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Chronic stress, allostatic load, and aging in nonhuman primates

DARIO MAESTRIPIERI AND CHRISTY L. HOFFMAN
University of Chicago

Abstract

Allostatic load is the "wear and tear" of the body resulting from the repeated activation of compensatory physiological mechanisms in response to chronic stress. Allostatic load can significantly affect the aging process and result in reduced longevity, accelerated aging, and impaired health. Although low socioeconomic status is associated with high allostatic load during aging, the effects of status-related psychosocial stress on allostatic load are often confounded by lifestyle variables. Chronic psychosocial stress associated with low dominance rank in nonhuman primates represents an excellent animal model with which to investigate allostatic load and aging in humans. Research conducted with free-ranging rhesus monkeys suggests that female reproduction can also be a source of stress and allostatic load. Female reproduction is associated with increased risk of mortality and hyperactivation of the hypothalamic–pituitary–adrenal axis. Reproduction is especially stressful and costly for aging females of low rank. Although many indicators of body condition and neuroendocrine and immune function are influenced by aging, there are marked and stable individual differences among aging females in body condition, plasma cortisol responses to stress, and cytokine responses to stress. These differences are consistent with the hypothesis that there are strong differences in chronic stress among individuals, and that allostatic load resulting from chronic stress affects health during aging. Comparisons between captive and free-ranging rhesus monkey populations may allow us to understand how differences in environmental stress and allostatic load affect rates of aging, and how these in turn translate into differences in longevity and health.

In order to survive and function properly, organisms must maintain their physiological parameters (e.g., temperature, blood pressure, glucose, and hormone concentrations in blood) within a certain range of values appropriate for their age, gender, and species. The state of equilibrium in which all of an organism's physiological parameters are within the normal range is referred to as homeostasis. The external environment, which includes both abiotic factors such as ambient temperature and humidity and biotic factors such as other organisms and their behavior, can cause perturbations of homeostasis so that some physiological parameters change and assume values that are either above or below the normal range. Perturbations of homeostasis can also be induced by pathological processes such as infectious diseases or by genetic alterations or physiological malfunction. In response to these perturbations of homeostasis, the organism makes adjustments in its physiological processes so as to bring the values of the parameters that have been altered back into their normal range. This dynamic process through which an organism adjusts its physiological parameters in response to perturbations of homeostasis is referred to as allostasis. Allostatic processes involve feedback mechanisms that detect a deviation from homeostatic equilibrium and trigger the appropriate compensatory responses.

Environmental perturbations of homeostasis are known as stressors. There are many types of stressors, acute or chronic. Responses to acute stressors help the individual survive and reestablish homeostasis. A sudden predator attack and aggression from a conspecific are good examples of stressors that can threaten survival or physical well-being. Areas of the brain such as the amygdala and prefrontal cortex play a crucial role in evaluating the threat and producing an emotional response that will help cope with it. Signals from the brain activate the release of catecholamines (epinephrine and norepinephrine) from the sympathetic–adrenal–medullary axis and of glucocorticoid hormones (cortisol or corticosterone) from the hypothalamic–pituitary–adrenal (HPA) axis. This allows the organism to mobilize energy and exercise muscle, increase cardiovascular tone to facilitate energy delivery, and temporarily inhibit other physiological processes such as growth, repair, digestion, and reproduction. Immune processes including the release of pro- and anti-inflammatory cytokines can also be part of acute responses to stressors. Although the general aspects of allostatic responses to stress are the same in all organisms of the same species, and often also in different species, there are marked individual differences both in the perception of threats and in the activation of allostatic mechanisms.

Chronic stress causes the repeated or continuous activation of compensatory allostatic responses. These responses have

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Address correspondence and reprint requests to: Dario Maestripieri, University of Chicago, 5730 South Woodlawn Avenue, Chicago, IL 60637; E-mail: dario@uchicago.edu.

an immediate benefit but also a cost. The wear and tear of the body resulting from chronic allostatic activation is referred to as allostatic load (AL; Juster, McEwen, & Lupien, 2010). Catecholamines, cortisol, and cytokines are considered primary mediators of AL. These primary mediators have direct effects on cellular activities as well as activate secondary mediators, that is, metabolic, cardiovascular, and immune parameters that change their ranges of action to maintain chemical, tissue, and organ function. Chronic stress and allostasis result in a permanent shift of physiological parameters away from their normal homeostatic ranges and toward abnormal values. The chronic activation of primary and secondary mediators of AL results in tertiary outcomes, such as permanent physiological dysregulation, brain changes (synaptic and dendritic remodeling, suppressed neurogenesis, structural atrophy/hypertrophy), accelerated aging, disease, or death (McEwen, 2007).

AL can be detected and quantified through the measurement of chronically altered physiological parameters. Specifically, researchers study the interactions between primary mediators and their effects, in conjunction with the use of secondary biomarkers, so as to identify individuals who are at risk of tertiary outcomes. Documenting AL is difficult because each mediator produces biphasic effects and is regulated by other mediators, often in reciprocal fashion, leading to nonlinear effects upon many tissues and organs (Juster et al., 2010). Assessing AL also requires documenting age effects with cross-sectional or longitudinal experimental designs. Describing the accumulation of AL over time and in relation to age, however, is also difficult because fluctuations in physiological mediators induce compensatory remediation over time (Juster et al., 2010).

Chronic Stress, AL, and Aging

Despite these difficulties, studies using a combination of AL biomarkers such as cortisol, catecholamines, cholesterol, blood pressure, and cytokines have shown that higher AL is associated with lower basal physiological functioning, greater aging-related decline in cognitive and physical functioning, greater risk of cardiovascular disease, and increased mortality risk in older adults (e.g., Gruenewald, Seeman, Ryff, Karlamangla, & Singer, 2006; Juster et al., 2010; McEwen, 2007). Some studies have reported gender differences in AL such that cardiovascular biomarkers of AL are more dysregulated in men while neuroendocrine biomarkers of AL are more dysregulated in women (Juster et al., 2010). Although in some cases specific biomarkers or clusters of AL mediators are linked to specific pathological outcomes, increased risk of mortality is generally predicted by a combination of all AL biomarkers (e.g., Gruenewald et al., 2006).

Although AL is presumably the result of chronic stress, the evidence specifically linking chronic stress and AL is mixed. For example, one study found no association between stressful life histories (marital status, group participation, coresidence with married son) and neuroendocrine AL parameters (Gersten, 2008) but reported an association with current perceived stress in women. In another study, subjective perceived stress, as opposed to objective environmental stress, was correlated to higher AL primary mediators (Clark, Bond, & Hecker, 2007). In yet another study, mothers of children with cancer and other diseases showed increased AL markers (higher norepinephrine, lower cortisol) and also had a smaller hippocampus (Glover, 2006; Glover, Garcia-Arcena, & Mohlman, 2008). Finally, it has been recently reported that individuals exposed to chronic psychosocial stress, such as victims of child maltreatment, exhibit signs of early cellular aging such as accelerated telomere length reduction (see below), presumably as a result of AL (Epel et al., 2004; Tyrka et al., 2010).

Chronic stress is also presumed to be the link between low socioeconomic status (SES) and high AL and its consequences. A large body of research has shown that aging individuals of low SES are generally more vulnerable to risk of cardiovascular, respiratory, rheumatoid, and psychiatric diseases, and mortality from all causes than aging individuals with more financial resources. Moreover, economically and socially disadvantaged minority groups such as African American women exhibit reduced life expectancy, accelerated cellular aging, and increased vulnerability to aging-related diseases (Crimmins, Kim, & Seeman, 2009; Epel, 2009; Geronimus, Hicken, Keene, & Bound, 2006; Geronimus, Hicken, Pearson, Seashols, Brown, & Dawson Cruz, 2010). Consistent with the AL model, older individuals with low SES have high values of AL, and African American women show the most consistently elevated AL across all age groups. What is less clear, however, is whether the high AL associated with low SES is the result of psychosocial stress associated with poverty, or of other factors linked to low SES.

In addition to lacking financial resources, low SES individuals also lack social support and exhibit unhealthy lifestyles. Lack of social support can contribute to high AL and its detrimental consequences because individuals who have strong close ties with relatives and friends and are embedded in larger and supportive social networks are generally healthier and live longer than individuals who lack these resources (e.g. Holmen & Furukawa, 2002; Kiecolt-Glaser et al., 1985; Seeman, 2000; Wright & Steptoe, 2005). Furthermore, low SES, at least in Western societies, is associated with a number of lifestyle variables that may affect health and the aging process such as smoking, alcohol, and drug abuse, less healthy diets, more sedentary life styles, greater exposure to violent crimes, and fewer coping outlets. Finally, economically and socially disadvantaged minority women also experience greater reproduction-related chronic stress, as they begin reproducing at an earlier age and overall produce more children than nonminority women of high SES. Both human and animal research suggests that reproduction is a significant physiological and psychosocial stressor for females, which may affect longevity, aging, and health.

Pregnancy and lactation entail dramatic increases in hormones of the hypothalamic–pituitary–gonadal and the HPA axis, along with suppression of immune function. Repeated

physiological activation in conjunction with frequent reproduction may be a significant source of AL in females and contribute to increased risk of disease and mortality. For example, in both humans and rhesus monkeys, female reproduction is associated with increased risk of mortality (Hoffman et al., 2008; Penn & Smith, 2007). In addition to neurendocrine and immunological processes, oxidative stress, which occurs when the production of "free radicals" from metabolic activities exceeds the capacity of antioxidant defenses and damages DNA, is also another important byproduct of reproduction that contributes to AL (Finkel & Holbrook, 2000). Oxidative stress can damage telomeres, the complex DNA–protein caps of chromosomes that function to maintain genome integrity (von Zglinicki, 2002). Human and animal studies suggest that both psychosocial stress (humans: Epel et al., 2004; Geronimus et al., 2010; Tyrka et al., 2010) and oxidative stress associated with frequent reproduction (mice: Kotrschal, Ilmonen, & Penn, 2007) increase the rate of age-related telomere length reduction, thus resulting in accelerated aging. The impact of the reproductive stress on AL, aging, and health, however, is generally underinvestigated, and studies simultaneously addressing the effects of chronic psychosocial and reproductive stress and their underlying mechanisms, are conspicuously lacking.

Primate Research on Chronic Stress and AL

Research with primate models offers the opportunity to investigate the effects of chronic stress associated with low social status or frequent reproduction without the confounding influence of life style variables. Moreover, research with primate models offers the opportunity to investigate AL accumulation across the life span using longitudinal and experimental approaches that would be difficult in humans. Finally, research on AL and aging in primates can be conduced at multiple levels of analysis, from social and behavioral to physiological, neurochemical, and genetic, thus using the approach that has been advocated for research in human developmental psychopathology (e.g., Cicchetti & Toth, 2009). Therefore, primate research can extend, complement, and validate current efforts to understand the relationship between chronic stress, AL, aging, and health in humans.

Primate research has produced evidence linking status-related chronic stress and AL, although this relationship has not been studied in the context of aging. Although low social status in monkeys is in many ways comparable to low SES in humans, in some primate societies high social status can be even more stressful than low status. Therefore, primate studies have suggested that it is stress, rather than status per se, that results in high AL. Sapolsky (2005) has argued that low status is associated with high stress in despotic primate species, in which high-ranking individuals maintain dominance through threats and other forms of psychological intimidation (e.g., macaques, baboons, chimpanzees). This is particularly true in groups in which dominance hierarchies are stable, rank is socially inherited from mothers and difficult to change, and low-ranking individuals are subjected to high rates of harassment, so that their daily lives are characterized by lack of control and predictability. In these species and social situations, however, high-ranking individuals can temporarily experience great psychosocial stress if the hierarchy becomes unstable and their rank is being challenged. High rank can be associated with greater stress also in despotic primate species in which high-ranking individuals frequently reassert their dominance through physical aggression (e.g., ring-tailed lemurs); in these species or societies, high-ranking individuals may be more stressed than their victims. In contrast, in nondespotic primate species, in which direct competition over resources is weak and dominance hierarchies are loose or nonexistent, social factors are not a significant source of psychological stress.

In primate species in which low-ranking individuals are highly stressed, psychosocial stress can be alleviated by the presence of strong networks of kin and the receipt of social support (grooming, physical contact, and agonistic aid), the effective avoidance of high-ranking individuals, or the use of so-called alternative social strategies (e.g., engaging in mating behavior without been seen by high-ranking individuals to avoid triggering their aggression). Individuals with "relaxed" personalities, who can effectively discriminate between threatening and neutral stimuli and do not hyperreact to novelty may also be less vulnerable to status-related psychosocial stress (Sapolsky, 2005).

The relationship between status-related stress and AL in primates has been investigated mainly with regard to neuroendocrine biomarkers (primarily cortisol; Abbott et al., 2003), and to a lesser extent with immunological and cardiovascular measures. Little is known about the relationship between status-related psychosocial stress and catecholamines. With regard to cortisol, work with wild baboons conducted by Sapolsky (2005) as well as studies of macaques and other primates have shown that stressed individuals show elevated basal levels of cortisol and ACTH, in some cases higher and in other lower cortisol responses to environmental or pharmacological challenges, and hyper- or hyposensitivity to negative feedback regulation (i.e., cortisol responses to dexamethasone suppression test; e.g., Gust, Gordon, Hambright, & Wilson, 1993). In groups of baboons or macaques that have been newly formed or in which there have been dominance upheavals, all individuals have high cortisol levels regardless of rank (Abbott et al., 2003). In both captive long-tail macaques and wild baboons, low-ranking males have lower testosterone levels, presumably a suppression effect resulting from high stress and cortisol (Sapolsky, 2005). One study of captive rhesus macaque females suggested that aging affects the basal activity of the HPA axis (particularly, circadian variation in cortisol levels) but this effect can be masked by acute psychosocial stress (Gust et al., 2000). This study, however, provided no information on social status or other types of chronic stress. Therefore, the relationship between the HPA axis, chronic stress, and aging remains uninvestigated in primates. Data on social behavior in aging macaques indicate that low-ranking females exhibit more social withdrawal, more time spent alone,

and reduced activity levels when compared to high-ranking females, possibly due to greater psychosocial stress (Veenema, Spruijt, Gispen, & van Hooff, 1997; Veenema, van Hooff, Gispen, & Spruijt, 2001).

In captive long-tailed macaques (a species in which low-ranking individuals are highly stressed), low rank is associated with higher basal blood pressure, a sluggish activation of the cardiovascular stress response after a challenge and delayed recovery when it abates, a pathogenic cholesterol profile, and increased vulnerability to the atherogenic effects of a high-fat diet (e.g., Kaplan, Manuck, Anthony, & Clarkson, 2002). However, there have been no studies of cardiovascular indicators of AL in aging primates.

Previous studies of immune function in relation to psychosocial stress and aging in primates have relied on two assessment methods: in vitro assays of natural killer (NK) cytolytic activity and quantification of plasma cytokine concentrations (typically interleukin [IL]-1, -6, and -8; the IL-1 receptor antagonist, or IL-1ra, is also used as a marker of inflammation and infection; Coe & Laundenslager, 2007). In general, moderate acute stress is expected to enhance immunity, whereas chronic stress is expected to be immunosuppressive. Studies of rhesus macaques have shown that stressful changes in housing conditions for captive animals (Coe & Ershler, 2001) or capture and handling of free-ranging animals (Laudenslager et al., 1999) are followed by a decline in NK cytotoxicity toward K562 targets in vitro for up to 24 hr later. Coe and collaborators (Coe, 1993, 2004; Coe & Ershler, 2001) have also documented aging-related declines in NK cytolytic cell activity (both in basal conditions and in response to acute psychosocial stress) as well as reduction in cytokine release in responses to antigen challenges. However, they reported a great deal of interindividual variation in the timing and the magnitude of this decline in immune function and showed that this variation is predictive of health and longevity (Coe & Ershler, 2001). Specifically, monkeys showing low cytolytic activity at 20 years of age lived only a few more years, whereas those sustaining high lytic responses continued to live on for as much as a decade longer (Coe & Ershler, 2001).

The brain is a major target of AL (Ganzel, Morris, & Wethington, 2010; McEwen, 2007). Data from rodents have shown that chronic stress results in neuronal loss, loss of synaptic connectivity, or impairment of synaptic function in the hippocampus, amygdala, and prefrontal cortex (McEwen, 2007). A longitudinal study of aging human subjects showed that progressive increases in salivary cortisol over a 5-year period were associated with reduced hippocampal volume and reduced performance on hippocampal-dependent memory tasks (Lupien et al., 1998). After preliminary studies by Sapolsky and collaborators 20 years ago suggested that chronic psychosocial stress may damage the hippocampus in vervet monkeys (Sapolsky, Uno, Rebert, & Finch, 1990; Uno, Tarara, Else, Suleman, & Sapolsky, 1989), no further studies have been conducted in nonhuman primates. Although research by Morrison and collaborators has investigated many aspects of brain aging in rhesus monkeys, including the effects of estrogen (e.g., Hof & Morrison, 2004; Morrison 2003; Morrison & Hof, 2007; Radley & Morrison, 2005), this work has not investigated the effects of chronic social stress. Information on aging-related changes in brain function, rather than in brain structure, in primates has been provided by measurements of monoamine metabolites and neuropeptides. In humans, alterations of the monoamines dopamine, serotonin, and norepinephrine have been implicated in aging-related changes in cognitive function as well as in aging-related disorders such as Alzheimer's and Parkinson's disease (e.g., Mohr, Li, & Heekeren, 2010; Volkow et al., 1998). As with humans, primate studies have shown that aging is accompanied by a reduction of monoamine content in various areas of the brain as well as in cerebral spinal fluid (CSF) concentrations of the monoamine metabolites 5-HIAA, HVA, and MHPG (Elsworth, Leahy, Roth, & Redmond, 1987; Goldman-Rakic & Brown, 1981; Mohr et al. 2010; Shelton et al., 1988). Brain oxytocin and corticotropin-releasing factor are involved in regulating social, affective, and cognitive processes and are known to be affected by chronic stress; therefore, they are good candidates as mediators of AL in the brain. However, no information is available on the effects of aging on these neuropeptides in primates.

Finally, body condition and metabolic variables provide information about health and disease, and therefore are good candidates as biomarkers of tertiary outcomes of AL during aging in primates. Body weight (BW) and body mass index (BMI) generally decrease with increasing age (see below), and are especially low in individuals who are known to be chronically sick. Being overweight or obese is also a health risk factor, and there is evidence that the metabolic syndrome occurs in primates (Kaufman et al., 2005; Schwartz, Kemnitz, & Howard, 1993). Finally, analyses of blood chemistry variables in rhesus monkeys have shown that serum albumin and creatinine levels, albumin/globulin ratio, serum calcium, and total serum proteins exhibit the greatest magnitude of change in relation to age (Smucny et al., 2001, 2004). Again, little or no information exists about the relationship between chronic stress and metabolic indicators of AL in nonhuman primates.

Free-Ranging Rhesus Monkeys as Model Organisms for Research on Chronic Stress, AL, and Aging

Rhesus monkeys have been used as effective models for human aging in many research areas including neurobiology and cognition, skeletal and reproductive aging, dysfunction of the endocrine and immune system, and cardiovascular disease and diabetes (Roth et al., 2004). Most, if not all, biomedical aging research with rhesus monkeys to date, however, has been conducted in captivity and with individually housed subjects. Aside from a few behavioral studies, virtually no aging research has been conducted with free-ranging rhesus monkeys.

Studying aging in free-ranging rhesus monkeys is necessary and important for at least two reasons. The first is that free-ranging rhesus monkeys do not live as long as their captive counterparts. In captivity, the median life span of

rhesus monkeys is 25 years and the maximum life span is 40 years (Roth et al., 2004). In food-provisioned, predator-free free-ranging populations, however, the median life span is 15 years and less than 5% of individuals reach 25 years of age (Johnson & Kapsalis, 1995; see below), and in wild populations longevity is even lower. Thus, as civilization and availability of health care have extended the human life span, captivity appears to have similarly increased the life span of rhesus monkeys. This has important implications for aging because many of the aging-related disorders that we observe in both contemporary humans and captive rhesus monkeys are disorders that did not occur in most of the evolutionary history of these species. Studying the aging process in the environmental conditions in which humans spent most of their evolutionary history is obviously no longer an option. Free-ranging rhesus monkeys, however, give us the unique opportunity to study the aging process in environmental conditions that closely approximate those in which these primates evolved. The extent to which the aging process may be qualitatively and/or quantitatively different in free-ranging and captive rhesus monkeys is unclear. For example, it is possible that fundamental aspects of aging are the same but they are accelerated in free-ranging animals when compared to captive individuals, due to the greater cumulative effects of physical, ecological, and psychosocial stressors (i.e., AL) experienced by the free-ranging monkeys. Variation in aging rates between captive and wild animals, as well as between wild populations exposed to different degrees of environmental stressors, has been demonstrated in other species of mammals (Austad, 1993, 1996; Miller, Harper, Dysko, Durkee, & Austad, 2002). Therefore, one reason for studying aging in free-ranging rhesus monkeys is that by comparing free-ranging and captive monkeys we can understand how rates of aging can vary in different environments as a result of differences in AL.

A related reason for studying free-ranging monkeys is that studying the effects of AL on aging would not be possible using captive monkeys that are individually housed in cages. Rhesus monkeys are highly social animals that live in large groups, in which daily social activities depend on complex behavioral transactions regulated by kinship, dominance, or friendship. These groups have a strong matrilineal structure and a rigid dominance hierarchy. Rhesus monkeys are considered one of the most despotic primate species, in which low-ranking individuals experience high levels of chronic stress (Maestripieri, 2007). This is especially true for females, because female dominance rank is socially inherited from mothers and is highly stable throughout the lifetime. Therefore, young females born to low-ranking mothers typically remain low ranking for the rest of their lives. Low-ranking females experience chronic psychosocial stress in the form of high rates of aggression as well as threats (Maestripieri, 2007). In addition, low-ranking females typically have fewer relatives in their group and receive less effective social support than high-ranking females. Therefore, low-ranking rhesus females are good model organisms for studying the effects of status-related chronic psychosocial stress on AL during aging.

Rhesus monkey females are also good model organisms for studying the effects of reproduction-related chronic stress on AL and aging. Rhesus females begin reproducing at 3 or 4 years of age and continue to do so into their 20s. Pregnancy lasts 5.5 months, and infants are usually weaned within 6 or 12 months. Some rhesus females produce one infant per year for 15–20 years, whereas others give birth every other year or with longer interbirth intervals. In addition to the energetic stress of pregnancy and lactation, motherhood is also associated with significant psychosocial stress. Rhesus infants are at risk of kidnapping, harassment, and possibly also infanticide from other conspecifics; therefore, concerns over infant safety and the need for protection are a cause of significant anxiety in rhesus mothers (Maestripieri, 1993a, 1993b). Females who reproduce almost every year probably experience significant chronic stress, above and beyond status-related stress, and such reproductive stress should result in physiological AL and increased risk of disease and mortality during aging.

Chronic Stress, AL, and Aging in the Rhesus Monkey Population on Cayo Santiago

The Caribbean Primate Research Center of the University of Puerto Rico maintains a free-ranging population of rhesus macaques on the island of Cayo Santiago, Puerto Rico, which includes approximately 900–1000 individuals. The population was established in 1938 and has been under continuous observation since 1956 (Rawlins & Kessler, 1986). The monkeys are free-ranging on the island, yet they are easily identifiable and fully habituated to human presence, facilitating behavioral observations. They live in several large social groups and maintain a social structure and behavior very similar to their counterparts in Asia. There are no predators on the island and the monkeys are daily provisioned with commercial monkey chow, which is readily accessible to all members of the population. Therefore, all monkeys in the population have essentially the same diet and very similar life style. Except for periodic culling of individuals, mostly juveniles and males, the social structure of this population has been intact for decades, and all individuals have a fully known genealogical, reproductive, and clinical history. All matrilineal relatedness is known for all females in the population from birth records and observations, whereas paternal relatedness has been determined through genetic analyses. Finally, all monkeys on the island are trapped once a year, allowing scientists to obtain biological samples or any physical measurements they might need for their research. In an ongoing study of aging in this population, we have obtained evidence that low social status and reproduction are associated with stress and AL, and that this has consequences for longevity and aging.

Female reproduction is risky, costly, and stressful

Analyses of the long-term colony records of the Cayo Santiago population for a period of over 40 years showed that the median age for females who survive to reproductive age

is about 15 years and maximum life span is about 30 years of age (Hoffman, Higham, Mas-Rivera, Ayala, & Maestripieri, 2010). Many aging females continue reproducing until they die, but reproduction becomes increasingly costly with advancing age. One of the costs of reproduction is reduced survival: females have a higher probability of dying during the period in which they produce and raise offspring (i.e., the last few weeks of pregnancy and the first few postpartum months, when females are lactating and their offspring are fully nutritionally and socially dependent on them) than at other times of the year. This was demonstrated by analyzing seasonal fluctuations in births and deaths in adult females and males (Hoffman et al., 2008). A total of 7,402 live births (3,805 males, 3,597 females) were recorded in 45 years (1961–2005). Most births (86%) were concentrated in a 5-month period, from November through March, whereas on average the mating season began in mid-May and ended in October. Seasonal reproduction in this population is regulated by climatic factors; the onset of the Spring rainy season triggers the beginning of mating activity, and the birth season begins about 6 months after the onset of mating (Hoffman et al., 2008; Rawlins & Kessler, 1985). In the period between 1961 and 2005, the mating season, and therefore also the birth season, have commenced increasingly earlier over time, due to the fact that the Spring rainy season has begun increasingly earlier, possibly as a result of global climate changes (Hoffman et al., 2008). Data from 922 adult deaths (526 males, 396 females) in relation to time of the year indicated that both females and males exhibited significant seasonal fluctuations in their monthly probability of mortality, and that these fluctuations were significantly different between the sexes. Female mortality probability peaked in February and March, that is, the last 2 months of the birth season, whereas male mortality peaked in August, September, and October, that is, during the mating season (Hoffman et al., 2008). In addition to this analysis of mortality probabilities, we also compared the total number of female and male deaths in the mating and the birth seasons and found that more females died in the birth season than in the mating season, whereas more males died in the mating season than in the birth season. Finally, we showed that changes in the timing of the onset of the birth season from year to year were mirrored by concomitant changes in mortality. As the birth season has commenced increasingly earlier in the year, the average dates of female and male deaths have steadily shifted as well (Hoffman et al., 2008). Although in most cases the exact causes of death were unknown, the peak in female mortality during the birth season appeared to be due to increased vulnerability to infectious diseases such as tetanus, which in turn, may have been the result of reproduction-related stress and impaired immune function (Hoffman et al., 2008).

Increased risk of mortality is one of the costs of female reproduction. Other costs are energetic and metabolic. Sustaining pregnancy and producing milk are expensive activities that require the use of resources the body normally uses for its own maintenance or growth. Young females typically compensate for these costs by increasing their food intake and body mass. Increasing food intake and body mass may not be an option for aging females, whose body weight and body mass are much lower than those of younger adults, and which continue to decline with advancing age. Aging females attempt to compensate for the increasing energetic costs of reproduction in three different ways: by resting more and saving energy, by producing infants less frequently, and by producing smaller infants that require less nutritional expenditure. We reported that after giving birth, older females spent a higher proportion of time resting than younger females did (Hoffman, Higham, et al., 2010). We also reported that interbirth intervals became longer with advancing age, so that between 4 and 18 years of age 85% of females gave birth annually, whereas at 22 years of age more than 50% of females skipped 1 year (Hoffman, Higham, et al., 2010). Finally, there was a tendency for older females to produce infants that were of low body mass for their ages. The old females' compensating strategies allow them to produce infants even at very late ages, but in doing so they may jeopardize not only their own survival but also that of their offspring. In fact, the probability of offspring survival decreased steadily as a function of increasing maternal age (Hoffman, Higham, et al., 2010).

The energetic and metabolic costs of pregnancy and lactation are accompanied by other physiological costs that stem from motherhood-associated psychosocial stress. In rhesus monkeys and other primates including humans, motherhood is associated with elevated anxiety resulting from concerns about the infant's safety (Maestripieri, 1993a, 1993b). In addition, motherhood and lactation are also accompanied by sleep disruption, and tension and conflict in social relationships with older offspring or other adults. Not surprisingly, increased anxiety and stress are accompanied by activation of the HPA axis. In our study, we found that basal cortisol levels, as measured through assays of fecal samples collected on a continuous basis, were higher in pregnant and lactating than in nonpregnant nonlactating females (Hoffman, Ayala, Mas-Rivera, & Maestripieri, 2010). In addition, lactation was accompanied by greater plasma cortisol responses to the stress of capture and individual housing. This was demonstrated with both between-subject analyses (i.e., by comparing plasma cortisol responses to stress in lactating and nonpregnant nonlactating females) and within-subject analyses (i.e., by comparing the same females who were nonpregnant nonlactating in 1 year and lactating in another year; Hoffman, Ayala, et al., 2010; Maestripieri, Hoffman, Fulks, & Gerald, 2008). This implies that reproducing females have elevated concentrations of cortisol 9–10 months per year, and that females who give birth every year have elevated glucocorticoid hormones most of their life. Given the glucocorticoid-cascade hypothesis (Sapolsky, Krey, & McEwen, 1986), frequent reproduction is a source of significant AL in primate females, and its deleterious consequences should be especially apparent during aging.

Social status, chronic stress, and AL in free-ranging rhesus monkeys

Despite the effects of changes in female reproductive state from 1 year to the next, individual differences in plasma

cortisol responses to stress among aging rhesus monkey females were highly stable across 2 consecutive years, suggesting that there may have been differences in chronic stress among individuals above and beyond those associated with reproduction (Hoffman, Ayala, et al., 2010). Although dominance rank did not affect basal levels of cortisol in feces (Hoffman, Ayala, et al., 2010), high-ranking females had lower cortisol responses to stress than low-ranking ones. Specifically, females who belonged to the top matrilines in their respective groups ($n = 21$) had significantly lower cortisol levels than females belonging to the middle- and bottom-ranking matrilines ($n = 40$; high rank: 29.02 $\pm$ 1.81 μg/dl; middle and low rank: 34.46 $\pm$ 1.49 μg/dl; $U = 272$, $p = .02$). As mentioned before, rhesus macaque society is highly despotic and low-ranking females probably live in a state of constant anxiety and fear given the frequent threats and the unpredictable aggression they receive from high-ranking females. On Cayo Santiago, where social groups are larger than in the wild, the benefits of high rank seem to be restricted to the members of the top-ranking matriline. Middle-ranking females are probably just as stressed as low-ranking females and that may explain their similarity in cortisol responses to stress. With regard to the psychosocial stress associated with lactation, however, low-ranking females seem to be worse off than middle-ranking females. In fact, low-ranking females had greater increases in cortisol from the cycling to the lactating condition than did middle- or high-ranking females (Hoffman, Ayala, et al., 2010). Therefore, reproduction is particularly costly and stressful for low-ranking females, and low-status females who reproduce a great deal during their lifetime may experience particularly high AL during aging. Cortisol responses to stress, however, are influenced not only by social status and reproductive condition but also by genotype. We genotyped aging females for the serotonin transporter gene polymorphism (a long, *l*, and a short, *s*, allele are present in both rhesus monkey and human populations) and found that, other things being equal, females with the *ls* (23% of the population) or the *ss* (11%) genotype had higher cortisol responses to stress than females with the *ll* (66%) genotype, analysis of variance, $F(1, 36) = 7.54$; $p = .0094$. This finding suggests that genetic risk factors should be taken into consideration when examining interindividual variation in AL in both rhesus monkeys and humans.

Although the main focus of our aging study was on endocrine markers of AL, we also gathered data on body condition, and neurobiological, immunological, and metabolic biomarkers of AL and aging. Among our aging rhesus monkey females, we found strong negative correlations between age and BW and the BMI. In addition, there were strong positive correlations between BW and BMI measured in 2 consecutive years, suggesting that differences in body condition among aging females were stable over time. BW and BMI were positively correlated with total bilirubin (BW: rs $= .31$, $n = 52$, $p = .03$; BMI: rs $= .27$, $n = 51$, $p = .05$), total protein (BW: rs $= .27$, $n = 52$, $p = .05$; BMI; rs $= .31$, $n = 51$, $p = .03$), and total triglycerides (BW; rs $= .29$, $n = 52$, $p = .03$; BMI; rs $= .31$, $n = 51$, $p = .03$) and negatively correlated with levels of gamma-glutamyl transferase (BW; rs $= -.42$, $n = 52$, $p = .002$; BMI: rs $= -.43$, $n = 51$, $p = .002$). Therefore, old age and poor body condition were associated with alterations in glucose and lipid metabolism (see also Kessler & Rawlins, 1983).

We collected samples of CSF from both aging females and younger controls to measure concentrations of monoamine metabolites and peptides. The CSF concentrations of serotonin, norepinephrine, and dopamine were not significantly different in relation to female age or rank, but CSF concentrations of oxytocin were significantly higher in aging females (Parker, Hoffman, Hyde, Cummings, & Maestripieri, 2010). The plasma concentrations of cytokines IL-1ra, IL-6, and IL-8 measured after the stress of capture and housing in a cage were generally higher and more variable in older (>15 years) than in younger (<15 years) females (Hoffman et al., 2011). As with plasma cortisol levels, the concentrations of IL-1ra and IL-8 measured in the same subjects in 2 consecutive years were significantly positively correlated (IL-1ra; rs $= .64$, $n = 15$, $p = .01$; IL-8; rs $= .85$, $n = 18$, $p = .0004$), whereas for IL-6 the correlation was not significant (rs $= .06$, $n = 19$, $p = .77$). There was no significant effect of rank or a significant interaction between rank and age on cytokines. Average concentrations of IL-8 were significantly positively correlated with those of plasma cortisol ($n = 69$, rs $= .29$, $p = .01$), whereas cortisol was not correlated with IL-1ra or IL-6. There were no significant correlations between cytokine concentrations and CSF concentrations of the serotonin metabolite 5-HIAA, the dopamine metabolite HVA, or the dopamine precursor tyrosine. There were, however, significant negative correlations between the serotonin aminoacid precursor tryptophan and IL-1ra ($r = .52$, $n = 32$, $p = .002$), IL-6 ($r = .38$, $n = 33$, $p = .02$), and IL-8 ($r = .35$, $n = 34$, $p = .04$). These correlations were independent of age. One female in particular, had extremely low levels of CSF tryptophan, suggesting significant inflammation associated with activation of indole-3-dioxygenase. This female also had very high concentrations of all three cytokines (IL-1ra = 1530.93; IL-6 = 82; IL-8 = 2329).

Although social status did not significantly affect all physiological markers of AL, we found stability of individual differences in BW and BMI, plasma cortisol responses to stress, and plasma cytokine responses to stress in 2 consecutive years. These differences are consistent with the hypothesis that there are strong differences in chronic stress among individuals, and that chronic stress affects many aspects of the aging process. Body condition and cytokine concentrations were affected by age, whereas plasma cortisol concentrations were affected by rank and genotype. However, there was a correlation between plasma cortisol and one of the cytokines, suggesting an interaction between psychosocial stress, HPA function, and immune function in aging females.

In conclusion, although the study of chronic stress and AL during aging in free-ranging rhesus monkeys is just be-

ginning, there is already suggestive evidence that stress associated with low social status and reproduction influences different physiological indicators of AL. Being of low dominance rank in a nonhuman primate society can be chronically stressful and comparable to having low SES in human societies. However, primate research suggests that there are important factors modulating the relationship between social status, AL, and aging. Low status is more likely to be stressful in despotic than in egalitarian societies, and if such despotic societies are large and highly stratified, individuals of the middle class can be as stressed as those at the bottom of the hierarchy. Primate research also suggests that the stress of reproduction may be higher in low status than in high status females, and that females of low status who reproduce frequently in their lifetime may experience particularly high levels of AL during aging, with negative consequences for health and longevity. Future primate research can address the cumulative effects of chronic psychosocial and energetic stress on longevity, the rate of aging, and health using a longitudinal life span approach. Furthermore, comparing the aging process in free-ranging and captive rhesus monkeys can enhance our understanding of variation in aging rates and longevity in populations of the same species exposed to varying amounts of environmental stress.

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