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REVIEW ARTICLE

Environmental enrichment and mouse models: Current perspectives

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Abstract

The provision of environmental enrichment to numerous species of laboratory animals is generally considered routine husbandry. However, mouse enrichment has proven to be very complex due to the often contradictory outcomes (animal health and welfare, variability in scientific data, etc.) associated with strain, age of the animal when enrichment is provided, gender of the animal, scientific use of the animal, and other housing attributes. While this has led to some suggesting that mice should not be provided enrichment, more recently opinion is trending toward acknowledging that enrichment actually normalizes the animal and data obtained from a mouse living in a barren environment are likely not to be representative or even reliable. This article offers an overview of the types of impact enrichment can have on various strains of mice and demonstrates that enrichment not only has a role in mouse husbandry, but also can lead to new areas of scientific enquiry in a number of different fields.

KEYWORDS
animal welfare, environmental enrichment, mouse behavior, research validity

1 | INTRODUCTION

The laboratory mouse is a ubiquitously used research subject whose genetics, anatomy, physiology, immunology, and behavior have been studied in detail for generations. Thus, it would seem that providing a housing environment that is species-appropriate would be a simple matter. However, it would be a serious mistake to approach mouse enrichment as a one-size-fits-all husbandry procedure. The laboratory mouse is still considered behaviorally similar to wild mice in many dimensions[1(p150)], though it differs somewhat from the wild-type ancestor in its behavior, with running behavior and open-field freezing behavior, and a general higher level of activity more evident in wild-type mice than the laboratory bred animals.[2] Over decades of purposeful breeding, a variety of characteristics (eg, ease of handling) were either deliberately or inadvertently introduced into the behavior profile of the laboratory mouse. Today, the increasing trend in the use of transgenic mice has only amplified the diversity of traits being bred for, and thus, the potential exists for both extant and subtle differences in mouse behavior and their response to their environment.

The behavioral breadth of the species may help to account for the fact that the literature is replete with contradictory findings and diverse conclusions about the potential benefits and unexpected consequences from providing enrichment to laboratory mice. Indeed, an argument has been made that enriched animals produce different results; enrichment may increase between-subject variability; and enrichment may reduce replicability across laboratories.[3(p47-48)] A simple response to these arguments could be that animals should not be provided enrichment. But, a counter-argument has been made that, as expected, the enriched animal model is different in many ways from the animal model living in a barren environment.[3(p47)] Indeed, it is not logical to accept the notion that

animals that are stressed due to environmental inadequacies are, in fact, a better research model, especially considering the fact that the normal state of the animal (and the human for which it is serving as a model) live in complex, stimulating environments. Given this, she suggests that the external validity of research animals living in minimalistic environments may not be as robust as is assumed.

Contradictions in results in the enrichment literature clearly signal both inadequate objective information regarding the (possibly changing) behavior of the mice we use in research and the need for additional basic studies to better characterize the animal model as its genome is modified. The reality is that mouse enrichment programs are complex; must be thoroughly researched; and the enrichment should be implemented based on input from the investigator, the veterinarian and husbandry personnel.

2 | IMPLEMENTING ENVIRONMENTAL ENRICHMENT

2.1 | The goal of enrichment

Environmental enrichment has been variously defined, but generally includes the goal of improving the welfare of the animal through the thoughtful inclusion of social and nonsocial features to the cage environment. More than 10 years ago, enrichment was described as "any modification in the environment of the captive animals that seeks to enhance its physical and psychological well-being by providing stimuli meeting the animals' species-specific needs".[4] More recently, the aim of enrichment has been described as a method "to enhance animal well-being by providing animals with sensory and motor stimulation, through structures and resources that facilitate the expression of species-typical behaviors and promote psychological well-being through physical exercise, manipulative activities and cognitive challenges according to species-specific characteristics".[5] In some cases, the objective of enrichment is to increase the expression of certain behaviors while in other cases, reduction of specific behaviors is intended. For example, reduction in the expression of stereotypic behaviors may be a goal which is achieved by providing resources such as a shelter.[6] In all instances, the provision of enrichment should not negatively impact the health and safety of the animal.

There are several general characteristics of nonsocial enrichments that are desirable and may drive the selection process among enrichment choices. Primary among these is that ideally there should be demonstrated value derived from the enrichment technique in enhancing the welfare of the animal.[7] Optimally, this evidence should be contained in the peer-reviewed literature and the results of the published data should be able to be extrapolated to the specific context of the institution considering implementing that type of enrichment. It is worthy to note that enrichment is typically intended to improve animal welfare over some established baseline. Often, the wild counterpart of the laboratory animal is held up as the standard for comparison. However, this comparison may be flawed due to the significant changes that have occurred in the laboratory mouse following generations of targeted breeding.

One reasonable approach is to base welfare assessments on a composite of types of mice that evidence similar behaviors, responses to experimental challenges, or fragility. In this manner, groupings of strains or lines of mice would be made and common approaches to assessing welfare would be applied. Needless-to-say, the success of such a strategy would be dependent on the accuracy of groupings of mice and, of necessity, relies on the availability of information to make these judgments. In some circumstances, behavioral phenotyping scoring systems facilitate the description of behaviors of transgenic and knockout mice. These systems typically involve analysis of a battery of responses to stimuli and resting activities,[8] as well as physical characteristics (eg, bald patches). This tool may aid in the grouping of mice for determination of when an animal differs from its prototype, which could be an indicator of altered welfare. In the absence of an obvious metric for assessing the welfare of the diverse range of mice used in research, there may be an inclination to rely on the wild-type mouse or on an inappropriate laboratory strain or line as the basis for comparison. While progress has been made in identifying pain and distress in mice (eg, the mouse grimace scale,[9] changes in activity[10] as well as changes in behaviors such as flinching, writhing, rear leg lift, and press[11]), strain differences continue to plague making some of these strategies broadly utilitarian, and the value of systems based primarily on behavior change for animals in a prolonged state of compromised welfare (eg, chronic pain) has not been determined.[12]

2.2 | Common types of mouse enrichment

2.2.1 | Nests

Nesting behavior appears to be an activity that is well preserved from wild-type progenitor mice.[1(p150)] The provision of nesting material to caged mice has received widespread support because there appears to be a strong motivation for individual mice to build nests (even among nonbreeding mice), it can enhance pup survivability, it is a behavior that is commonly performed by numerous strains of mice, and it offers the opportunity for mice to better thermoregulate in their environment.[13,14] Numerous studies have assessed the relative merits of different kinds of nesting material, including commercially available Nestlets™, paper strips, tissue or paper towel, cotton string, wood wool, and wood shavings. The value of the nesting material to the mouse has also been critically evaluated, using the complexity or architecture of the nest as a metric for the quality of the nesting material provided[15,16(p29)] or the mouse's willingness to work to access nesting material.[17] Some kinds of nesting material (eg, corn husks) reduce aggressive behavior in a line of BALB/c mice, as indicated by reduced wounding of the animals,[18] possibly due to the availability of areas to escape from aggressive animals. Clearly, the type of nesting material impacts this welfare benefit, as aggression was decreased in 7-week-old male BALB/c mice provided tissue torn in strips[19(p71)], though intracage fighting was not reduced by

providing wood wool as nesting material to BALB/c and C57BL/6J mice[20] and actually increased fighting in NIH/S male mice.[21] Yet, there is evidence that some strains of mice, such as BALB/c and CD-1 mice, show reduced signs of stress, to include lower urine corticosterone levels and heavier thymuses, if they are provided nesting material and if the nest is transferred during cage cleaning procedures.[22] Although there are contradictions in the literature regarding optimal nesting material (eg, paper strips[16] vs tissue or paper towel[23]), an important consideration is the planned use of the mice. For example, a tissue nesting material can be a confounding variable for studies of allergic asthma in BALB/c mice, resulting in increased total cell number, eosinophil number, and IL-13 concentration in bronchoalveolar lavage fluid as compared with nonenriched control animals.[24] Cautions have been made regarding some types of nesting material that can entangle the limbs of pups.[25] More recently, the provision of a nest-building material is considered an important element of the mouse's cage environment.[16(p26)] The manifestation of nest-building behavior by mice is considered a reliable indicator of health and welfare, with its absence reflecting pain or discomfort in the mice.[26]

2.2.2 | Nest boxes/Shelters

As a prey species, wild-type mice will attempt to flee and hide from predators and it may be that laboratory mice retain this fear response behavior. For example, laboratory mice may exhibit aggression to handlers if startled or fearful, and thus the provision of shelters has been suggested to reduce the mouse's fear response.[27] The inclusion of shelters or nest boxes has been evaluated as a single enrichment and in association with other enrichments (eg, nesting material, running wheels). As has been demonstrated by investigations into other forms of enrichment, varying results have been obtained on the merits of providing shelters, depending on the strain of mouse, whether nesting material was also present, the number of openings in the nest box, and the material from which the nest box or shelter was constructed (eg, metal, plastic, wood, paper product). In fact, the material of which the nest box is constructed has been proposed as a significant factor in preferences expressed by mice.[28]

In some cases, the shelter provided is a tube (perforated along the sides of the tube or nonperforated), while in others it is designed to function more specifically for nesting. Partitioning the cage space up with structures like shelters allows mice to separate areas for feeding, resting, and urination/defecation, thereby aiding mice in controlling their environment, such as exposure to illumination.[29] The location of a tube-shaped shelter within the cage may vary, being situated either directly on the cage floor or suspended from the cage wall. Indeed, the location of the nest box has been shown to be important in individually ventilated cages, with nest boxes placed on the floor preferred by female Crl:CD1 (ICR) mice, the majority of whom also moved the nest box toward the front of the cage, under the food hopper.[30] Proposed reasons for this strong trend included the reduced ventilation exposure and/or reduced illumination exposure for mice if the nest box was moved under the feeder. But, there are strain-dependent responses to tubes, as individually housed male TO mice do not use a tube for sleeping if sawdust is made available as bedding in the cage. Rather, these mice used the tube for refuge and as a latrine.[31]

Recently, it has been shown that the number of days of survival of Tabby jimpy mice was increased in those animals provided a nest box constructed of paper boxes.[32] These animals also had a higher weaning rate, had a statistically significant higher weaning weight, and developed few abnormal jumping behaviors. This type of nest box allowed the dams to create additional holes and to use the shredded paper as a component in their nest-building activity. Male BALB/c mice also had increased longevity if they had access to a shelter.[33] However, it should be noted that for some strains of mice, inclusion of a nest box or shelter has been implicated with increased aggression levels in animals[19(p74)], though this is not always the case.[34(p367)] Yet, mice living in cages containing a nest box, nesting material, chew blocks, and a running wheel consumed less of the anxiolytic agent than mice in standard cages and spent less time performing bar-related behaviors and bar-circling stereotypies.[35]

3 | EFFECTS OF ENRICHMENT

3.1 | Effects on the animals

One of the challenges associated with cataloguing the effects of environmental enrichment on mice is that reports of effects from studies using "enrichment" may be confounded by the fact that the items provided in the cage to increase structural complexity were not objects that actually enhanced the welfare of the animals. Clearly, semantics play a role in this problem as any addition to the cage environment seems to be automatically labeled as an enrichment, whether the definition of enrichment is achieved or not. Many preconceived notions about the benefits of certain cage structures must be discarded as evidence mounts regarding their value as true enrichments. Further complicating the picture is the variability among strains of mice in terms of responses to enrichment items or structural additions to the cage environment. For example, the number of litters produced by female mice living in enriched or standard housing can vary due to the presence of enrichment.[1(p157)] In these studies, the enriched cages included a ladder and jar with nesting material, while the standard cage had bedding. BALB/c and Swiss Webster females produced significantly fewer litters ($P < .001$) and had fewer pups per litter when housed in the enriched cage as compared to the standard cage. However, CB17-Prkdc^{scid}, B6D2F2, and ICR mice did not show any difference in number of litters or pups per litter when housed in standard or enriched cages. There are also striking gender-dependent immunological differences in BALB/c and Swiss Webster mice. Specifically, females of these 2 strains (but not males) demonstrated significantly lower levels of thymocytes when living in an enriched cage as compared to the standard cage. In addition, the age at which the mouse is exposed to the enrichment and the duration of exposure may influence the effect on the animal.[36,37(p95)]

An understanding of the effects of providing an enriched or stimulating environment to rodents has roots in studies done with rats and assessing effects of handling and maze training on brain chemistry and anatomy.[38] Since then, the body of information regarding the influence of cage complexities on the mouse has grown considerably and new findings continue to be published. These findings can generally be categorized into effects on the behavior or biology of the animals, often described in the context of changes in a specific animal model.

3.1.1 | Behavior

The standard cage provides limited scope for the expression of species-appropriate behaviors in the laboratory mouse. Therefore, it is not unexpected that the addition of complexities to the cage environment evokes a change in behavior. It has been theorized that exposure to enriched environments early in the postweaning period may offset the expression of some abnormal behaviors, such as stereotypy, in animals subsequently housed in more limited environments,[39] though minimal effects were observed in mice provided an enriched cage preweaning on adult behavior.[37(p95)] General activity level, which in some studies is dissected into the more specific behaviors of exploration and locomotion, as well as sleep, stress or anxiety related behaviors (sometimes referred to as emotionality), social behaviors, appetitive behavior, and grooming are among the parameters evaluated when one or more objects is introduced to the cage environment. Results vary among strains, gender, and type of object(s) introduced. The data converge in demonstrating increased activity, frequently expressed as exploratory behavior in the home cage,[40] but an inhibition of exploration in experimental settings, with some gender differences, such as an open-field test or elevated T-maze;[41-43] increased aggression between animals with many types of enrichment[19,44(p74)], though not in the ABG inbred strain which is known to be very docile;[45] and often a reduction in time spent sleeping.[46]

3.1.2 | Neurological effects

Morphological changes to the brain are perhaps among the most well-known effect of enrichment on rodents. The brain evinces numerous responses to environmental complexity.[47] Typically, greater cerebral weight and length, as well as increased cortical depth, are measured in rodents living in an enriched environment.[48,49] Recently, the specific regions of the rodent brain affected by living in an enriched environment have been determined. In the hippocampus, CA1 and dentate gyrus cells were affected; however, changes were not observed in layer V pyramidal neurons of the cerebral cortex or in the spiny neurons in the striatum.[50(p57)] When the histological changes in the brains of rats provided with social and inanimate enrichments have been compared with rats that are socially housed without inanimate enrichments, the number of oligodendrocytes and astrocytes in the occipital cortex have reflected an increase in the former group. With rats that were handled daily, only the number of astrocytes increased.[51]

Increases in dendritic spines and branching, synaptic connections, and neural cell size have long been recognized to result from enriching the environment of rodents.[52,53] Initially, these effects on brain morphology cannot be attributed to the enriching effects of social housing, but rather appear to be related to the presence of the inanimate enrichments[54,55] and, more specifically, to direct contact with the inanimate enrichments.[56] Although enriched mice move longer distances and spend more time in the center of an open-field testing apparatus,[57] increased activity associated with exercise (eg, a running wheel) and exploration may not be responsible for the histological changes in the brain.[50(p57)]

An examination of gene expression in the brain, relative to the availability of enrichment items in the home cage, reveals that enrichment affects the expression of several genes that regulate neuronal structure, synaptic signaling, and brain plasticity[58] which have a role in learning, memory, and age-related memory deficits through upregulation of certain neural proteins. In fact, the transgenic R6/1 and R6/2 mice, which are used to model Huntington's disease—a genetic disorder that results in motor dysfunction, dementia, and death—exhibit less decline in select motor function tasks and delayed loss of cerebral volume in those transgenic mice living in an environment that includes both social and inanimate enrichment.[59,60(p238)] Similarly, female mutant mice used to study Rett syndrome had enhanced motor skills and learned tasks at the same level as normal mice if they lived in an enriched environment.[61] These effects were correlated with upregulated brain-derived neurotrophic factor (BDNF) in the female mice (though not the males). Increased striatal expression of BDNF, along with an increase in striatal levels of delta-Fos B and a decrease in striatal levels of the dopamine transporter, also results in increased resistance to the neurotoxic effects of MPTP in mice.[62] Housing Alzheimer's disease transgenic mice in an enriched environment results in significantly reduced levels of amyloid deposition and cerebral β-amyloid peptides, two hallmarks of the disease in human patients and the mouse model.[63] This has been attributed to increased activity of a β-amyloid degrading endopeptide, neprilysin which is elevated in the brains of enriched mice. Other effects on the nervous system have been observed after an exposure of 10 days duration of enrichment to 16-week-old C57BL/6 mice that had streptozotocin-induced diabetes. The enrichment exposure resulted in neural cell proliferation, differentiation, and retention; vascularization of the dentate gyrus; and enhanced dendritic complexity of hippocampal neurons.[64] Recent evidence suggests that the mode of action for enrichment on slowing the course of the disease is mediated through reducing protein deficits in the brain,[65] because nonenriched mice have significant decreases in BDNF as well as reductions in dopamine levels. Not only is BDNF higher in the brains of enriched animals, but so too are nerve growth factor and neurotophin-3 proteins.[66] It has been proposed that standardization of housing conditions should be considered in therapeutic trials.[60(p235)] However, the survivability of R6/2 mice was improved whey they were used in behavioral testing as a means of providing enrichment (rather than housing them in enriched cages).[67] So, it

appears that there are a number of potential confounding variables, some of which may not have even been identified to date, that can alter the course of experimentally induced or modeled disease research.

In rodents, a septal lesion produces a phenomenon known as septal rage, which is characterized by hyperemotionality and aggressiveness by the rodents. Enriched mice have been shown to be less "reactive" than nonenriched mice, and mice living first in an enriched environment and later transferred to the nonenriched environment showed an immediate increase in reactivity.[68] Thus, it appears that enrichment may also modulate the emotionality of some mice.

A discussion of possible neurological changes would not be complete without mentioning the effects of enrichment on memory and learning because these effects reflect a functional change that can occur in rodent brains concomitant to the anatomical changes already described. Learning rate is enhanced across a variety of tests in enriched BXSB mice, with and without ectopic cell clusters in the neocortex.[69] Additionally, spatial memory is positively affected by an enriched environment,[70,71] even when the enrichment is provided to the animals when they are adults.[72] For example, mice living in enriched cages exhibited faster and better learning and search strategies in a water maze.[73] The effect on memory in the mouse model of post-traumatic stress disorder is complex,[74] but appears to contribute to retention of the memory when a situational reminder of the trauma was sufficiently long (ie, 10 minutes), but had no effect when the situational reminder was shorter (ie, 1 minute). Although the precise mechanism of the memory enhancement has not been identified fully, recent evidence suggests that enrichment affects cAMP-dependent protein kinase long-term potentiation in the hippocampus.[75] Huang and colleagues have demonstrated that Neurogranin ($Ng^{+/+}$ and $Ng^{+/-}$) mice show enhanced long-term potentiation in the hippocampus and performed significantly better in a Morris water maze as compared to controls, though $Ng^{-/-}$ mice did not.[76] In addition, Ng $^{+/-}$ mice showed improved performance in a radial maze test. The authors suggest that enrichment causes a significant increase in hippocampal Ng levels. More recent research has demonstrated that an enriched environment may result in enhancing memory by accelerating the activity of the medial prefrontal cortex, which has a role in processing spatial memories, and results in the recruitment of additional cortical areas into the network sustaining spatial memories.[77]

3.1.3 | Organ weights

Organ weights also appear to be influenced by the presence of environmental enrichment in the cage, for example, the heart, liver, kidney, adrenal, spleen, and uterus of three inbred strains of mice (BALB/c, C57BL/6, and A/J) living in enriched and nonenriched cages.[78(p415)] In comparisons with control animals, they found that the weights of the spleen from enriched animals were slightly, but not significantly, increased; and the weights of the adrenal from enriched animals were slightly, but not significantly, decreased. However, no significant differences in the organ weights (kidneys, liver, heart, spleen, testes, prostrate, adrenals, thyroid and parathyroids, pituitary, and brain) were observed in CD-1 mice provided a gauze pad in the cage as an enrichment compared with mice without a pad or in male Swiss albino mice provided a nest box and cotton.[79,80] Similarly, no increase in organ weights was detected in C57BL/6JIcoU or BALB/cAnCrRyCpbRivU mice enriched with objects or enriched with nesting material.[81] A more recent study of B6C3F1/N mice further confirmed no significant increase in organ weights (liver, spleen, thymus, adrenal glands, lung, kidneys, and gastrointestinal tract) of either male or female mice when they were provided with nesting material (Crink-l'Nest^{TM}).[82]

3.1.4 | Physiological changes

The cardiovascular system and hematology of mice from enriched and nonenriched environments have also been assessed. A nonsignificant decrease in red blood cell count and hematocrit and a nonsignificant increase in hemoglobin has been recorded in enriched mice (BALB/c, C57BL/6, and A/J) compared with nonenriched controls.[78(p414)] This same study also demonstrated a nonsignificant increase in the level of white blood cells in enriched C57BL/6 and A/J mice, but not in enriched BALB/c mice.

The mechanism for wound repair and lifespan extension in a mouse model with colon cancer has been elucidated.[83] Mice with a $Tcf4^{Het/+}$- and $Apc^{Min/+}$-mediated colon tumorigenesis that were provided environmental enrichment had improved survival by eliciting a wound repair process (revascularization, plasma cell recruitment and IgA secretion, replacement of glandular tumor tissue with pericytes, and normalizing the microbiota). Male mice had reduced expression of circulating inflammatory cytokines and induced nuclear hormone receptor signaling, which are related to wound healing.

The effect of enrichment in the environment has been measured for several other physiological parameters. Higher levels of testosterone and immunoglobulin G levels have been detected in enriched mice compared with control animals, although there is some strain variability in these findings.[34(p370)] However, no difference in corticosterone (or thyroxine) levels was observed in enriched vs nonenriched DBA/2 mice.[84] Enrichment items are not the only environmental factors that have the potential to influence the physiology of a mouse. For example, the depth and type of bedding placed in the cage influence body temperature.[85(p64)] Mice housed in deep wood bedding were noted to have a significantly higher temperature than comparable mice housed on a layer of beta chips or thin wood bedding, although this difference was time dependent because it was observed only during the daylight hours. Such a difference in body temperature based on bedding depth and type would be of concern in toxicological studies in which determination of the endpoint is based in part on the animal's body temperature.[85(p67)]

3.1.5 | Effects on cancer development

A pattern has been observed over the last several years that environmental enrichment negatively impacts several types of cancer growth. These findings are yielding new avenues of exploration for cancer treatment. One pathway for this beneficial effect is proposed to be upregulation of hypothalamic BDNF which, in turn, downregulates leptin production in adipocytes via sympathoneural β-adrenergic signaling.[86] They have demonstrated that mice living in enriched environments have reduced susceptibility to melanoma and colon cancer. The activation of the hypothalamic–sympathoneural–adipocyte (HSA) axis is influenced by environmental enrichment, perhaps in part due to the reduction in serum leptin levels following exposure to environmental enrichment. This same effect has been demonstrated using a mouse model of breast cancer.[87] Specifically, enrichment delayed onset of the cancer through a reduction in leptin levels. Enrichment consisting of inanimate objects, social stimulation and exercise was found to inhibit pancreatic cancer growth in both subcutaneous and orthotopic models.[88(p3)] The same impact on BDNF was observed as had been reported by other laboratories, and it was observed that enrichment induced differential expression (downregulated) of genes, mostly located in the mitochondria of the tumors. Inhibition of mitochondrial metabolic genes may promote cancer cell death.[88(p5)] A third potential pathway for cancer development has been illuminated. They demonstrated that C57BL/6 mice housed in an enriched environment that received transplanted murine or human glioma cells had reduced tumor volume and longer survival time, as well as increased resistance to developing the tumor.[89(p7)] Indeed, interleukin-15 (which increases natural killer cell activity) and BDNF are key to this effect because levels are increased in the brains of enriched mice and they have a tumor-reducing effect.[89(p3,5)]

3.2 | Is enrichment beneficial or a confounding variable?

The scientific literature provides abundant evidence that the welfare of laboratory mice may be seriously impaired by housing them in barren standard laboratory cages, and their welfare may be improved significantly by providing adequate environmental enrichment. Signs of poor welfare in barren standard cages include abnormal behaviors such as stereotypies (eg, bar-mouthing, jumping, circling) and compulsive behaviors such as barbering, elevated stress hormone levels, fearful and anxiety-like behavior, anhedonia and impaired thermoregulation. Attenuating these adverse effects through appropriate environmental enrichment is likely to improve not only the animals' well-being, but also the scientific validity of a wide range of experiments conducted with them.[90] Abnormal behavior, stress, fear and anxiety, and impaired thermoregulation are all confounding variables that may adversely affect the outcome of animal experiments and potentially also increase variation in the data. It therefore appears that providing suitable enrichment is in the best interest of both the animals and the research conducted with them, supporting Trevor Poole's famous quote that only "happy animals make good science".[91]

Nevertheless, environmental enrichment is still far from being a standard husbandry procedure in most mouse facilities. Ironically, one reason for this reluctance is the concern that environmental enrichment itself could be a confounding variable which adversely affects the scientific validity of animal experiments. In particular, it has been argued that environmental enrichment might disrupt environmental standardization in ways that are detrimental to the precision and reproducibility of results from animal experiments.[92] If true, this would mean that environmental enrichment creates a conflict between the welfare of the animals and the validity of the research, and that the benefits of enrichment in terms of better animal welfare need to be measured against its costs in terms of poorer scientific validity to achieve an optimal compromise. However, this perspective is likely a result of the ambiguity of the term "enrichment", which has been defined in diverse—and sometimes inaccurate—ways. The key is to provide "beneficial" enrichment to the animals, distinguishing these as species-relevant approaches that improve welfare, rather than simply putting any item into a cage and referring to it as "enrichment". Indeed, these latter items can be referred to as "pseudo-enrichments".[93] Based on an evaluation of multiple laboratories to assess the effect of enrichment on variation in behavioral endpoints and reproducibility of behavioral differences in three strains of mice, it has been determined that within group variability contributed an average of 60% of total variability and was unaffected by enrichment.[94] Thus, nonenriched cage environments fail to reduce individual variability in behavioral endpoints.

4 | CONCLUSIONS

The scientific evidence overwhelmingly supports the use of enrichment to improve the welfare of mice used in research. However, the type of enrichment used must be biologically relevant, safe for the animal, improve the animal's welfare, and not interfere with the scientific measures taken from the animals. When these criteria are met, the data produced by the animal will be more valid and reliable. Of note, use of environmental enrichment has led to new areas of scientific enquiry.

CONFLICT OF INTEREST

None.

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