Exp. Anim. 67(1), 31–39, 2018

—Original—

Larger cages with housing unit environment enrichment improve the welfare of marmosets

Takuro YOSHIMOTO[1)], Eiki TAKAHASHI[1)], Shunji YAMASHITA[2)], Kiichi OHARA[2)], and Kimie NIIMI[1)]

[1)]*Research Resources Center, RIKEN Brain Science Institute, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan*
[2)]*O'HARA & CO., LTD., 4-28-16 Ekoda, Nakano-ku, Tokyo 165-0022, Japan*

Abstract: The provision of adequate space for laboratory animals is essential not only for good welfare but accurate studies. For example, housing conditions for primates used in biomedical research may negatively affect welfare and thus the reliability of findings. In common marmosets (*Callithrix jacchus*), an appropriate cage size enables a socially harmonious family environment and optimizes reproductive potential. In this study, we investigated the effects of cage size on body weight (BW), behavior, and nursing succession in the common marmoset. Large cages (LCs) with environment enrichment led to an increase in BW while small cages (SCs) caused stereotypic behaviors that were not observed in LCs. In addition, the BW of infants increased with aging in LCs. Our findings indicate that the welfare of marmosets was enhanced by living in LCs. Research on non-human primates is essential for understanding the human brain and developing knowledge-based strategies for the diagnosis and treatment of psychiatric and neurological disorders. Thus, the present findings are important because they indicate that different cages may influence emotional and behavioral phenotypes.

Key words: body weight change, cage size, common marmoset, nursing success, stereotyped behavior

Introduction

The common marmoset (*Callithrix jacchus*) is a small New World primate native to eastern Brazil that has been used in biomedical fields such as neuroscience, reproductive biology, infectious disease, and drug development [20]. The common marmoset has several advantages relative to *Macaca* species including a smaller body size, availability, easy breeding in captivity, low husbandry cost, avoidable zoonotic issues, early sexual maturation, and a short gestation period [1, 31]. In addition, the development of transgenic marmosets has become possible [29]. As with the Human Genome Project almost 25 years ago, there is an emerging interest in brain-mapping projects such as the Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) initiative in the United States, the Human Brain Project (HBP) in Europe [17], and the Brain Mapping by Integrated Neurotechnologies for Disease Studies project (Brain/Minds) in Japan [23]. The Brain/Minds project aims to map the structure and function of neuronal circuits to ultimately understand the vast complexity of the human brain and to this end studies the common marmoset. This has increased the number of studies using common marmosets as a laboratory model [20, 25].

At the same time, there has been a substantial increase

(Received 15 May 2017 / Accepted 24 July 2017 / Published online in J-STAGE 18 August 2017)
Address corresponding: E. Takahashi, Research Resources Center, RIKEN Brain Science Institute, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan

in the recognition of the importance of the welfare of nonhuman primates in recent years. Several studies on common marmosets have indicated that marked changes in the range and frequency of behavior are associated with changes in the physical dimensions of their natural environments [18]. The provision of adequate space for laboratory animals is essential for good welfare; in common marmosets, it helps to create a socially harmonious family environment and optimizes their reproductive potential. However, there are differences on the recommended cage size for marmosets between the Institute for Laboratory Animal Research (floor area: 2,000 mm^2, height: 762 mm) and the European Union Directive (floor area: 5,000 mm^2, height: 1,500 mm).There is also some debate over standards of cage size [10, 22]. Nonetheless, experimental designs need to quantify the possible influences of environmental conditions on the physiology and behavior of common marmosets. Because it is impossible to conduct a detailed comparison of captive (in the laboratory) and wild (in nature) behavioral repertoires using non-human primates, an accepted alternative involves investigating the frequencies of abnormal behavioral patterns, such as stereotypical motor acts. When keeping common marmosets in the laboratory, the goal should be to provide an environment that minimizes abnormal behaviors, and cage size is an obvious variable that should be taken into account. Thus, we investigated the influence of cage size on the body size, stereotypical behaviors, and nursing success of common marmosets housed in a laboratory setting.

Materials and Methods

Ethical declaration

This study was conducted in accordance with the Declaration of Helsinki and approved by the Animal Experiments Committee of the RIKEN Brain Science Institute. All animals were cared for and treated humanely in accordance with the Institutional Guidelines for Experiments using Animals.

Animals

Common marmosets were reared at the RIKEN Brain Science Institute (Saitama, Japan) and housed in a temperature- (27 ± 3°C) and humidity-controlled (50 ± 20%) environment with a 12 h light/dark cycle (light period: 8:00–20:00). The monkeys were allowed *ad libitum* access to tap water and food pellets (CMS-1M; CLEA Japan Inc.; Tokyo, Japan) and were given either a piece of Calorie Mate (Otsuka Pharmaceutical Co., Ltd.; Tokyo, Japan) or Castella (Imuraya Co., Ltd.; Mie, Japan) as a treat each day [32, 33].

Cages

We compared the effects of two cage sizes: small cages (SCs; 600 W × 430 D × 660 H mm, Fig. 1A; CLEA Japan Inc.) and large cages (LCs, 1,200 W × 750 D × 2,100 H mm [including roof parts], Fig. 1B; O'HARA & CO., LTD.; Tokyo, Japan). SCs consisted of wire walls and a floor and contained two perches, a removable step, a feedbox holder, and a feed-water inlet. LCs consisted of lattice punching panel walls and a floor and contained four long wooden sticks with two perches, four removable steps, four nest boxes, four feedbox holders, and four feed-water inlets.

BW measurements and behavioral observation in the relocation test

Single-living adult males (3–6 years old) that had been reared in SCs for at least 6 months were relocated to either an LC (SC>LC; n=8, Fig. 2A) or another SC as a control (SC>SC; n=8, Fig. 2B) and kept in single-living conditions. To avoid the influence of movement stress on body weight (BW), the 3-month period after moving was considered an acclimation period and data from this period were excluded from the study. Comparisons of BW and behavior and before and after relocation were performed. BW was measured using an SH-2000 scale (A&D Co., Ltd., Tokyo, Japan). Video recordings (EosKissX4; Canon Inc., Tokyo, Japan) of the behaviors of each animal were conducted two separate times: 2 months prior to, and 4 months after, the moving day. The video recorders were set up in front and outside of the cages and recording was conducted throughout the 12 h light phase of the light/dark cycle. Video data were analyzed with Matlab Software (The MathWorks, Inc., MA, USA).

BW changes in infants and parents

To measure the effects of cage type on the growth of infants, we measured changes in the BWs of parents (SC; n=4 pairs, LC; n=10 pairs, each of which had been reared in one particular cage type for at least 6 months) and their infants born in the different cage types (SC; n=5, LC; n=17, Table 1). The BW measurements were taken on the day of birth (DOB) of the infants and at 1, 2, 3,

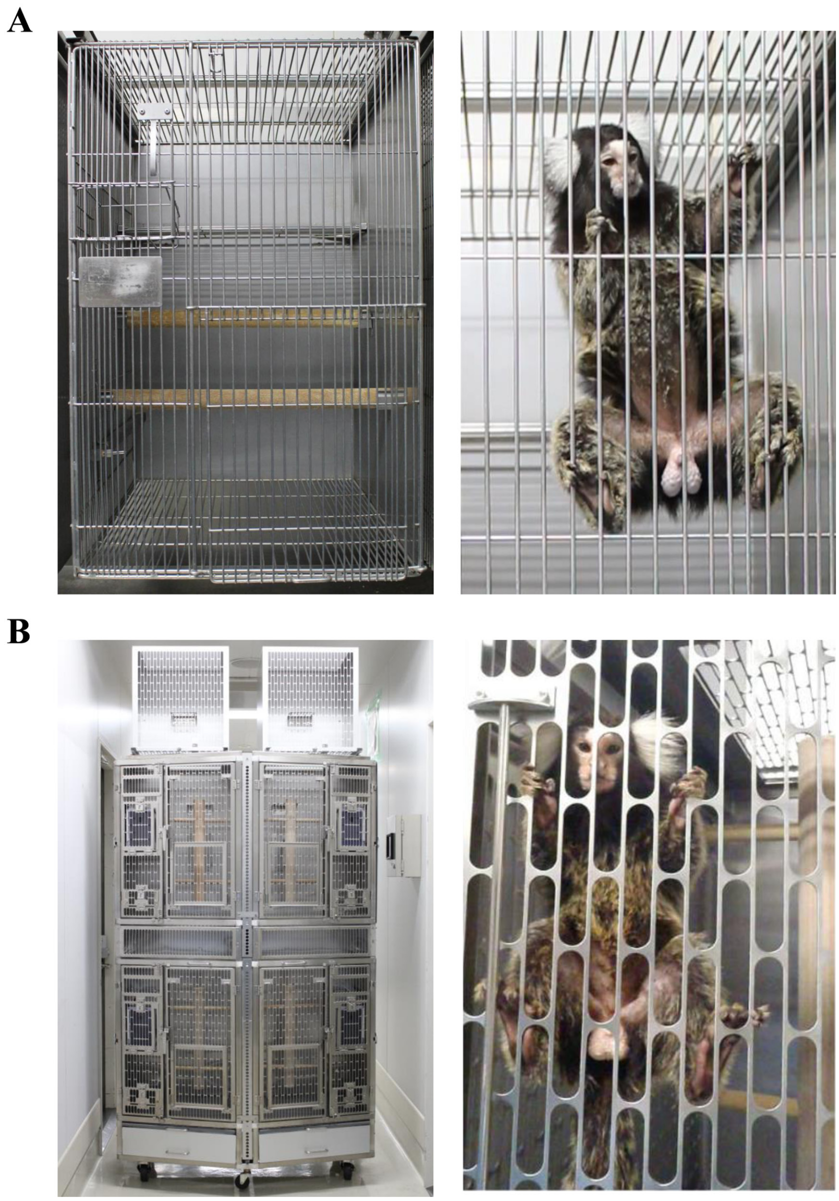

Fig. 1. Marmoset cages and marmosets in each cage. A) Small cage (SC). B) Large cage (LC).

and 4 months after the DOB. None of the animals were relocated from their cages for the duration of the experiment.

Data analysis

All statistical analyses were performed using GraphPad Prism Software version 6 (GraphPad Software Inc., CA, USA). Wilcoxon matched-pairs signed rank tests were used to compare the BWs of adult males in each cage type before and after relocation, and two-way repeated measures analysis of variance (ANOVA) tests with Sidak's multiple comparisons analyses were conducted to compare the changes in BW of all monkeys during the 4 months after the DOB. P-values<0.05 were considered to indicate statistical significance, and all data are presented as means ± SEMs.

Results

BW in the relocation test

The mean BW of the SC>LC group significantly increased after relocation (before: 362.2 ± 8.1 g; after:

Table 1. The number and sex of infants in each pair are presented

Pair No.	LC 1	LC 2	LC 3	LC 4	LC 5	LC 6	LC 7	LC 8	LC 9	LC 10	SC 1	SC 2	SC 3	SC 4
Male	1		2		1	2	1	2	1	2	1	1	1	2
Female		2		2					1		1			

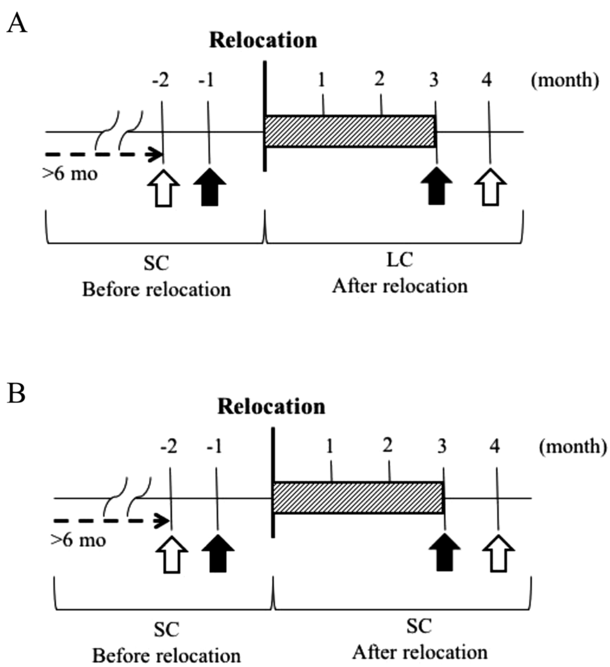

Fig. 2. Schematic of the relocation procedure. A) Animals were relocated from SCs to LCs. B) Animals were relocated from SCs to other SCs. Solid squares represent the acclimation period, open arrows represent the day of video recording, and solid arrows represent the day of BW measurement.

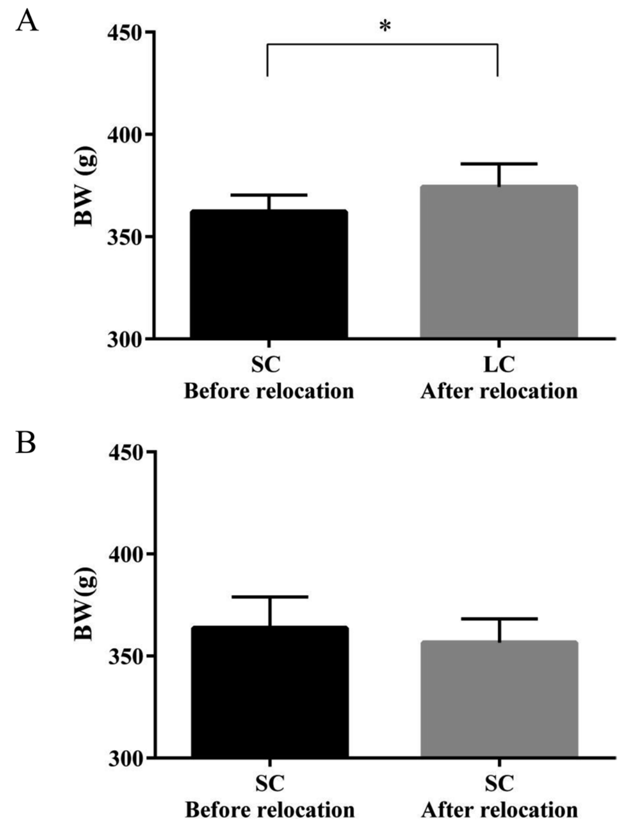

Fig. 3. BWs of male adults before and after relocation. A) BW significantly increased after relocation from SCs to LCs. B) There were no significant differences in BW before and after relocation to other SCs. *P<0.05: significantly different from controls (Wilcoxon matched-pairs signed rank test).

374.4 ± 11.2 g; P<0.05, Fig. 3A), whereas that of the SC>SC group did not change (before: 363.7 ± 15.3 g; after: 356.6 ± 11.6 g; P>0.05, Fig. 3B).

Behavior in the relocation test

The behavioral observations revealed that animals in SCs showed repeated vertical circling behavior, which was considered a stereotypical behavior, both before (data not shown) and after relocation (Figs. 4A and B). However, after moving to LCs, this behavior was no longer observed in any of the animals (Fig. 4C).

BW changes from DOB

Figure 5A details the BW measurement protocol. A 2 (group: SCs and LCs) × 5 (time: DOB and 1, 2, 3, and 4 months after DOB) ANOVA was conducted to assess the BWs of fathers, mothers, and infants. In fathers, there was a significant main effect of time and a significant group × time interaction (time effect: $F_{(4, 48)}$=3.93, P<0.01; group × time interaction: $F_{(4, 48)}$=4.58, P<0.01) but the group effect was not significant ($F_{(1, 12)}$=1.82, P>0.05, Fig. 5B). In mothers, there were no significant main or interaction effects (group effect: $F_{(1, 12)}$=0.11, P>0.05; time effect: $F_{(4, 48)}$=2.00, P>0.05; and group × time interaction: $F_{(4, 48)}$=1.86, P>0.05, Fig. 5C). In infants, there were significant main effects of group and time and a significant interaction (group effect: $F_{(1, 21)}$=10.36, P<0.01; time effect: $F_{(4, 84)}$=228.0, P<0.01; and group × time interaction: $F_{(4, 84)}$=5.35, P<0.01). At

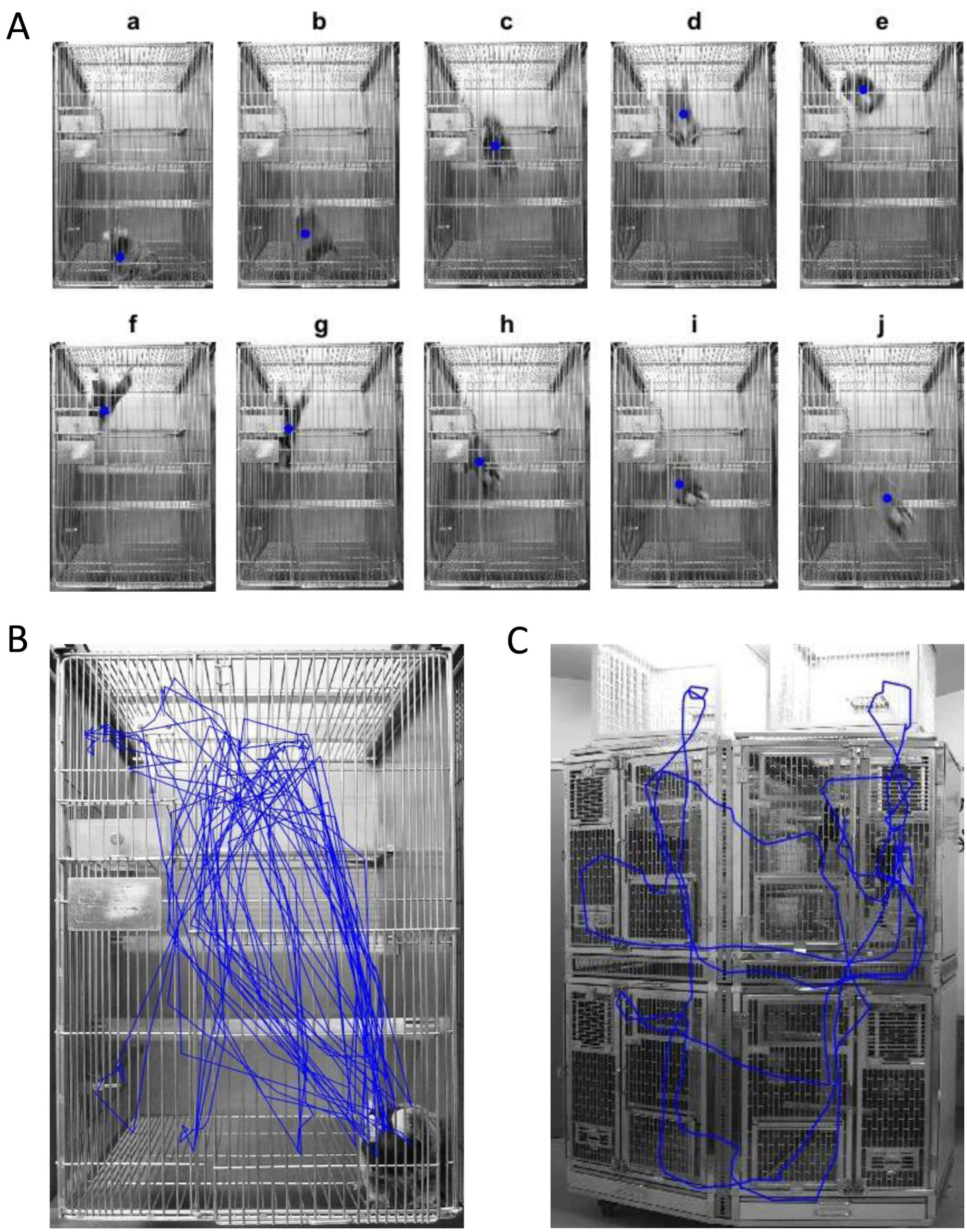

Fig. 4. Representative behavioral traces of the marmosets. A): Representative stereotypical behavior in SCs shown by continuous photos (a-j; every 100 ms). B) Representative behavioral trace (every 200 ms) in SCs shown for 1 min. C) Representative behavioral trace (every 200 ms) in LCs shown for 1 min.

3 and 4 months after DOB, the mean BW in the LC group was significantly higher than that in the SC group (*P*<0.01, Sidak's comparison, Fig. 5D).

Discussion

Appropriate housing is important for all laboratory animals and cage size in particular could have an important effect on animal welfare in terms of additional suffering and distress; this in turn could potentially affect

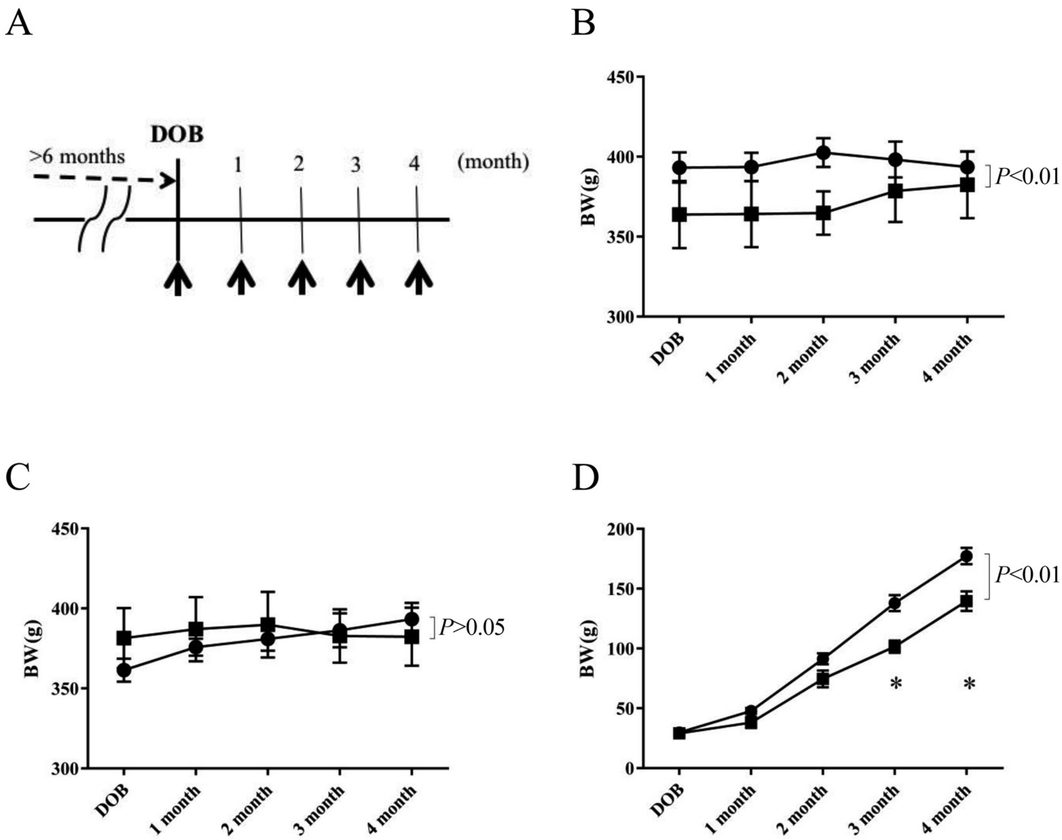

Fig. 5. Changes in the BWs of fathers, mothers, and infants according to 2 (group: SCs and LCs) × 5 (time: the day of birth [DOB] and 1, 2, 3, and 4 months after DOB) ANOVA analyses. Solid squares represent the SC group and dots represent the LC group. A) BW measurement protocol; arrows represent the day of BW measurement. B) Fathers: although there were significant effects of time and the group × time interaction, there were no significant effects of group. C) Mothers: there were no significant main effects or interaction effects. D) Infants: There were significant main effects of group and time as well as a significant interaction effect. *$P<0.05$: significantly different from controls (Sidak's multiple comparison; $P<0.01$).

the reliability of the research. Accordingly, the refinement of laboratory housing for animals to minimize suffering and distress and enhance well-being is an important and internationally accepted principle. Our findings indicate that a larger cage size in the laboratory reduces stereotypic behaviors and increases BW in common marmosets.

Stereotypic behaviors are repetitive and apparently functionless behavior patterns that captive animals often exhibit in response to being confined, a lack of stimulation, insufficient exercise, or inescapable fear or frustration [21]. They can be reduced by environmental improvements and this reduction is widely considered an index of increased well-being [4]. Kitchen *et al*. investigated the effects of cage size on animal behavior and found that animals in larger cages exhibited significant increases in activity levels and the frequencies of specific behaviors such as foraging, allo-grooming, and branch usage compared to animals in smaller cages [18]. Furthermore, they reported that stereotypic behaviors were never exhibited by animals in larger cages. In the present study, vertical circling behavior, which is categorized as a stereotypical locomotor behavior in non-human primates [5], disappeared when animals were moved from SCs to LCs. These behavioral changes suggest that the provision of larger cages may enhance the welfare of captive marmosets and that more attention should be paid to the relationship between cage size and animal welfare-related issues whenever captive marmosets are used for research.

BW is generally accepted as a useful health indicator in several species, including non-human primates such as macaques [2]. In captive marmosets, low BW is a reliable factor that is predictive of gastrointestinal dis-

Fig. 6. Enrichments for marmosets in LCs.

Fig. 7. Space separators in LCs.

eases such as wasting marmoset syndrome, which is considered one of the biggest issues in marmoset colonies [3]. In addition, bone mineral density is proportional to BW [12]. Thus, particularly in a marmoset colony, BW is an important health indicator and the maintenance of high BW in a colony could improve its health status as a whole. In the present study, adult male marmosets that were relocated from SCs to LCs exhibited a significant increase in BW and infants born in LCs had higher BWs than those born in SCs at 3 and 4 months after the DOB. Marmosets in larger cages exhibit increases in general activity levels [18], and thus the increase in BW in the LC group in the present study may have been due to increases in muscle mass resulting from higher levels of activity. To the best of our knowledge, this study is the first to report enhancing effects of larger cage sizes in terms of BW.

Male marmosets tend to gain weight during the gestation of their mates, which helps them alleviate the energetic cost of fatherhood, with the greatest increases occurring during the final month of gestation [34]. Similarly, in the present study, there was a significant effect of time on BW changes in fathers, which suggests that fathers might also gain weight during the lactation period of infants regardless of the size of their cage.

Stressful situations such as repeated blood sampling significantly reduce semen volume and sperm concentration in male adult marmosets [9] and elevations in cortisol, a stress hormone, impair maternal behavior in marmoset mothers [26]. Thus, there is a close relationship between reproductive ability and stress in marmosets. Taken together, these findings indicate that stress reduction is necessary for better reproduction and breeding management of marmosets. Many mammals, including non-human primates, experience stress in restricted environments, but environmental improvements can meet the behavioral needs of animals and lead to reductions in stress [24]. Cage configuration plays an important role in environmental enrichment for marmosets and this is particularly true for height; no housing would be too high for marmosets because they live 10 m above the ground in natural habitats [11] and prefer to look down on potential ground predators [24]. Therefore, the height of the LCs in the present study, with roofs that were three times as high as those of SCs, were beneficial for the environmental enrichment of marmosets. The sizes of LCs also made it possible to increase the complexity of the housing units (Fig. 6). Enrichment with objects such as wooden branches, cups, plastic bottles, and/or film cases suppresses stress-related behavior in marmosets [18, 19]. Thus, these two features of LCs, height and a high capacity for enrichment, are considered advantages over SCs.

In addition to size and height, the LCs used in our study have other useful features. All of the lattice punching panel walls and floors are made of stainless steel plates (2 mm thick) that were perforated using a laser process; there are no intersecting steel wires on the wall and the surface of the wall is flat so cameras, sensors, and other devices can be installed for future behavioral experiments. In addition, the LCs can be broken down into smaller parts without special tools or techniques and researchers can easily replace the cage parts. For example, researchers can change a cage door made of lattice punching panel to a door made of transparent plastic to observe the inside of the cage. Such features allow for more flexible experimentation methods when using marmosets.

Other differences between LC and SC include wash procedures and animal capture. For washing, SCs (animals kept inside) are brushed with hot water in husbandry rooms; in contrast LCs (animals kept inside) have nest boxes into which animals can escape during cage washing, this often leaves large spaces uncleaned and debris can accumulate. To remedy the situation the LCs (animals removed) are moved into a cleaning room and washed with a special cage washer after biweekly cage changes. Therefore, in rooms with LCs, there are no fluctuations in humidity caused by the use of hot water during wash procedures. In animal capture, another distinct cage challenge, as Kitchen *et al.* showed that capture time was significantly longer in larger cages [18], difficulties of animal capture can be a problem with larger cages. However, with the use of separators (Fig. 7) the space in LCs can be divided in quarters, so animal capture in LCs is not thought to be a substantial problem in our facility.

Although concentrations of plasma cortisol have been widely used to quantitatively assess the stress levels of animals [7, 13, 14, 27], capture and restraint have been shown to significantly increase HPA activity and potentially effect plasma cortisol levels in some species [6, 8, 16, 28]. Capture method discrepancies between the SCs and LCs could affect plasma cortisol levels, so we thought plasma cortisol under restraint conditions would be unsuitable for the purpose of our study. For this reason body weight gain was selected to be an index for stress reduction instead of plasma cortisol level, because body weight changes have a trend for a negative correlation with basal morning plasma cortisol concentrations [15]. It is known that urinary cortisol excretion can be a valid and sensitive index of the HPA response to stressors in marmosets [30], more quantitative correlation between stress and cage size could be assessed with measurements of urinary cortisol levels in further studies.

The SCs used in the present study were traditional types of cages also used in Japanese marmoset husbandry facilities. Their heights are lower than the level recommended for non-human primates by the National Research Council of the National Academies Guide for the Care and Use of Laboratory Animals [22]; in fact, most marmoset cages in Japan have an insufficient height. Considering the increase in studies using common marmosets as subjects, as detailed above, the need for animal welfare-conscious equipment has also increased. The LCs in the present study had a sufficient height that was near the maximum height considering the building conventions in Japan. Based on the positive effects of LCs on BW and behavior observed in the present study, this type of cage is a superior housing method that maintains and even promotes the health and well-being of common marmosets.

Acknowledgments

We thank the rearing staff of the animal facility for their generous help.

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