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Research report

Effects of exercise and enrichment on behaviour in CD-1 mice

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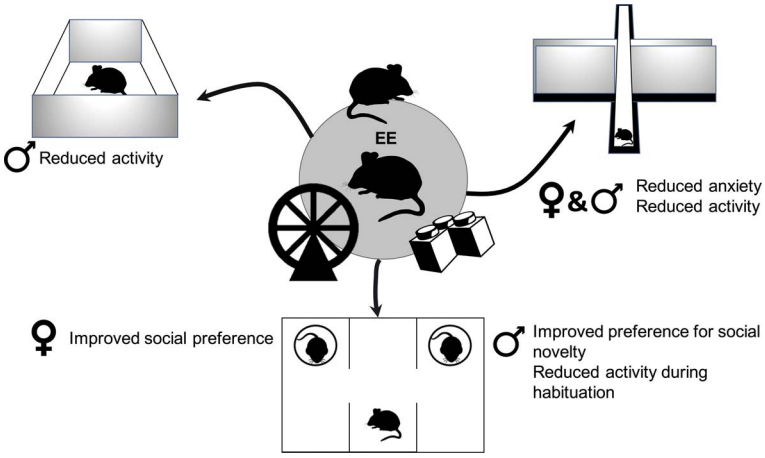
GRAPHICAL ABSTRACT



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ABSTRACT

A host of scholarly work has characterized the positive effects of exercise and environmental enrichment on behaviour and cognition in animal studies. The purpose of this study was to investigate the uptake and longitudinal impact of exercise and enrichment on the behavioural phenotype of male and female CD-1 mice. CD-1 mice housed in standard (STD) or exercise and enrichment (EE) conditions post-weaning were tested in the 3-chamber sociability test, open field, and elevated plus maze and exercise activity was monitored throughout the enrichment protocol. Male and female EE mice both showed reduced anxiety and activity in the open field and elevated plus maze relative to sex-matched STD mice. EE altered social behaviours in a sex-specific fashion, with only female EE mice showing increased social preference relative to female STD mice and a preference for social novelty only present in male EE mice. This sexual dimorphism was not observed to be a product of exercise uptake, as CD-1 mice of both sexes demonstrated a consistent trend of wheel rotation frequencies. These findings suggest the importance of considering variables such as sex and strain on experimental design variables in future work on environmental enrichment.

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1. Introduction

The field of exercise and enrichment has been gaining momentum in preclinical study of murine models. Though it is problematic to define a standard definition of an enriched environment, Rosenzweig et al. [1] suggested enrichment as "a combination of complex inanimate and social stimulation". Research exploring the positive effects of environmental enrichment has provided evidence that the complexity of the rearing environment elicited profound alterations on the anatomy and biochemistry of the brain [2,3]. Analogous to environment enrichment, voluntary exercise has been shown to enhance spatial learning [4–6]. As a result, there is an extensive body of preclinical literature characterizing the positive effects of environmental enrichment and voluntary exercise in tandem, a model for a cognitively- and physically-active lifestyle in humans [7], in the context of neurodevelopmental disorders [8–10] as well as later life brain plasticity and health [11–13].

Studies have demonstrated that sensory, motor, and cognitive stimulation elicited by exercise and enrichment exerts its positive outcomes through the induction of neuroplastic mechanisms observed through increased expression of neurotrophic factors [14,15] and neurotransmitter receptors [16,17]. The observed neurochemical and neuroanatomical findings in enriched animals have been linked to alterations to behavioural outcomes [3] in the context of social [18], anxiety-like [9,19] and activity [20] behavioural measures. Recent work has shown that environmental enrichment and physical exercise improved object recognition memory and contextual fear conditioning in transgenic Gfap-hsv-tk mice with ablated neural progenitors [21], beneficial cognitive and emotional regulation findings paralleled in work with rats [22,23]. In studies with C57BL/6 mice, the anxiolytic effects of environmental enrichment [24] have been shown through increased center time in the open field [25] as well as increased open arm time in the elevated plus maze [26]. In the 3-chamber sociability test, exposure to more complex exercise and enrichment environments has been shown to manifest increased social preference in female BALB/c and 129/Sv mice, an effect not seen in strain-matched male mice [27]. The interaction of sex and strain on the behavioural outcomes of exercise and enrichment has a potential influence on the heterogeneity of findings in the field [28]. Thus, this study aimed to assess the effects of voluntary exercise and environmental enrichment on social, anxiety-like, and exploratory behaviour in male and female CD-1 mice.

2. Materials and methods

2.1. Animals

Male and female CD-1 mice, 6 weeks of age, were purchased from Charles River Laboratories (Kingston, NY). Mice were housed in a 12-hour light/dark controlled environment, lights off at 5 p.m., and fed the standard mouse diet *ad libitum*. Male mice were housed singly for one week to habituate them. After habituation, one female was bred with each male and given a period up to 72 h to mate. At the beginning of each light cycle, the female mice were checked for the presence of a sperm plug, indicating pregnancy. When a sperm plug was detected, the pregnant dam was transferred to a separate cage. Day of birth was defined as postnatal day 0 (P0) and litters culled to 12 pups on P1. At P21, mice were weaned; separated 2 littermates per cage based on sex. Mice were housed in either standard (STD) or exercise and enriched (EE) housing. 8 mice from each litter (6 litters total) were used in the experiment – 2 M STD, 2 M EE, 2 F STD, 2 F EE per litter. STD cages were 26.7 cm × 16.5 cm × 12 cm and EE cages were 33 cm × 20.3 cm × 19 cm. Mice were subjected to a battery of common behavioural tests starting at 8 w (Fig. 1). All experimental procedures were approved by the Animal Research Ethics Board, McMaster University in accordance with the guidelines of the Canadian Council of Animal Care.

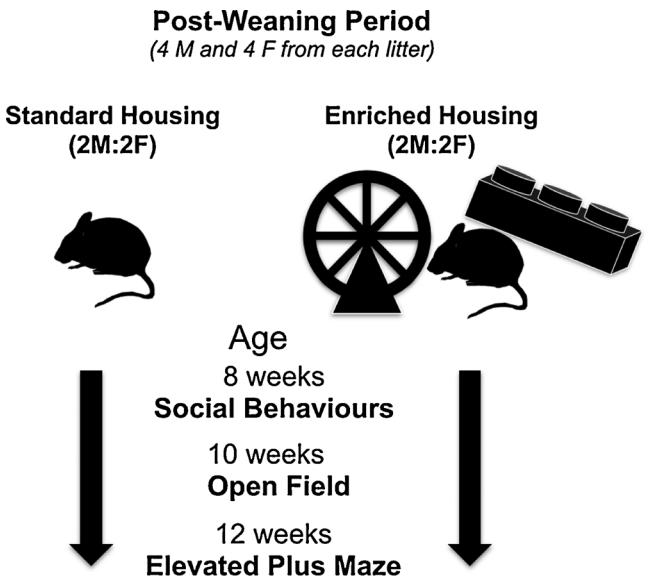

Fig. 1. Timeline for experimentations. After weaning on P21, 4 males and 4 females from each litter of CD-1 mice were randomized into either standard (STD) or exercise and enrichment enrichment (EE) housing with a sex-matched littermate (n = 2 per cage). At the ages of 8, 10, and 12 weeks, mice from STD and EE housing were subject to a battery of behavioural assays: the 3-chamber sociability test, open field and elevated plus maze respectively.

2.2. Post-weaning housing

Mice were housed two littermates per cage, sex matched in either STD or EE housing conditions from weaning to end of experiment. There were three sets of enrichment toys that were cycled weekly to promote novel sensorimotor stimulation (Fig. 2). Exercise wheels were cleaned weekly. Wheel activity was monitored with the activity wheel monitoring (AWM) software as the count of rotations (intervals) of the exercise wheel (Lafayette Instrument Company). Data was collected for each cage that housed 2 sex-matched littermates. Mice were handled 5 min each 3 times a week, beginning 1 week prior to behavioural testing and throughout the subsequent experimental period.

2.3. Behavioural testing

2.3.1. Social behaviour

Sociability and social novelty was assessed using a three-chamber assay [29,30]. At 8 w of age, mice were individually tested during the active period (6 p.m.– midnight). Mice were habituated for 20 min in a non-colony behavioural room prior to testing. The apparatus had three chambers with the outside chambers containing an upside-down wire pencil holder (Galaxy Cup, Spectrum Diversified Designs, Inc.). This configuration allowed the stranger and experimental mice to have some physical contact. There were three stages in this test; habituation, sociability, and social novelty. For habituation, the test mouse was placed in the center chamber without access to either side chamber for 5 min. In the next 10 min, a stranger mouse was placed in the inverted cup in one of the side chambers (randomized) and an empty cup in the other side. The test mouse had access to the entire apparatus. This tested sociability, in terms of preference for the stranger chamber compared to empty chamber. In the final 10 min, preference for social novelty was tested by placing a novel stranger in the cup in the empty chamber and examining the test mouse's preference for the novel relative to familiar (original) stranger. Behaviours were recorded with the Ethovision software using live tracking (EthoVision XT; Noldus). Behavioural apparatus was washed with wet paper towels (water only) and dried between tests. Outcome measures included time spent in 3 chambers – stranger, center, and empty for sociability test; familiar,