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# Effects of Rat Visual, Olfactory, or Combined Stimuli during Cohousing on Stress-Related Physiology and Behavior in C57BL/6NCrl Mice

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**The *Guide for the Care and Use of Laboratory Animals* recommends housing rats and mice separately to reduce the potential for environmental stress to mice. The literature presents equivocal support for this practice, and housing practices vary widely. According to the existing literature, it is unclear whether visual, olfactory, or combined stimuli are responsible for stress-related changes in mouse physiology and behavior. To determine the extent to which exposure to visual, olfactory, or combined stimuli produce stress-related changes, measures of physiologic and behavioral stress were evaluated in mice after cohousing them in a room with rats. Adult, male C57BL/6NCrl mice ($n$ = 8 per group) were randomly assigned to control, isolator cage, visual stimuli, olfactory stimuli, or visual+olfactory stimuli groups. After 15 d of exposure, body, and adrenal weights did not differ between groups. None of the groups of mice experienced significant increases in corticosterone or stress-related behavior in the open-field test after exposure to rat stimuli. These results suggest that the stress-related effects of cohousing with rats are negligible in mice and have implications for housing rats and mice in shared rooms, thereby allowing efficient use of research resources.**

Minimizing environmental sources of stress in animal facilities that house multiple species is a challenge faced by many research facilities and must be balanced with needs for space and competing resources. One strategy that may be useful in optimizing space and resources is to house rats and mice in the same room, as is common practice in commercial breeding facilities.[5,24] However, this practice raises concerns about the effect of the continued presence of a potential predator species (rats) on the stress behavior and physiology of a potential prey species (mice). The *Guide for the Care and Use of Laboratory Animals* recommends physically separating species to eliminate the potential for environmental stress caused by the presence of predators in prey housing areas, but *The Guide* does not provide specific guidance with respect to housing rats and mice in the same rooms.[16] As a result, housing practices vary widely. A growing body of literature has examined murine stress after housing in the same room with rats, but the results of existing studies are equivocal. Furthermore, the roles of rat visual, olfactory, or combined stimuli in producing murine stress in shared animal rooms are unknown. Understanding the roles of various stimuli could help to guide future housing practices. For example, limiting visual contact or housing mice in isolator cages may be one way to reduce the effects of exposure to rat stimuli on stress-related outcomes in mice housed in the same room.

Early research described rat attacks of mice as "predatory."[20] This initial research influenced the practice of separating rat and mouse housing areas, to reduce presumed stress of mice exposed to visual, olfactory, or other stimuli associated with rats. However, some researchers suggested that this behavior was a rat species-specific act of aggression that could be attenuated by prior exposure to mice.[11,12,28] Additional research suggested that mouse defensive behaviors in the presence of rats are strain- and experience-dependent as well.[30] Currently, the predatory nature of rat–mouse interspecies interactions is unclear.

More recent research supports the potentially stressful effects of shared housing rooms on mouse health and behavior. Mice housed in the same room with rats demonstrated increased behavioral and physiologic changes related to acute and chronic stress.[5] C57BL/6ByJ and BALB/cByJ mice exhibited neurochemical changes consistent with a stress response after brief (10 to 20 min) visual, olfactory, and auditory exposure to rats.[13] Similarly, mice with brief (5 min) exposure to rat visual, olfactory, and auditory stimuli experienced increased corticosterone and stress-related behavior changes.[2] Mice housed in rooms with olfactory and visual stimuli from rats demonstrated increased anxiety-like behavior and attenuated sucrose intake; however acute exposure produced no change in these behaviors.[8] Interpreting these results, the authors of the study suggested that the prey response differed according to acute compared with chronic exposure to rat stimuli.[8] Increased stress response and sympathetic nervous system activation were present in mice single-housed (but not group-housed) in the same room with rats.[10] The authors of the study suggested that these results highlighted "the need for better management of animal housing conditions and the need to reduce exposure to stressors."[10]

In contrast, other researchers have reported few or no adverse effects on stress and general health outcomes of mice housed in the same room with rats. There was no effect on physiology of C57BL/6Jico mice that were housed in a room with Wistar rats.[19] The authors concluded that the separate cage cohousing environment produced no long-term changes in physiologic parameters and critiqued prior studies in which cohousing included impractical housing measures, such as placing rats within or on top of mouse cages.[19] Other researchers found no effect of rat olfactory stimuli exposure on mouse exploratory behavior in an empty cage.[1] There was no effect on pup growth or reproductive success among several strains of mice housed

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long-term (more than 30 d) in the same room with rats.[24] In discussing the implications of this work, the authors noted that their results did not support "a ban on housing rats and mice" nor "the contention that such housing is stressful."[24] Finally, a recent review summarized related studies that failed to find significant effects of predator odor on prey health and behavior.[4]

Altogether, research investigating the anxiogenic-like or stress-inducing effects on mice chronically housed in the same room with rats is equivocal. Furthermore, it is unclear whether exposure to visual or olfactory (or both) predator stimuli is most important in potential effects. Therefore, the present research sought to evaluate the effects of visual, olfactory, and visual+olfactory predator stimuli on the stress-related health and behavior of mice, with the intention of contributing to the literature regarding best practices for housing rats and mice.

## Materials and Methods

**Animals and housing conditions.** All procedures involving rats and mice were approved by the IACUC of Northern Arizona University.

Male C57BL/6NCrl mice ($n$ = 40; age, 8 to 9 wk; Charles River Laboratories, Wilmington, MA) were singly housed and randomly assigned to one of the following groups ($n$ = 8 each) after a 3-d habituation period: control; isolator cage; visual stimuli; olfactory stimuli; and visual+olfactory stimuli. Mice were housed singly to facilitate feces collection (from individual animals) that was used in a separate experiment (data not shown). All mice were housed in transparent polycarbonate cages (19 × 28 × 12.70 cm; Ancare, Bellmore, NY) containing cellulose-fiber wood-pulp bedding (Ultra CareFRESH, Absorption, Ferndale, WA) and cardboard tubes for enrichment. Cages were covered with either wire or filter cage tops (Figure 1). Mice in the control group were housed in cages with filter cage tops and in a separate room, with no access to any predator stimuli. All handling, husbandry, and testing was conducted first by using this group to eliminate the potential for cross contamination and exposure to unintended stimuli.

Mice in the isolator cage group were housed in isolator cages (19 × 28 × 12.7 cm, Ancare) with filter cage tops and were placed in the back of the room, to prevent visual and olfactory access to rat predator stimuli (Figure 1). Mice in the visual stimuli group were housed with cage tops with filters on cage racks adjacent to rat cages with open wire tops. All cages were transparent, and mice had access to rat visual stimuli only. Mice in the olfactory stimuli group were housed in cages with wire tops on racks adjacent to rat cages with wire tops, but opaque barriers between cages prevented access to visual stimuli; mice in this group had access to rat olfactory stimuli only. Mice in the visual+olfactory group were housed in transparent cages with wire cage tops and adjacent to transparent rat cages with wire tops; mice in this group had access to both visual and olfactory rat stimuli. Mice in the control group has no exposure to potential auditory stimuli from rats, but mice in the isolator, visual stimuli, olfactory stimuli, and visual+olfactory stimuli groups had exposure to potential auditory stimuli from rats.

After a 3-d habituation period, 12, male CD rats (Charles River Laboratories; 8 to 9 wk of age) were socially housed (2 per cage; 26.70 × 48.25 × 20.30 cm, Ancare cages with Ultra CareFRESH cellulose-fiber wood-pulp bedding, Absorption) in the same room with mice in the isolator cage, visual stimuli, olfactory stimuli, and visual+olfactory stimuli groups. Rats were housed on the middle shelves of a cage rack shared with mouse cages. Housing conditions are illustrated in Figure 1.

**Procedure.** Food (Purina LabDiet 5001, PMI Nutrition International, St Louis, MO) and purified water were provided ad libitum to all animals in the study, and all rooms were maintained on a 12:12-h light:dark cycle (lights on, 0700 to 1900) at approximately 22 °C. Cage changes were performed twice each week in a separate room, with soiled bedding placed into a horizontal bedding disposal unit (model DS400ADS, Allentown). Cage changes (by CR and TG), husbandry (CR, TG, and MB), animal handling (CR, TG, and MB), behavior testing (MB), and euthanasia (TG) were performed by the authors. All animals were maintained in their respective housing environments from day 0 to day 15 of the experiment. Submandibular blood samples were collected on day 0. Mice were habituated to daily handling and were weighed every 3 d to assess general health and body weight.

Immediately after behavioral testing on day 15, animals were euthanized ($CO_2$ inhalation), final blood samples were collected via cardiocentesis, and adrenal glands were removed and weighed. Recommended by the *American College of Laboratory Animal Medicine*, $CO_2$ euthanasia was selected as a humane method of euthanasia that was unlikely to confound corticosterone measurements as compared with rapid decapitation, which can increase stress hormone concentrations.[6] Mice were euthanized in accordance with the *AVMA Guidelines for the Euthanasia of Animals*.[17] To replace 20% of the overall chamber volume per minute, 100% $CO_2$ was gradually introduced at 4.6 L/min; gas flow was maintained for at least 1 min after apparent death of the animal. Mice were removed from the chamber, and final blood samples were collected via cardiocentesis. Assurance of death was performed via cervical dislocation.

**Stress measures.** ***General health.*** Body (in grams) and adrenal (in milligrams) weights were recorded by using a digital scale (Scout II, Ohaus, Parsippany, NJ) as measures of general health indicative of environmental stress. Two values were missing from the final data set due to scale malfunction. The missing values (one each from the control and olfactory stimuli groups) were imputed based on the group mean.

***Corticosterone.*** After collection on days 0 and 15, blood samples were centrifuged at 13,625 × $g$ (4 °C) for 15 min in EDTA-coated tubes. Plasma was removed and stored at −80 °C until assayed. Submandibular blood collection on day 0 did not yield sufficient volume to assay plasma in duplicate for each animal; therefore samples were pooled from 2 animals in the same group, similar to the pooled sample technique used previously for the mouse corticosterone assay.[15] Plasma corticosterone concentrations (in nanograms per milliliter) were assayed by using a commercially available ELISA kit (ALPCO Diagnostics, Salem, NH) according to the manufacturer's directions. Intraassay coefficients of variance were less than 10% ($n$ = 40 samples). Interassay coefficients of variance were less than 15% ($n$ = 3 plates). Values for 4 samples (control day 0 and olfactory stimuli day 15, one value each; control day 15, 2 values) were missing because they were beyond the range of detection. Missing values were imputed based on the group mean. In an attempt to control for circadian variation in corticosterone concentrations, all blood samples were collected during the first half of the light phase, between 0800 and 1330.

***Behavioral measures.*** On day 15, mice were weighed and transported to a separate behavioral testing room, where a 10-min open-field behavioral test was conducted. Open-field testing was conducted in a 27.5 × 27.5 × 20 cm opaque acrylic arena. The arena was cleaned with 70% ethanol between uses. The arena was lit with two 40-W bulbs suspended approximately 1.5 m above the arena. Behavioral testing was conducted

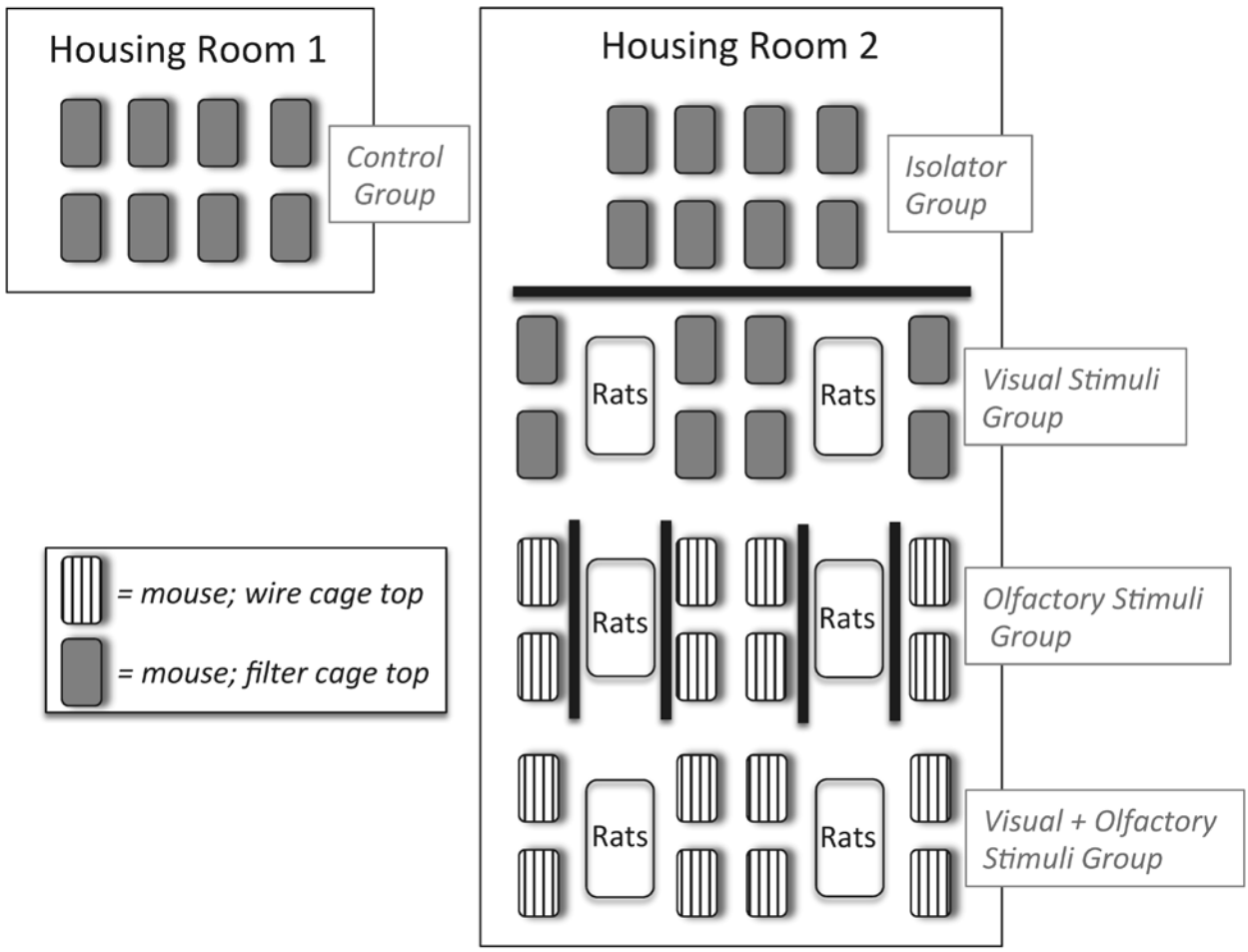


**Figure 1.** Housing conditions for groups (control, isolator cage, visual stimuli, olfactory stimuli, and visual + olfactory stimuli).

during the first half of the light phase, between 0800 and 1230. Behavior was videorecorded (EthoVision System, Noldus, Leesburg, VA) for subsequent analysis of time in the center of the arena (in seconds; 14 × 14 cm central section) and total distance traveled (in centimeters).

**Statistical analysis.** All statistical analysis was conducted by using SPSS software (version 21, SPSS, Chicago, IL). One-way ANOVA was used to assess group differences in adrenal weight, time in center, and distance traveled in the open-field test. Two-way repeated-measures ANOVA (group × day) was used to assess group differences in body weight across days 0, 3, 6, 9, 12, and 15 and plasma corticosterone concentration between days 0 and 15. *P* values of less than 0.05 were considered statistically significant, and Fisher Least Significant Difference post hoc tests were used to investigate significant main effects.

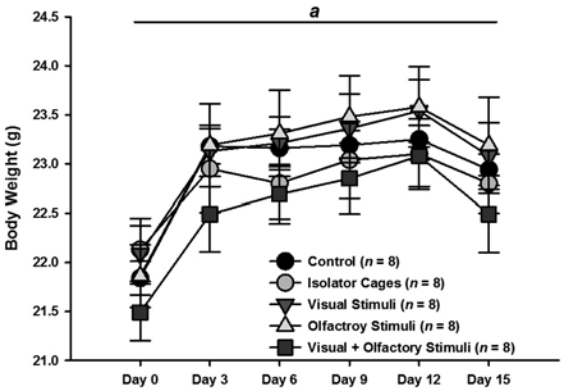


**Figure 2.** Body weights (g; mean ± SEM). The data show a main effect of time (*a*, $P < 0.05$) but not of group nor the interaction of time and group.

## Results

**General health.** Body and adrenal weight data (mean ± SEM) are presented in Figures 2 and 3, respectively. Body weights did not differ between groups at any of the time points examined, but there was a main effect of time ($F_{5,31} = 60.36$, $P < 0.05$), with body weights increasing over time. On day 15, adrenal weights in all groups were significantly ($F_{4,35} = 18.28$, $P < 0.05$) decreased relative to control values.

**Corticosterone.** Corticosterone concentrations (mean ± SEM) are presented in Figure 4. There was a main effect of time, with concentrations significantly ($F_{1,35} = 31.87$, $P < 0.05$) increased on day 15, and a main effect of group ($F_{4,35} = 4.82$, $P < 0.05$), with corticosterone concentrations lower in the olfactory stimuli group than the control group and concentrations higher in the isolator group than in the visual, olfactory, and visual+olfactory stimuli groups. Investigating the significant day × group interaction ($F_{4,35} = 2.88$, $P < 0.05$) revealed increased corticosterone concentrations from day 0 to day 15 in the Control ($t_7 = 5.86$, $P < 0.05$), visual ($t_7 = 3.08$, $P < 0.05$), and visual+olfactory ($t_7 = 3.80$, $P < 0.05$) groups. On day 1, corticosterone concentrations were increased ($F_{4,35} = 6.95$, $P < 0.05$) in the isolator and visual+olfactory groups relative to control values, but this difference was not present on day 15. On day 15, corticosterone

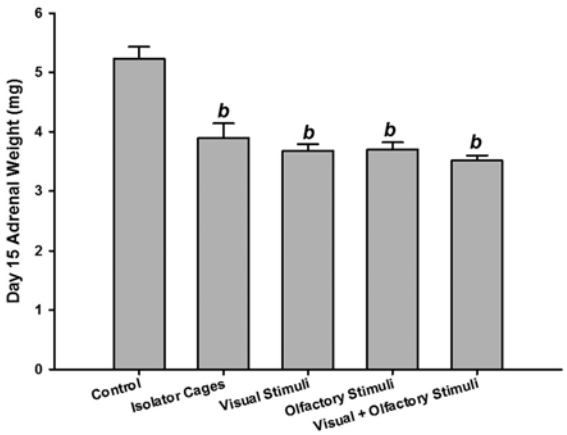


**Figure 3.** Adrenal weights on day 15 (mg; mean ± SEM). *b*, Value significantly ($P < 0.05$, Fisher Least Significant Difference test) different from that of control group.

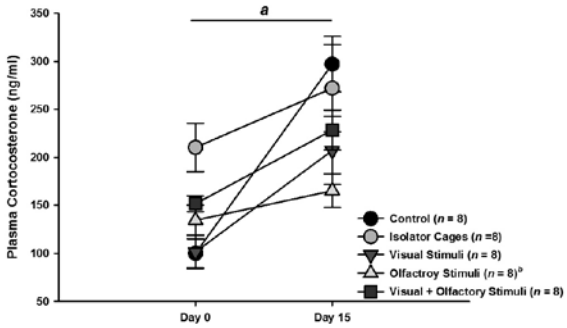


**Figure 4.** Corticosterone concentrations on day 15 (mg/mL; mean ± SEM). The data show a significant main effect of time (*a*, $P < 0.05$), a significant ($P < 0.05$) group × time interaction, and a significant main effect of group (*b*, $P < 0.05$).

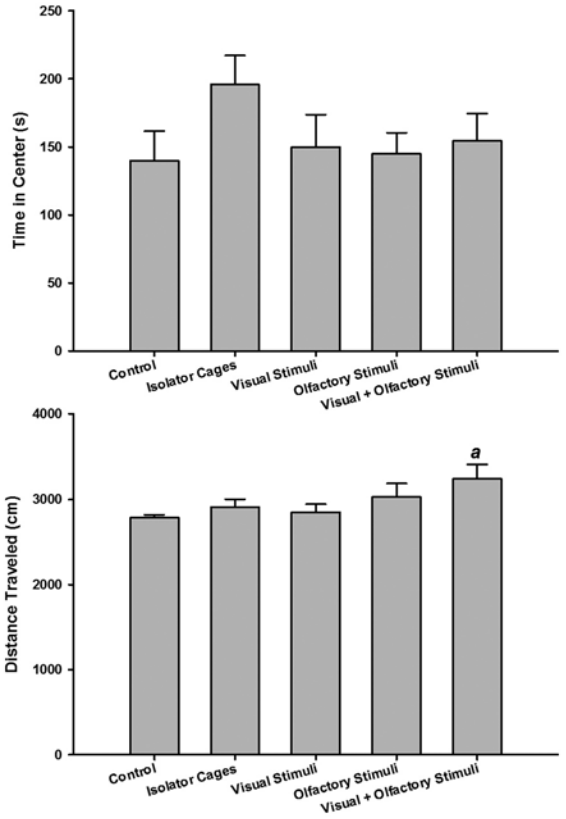


**Figure 5.** Performance (time [s; mean ± SEM] in center and distance traveled [cm; mean ± SEM]) in the open-field test. *b*, Value significantly ($P < 0.05$, Fisher Least Significant Difference test) different from that of control group.

concentrations were decreased ($F_{4,35} = 2.79$, $P < 0.05$) in visual and olfactory stimuli groups relative to control values.

**Behavioral measures.** Data (mean ± SEM) regarding time in the center and distance traveled in the open-field test are presented in Figure 5. Time in the center was similar among all groups. Compared with the control group, the visual+olfactory stimuli group exhibited significantly ($P < 0.05$) increased distance traveled.

## Discussion

Altogether, the results of this study suggest that cohousing rats and mice in the same room had little effect on the stress-related behavior and physiology of mice. Furthermore, these results suggest that exposure to visual, olfactory, or the combination of visual+olfactory stimuli failed to produce significant effects on mouse body weight gain, corticosterone response to an acute stressor (open-field testing), or behavioral performance in the open-field test.

A lack of effect of rat stimuli on body weight is consistent with previous results.[5,24] The present study extends this finding to separately evaluate the effects of isolated housing in the same room and exposure to visual, olfactory, and visual+olfactory rat stimuli. Regardless of exposure to visual, olfactory, or the combination of stimuli, being in the presence of rat stimuli had no effect on the body weight of mice. Interestingly, exposure to visual, olfactory, or combined rat stimuli did not differ from the isolator cage condition with regard to adrenal weight, and all groups experienced decreased adrenal weight relative to the control group. This result is in contrast to previous findings[5] in which adrenal weight was increased among mice housed in the presence of rats; however, whether mice were exposed to visual, olfactory, or combined stimuli in that study is unclear. The finding of increased adrenal weight in the control group of the present study was unexpected, but it is consistent with the increase in corticosterone in this group after exposure to an acute stressor (handling and completion of the open-field test). One possible explanation for the difference in adrenal weights is that mice that were chronically housed in the room with rats (regardless of stimuli exposure type) experienced their environment as enriched. In another study, mice in enriched environments exhibited trends toward reduced adrenal weights relative to animals in a standard housing condition.[26]

The finding of increased corticosterone on day 15 after completing the open-field test in the present study was consistent with previous results,[7] in which corticosterone was increased in mice after completing a similar test. The open-field test is commonly used to assess stress and anxiety-like behavior in rodent models and uses species-typical rodent behavior of spending less time in the well-lit and exposed area (center of the testing arena).[9] The percentage change in corticosterone after open-field testing did not differ between any of the groups. Exposure to rat stimuli had no effect on corticosterone concentrations in response to this acute stressor, but it is interesting to note that 15-d exposure to olfactory stimuli produced the smallest increases in corticosterone after open-field testing. One possible confound in comparing the results of the present study with those of a previous one[7] is that the method of euthanasia differed between the studies. $CO_2$ inhalation was used in the present study,

whereas the previous one[7] used rapid decapitation without $CO_2$. Other researchers[6] report that decapitation can result in increased corticosterone concentration, whereas $CO_2$ inhalation prior to trunk blood collection is associated with no effect on corticosterone levels.[16] Similarly, another study[27] reported that exposure to $CO_2$ did not significantly increase corticosterone concentrations compared with trunk blood collections without $CO_2$. Another possible confound in interpreting corticosterone concentrations from day 15 is the order in which blood samples were collected. Samples were collected from the control group first (mean concentration, 297 ng/mL), followed by the isolator (272 ng/mL), visual stimuli (207 ng/mL), olfactory stimuli (165 ng/mL), and visual+olfactory stimuli (228 ng/mL) groups, beginning at approximately 0830 and ending at approximately 1330 (first half of the light phase). This time period corresponds with a period of asymptotic circadian decline in corticosterone concentrations in mice.[21,22] Although efforts were made to restrict blood collection to a limited period of time (morning), the relatively rapid circadian changes in corticosterone concentration during this period may partially or potentially mask the effects of treatment group. Future research should address the confounding effect of order of collection due to influence by a circadian rhythm and adopt a randomized collection procedure during a limited time period.

Exposure to rat stimuli had no effect on performance within the open-field test, consistent with previous results.[5] However exposure to visual+olfactory stimuli significantly increased distance traveled and tended to increase time in the center relative to control values; these measures are indicative of increased exploration and reduced anxiety-like behavior. This result suggests that 15-d exposure to visual+olfactory stimuli reduced the acute stress response in this group.

Limitations of our study include the use of a single strain each of mice and rats. Our use of the C57BL/6NCrl mouse and CD rat strains was a purposeful attempt to generate data about widely used laboratory models that would be applicable in informing common housing practices. Future research should examine the effects of cohousing on reactive strains (for example, BALB/c), between sexes, and across the lifespan. Prior to their purchase by research facilities, many commercially available mice are cohoused with rats in breeding facilities. This practice is standard at Charles River Laboratories, where the mice in the present study originated. The mice used in our study may have had exposure to rats prior to participating in this research. Whether prior exposure to rat stimuli affected the mice's response to these stimuli in the present study is unknown. Predicting the effects of prior exposure is complicated by the magnitude of stress or enrichment provided and the length of exposure.[3,18] To date, few studies have examined the effects of cohousing on rats.[5,24] In addition, the present study did not adequately control for the effects of auditory stimuli. Stimuli conditions in the isolator, visual, olfactory, and visual+olfactory groups were confounded by potential exposure to rat auditory stimuli, but data from the control mice (with no auditory exposure) suggest that the potential presence of auditory stimuli did not produce significant effects. Future research could incorporate sound attenuation to confirm the specific effect of auditory stimuli on stress-related variables.

Altogether, our results suggest that exposure to visual or auditory (or both) rat stimuli had no effect on physiologic and behavioral measures of stress in C57BL/6NCrl mice. This mouse strain is considered to have normal vision and can accurately discriminate visual patterns at a distance of 140 cm, suggesting that the mice were able to perceive visual cues across a transparent cage wall under the visual and visual+olfactory conditions.[25,29] In addition, the mouse audiogram ranges from approximately 2 to 64 kHz.[14] Adult rat vocalizations occur at 18 to 32 kHz (under aversive conditions) and 32 to 96 kHz (under nonaversive conditions).[23] Therefore, mice in the present study likely were able to perceive the majority of rat auditory stimuli. However, there was no physiologic or behavioral difference between groups with (in cohousing room) or without (housed in control room) exposure to rat auditory stimuli. The results of this research suggest that cohousing rats and mice in separate cages within the same room produces no significant effect on stress-related physiologic or behavioral measures in mice, despite exposure to visual, olfactory, and auditory stimuli. These results are consistent with previous work[1,4,19,22] and support the use of cohousing these species as needed, according to the rationale that cohousing does not affect stress-related measures in C57BL/6NCrl mice.

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