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Improving transparency – a call to include social housing information in biomedical research articles involving nonhuman primates

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Accurate, transparent, and complete reporting of research methods are basic and essential scientific principles that enable investigators to evaluate the published research (Koroshetz, Behrman et al. 2020, Bliss-Moreau, Amara et al. 2021). Some information, such as the number of animals utilized in a study, the statistical method, and the types, and models of various assays, generally appear in scientific publications. Authors who submit manuscripts to peer-reviewed journals that lack this type of information will probably be asked either by a reviewer or the journal editor to add it before the manuscript can be published. However, data regarding the social housing conditions that the animals experience during the study are usually absent. In this commentary, we will demonstrate the profound biological implications of housing research nonhuman primates (NHPs) under different social conditions. Due to these known effects of housing conditions on the biological output of NHPs, we will then suggest that failure to include pertinent details in manuscripts is likely to reduce the readers' ability to properly assess the study's strength, interpret the results in the appropriate context and attempt replicating it. Finally, we will call on the

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Ethics statement

All research complied with the US Department of Agriculture Animal Welfare Regulations and adhered to the American Society of Primatologists (ASP) Principles for the Ethical Treatment of Non-Human Primates.

Conflict of interest

The authors declare that there is no conflict of interest.

scientific community to adopt a requirement to include specific information regarding the social housing conditions of NHPs that are used in biomedical research.

Sociality is a fundamental feature that is evident in every aspect of the lives of gregarious NHP species with both direct and indirect impacts on the animals' fitness (Archie, Tung et al. 2014, Brent, Ruiz-Lambides et al. 2017, Ostner and Schülke 2018). For example, during female-female conflict, male rhesus macaques (*Macaca mulatta*) were more likely to support and father the offspring of females with which they shared a higher sociality index (i.e. engaged in more affiliative behaviors) than females with which they affiliated less frequently (Kulik, Muniz et al. 2012). Similarly, adult female baboons (*Papio cynocephalus*) that maintained strong and stable social bonds with members of their troop lived longer (Archie, Tung et al. 2014), and infants of females that remained in proximity with and groomed other females had a higher survival rate than infants of more isolated dams (Silk, Alberts et al. 2003).

The understanding of the critical role of sociality in NHP societies has contributed to the allocation of substantial resources and efforts toward maximizing the number of socially housed NHPs in research facilities. Reflecting these efforts, surveys conducted in recent years demonstrated an increase in the number and proportion of socially housed research NHPs in the U.S (almost exclusively in pairs. From 46% of the indoor housed population in 2003 to 65% in 2014). (Baker, Weed et al. 2007, Baker 2016). However, despite this saluted progression, large species-appropriate social groupings that provide the full range of social interactions are not typical for NHPs in biomedical research. Instead, research requirements dictate that a significant majority of socially housed NHPs are housed either in small groups or in pairs. Additionally, some research primates are housed singly with appropriate regulatory exemptions. (Baker 2016, Bennett 2016). Since the social aspect has a substantial impact on the fitness of wild NHPs it is plausible that maintaining research NHPs under social conditions which differ significantly from the species-typical social setting will affect the animals' biological output and influence data attained from the animals. Thus, one can expect to detect differences in biological parameters between singly, pair, or group-housed NHPs.

Indeed, there is ample evidence supporting the notion that different social housing conditions are associated with behavioral and physiological variability. If ignored, such variability has the potential to confound studies, reduce validity, and impair the interpretation of results. Behaviorally, the homeostasis of research subjects has been shown to be perturbed by single housing. For example, a study involving 3,823 rhesus macaques found that animals were 49% more likely to exhibit motor stereotypic behaviors that generally indicate poor welfare when singly housed than when housed in continuous full contact with a compatible social partner (Gottlieb, Maier et al. 2015). Macaques' tendency to develop both self-injurious behavior (SIB) and alopecia (hair loss) was positively correlated with the number of days the animals had been singly housed (Bellanca and Crockett 2002, Lutz, Well et al. 2003, Lutz, Coleman et al. 2016). Interestingly, both stereotypic behaviors and SIB were associated with physiological consequences, including suggested malfunction of neurological loops connecting the cortex and the basal ganglia (Pomerantz, Paukner et al. 2012), altered dopamine receptor levels in various brain regions

(Freeman, Rice et al. 2015), and altered serotonin and opioid measures, in addition to changing responses to stress (See Tiefenbacher, Novak et al. 2005 for a review). The variation introduced by social housing conditions may be also be manifested in by additional outcome measures, including urinary cortisol (Hannibal, Cassidy et al. 2018), fecal cortisol and heart rate (Doyle, Baker et al. 2008), proliferating B cells (Pahar, Baker et al. 2020), neuroendocrine function (e.g., see review by Cacioppo, Cacioppo et al. 2015), and the ratio of CD4 to CD8 lymphocytes (Schapiro, Nehete et al. 2000). Furthermore, several serum biochemical and hematological parameters, such as blood urea nitrogen, glucose, alanine aminotransferase, and serum calcium concentrations, differed significantly between singly housed and socially housed cynomolgus macaques (*Macaca fascicularis*) (Xie, Zhou et al. 2014, Koyama, Tachibana et al. 2018). Recently, Guerrero-Martin, Rubin et al. (2021) reported that singly and socially housed pigtailed macaques (*Macaca nemestrina*) infected with simian immunodeficiency virus exhibited marked differences in disease progression. Thus, single housing was associated with a higher viral load in the plasma and cerebrospinal fluid, a greater decline in CD4 and CD8 T-cells, and a lower CD4/CD8 ratio compared with socially housed macaques. Failure to report the different housing conditions would have compromised the ability of other investigators to effectively evaluate the robustness of this study. Perhaps more importantly, without information about the social housing conditions of the study animals, the results of the study may have been misinterpreted, attributed to other factors, or clouded by this confounding factor.

The ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines are a checklist of standards intended to “ensure transparent and thorough reporting. This enables readers and reviewers to scrutinize the research adequately, evaluate its methodological rigor, and reproduce the methods or findings” (Percie du Sert, Hurst et al. 2020). The guidelines are proposed for all research animals and should be applied throughout the course of each project, from the initial study planning to publication. The original publication of the ARRIVE guidelines in 2010 aimed to increase transparency by providing a framework for standardized reporting of data in studies using live animals (Kilkenny, Browne et al. 2010). However, data from recent years show that across scientific disciplines, implementation of the ARRIVE guidelines has been only partially met (Percie du Sert, Hurst et al. 2020). This outcome prompted an update to the guidelines, which intended to increase their implementation by providing more justification and clarification (Percie du Sert, Hurst et al. 2020). Minimum requirements of the 2020 ARRIVE guidelines include reporting on study design, sample sizes, inclusion/exclusion criteria, randomization, blinding, outcome measures, statistical methods, experimental animal information (specifically, age, sex, strain, and weight), experimental procedures, and results. In addition to the requirements, the guidelines also incorporate a set of recommendations for reporting, which includes animal housing, husbandry, and enrichment, and the social setting is mentioned as an example of information that the guidelines recommend be reported. We contend that this should be promoted to a requirement for NHP biomedical research.

Social housing conditions will inevitably vary among experiments, laboratories, and facilities. This variability and the known impacts of variation in housing condition places a premium on providing this information in manuscripts. We argue that including this information in scientific publications is crucial for the interpretation of research findings in

the appropriate context, for understanding some unexplained variability in study findings, and ultimately for enhancing the transparency of NHP biomedical research.

The Behavioral Management Consortium (BMC) consists of coordinators of the behavioral management programs at the seven US National Primate Research Centers, as well as the Centers for Disease Control and Prevention (CDC) and Johns Hopkins University. Its members, who author this commentary, call for incorporating descriptions of the duration and/or phases of the study in which animals were housed in different social conditions in the resulting publication. An appropriate approach for reporting is including a description of social housing conditions in relation to study design, i.e., the intended setting for each study phase and treatment group, as well as significant deviations from the predetermined types of housing employed. For example, one may need to report that 40 animals were assigned to a 6-month long study, 38 of which were housed in continuous full contact for the duration of the study, and two animals were paired for one month, then separated due to behavioral incompatibility and remained singly housed for the remainder of the study.

Whereas our goal in this commentary is to promote a policy change, additional benefits to this initiative are likely to ensue. Including this information in publications will also familiarize scientists with the manner by which other investigators conducting similar studies are housing their animals, and encourage them to consider the implications of various housing conditions on their research outcomes. Notably, the sharing of information is likely to encourage the increased use of social housing of research NHPs when investigators realize that it has been successfully implemented in research similar to their own. Access to social housing data will demonstrate not only the feasibility of socially housing NHPs in types of studies that traditionally required single housing but also by understanding its superiority over single housing in terms of the animals' welfare and enhanced translational value of the research (Graham and Schuurman 2015).

We do note that additional elements can impact the animal's biological output such as the animal's ontogeny and rearing environment influencing factors such as brain structural integrity (Howell, McCormack et al. 2013) and CD8 cells and natural killer cell activity (Lubach, Coe et al. 1995). Although reporting the animal's early rearing environment may improve the ability to properly evaluate research studies, such information is often unavailable to investigators and may be complex to report concisely. In contrast, the social housing conditions of the animals while on the study is more readily available, and including it is more practical. Finally, although we acknowledge that accurate reporting is crucial whether the research was conducted in the laboratory, zoo, sanctuary, or other settings, here we focused solely on the biomedical research environment.

Recently, the editorial board of the *American Journal of Primatology* decided to incorporate this requirement for all authors who submit a manuscript to their journal involving captive nonhuman primates. The BMC commends this recent change and calls for other peer-reviewed journals to follow suit.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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