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An overview of nonhuman primates in aging research

Julie A. Mattison[a,*] and **Kelli L. Vaughan**[a,b]

[a]Translational Gerontology Branch, National Institute on Aging, NIH Animal Center, 16701 Elmer School Road, Bldg 103, Dickerson, MD 20842

[b]SoBran, Inc., 4000 Blackburn Lane, Suite 100, Burtonsville, MD 20866

Abstract

A graying human population and the rising costs of healthcare have fueled the growing need for a sophisticated translational model of aging. Nonhuman primates (NHPs) experience aging processes similar to humans and, as a result, provide an excellent opportunity to study a closely related species. Rhesus monkeys share >92% homology and are the most commonly studied NHP. However, their substantial size, long lifespan, and the associated expense are prohibitive factors. Marmosets are rapidly becoming the preferred NHP for biomedical testing due to their small size, low zoonotic risk, reproductive efficiency, and relatively low-cost. Both species experience age-related pathology similar to humans, such as cancer, diabetes, arthritis, cardiovascular disease, and neurological decline. As a result, their use in aging research is paving the way to improved human health through a better understanding of the mechanisms of aging.

Keywords

monkeys; macaques; marmoset; cognition; reproduction; sarcopenia

1. Introduction

Aging is a complex phenomenon affecting every organ system of the body. Our understanding of the aging process is further complicated by the observation that no two individuals age at the same rate or in the same manner. To date, cells, worms, flies, and rodents have provided an extensive groundwork for aging research. However, taking this science from the bench to the bedside requires a more complex species, one with a physiology and aging process that more closely resembles the human experience. Nonhuman primates (NHPs) demonstrate parallel aging characteristics and experience many of the same diseases and pathophysiology as humans. In addition to their phenotypic similarities, NHPs share >92% genetic homology with humans. As a result, they may provide the best opportunity to study the actual mechanisms that lead to the age-related decline seen universally, across species.

*Corresponding author. Julie.Mattison@nih.gov.

The history of NHPs in research is rich with significant contributions to diseases such as HIV/AIDs, Ebola, and Zika, as well as the development of vaccinations, and advancements in organ transplant technology. Phillips et al., (2014) present a comprehensive review of the advantages of a primate model in many areas of biomedical research. This review highlights the contributions to aging research made by two commonly used nonhuman primate species---the Old World rhesus monkey and the New World marmoset.

Old World and New World are geographically based general classifications given to NHPs. Old World monkeys originate from Africa and Asia and consists of at least 132 species, including baboons and macaques. These animals range in size from medium to large and typically weigh between 4–20 kg. The presence of a tail differentiates monkeys from apes. Whereas, downward-pointing nostrils and only two pre-molars physically distinguish Old World from New World species (Lawrenc and Cords 2012). There are also several physical classifications that distinguish the New World and Old World groups (see Table 1).

New World monkeys originate from South America and are commonly divided into two families; the *Callitricidae and the Cebidae*. Where, the *Callitricidae* are the most primitive group of New World monkeys, and include marmosets and tamarins. The *Cebidae* are larger and are the only monkeys with a prehensile tail. Squirrel monkeys and capuchins are two examples of monkeys in this family.

2. Old World Macaques

The macaques are the most widely used NHPs in biomedical research and are now purpose-bred at dedicated facilities. Rhesus macaques (*M. mulatta*) have been extensively studied and are the predominant species used in aging research. Other macaque species, such as cynomolgus (*M. fasicularis*), pigtails (*M. nemestina*), stump-tails (*M. arctoides*), and bonnets (*M. radiate*), are studied to a lesser extent. Although the various macaque species are certainly similar, information here is specific to the rhesus macaque, unless otherwise specified.

Overall, rhesus monkeys share 92% genetic homology with humans (Magness et al., 2005). And, their phenotypic similarities extend to almost all aspects of anatomy, physiology, endocrinology, immunology, neurology, behavior, and aging processes. Rhesus monkeys have a relatively long lifespan, with an average of 25 years and maximum of 40 years in captivity. As a result, age-related changes in NHPs more closely approximate the experience of humans, as compared to that of shorter-lived research models (e.g. mice, rats, etc.). The rate of aging is commonly considered to be three times that of humans, although this ratio is not consistent across every stage of life.

Moreover, rhesus monkeys sexually mature around the ages of 2.5 – 3.5 years, they reach adult stature by 8 years of age, and females undergo menopause by about 25 years. Thus, the rate of aging ratio of human to monkey years can be summarized as follows: 1:4 from birth to sexual maturity, 1:3 during young adulthood, and 1:2 for females before menopause. In general, rhesus monkeys aged 15 – 22 years are deemed middle aged, while those over 30 years are considered old or elderly.

While offering a robust model, rhesus longevity also poses one of the greatest challenges for aging research. For example, it takes decades before age-related conditions are apparent, resulting in lifespan studies extending beyond a typical scientific career. Moreover, maintaining monkeys for life-span studies is extremely expensive, requiring specialized facilities staffed with dedicated veterinary and husbandry personnel. Thus, monkey studies often suffer from small sample sizes and are generally cross-sectional rather than longitudinal. Another complication is the considerable individual variation between monkeys; because they are not an inbred species, any two monkeys are as different as two humans. Yet, despite the challenges, rhesus monkeys still provide the best translational approach to understanding human aging, age-related diseases, and test interventions.

2.1 Endocrine and Reproductive

The neuroendocrine system plays a key role in the coordinated regulation of physiological signaling and function. In conjunction with altered hormone levels, aging results in a disruption of circadian patterns, which in turn may contribute to age-associated dysfunction at multiple systemic levels. For example, both male and female monkeys experience an age-related decline in the Hypothalamic-Pituitary-Gonadal (HPG) axis (the central core of many hormone feedback loops); a process occurring more gradually in males.

Male rhesus monkeys undergo puberty between the ages of 2.5 – 3.5 years. Although the gonadal axis and the existence of an andropause are not well characterized for males, it is clear that the diurnal patterns of hormone secretion change with age. With age, daytime pulses of luteinizing hormone are significantly reduced, leading to a lower daytime androgen level. In spite of this, levels over a 24-hour period are not significantly affected (Schlatt et al., 2008).

Similarly, hormone profiles for cortisol and dehydroepiandrosterone sulfate (DHEAS) steroids produced by the adrenal cortex, and testosterone, an androgenic steroid produced in the testes, taken from adult (10 years) and aged (26 years) male rhesus monkeys, demonstrate a clear 24-hour rhythm (Downs et al., 2008). Here, testosterone shows a peak at night while DHEAS and cortisol peak in the early morning. There is a significant decline in the amplitude of both testosterone and DHEAS in aged monkeys, while cortisol generally remains unchanged or is slightly increased. In fact, baseline levels of cortisol are elevated, which may be a contributing factor to age-related sleep and metabolic disorders (Downs et al., 2008). A lower DHEAS level has been linked to cognitive decline in rodents and humans but has not been directly demonstrated in NHPs. Although there is a decline in the circulating testosterone level, it is maintained above pre-pubertal levels and, therefore, its decrease may not be as physiologically relevant. Yet, the dampened circadian pattern may contribute to overall hormonal deregulation in aged monkeys (Urbanski and Sorwell 2012).

Female NHPs are unique in that they are the only mammals that menstruate. In fact, rhesus monkeys have been a model for reproductive studies in women since the early 1900s. In female monkeys, puberty also occurs between the ages of 2.5 – 3.5 years and their menstrual cycles are ~28 day in length. Similar to humans, aging female rhesus monkeys undergo a decrease in serum estradiol, an increase in follicle stimulating hormone, and have decreased inhibin B accompanied by amenorrhea, the hallmark sign of menopause. A period of

irregular cycling, termed peri-menopause, is characterized by a decrease in the total number of regular menstrual cycles and percentage of normal length cycles, precedes menopause (Downs and Urbanski 2006). Paralleling humans, female rhesus commonly experiences normal cycling through the age of 22 years, with the onset of perimenopause at about 24 years, and become postmenopausal at 25 years. The average age of menopause in women is 51 years. Compared to humans, female monkeys have a shorter post-reproductive period of life.

2.2 Musculoskeletal

Age-related bone loss and deterioration are the hallmark changes associated with osteoporosis. These changes lead to bone fragility and fractures, which is a significant health concern among the aging population. Compared to men, women are at greater risk for bone loss due to a lower peak bone mass, as well as accelerated bone loss occurring at menopause. However, both elderly men and women experience a significant number of hip fractures. These osteoporotic fractures result in reduced mobility and independence, and increased health care costs and mortality rate.

Rhesus monkeys experience age-related structural and body composition changes similar to humans. Among humans and NHPs, postural changes seen with aging are associated with reduced bone mineral density and a break down in cartilage, leading to reduced intervertebral space and subsequent osteoarthritic characteristics. The pattern of disc degeneration observed in NHPs is similar to humans (Bailey et al., 2014), and both age-related and hormone-deficiency induced loss of bone density and strength are evident in rhesus monkeys.

In female monkeys, loss of bone mass occurs with the menopause transition, beginning during perimenopause. As measured by lumbar spine and proximal radius, post-menopausal monkeys have 11–13% lower bone density than their younger counterparts (Colman et al., 1999a). Elevated osteocalcin also indicated increased bone turnover in post-menopausal females, similar to the human condition. For these reasons, female rhesus monkeys provide a valuable model for understanding the effect of hormone loss due to natural menopause, as well as loss resulting from surgical interventions (Colman et al., 1999a).

In males, the effect of age-related changes in bone mass is not as well studied but is apparent at the lateral spine and radius after 10 years of age in monkeys. Similarly, with age, males have a reduction in serum osteocalcin and carboxyterminal telopeptide of type I collagen, indicating lower bone turnover (Black et al., 2001). However, there is no obvious change in parathyroid hormone, Vitamin D, follicle stimulating hormone, or testosterone; the latter indicates that bone mass loss in males is independent of gonadal hormones (Colman et al., 1999b).

Skeletal muscle is the functional partner to bone and also undergoes major changes with age, contributing to frailty. Sarcopenia is the term used to describe the skeletal muscle atrophy and loss of function that occurs with age and the resulting decline in both muscle mass and quality. Age-specific changes in monkey muscle are similar to the muscle wasting seen in humans, in which approximately 3 – 8% of muscle mass is lost each decade after the age of

30 years, and the rate of decline accelerates after the age of 60 years (Kyle et al., 2001). As seen in both cross-sectional and longitudinal studies with rhesus monkeys, males continued to gain muscle up to about 15 years of age, but after the age of 20, estimated skeletal muscle mass (the sum of lean mass in the arms and legs) decreases significantly (Colman et al., 2005). Cross-sectional data revealed that, by the age of 25 years, total muscle mass loss was nearing 27% in males (Colman et al., 2005).

Compared to males, muscle mass peaked about one year earlier in rhesus females, who experienced a subtle age-associated decline (Colman et al., 2005). In the cross-sectional analysis, significant effects were not apparent until they were >25 years old and, in the longitudinal analysis at this age, females had lost only 20% of their muscle mass compared to the 27% in males (Colman et al., 2005). This sex difference, with a dampened decline in females, has been demonstrated in human studies as well (Kyle et al., 2001), and overall, suggests that macaques provide an important model for studying the pathogenesis of sarcopenia and potential interventions.

2.3 Cognitive Function and Brain Aging

Cognitive function declines with normal aging in monkeys, and just as in humans, pathological conditions accelerate the rate of decline. Although the development of the brain is similar between the two species, in particular the cortex, aging patterns can be different and NHPs do not spontaneously develop the same diseases. For example, experimental models of Alzheimer's Disease (AD) have been created to study specific aspects of this disease, which do not occur naturally in NHPs.

There is now a vast amount of research characterizing cognitive function in rhesus monkeys and several behavior tasks developed for humans have been adapted for use in NHPs. With improved imaging techniques and cognitive testing, we know that brain mass does not decline in rhesus monkeys (Herndon et al., 1998), but regional volumes do, and these region specific changes are likely responsible for the cognitive decline observed with age.

As identified in human populations, aged monkeys show significant impairment on cognitive tasks compared to their younger counterparts. These impairments are seen in areas such as working memory, declarative memory, executive function, cognitive flexibility, and motor skills (Voytko and Tinkler 2004). However, much like the human population, the degree of impairment varies greatly between monkeys, with some showing no signs of deficiency to others with a severe functional decline.

Not surprisingly, old monkeys take longer to learn new things. Teaching old monkeys new memory tasks is not impossible but certainly more difficult. In one of the most basic and simple paradigms, object discrimination, old monkeys needed four times as many trials as young monkeys to execute a task (Voytko and Tinkler 2004). For a delayed response task, the monkey must remember a previously cued spatial location following a delay. Old monkeys require significantly more trials to reach the criterion and make almost three times as many errors as young monkeys. Yet when the old monkeys are trained and have had previous behavior testing, the learning impairment is reduced and their performance is closer to that of young monkeys (Voytko and Tinkler 2004).

The cognitive decline associated with age in monkeys may be correlated with specific structural changes occurring within the brain. Although total brain weight and the size of most parts of the cerebral cortex do not change with age, the volumes of specific regions are reduced. These include the basal ganglia, dorsal prefrontal cortex, area 46, and anterior cingulate cortex. Additionally, there is a loss of nerve fibers from white matter within the forebrain seen with aging. A few of these tract losses have been correlated to cognitive decline; a correlation that appears to be most related to the extent of the fiber loss (reviewed in Hara et al., 2012).

Although rhesus monkeys develop pathological characteristics of AD, they do not develop the disease. For example, the frequency of senile plaques increases with age in rhesus, but there is no apparent effect on cognitive function. For this reason, rhesus monkeys offer us the ability to study normal age-related changes in function that are not confounded by the disease state. In non-diseased humans and in monkeys, Aβ-40 is the predominant plaque present. As the disease progresses in humans, the Aβ-42 form predominates, a change that does not occur in monkeys. Also of note, monkeys do not develop neurofibrillary tangles, which are associated with neuronal loss in humans (reviewed in Hara et al., 2012). Research efforts are underway to model the characteristics of AD in rhesus monkeys to better understand its pathogenesis and potential for drug development.

3. New World Marmosets

The common marmoset (*Callithrix jacchus*) is a New World primate with an average lifespan of 5 to 7 years and maximum of 16.5 years. With a compressed lifespan in comparison to rhesus, marmosets are fully mature by about 2 years of age and considered aged by 8 years (Abbott et al., 2003). Thus, for aging studies, this nonhuman primate species offers many advantages.

First, marmosets are small, averaging only 350 to 400 grams as adults. They live in multi-generational family units, which allows them to be easily maintained in social housing in the laboratory setting. There are well-established colonies of marmosets at the National Primate Research Centers and other private facilities; as such, they are generally widely available for research use. Marmosets experience age-related pathology similar to humans. These include cancer, diabetes, chronic renal disease, and amyloidosis. Due to its small size, low zoonotic risk, reproductive efficiency, and relatively low cost to maintain in a laboratory, marmosets are becoming the preferred NHP for biomedical testing.

At 8 years of age, marmosets are aged and experiencing fibrous changes in the intra-articular discs, β-amyloid deposition, reduced neurogenesis, renal pathology, weight loss, increased insulin resistance, and increased incidence of neoplasia. Descriptions of age-associated pathology in marmosets resemble the human experience in which neoplasia, infections, renal disease, amyloid accumulation, and diabetes are common contributors to death. A survey of pathology incidence in the marmoset population at the New England Primate Research Center, reported on 77 cases for animals over 1 year of age. The major contributors to death of young monkeys (<5.8 years of age) was trauma, inflammatory bowel disease, sepsis, and bacterial infections of the gastrointestinal tract, liver, and kidneys. Older monkeys more

commonly died from neoplasia, chronic renal disease, amyloidosis, and diabetes mellitus. Adenocarcinoma of the small intestine was the most common neoplasia but rarely observed in animals younger than 6 years of age (Tardif et al., 2011).

3.1 Bones, Body Weight, and Metabolic Syndrome

Osteoporosis is a serious health challenge for older humans, often leading to limited mobility and loss of independence. A study by Bagi et al., (2007) suggests that marmosets may be an excellent model for testing treatment modalities. Adult marmosets lack growth plates, have coordinated remodeling of the bone, undergo age-related structural changes similar to humans, and have more similar mechanical loading compared to rodents. When treated with alendronate, an FDA approved bisphosphate therapy for osteoporosis, trabecular bone volume and number were improved via mechanisms similar to humans (Bagi et al., 2007).

Similar to aging and frail humans, older marmosets lose weight at a rate that accelerates after late middle age, which is approximately 8 years old in marmosets (Tardif et al., 2011). Power et al., (2001) also reported a drop in body weight with age and, using labeled water dilution, demonstrated that it was associated with loss in fat free mass. In a larger cohort, Tardif et al., (2011) showed a negative association between body mass and lean mass with age but there was no association with fat mass. Appendicular muscle loss was also seen in older aged marmosets, similar to that seen in humans.

Although a relationship between obesity and aging have not been established, in marmosets, age and weight are independently associated with insulin sensitivity. Thus, marmosets may be a valuable model to study the complex relationship between obesity and aging that is also seen in humans. Although aged marmosets experience an increased incidence of insulin resistance, they are not an ideal model for experimentally induced diabetes. Steptozotocin administration resulted in secondary acute renal and liver toxicity and immunostaining revealed reduced expression of pancreatic GLUT2 receptors compared to Old World species (Kramer et al., 2009).

3.2 Reproductive Aging

Interestingly, although female marmoset reproductive cycles are similar to humans, they may not be a very good model for menopause. Steroid hormone profiles are similar, although not exact, between humans and marmosets. In addition, the marmoset ovarian cycle lasts 28 days, with ovulation at about day 10. Marmosets have large litter sizes, often twins or triplets, and postpartum ovulation generally occurs within 10–20 days resulting in pregnancy (Tardif et al., 2003). One report suggested no decline in antral follicles with age and no decline in ovulation rate (Tardif and Jaquish 1997). However, in a larger cohort, Gilchrist et al., (2001) demonstrated a significant logarithmic decline with age that is comparable to humans. Additionally, older, high-parity moms give birth to larger infants regardless of litter size. As marmosets age, their ovaries continue to produce steroids. Yet, even if the ovaries are surgically removed, eliminating the release of gonadal estrogen, marmosets maintain bone mass (Abbott et al., 2003). This represents a completely different scenario than the post-menopausal human woman.

Similarly, male marmosets maintain reproductive vitality into old age despite a slight decrease in androgen levels. Testosterone levels increase until approximately 7.5 years of age and then begin to drop (Tardif et al., 2008). Older males remain responsive to GnRH stimulation. In fact, with increasing age, there is a greater increase in testosterone release when stimulated. This observation indicates that, although basal androgen levels are lower in older monkeys, the Leydig cells have not lost the ability to synthesize and release hormone when stimulated (Tardif et al., 2008).

3.3 Neurobiology

The marmoset is an important model of normal age-related brain changes and psychological stress, and is becoming a widely-used model for experimentally induced neurological diseases. Marmoset neural anatomy is similar to commonly used Old World monkeys, as both have a well-developed cerebral cortex and cerebellum. And unlike rodents with a single structure striatum, the marmoset has a discrete putamen and caudate region. Moreover, the marmoset's brain represents 2.7% of its body weight, which is equivalent to the brain-body mass relationship in humans (Abbott et al., 2003).

In humans, normal aging results in a decline in newly generated neurons in the dentate gyrus of the hippocampus, an observation which has also been demonstrated in rodents. Adult marmosets experience this same decline in neurogenesis, a change that occurs before an age that is commonly considered to be old (Leuner et al., 2007). This decline was evident using BrdU-labeled cells in the dentate gyrus. However, the oldest marmoset in this study was 7 years of age, so changes into old age are still unknown. It is likely that this loss of neurogenesis is one component of the aging brain that is also subject to loss of synaptic connectivity and altered plasticity, each of which are contributing to a decline in cognitive function.

In addition to general aging processes, psychological stress negatively impacts hippocampal neurogenesis in adult marmosets. With BrdU-labeling, it was shown that a single one-hour exposure to a stressful environment impairs hippocampal function and reduces the number of proliferating cells (Gould et al., 1998). This phenomenon has been used to help explain why human patients suffering from post-traumatic stress disorder or depression have a reduced hippocampal size on MRI scans.

Consistent with many other NHP species, marmosets accumulate β-amyloid with age, occurring at 7 – 15 years compared to 22 – 31 years in Old World species (Tardif et al., 2011). Diffuse Aβ-42 positive cortical plaques accumulate in small cortical vessels and, less frequently, in para-limbic areas (Ridley et al., 2006). However, as with several other aging animal models, neurofibrillary tangles have not been identified. Thus, marmosets represent an interesting opportunity for the study of specific aspects of AD, but do not represent the whole disease spectrum.

Nevertheless, the structure of the marmoset striatum makes this species an ideal model for studies of Parkinson's Disease (PD) as the striatum is often the treatment target. Thus far, marmosets have been used to study several PD treatments such as neurotrophic factors, dopamine agonists, dopamine reuptake inhibitors, and neuro-transplantation. Induction

models of PD have been valuable for the study of the disease, and marmosets have been reliably used in this context as well (Eslamboli 2005).

Models of PD rely on neurotoxin induced dopaminergic cell death using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-hydroxydopamine (6-OHDA). A five-day course of subcutaneous MPTP administration is the most commonly used protocol and results in a 95% loss of tyrosine hydroxylase mRNA in portions of the substantia nigra. The effect that this procedure has in marmosets mimics the end stages of human PD. This particular model is useful for assessing treatments that target a reduction in L-dopa induced dyskinesia and other therapeutic agents such as glial derived neurotrophic factor, and dopaminergic and non-dopaminergic agonists. A lower dose MPTP administration over 3 days has been shown to produce less severe nigrostriatal lesions in marmosets and is proving to be useful for assessing treatments aimed at the earlier stages of PD as seen in humans (reviewed in Eslamboli (2005)).

4. Conclusions

Even though the rhesus monkey remains the most commonly used NHP in aging research, development of the marmoset as an aging model continues and resources are improving. With colonies dedicated to aging research and advanced molecular tools, marmosets have become a valuable research model. And, in 2014, the marmoset genome was sequenced (Marmoset Genome and Analysis 2014) and the possibility for transgenic applications has already been realized (Sasaki et al., 2009). Indeed, the ability to create a transgenic primate increases the value of this animal model for translational research.

Nevertheless, how should one determine which species to use for a particular project? Perhaps the most useful method to determine the appropriate species is to search the literature for models that have been successfully used in previous studies. For example, rhesus macaques are great models for age-related macular degeneration (AMD), the most common cause of vision loss in the elderly. Macaques have eyes that closely resemble the human eye in almost all respects. In fact, the macaque retina has a macula and age-related pigmentary and drusen changes occur spontaneously in rhesus monkeys, which closely resembles human AMD. Conversely, the marmoset provides a robust model of age-related (peripheral) hearing loss, or presbycusis, which is quite common in elderly humans. The marmoset cochlea are anatomically similar in structure compared to humans.

There are several other important factors to consider when selecting the appropriate model. First, define the required characteristics for the specific experiment and consider the available methods for monitoring disease progress. For example, a requirement for large volumes of blood or repeat sampling may preclude smaller NHPs from consideration or, if performing MRI or PET scans, one must consider the availability of a human versus rodent machine. Next, consider the (perceived) similarities of the disease pathogenesis as well as which species has similar biomarkers as the human disease. Finally, if an experimental drug is to be used, consider any known toxicities as well as the use of allometric scaling for dose conversions from other species. NHPs may not be appropriate for every experimental question, but they are a crucial component for taking the bench to the bedside.

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Highlights

- NHPs have aging characteristics and pathogeneses that closely resemble humans
- Rhesus monkeys provide a robust model for translational aging research
- The marmosets comparatively shorter lifespan is advantageous for aging studies
- NHP studies are a crucial component in the progression of bench to bedside research

Table 1

Comparison of Old World and New World Monkeys

Feature	Old World Monkeys	New World Monkeys
Origin	Africa & Asia	Americas
Body Size	Medium to large	Small to medium
Nose	Downward facing nose (catarrhine) and nostrils	Flat nosed (platyrrhine) with nostrils facing sideways
Tail	Non-grasping; Ischial callosities (sitting pads)	Prehensile
Teeth	8 premolars	12 premolars
Hands	Opposable thumbs; fingernails & toenails	Thumb is in same plane as other digits; no fingernails
Ears	Tympanic membrane connected by bony tube	Tympanic membrane connected by bony ring
Habitat	Wide range, mostly on ground, tendency for single male multi-female social groups	Small range, arboreal, tendency for single-female and multi-male social groups
Infant Care	Males rarely contribute	Males contribute
Diet	Omnivores, foraging plants, insects, small animals	Nuts, berries, insects