ovariectomized monkeys, we predict that medial temporal regions retain their plasticity even

years after estrogen deprivation, but that plasticity in the frontal cortex may be timed to a temporal window that remains to be identified.

Adrenal Hormones

In addition to gonadal hormones, adrenal hormones such as glucocorticoids and dehydroepiandrosterone and its sulfate DHEA(S) have been implicated in the maintenance of cognitive function during aging. Indeed, cortisol levels increase linearly with aging in men and women (*128*) and there is a substantial decrease of DHEA(S) plasma levels with aging in both sexes (*129, 130*). In addition, glucocorticoids have been shown to play a crucial role in age-related hippocampal atrophy (*131–135*). For example, in elderly people, prolonged exposure to elevated glucocorticoid levels resulted in hippocampally dependent memory deficits and a 14% reduction in hippocampal volume (*131, 132*).

The role of DHEA(S) is less clear, with most studies failing to find a relationship between DHEA(S) and cognitive impairment (for reviews see (*136, 137*)). Nevertheless, DHEA(S) may have beneficial effects on well-being, mood (*128, 138–140*), and major depression (*139, 141*).

Although basal levels of cortisol do not appear to be significantly different between young and aged macaques, the hypothalamic-pituitary-adrenal (HPA) system of aged animals shows a relative resistance to the suppressing effects of glucocorticoids via negative feedback (*142–144*). However, the hypothesis that chronic exposure to glucocorticoid levels results in hippocampal damage was not supported when tested in aged macaques: Leverenz et al. (1999) (*145*) failed to find a change in hippocampal volume or neuron numbers in pigtail macaques treated daily for 12 months with high levels of oral cortisol, in the absence of stress. These findings suggest that other factors related to stress could account for changes in hippocampal neuronal integrity. Elevated plasma cortisol has been associated with anxious temperament in macaques (*146*), but there is no published report on the effects of glucocorticoids on cognition in macaques.

Studies in the rhesus monkey have found marked reduction in DHEA(S) in old compared to young monkeys, similar to findings in humans (*142, 146–149*). As in human studies, no relationship was found between endogenous DHEAS levels and cognitive impairment in the rhesus monkey (*146*).

Advantages and Drawbacks

Although macaques have proven to be very useful to further our understanding of age-related decline in brain function, the use of these species as models for human aging presents a number of drawbacks (*10, 150, 151*). One of these is the great expense associated with acquisition and maintenance of macaques in the laboratory. Health issues pose another problem, as special precautions must be followed

when working with a species that is a Herpes B virus carrier (152). Also, the limited availability of old macaques makes future aging research with macaques particularly challenging. For example, access to naturally menopausal monkeys is seriously impeded by the short post-reproductive life of the female macaque, which in turn makes the study of the effect of menopause on cognition very difficult. As a result, premenopausal ovariectomized monkeys serve as the primary models for human menopause (6, 119, 153). As it is becoming increasingly clear that the effects of estrogen on cognition differ in young and aged animals (119), the value of young ovariectomized monkeys as models for menopause is questionable. Finally, seasonal cessation of reproductive function in certain species of macaques, such as rhesus monkeys (154), may potentially interfere with endocrine studies. Although efforts are underway to counteract some of these shortcomings (151), researchers might consider alternative primate models of human cognitive aging.

In the next sections, we first examine the potential of other large monkey species as models, before we discuss the usefulness of small-sized primate species (less than 500 g). Great ape species, which have been largely ignored in cognitive aging research, will be reviewed in the final section of this chapter.

Other Medium-Sized Monkey Species

Old World Monkeys

Baboon

Baboon species (genus *Papio*) are well characterized genetically and show over 90% similarities with the human genome (155, 156). Their life span is about 25–30 years in the wild (157). Baboons are of particular interest for cognitive aging research for several reasons. First, they are capable of performing a variety of complex cognitive tasks and can be tested in settings almost identical to those used with humans (158–163). Second, baboons are unique among nonhuman anthropoids in that they exhibit a characteristic age-related increase in amyloid deposition and in neuronal and glial tau pathology (25, 164, 165), which makes them excellent models for age-related human tauopathies. Finally, the reproductive endocrinology of female baboons is very similar to that of women (166), with aged baboons undergoing menopause around 26 years of age (153, 167, 168). If aged female baboons prove to be more readily available than aged female macaques, studies in naturally postmenopausal baboons could be carried out. Less is known about the reproductive endocrinology of male baboons, but nonsignificant increases in luteinizing hormone and decreases in testosterone were noted in male *P. hamadryas* (169). Like humans, baboons undergo age-related changes in adrenal hormones such as cortisol and DHEA (144, 169–171), but the relationship between these changes and age-related cognitive decline has not yet been examined.

The similarities in cognitive processes, brain aging, and physiological parameters between baboons and humans suggest that baboons may be excellent models for human cognitive aging. Thus, it is quite puzzling that aged baboons have not been cognitively characterized. One disadvantage of using baboons is their relatively large size, with adult males of certain species reaching more than 25 kg. Nevertheless, it would be of particular interest to determine whether the unique feature of combined tau pathology and amyloid deposition in the aged baboon brain – reminiscent of human AD pathology – is systematically accompanied by cognitive impairments not observed in other nonhuman primates. In addition, the impact of the age-related endocrine changes on brain function should be examined, in particular in naturally postmenopausal baboons.

Vervet Monkey

The vervet monkey (*Chlorocebus aethiops*) weighs between 3 and 7 kg and has a life span of about 20 years. This species has seldom been used in aging research. However, a recent study (172) has shown that Caribbean vervet monkeys may be useful as model of A β deposition in the brain. It was found that vervets develop cerebral A β plaques with aging that can be significantly reduced by prior immunization with A β peptides. Cognitive assessments are required to determine whether these amyloid plaques deposits are associated with cognitive impairments.

New World Monkeys

Squirrel Monkey

Squirrel monkeys (*Saimiri sciureus*) are relatively small primates weighing about 1 kg in adulthood, with a life span of about 20–30 years in captivity (173). This species serves as a model for human aging in caloric restriction studies (174, 175), but cognitive assessments have yet to be carried out. Neuromorphological studies have investigated amyloid deposition in *Saimiri*, revealing that aged individuals exhibit pronounced A β accumulations (176). However, these accumulations are almost entirely associated with blood vessels, and are reminiscent of cerebral amyloid angiopathy rather than AD. Other studies have investigated motor aging, as there is a significant decline of the nigrostriatal system in this species (177). Only two studies have investigated aspects of cognitive aging in *Saimiri*, as assessed by inhibitory motor control (178). Old females made more errors than young females when reaching into a box the opening of which had been placed in a different orientation from that used during training. Moreover, old adults had greater HPA responses following stress (restraint) and a modest reduction in glucocorticoid feedback sensitivity. Finally, white matter volume in the anterior brain region, as measured by MRI, was larger in old than in young adults and correlated with impaired inhibitory

control. Such findings should encourage further investigations of cognitive aging in *Saimiri* species.

Capuchins

Capuchins (*Cebus* species) are medium-sized monkeys ranging in weight from 2.5 to 5 kg. They are more encephalized than any other monkey species (179–181), and are known for their highly developed manipulative skills, tool usage, and high cognitive abilities (182), which could make them interesting models for human cognitive aging. Indeed, early work of Bartus and collaborators (183–185) employed aged capuchins as models for age-related memory impairment. However, probably due to their long life span of up to 46 years in captivity, capuchins are not currently used as models for human cognitive aging.

What Can Be Gained from Small-Sized Primates?

The usefulness of small primate species (<500 g) as models for human aging has been discussed in depth by Austad (186). These species, although phylogenetically more distant from humans, present important advantages compared to larger primates, as they are generally less costly to maintain and easier to handle. They are usually short-lived (no more than a decade or two), and some species exhibit cognitive behavioral traits that are particularly relevant for human aging. In this section we focus on small primate species relevant to cognitive aging research.

Strepsirrhini

Strepsirrhini are the primate group phylogenetically most distant from humans, having diverged from the rest of the primates about 60 to 70 millions years ago (187). One member of this group, the gray mouse lemur (*Microcebus murinus*), has received particular attention as a potential model for human cognitive aging. *M. murinus* is a small nocturnal and solitary primate whose life span reaches about 12–14 years in captivity. Aged mouse lemurs have been shown to exhibit a decline in working memory (188), spatial memory (189), and executive function (190) that resemble the cognitive deficits seen in other primates. Gray mouse lemurs also show many age-related changes in the brain, including cerebral atrophy, amyloid deposits in several regions of the brain, gliosis, and changes in all neurotransmitter systems (for review see (191)). An additional important feature of this primate is that aging is associated with hyperphosphorylated tau pathologies that have only been observed in humans. Of particular interest, a subgroup of about 20% of aged individuals demonstrates a particularly severe pattern of neuropathology that is

accompanied by aggressiveness, social withdrawal, and inability to perform cognitive tests (191). Such traits are reminiscent of AD and suggest that the gray mouse lemur may be especially useful as a model for the disease (191).

The reproductive endocrinology of gray mouse lemurs is quite different from that of humans, however, possibly limiting their usefulness for understanding the impact of human reproductive senescence on brain function. Gray mouse lemurs are seasonal breeders, and while males show a significant age-related decline in testosterone levels (192), females do not show menopause or fertility loss with advancing age (193). As far as adrenal steroids are concerned, aged males show a decline in DHEA-S after the age of 3 years that accelerates after the age of 6 (194), but it is not known whether females experience a similar decline. Unfortunately, the potential link between these endocrine decreases and age-related cognitive impairment has not been investigated. To our knowledge, age-related changes in cortisol have not been investigated in this primate.

Finally, even though the gray mouse lemur has successfully been used in several cognitive tasks, as described above, the range of cognitive abilities that can be explored in a lemur species may be limited. For example, *M. murinus* was among the species performing the poorest in reversal learning tests, a measure of cognitive flexibility and obtained the lowest scores on an overall measure of cognitive ability in the meta-analysis of (195).

Callitrichidae

Common Marmoset

The common marmoset (*Callithrix jacchus*) is a social and diurnal species that can live up to 12 years in captivity. Marmosets are extensively used in biomedical research because of attractive advantages conferred by their small size, high fertility, and ease of handling. Several studies have demonstrated that the marmoset can perform at a high level on a range of cognitive tasks administered either in the WGTA (196) or in computerized settings (197–199). However, they appear unable to master tasks of visual recognition memory such as the delayed nonmatching to sample (DNMS) (197) and perform poorly on a global measure of cognitive ability (195). Of particular interest for cognitive aging research is the fact that marmosets can be successfully trained for conscious functional neuroimaging studies (200–202). They also may provide a very exciting model for studying the effects of different drugs on the activity of the aged primate brain.

The use of the marmoset as a model for cognitive and brain aging is in its infancy and we know relatively little about age-related changes in brain anatomy in this primate. Several studies have reported amyloid deposits in the brain of aged marmosets (203, 204) and a recent article identified an age-related loss in basal forebrain cholinergic neurons calcium-binding protein (205). It is worth noting that the sequencing of the marmoset genome is underway. The genetic information

provided should help determine the molecular bases for neuropathological processes associated with aging in this primate.

The reproductive endocrinology of the marmoset has been well characterized and differs in many respects from that of other primates (206–209). Callitrichids are the only primates that may ovulate more than one follicle per cycle. An important advantage of marmosets for aging research is their high fertility, with breeding females typically producing dizygotic twins every 6 months. Although there is a decline in ovarian follicles with age, there is no evidence of reproductive senescence or in ovulation rate. Concerning adrenal steroids, there is a diurnal variation in cortisol levels in the marmoset, with higher levels in the morning than in the evening (210), but it is not known whether aged individuals show increases characteristic of human aging. As far as we know, changes in DHEA(S) levels with age have not been investigated in this species.

Cotton-Top Tamarins

Another potentially interesting small-size primate for cognitive aging research is the cotton-top tamarin (*Saguinus oedipus*). It is a diurnal and social primate that lives up to 20 years in captivity. Although cognitive aging data are not available for this species, the cognitive abilities of young cotton-top tamarins have been thoroughly investigated. Despite their small brain, these primates are able to master a range of cognitive tasks from numerosity discrimination (211) to tool competence (212). Like marmosets, they have great potential for future use in functional neuroimaging studies.

In one study (213), female tamarins (*S. oedipus* and *S. fuscicollis*) were found to ovulate up to at least 17 years of age, but females over 17 showed signs of cycling cessation or aberrant cycles, suggesting that reproductive senescence might occur till close to the time of death in these species. However, unlike Old World monkeys and women, old anovulatory females had measurable concentrations of progesterone and estrone. Although several studies have investigated testosterone and cortisol levels in this species (e.g.), they were not studied in the context of aging.

Great Apes

Many of the studies on aging of monkeys and prosimians described above have been motivated by the relative evolutionary proximity of these primates to our species. In contrast, humans' closest relatives, the apes, have been largely neglected in studies on aging and cognition. If evolutionary pressures actively shaped our species' aging phenotype (see for alternative views (214, 215)), it is imperative that age-related processes in our closest relatives be investigated. The need for information on aging in the apes has been widely recognized, particularly with regard to the chimpanzee (188, 216), which shares 98% of its genetic material with humans. In this section, we will examine the literature on aging, cognition, and the brain in apes and outline some of our ideas for future research.

Cognitive Aging

The only species of apes in which cognitive aging has been studied are the chimpanzee and the gorilla, and these studies are few; for bonobo, orangutan, and gibbon there are none. In contrast to the sparse literature on cognition in *aged* apes, that on cognitive function in general is a rich one, especially for the chimpanzee. Many studies within this field of psychological research, beginning with those of Wolfgang Köhler, have demonstrated that chimpanzees have remarkable cognitive capacities. Among them are the ability to recognize themselves in a mirror (217, 218), performance on tasks involving concept formation (219, 220), tool use and understanding of causal relations (221), and some understanding of the psychological states of others (but see for an alternative view). Apes are also able to perform complex linguistic tasks.

Despite the rich cognitive repertoire of the chimpanzee, only relatively mundane tasks have been examined in the context of aging, and only three studies have actually been conducted. The first of these (222) compared the performance of eight young (11–19 years of age) and eight old (28–40 years of age) chimpanzees of unspecified sex in rate of learning, memory, and response variability. The tasks employed included object discriminations in which trials with novel objects were interspersed, a wheel-rotating task that became more difficult if the chimpanzee did not change direction of rotation in successive trials, and a series of object discrimination tasks with a contingency cue present. No differences between the age groups were found in any of the tasks.

Riopelle and Rogers (223) studied 19 chimpanzees of unspecified sex, ranging in age from 7 to 41 years. Confirming the Bernstein study, they found no effect of age on two different object discrimination tasks designed to stimulate novel responses. However, they did observe poorer performance with age on two tasks. In a version of the DR, a decline in performance was observed with age, similar to that reported in monkeys. However, age differences were observed only at the short delays of 0 or 5 s. In contrast to the monkey studies, in which performance was most impaired at the longest delays, this chimpanzee study found that at the longest delay, 10 s, the performance of the young subject declined to the same level as that of the older subjects. The second task in which a significant decline with age was noted was a four-choice oddity task, in which chimpanzees were presented with one odd and three identical stimuli and were required to select the odd one. The third study was an attempt to replicate the findings of Riopelle and Rogers, but this study revealed no differences in performance as a function of age.

Two studies have been published on aging and cognition in the gorilla. In the first (224), 16 gorillas (seven females and nine males) were tested on the DR, with delay intervals up to 90 s and with two, three, or four food wells to choose from in the test. Although performance worsened with lengthening delays and increasing number of food wells, no effect of age on these measures was detected. There was, however, a nonsignificant tendency toward increased side bias with age. Anderson and colleagues (225) examined the ability to detect “numerousness” in 11 gorillas ranging in age from 6 to 43 years. They tested whether gorillas would select the larger of two food quantities of food from food wells. While neither young nor old gorillas relia-

bly selected the larger quantity without training, they all could be trained to do so. Following this training, they also reliably selected the larger of two pairs of quantities, suggesting the ability to summate the two quantities. While there was no relationship between age and the correctness in choosing the larger quantity, the old gorillas did respond significantly more slowly than the young. The authors attribute this slower responding to cognitive slowness rather than motor speed differences because the two age groups responded at the same speed prior to training.

Changes in Brain Anatomy and Function

The brain of the chimpanzee has been far more thoroughly investigated than that of any other apes. This is in part because the chimpanzee is thought to be the most similar of the great apes to humans, as noted above, but is also a consequence of the development of several research stations with a particular focus on chimpanzees (226). With regard to aging of the brain, the preponderance of research on chimpanzees is extreme; there is almost no information on the other species. For this reason, we will not present separate subsections for the four ape genera: *Pan*, *Gorilla*, *Pongo* (orangutan), and *Hylobates* (gibbon and siamang).

The most obvious distinguishing characteristic of the great ape brain is its size. The chimpanzee brain, with an average adult weight of about 370 g for females and 405 g for males (227), is about four to five times the size of the rhesus brain (27). While the bonobo, gorilla, and orangutan have brains of comparable size to that of the chimpanzee, the brains of gibbons and siamangs are about 100 g (228), near the 86 g reported for the rhesus monkey (27).

With respect to age-related differences in the brain, we previously reported a nonsignificant trend toward a decrease in brain weight at death among chimpanzees (227). Additional data accumulated since that publication, as well as volumetric MRI data collected by Dr. William Hopkins (personal communication) extended our original observation by showing the modest cross-sectional decline in brain size with age to be statistically significant. There may be no neuron loss however, as a stereological study of a series of six chimpanzee brains, aged 11 to 45 years (229), suggested that neuron number may be conserved with age, a finding similar to that in rhesus monkeys (49, 230).

Like rhesus monkeys, the aged great apes also have amyloid plaques without the tau-associated neurofibrillary tangles found in humans. Gearing (231) examined three chimpanzees aged 45, 56, and 59 years. Vascular amyloid was observed in the two oldest specimens. In addition, the 59-year-old exhibited sparse amorphous plaques in the cortex and hippocampus. Neurofibrillary tangles were not observed in any of the chimpanzees. An examination of three orangutans, aged 28, 31, and 36 years revealed sparse plaques in restricted locations in the 28- and 36-year-old individuals, and the 36-year-old animal also exhibited vascular amyloid (232). As with the chimpanzees, no neurofibrillary tangles were observed. Kimura (233) reported that the brain of a 44-year-old gorilla contained amyloid plaques, but this great ape also lacked neurofibrillary tangles.

One remarkable similarity of the human brain to those of the great apes is the presence of a large spindle-shaped neuron in the anterior cingulate gyrus. These spindle cells are abundant in humans, bonobo, and chimpanzee, less frequent in gorilla, but altogether absent in gibbon and in all monkey species studied (234, 235). While age-related loss of these cells has not yet been demonstrated in apes, their frequency is substantially decreased in humans afflicted with AD (236, 237). The existence of this cell type and its vulnerability in AD clearly underscore the importance of understanding the aging process and its effect on the brain in the great apes.

Endocrine Influences on Cognitive and Brain Aging

Endocrine studies in apes are logistically difficult and quite expensive. For this reason there have been very few of them. Although some studies have reported age-related declines in testosterone levels (238, 239), cortisol (240), and DHEAS (241) in apes, none of them has related these hormones to cognition or to aging. Aging of ovarian function, i.e., the question of menopause, has received a reasonable amount of attention, although any effects of reproductive aging in the female remain to be elucidated.

The chimpanzee was reported not to undergo menopause (241, 242), but this observation was based on only 12 individuals. In contrast, cessation of menstrual cycles was observed in a study of wild chimpanzees (Mahale, Tanzania), where 7 out of 25 females above 30 years had ceased cycling for 3 years before their death (243). Moreover, Videan and colleagues recently concluded that menopause occurs between 35 and 40 years of age in the chimpanzee, based upon FSH and LH levels taken twice per year from 14 individuals studied longitudinally (244). Although only very little endocrine data were available to support the prior belief that chimpanzees did not normally experience menopause, we caution that this new finding suggesting a relatively early menopause be considered tentative since it includes only FSH and LH measurements and does not actually identify ovulatory cycles and determine their disappearance. A thorough characterization of the menstrual cycle is critical if future studies are to reveal any influence of female reproductive hormones on cognitive and brain function in the chimpanzee. Our analysis of archival menstrual records from the Yerkes chimpanzee colony indicates indeed that even much older female chimpanzees (>50 years) appear to cycle until their death. Thus, additional studies need to be undertaken before firm conclusions can be reached.

Little is known about menopause in the other great apes. A recent study in captive western lowland gorillas indicated that menopause occurs around 35 years of age in this species based upon analysis of fecal estrogens and progestogen metabolites (245).

Advantages and Drawbacks

The most important advantage of the great apes as a model of the influence of aging on cognition, brain, and endocrine functions and their interactions is their especially close evolutionary relationship to humans. Thus, they may not only

show age-related changes that are particularly enlightening with respect to the similarities with humans but also with respect to differences that may be observed between this group of nonhuman primates and our own species. These advantages of study of the apes are offset by a large number of challenges that make observations on these species particularly difficult. Among the problems encountered are the rarity of the apes, the expense and difficulty of maintaining them, and the special adaptations of cognitive tests and equipment that are required to apply standard cognitive tests to the great apes. However, perhaps the most difficult challenge is that any differences between old and young apes cannot automatically be attributed merely to differences in their age, but could instead result from other differences between the young and old cohorts tested in any particular study. This type of interpretational difficulty, a special case of the cohort effect, which commonly plagues cross-sectional studies of aging, may be particularly problematic in long-lived species such as chimpanzees and gorillas, in which the younger members of the species may have experienced completely different lives, and even different birth circumstances. This problem can best be addressed by longitudinal studies in which contemporaneous comparisons between age groups are viewed in the light of observations of changes that occur with aging within the same individual. With the development of non-interventionist methods, such as Magnetic Resonance Imaging (MRI), through which changes in brain morphology can be observed over time, the possibility now exists for future studies in which brain and cognitive changes are observed simultaneously.

As pointed out by Erwin and Hof, researchers now have an important opportunity to study the effects of age on the chimpanzee; although the overall number of chimpanzees available is quite small, a large proportion of these are reaching relatively advanced ages (246). We and other researchers are soon embarking upon studies in which we plan to undertake a focused investigation of cognitive aging of chimpanzees. The work will involve investigators with backgrounds in chimpanzee research, human cognitive aging, human and nonhuman primate anatomy, and other disciplines who will observe the cognitive behavior of young and aged chimpanzees. Our group will investigate longitudinal cognitive changes by administering cognitive tasks that have been the mainstay of studies of the rhesus monkey, the species that served as the “workhorse” among primate models of aging. Chimpanzees will not only be tested on these tasks, but will also undergo periodic MRI examinations so that changes in behavior can be examined in the light of specific anatomical characteristics. Given the dwindling population of chimpanzees, now may be the only time in history that such a study can be undertaken.

Conclusions

This overview of nonhuman primate models of cognitive aging points to a few primate species that have great potential to further our understanding of human age-related cognitive decline. The list is by no means exhaustive, but highlights species for which the most information is available.

It is likely that macaque species will remain primary models of human cognitive aging, as our knowledge of aging in the macaque, from cognitive, behavioral, physiological, and endocrine perspectives, is more detailed than the limited knowledge that we have gained so far from other species. If cognitive aging is indeed a consequence of a multitude of factors, it is crucial to seek an understanding of aging at different levels of organization, from behavioral to molecular processes. As such, the macaque remains to date the model of choice.

Nevertheless, we have shown that other primate species may complement studies on the macaque. Medium-sized nonhuman primates that present particularly interesting features in brain and endocrine senescence, without having some of the drawbacks associated with macaques, are baboon species. The investigation of cognitive aging in the baboon should provide some new insights into the neural bases of cognitive impairment, in particular in relation to neuropathology associated with tau and A β accumulation. Another possible avenue of research for this species concerns the cognitive deficits associated with natural menopause.

From a practical point of view, however, small-sized species are probably most attractive as potential models for human cognitive aging. Gray mouse lemurs and marmosets exhibit some aspects of age-related cognitive and brain declines that appear similar to those of humans and present obvious advantages over larger primates in terms of purchase and maintenance costs. However, important differences in reproductive systems and brain function between humans and these phylogenetically distant species suggest caution in extrapolating findings to humans. In spite of these limitations, they present interesting alternative models in which species-specific aging mechanisms can illuminate our understanding of human cognitive aging. One exciting opportunity for future research is the further development of these primate models for functional neuroimaging studies.

At the opposite end of the size spectrum, the great apes are the most expensive and also most difficult to study. In spite of these hurdles, studying great apes' cognitive aging is critical to understanding potentially unique features of human senescence. Studies are underway to gather important data concerning brain and cognitive aging in our closest relative, the chimpanzee.

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