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The Well-Being of Laboratory Non-Human Primates

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Abstract

The well-being of non-human primates in captivity is of joint concern to scientists, veterinarians, colony managers, caretakers, and researchers working with non-human primates in biomedical research. With increased regulatory, accreditation, and research focus on optimizing the use of social housing for laboratory primates, as well as the advent of techniques to assess indices of chronic stress and related measures of well-being, there is no better time to present the most current advances in the field of non-human primate behavioral management. The collective body of research presented here was inspired in part by a 2014 symposium entitled, “Chronic Hormones and Demographic Variables: Center-Wide Studies on Non-Human Primate Well-Being” held at the American Society of Primatologists’ 37th Annual Meeting in Decatur, GA. By aiming to target readership with scientific and/or management oversight of captive primate behavioral management programs, this special issue provides badly-needed guidance for implementing social housing programs in a research environment and leverages collaboration across multiple facilities to address key components of behavioral management, explore refinements in how well-being can be measured, and identify the interrelationships between varying indices.

Keywords

pair housing; psychological well-being; chronic stress; behavioral management; primate

Introduction

The well-being of non-human primates (NHPs) in captivity is of joint concern to scientists, veterinarians, colony managers, caretakers, and researchers working with NHPs in biomedical research. Federal laws in the United States have been in place for over 50 years that set the minimum standards of care and treatment for research animals, including but not limited to the United States Department of Agriculture (USDA) Animal Welfare Act of 1966 [USDA, 1966], the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals of 1985 [National Institutes of Health, 1986], and the National Institutes of Health (NIH) Office of Laboratory Animal Welfare's (OLAW) Guide for the

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Care and Use of Laboratory Animals, originally published in 1963 [Animal Care Panel, 1963]. Each of these has been revised numerous times, and along with changing regulatory and accreditation expectations and advances in the research on behavioral management techniques, best practices continue to evolve. These practices are best guided by the applied scientific literature. However, there are several notable gaps in this literature pertinent to essential issues in the field of behavioral management.

First, while social housing is widely held to be the most effective technique for enhancing psychological well-being, the body of literature on the topic [e.g., Baker et al., 2012a, 2014; Doyle et al., 2008; Eaton et al., 1994; Lee et al., 2012; Schapiro et al., 1996] has several limitations. Perhaps most significantly, studies on pair housing of NHPs currently used in biomedical research are primarily restricted to a few macaque species, namely the rhesus macaque *(Macaca mulatta)* and the long-tailed macaque *(Macaca fascicularis).* There is little guidance available for the social management of other taxa commonly housed in laboratories. Second, the literature focusses on the behavioral effects of housing in successfully established pairs, and less on the process and outcome of attempting to move animals from single housing to a social setting. Last, relatively unaddressed are issues relating to long-term management and the impact of post-introduction changes in social housing.

Second, other aspects of well-being, including physiological stress, self-injurious behavior (SIB), alopecia, and anxious behavior—though relatively widely reported on—have not been considered with respect to each other. For example, we do not know whether NHPs that exhibit SIB are also those that exhibit anxious behavior, or whether alopecia is also an indicator of chronic stress.

This special issue, aims to address these aspects of NHP behavioral management by first presenting the most recent findings as they relate to social housing, including empirical research articles on social housing in species under represented in the literature and reviews of pair-housing techniques and management in macaques. Additionally, this issue for the first time presents research on a long-term index of hypothalamic—pituitary—adrenal (HPA) axis activity, hair cortisol, as it relates to behavioral indices of well-being, including SIB, anxious behavior, and alopecia. The issue closes with a review article highlighting the utility of applied behavior analysis in animal behavior management. Collectively, this issue aims to move the field of NHP well-being forward by filling gaps that currently hamper the optimal use of social housing across NHP species, by refining our understanding and interpretation of several behavioral and physiological attributes used as indices of welfare, and by identifying a theoretical framework for addressing deficits in welfare. The findings presented here will ensure that laboratory researchers embody the American Society of Primatologists, 2001 Policy Statement, “Principles for the Ethical Treatment of Non-Human Primates” by making use of “information on a species’ natural history to improve management and enrich environments,” as well as the American Society of Primatologists, 2014 Policy Statement “Social Housing for Nonhuman Primates Used in Biomedical or Behavioral Research in the United States.”

Overview of Part I: Pair Housing in Laboratory Primates

This section of the special issue begins with two extensive review articles that review the scientific literature concerning social introductions, and address both practical numerous aspects of introducing and maintaining macaques (genus *Macaca)* in pairs and the interface between the social environment and biomedical research [Hannibal D, Bliss-Moreau E, Vanderleest J, McCowan B, Capitanio J. Unpublished. Laboratory rhesus macaque social housing and social change: Implications for research. American Journal of Primatology; Truelove M, Martin A, Perlman J, Wood J, Bloomsmith M. Unpublished. Pair housing of macaques: A review of partner selection, introduction techniques, monitoring for compatibility, and methods for long-term maintenance of pairs. American Journal of Primatology]. Truelove M, Martin A, Perlman J, Wood J, Bloomsmith M. Unpublished. Pair housing of macaques: A review of partner selection, introduction techniques, monitoring for compatibility, and methods for long-term maintenance of pairs. American Journal of Primatology provide a thorough literature review and set of recommendations for a number of key issues involved in the management of macaques, including the selection of social partners, methods for introducing partners (including those employing gradual steps, novel caging, and anesthetization), strategies for monitoring and maintaining compatible pairs, and other programmatic issues. Last, they provide a detailed descriptive overview of a successful social housing program.

Hannibal D, Bliss-Moreau E, Vanderleest J, McCowan B, Capitanio J. Unpublished. Laboratory rhesus macaque social housing and social change: Implications for research. American Journal of Primatology highlight the essential point that a transfer from single housing to successful social housing represents only a fraction of the social changes to which laboratory NHPs are exposed. In the face of the propensity for the applied social housing literature to focus on the transition from single to pair housing, this article assists with harmonizing social management and research aims, by pointing out that changes in the social setting can exert physiological and health effects with the potential impacts on research outcomes. Social housing may strengthen the research model, but both successful social housing and negative changes in social housing (destabilization or social separation) can introduce significant physiological confounds involving alterations to the hormonal and immune systems and resultant effects on disease progression. These points, illustrate the necessity of aligning over time procedures to address animal and research needs. The authors, also present a convincing case for biomedical scientists to take into account not only the implications to their research goals of social housing *per se* but changes in the social status of their subjects.

The remaining articles in this section of the special issue present empirical research, involving large numbers of subjects, that examines how pair introductions are influenced by species, demography, partner selection techniques, and early interactions that may predict introduction outcome. Capitanio JP, Blozis SA, Snarr J, Steward A, McCowan BJ. Unpublished. Do “birds of a feather flock together” or do “opposites attract?” Behavioral responses and temperament predict success in pairings of rhesus monkeys in a laboratory setting. American Journal of Primatology point out that the literature available to guide the selection of potential partners, on the basis of characteristics predictive of introduction

success has predominantly taken the form of conference abstracts and employ a number of different behavioral screening tools (e.g., involving measurements of behavioral inhibition, response to humans, or assigning perceived potential social rank), in attempt to meet this goal. Perhaps not surprisingly, there is little consensus as to the characteristics of individuals or the disparity in characteristics between potential partners that may predict introduction outcomes. The authors address these gaps in the literature with a retrospective analysis of 340 pairing attempts of rhesus macaques (*Macaca mulatta*), using a well-characterized tool, the BioBehavioral Assessment [Golub et al., 2009].

Jorgensen M, Lambert K, Breux S, Baker K, Weed J. Unpublished. Pair housing of vervets/ African Green Monkeys for biomedical research. American Journal of Primatology, address the social management of vervet monkeys (*Chlorocebus aethiops*) through a cross-facility comparison of the introduction methodology and introduction outcomes of 271 pairing attempts. Anecdotally, inquiries for assistance between colleagues for introducing this species are relatively frequent in comparison to queries concerning other species [pers. Obs]. This article has significant implications for identifying the role of alternative introduction techniques in the widely disparate results across facilities, and illustrates the potential pitfalls of applying methodologies developed for macaque social management to other taxa.

Williams LE, Coke CS, Weed JL. Unpublished. Socialization of adult owl monkeys (Aotus spp) in captivity. American Journal of Primatology report the outcome of 477 pair introductions involving two species of owl monkeys (*Aotus nancymaae* and *A. azarae*). While naturalistic social groupings (i.e., monogamous pairs with associated juveniles or infants) are preferable, colony demographics (e.g., the number of available males and females) or research requirements (e.g., the need to avoid breeding) can severely limit the pool potential partners. In these circumstances, configurations not found in the wild such as isosexual pairings, are the only means to provide a social environment. The authors compare outcomes of species-typical male-female pairs with isosexual pairings, describe an introduction protocol for this species and identify several behaviors whose observation during the first hour of pairing predicts a successful introduction.

Finally, Worlein JM, Kroeker R, Lee GH, Thom JP, Bellanca RU, Crockett CM. Unpublished. Socialization in pigtailed macaques (Macaca nemestrina). American Journal of Primatology describe a methodology for introducing pigtailed macaques (*Macaca nemestrina*) and analyze the results of 674 pair introductions. Specifically-defined compatibility scores based on levels of affiliative, agonistic, and tension-related behaviors were assessed as predictors of introduction outcome and the incidence of wounding. This article also compares the result of introductions into full contact pair housing and protected contact (also termed grooming contact) housing, which involves the separation of individuals by a barrier that prevents cage entry but permits social contact, not only in terms of introduction success but long-term compatibility as well. In terms of behavioral benefits, protected contact housing has been found to be inferior to full contact in rhesus macaques but not in long-tailed macaques [Baker et al., 2012b, 2014; Lee et al., 2012]. This article adds to this literature for a third macaque species widely used in biomedical research. Comparing full versus protected contact introduction, is particularly important because the current edition of the Guide for the Care and Use of Laboratory Animals uses language that

categorizes protected contact housing as a form of single housing [National Research Council, 1996] but more recently categorizes it as a form of social experience [http://www.aaalac.org/accreditation/faq_landing.cfm#C6].

Collectively, this part of the special issue is intended to assist both with navigating constraints and strengthening social management programs in the laboratory setting. The behavioral management field will benefit from objective testing of the utility and value of the various methods discussed in this special section, as well as recommendations for successful social housing programs, in order to harmonize the care and use of laboratory NHPs and ensure their psychological well-being.

Overview of Part II: Long-Term Cortisol, Hair Loss, and Behavioral Indices of Well-Being in Laboratory Primates

Part II of the special issue is comprised primarily of empirical research articles, aimed at elucidating the complex relationships between several indices of NHP well-being. Importantly, the research in this section relies on collaborations between several primate facilities across the United States. One highlight of this section is the cross-disciplinary application of the hair cortisol assay, which was developed nearly ten years ago to assess long-term HPA axis activity [Davenport et al., 2006]. Though the development of this assay has led to its widespread application as a biomarker of behavioral health in both human and nonhuman primates [for reviews, see Meyer & Novak, 2012; Staufenbiel et al., 2013], little is known about hair cortisol values as they relate to commonly relied upon behavioral indices of NHP well-being, such as alopecia, anxious behavior, and SIB.

The first three papers describe risk factors for and long-term changes in alopecia in rhesus macaques. Novak MA, Menard MT, El-Mallah SN, Rosenberg KL, Lutz CK, Worlein JM, Coleman K, Meyer JS. Unpublished. Hair loss as a possible biomarker for stress in captive rhesus monkeys (Macaca mulatta). American Journal of Primatology examine rates of change in alopecia across 8 months as they related to changes in hair cortisol values in monkeys housed at three different facilities. Importantly, they found that the relationship between hair cortisol and changes in alopecia was different for monkeys that regained their hair versus those that remained alopecic, and that these relationships were facility specific. Kroeker R, Lee GH, Bellanca RU, Thom JP, Worlein JM. Unpublished. Prior facility affects alopecia in adulthood for rhesus macaques. American Journal of Primatology assess prior facility origin effects on rates of alopecia in adult monkeys currently housed in the same facility. Despite the fact that the majority of animals in this study left their prior facility over 2 years before the onset of the study, facility origin effects remained, indicating that prior experiences may have long-lasting effects on rates of hair loss. Dettmer AM, Rosenberg KL, Menard MT, El-Mallah SN, Woodward RA, Suomi SJ, Meyer JS. Unpublished. Differential relationships between chronic hormone profiles in pregnancy and maternal investment in rhesus monkey mothers with hair loss in the neonatal period. American Journal of Primatology focus on alopecia in a particularly at-risk group of captive NHPs, pregnant rhesus monkeys, and present findings linking hair loss in pregnancy with higher hair cortisol values and differential maternal investment in the neonatal period. Collectively, the authors of the first three papers in this section present alopecia as a commonly occurring

phenomenon in captive NHPs that is relatively stable over time. They also highlight the value of conducting research across multiple facilities.

The next three articles, provide unique information about multiple behavioral and hormonal indices of well-being across facilities. Hamel AF, Lutz CK, Coleman K, Worlein JM, Peterson EJ, Rosenberg KL, Novak MA, Meyer JS. Unpublished. Responses to the human intruder test are related to hair cortisol phenotype and sex in rhesus macaques (Macaca mulatta). American Journal of Primatology begin by examining the relationship between hair cortisol and behavioral responses to a common assessment given to laboratory NHPs, the Human Intruder Test [HIT; Kalin & Shelton, 1989]. The HIT is a reliable behavioral assay that provides information about a monkey's temperament and trait-like behavioral reactivity [Kalin & Shelton, 1989]. Previous studies examining HIT responsivity and HPA axis activity have relied on plasma cortisol levels, however, which may be confounded by the capture and sampling stress required by the HIT. Hamel AF, Lutz CK, Coleman K, Worlein JM, Peterson EJ, Rosenberg KL, Novak MA, Meyer JS. Unpublished. Responses to the human intruder test are related to hair cortisol phenotype and sex in rhesus macaques (Macaca mulatta). American Journal of Primatology study represents the first examination of HIT responsivity as it relates to chronic HPA activity (i.e., hair cortisol). Coleman K, Lutz CK, Worlein JM, Gottlieb DH, Peterson EJ, Lee GH, Robertson ND, Rosenberg KL, Menard MT, Novak MA. Unpublished. The correlation between alopecia and temperament in rhesus macaques (Macaca mulatta). American Journal of Primatology then describe their study examining alopecia and temperament in rhesus monkeys across the same four facilities as in Hamel AF, Lutz CK, Coleman K, Worlein JM, Peterson EJ, Rosenberg KL, Novak MA, Meyer JS. Unpublished. Responses to the human intruder test are related to hair cortisol phenotype and sex in rhesus macaques (Macaca mulatta). American Journal of Primatology, filling an important gap in the literature. Importantly, they rely on a cage side version of the HIT that helps to minimize potential reactivity resulting from separation from the social partner [Gottlieb & Capitanio, 2013]. Peterson EJ, Worlein JM, Lee GH, Varner EK, Dettmer AM, Novak MA. Unpublished. Rhesus macaques (Macaca mulatta) with a history of self-injurious behavior show a blunted affect in response to a behavioral anxiety assessment. American Journal of Primatology end the collection of empirical research articles with a study examining the relationship between SIB and anxious temperament in rhesus monkeys, a relationship that has heretofore not been fully established. In addition to yielding important new information about the relatedness of multiple physiological and behavioral indices of well-being, these articles also highlight the importance of cross-facility collaborative research.

This section ends with a review by Martin AL. Unpublished. The primatologist as a behavioral engineer. American Journal of Primatology describing the utility of a behavior analytic theoretical framework in studies of NHP well-being, with particular emphasis on the prevention and treatment of abnormal behaviors. This manuscript takes human clinical approaches and applies them to primatology, which is a unique reversal of translation of research methodologies.

In sum, this section of this special issue provides insight into recent advances in NHP well-being, and will advance the field by highlighting the utility of multi-faceted approaches to assessing well-being across multiple facilities.

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