INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Anxiolytic effects of environmental enrichment for mice

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Review question / Objective: **The main aim of this review was to critically identify which environmental characteristics consistently improve mice welfare from an affective state perspective. We asked if environmental enrichment versus standard housing would affect anxiety-like behavioural responses in laboratory mice.**
Condition being studied: **Laboratory mice are commonly housed in cages containing bedding materials and, at most, nesting materials and a hiding tube or hut. This type of housing restricts the ability of mice to perform natural behaviours, such as segregation of spaces for elimination and nesting. Compared to mice housed in more complex environments, standard-house mice show a higher incidence of stereotypies, alopecia, and aggression (depending on the type of enrichment). There is abundant evidence that indicate that mice exposed to higher cognitive, sensory and motor stimulation cope better with anxiety-eliciting environments and can recuperate better from chronic stress, pain and stress-induced depression. This evidence indicates that environmental enrichment has a positive effect on affective states in mice.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 January 2023 and was last updated on 10 January 2023 (registration number INPLASY202310024).

INTRODUCTION

Review question / Objective: **The main aim of this review was to critically identify which environmental characteristics consistently improve mice welfare from an affective state perspective. We asked if environmental enrichment versus standard housing would affect anxiety-like behavioural responses in laboratory mice.**

Rationale: **There is great methodological variation between studies using environmental enrichment – for example,**

environmental enrichment sometimes consists in the addition of a single acrylic tube into a standard cage, and in other cases consists in bigger cages with plastic containers, platforms, hiding structures, plastic objects and tubes – such that, straight forward recommendations to refine housing conditions, are difficult to make.

Condition being studied: Laboratory mice are commonly housed in cages containing bedding materials and, at most, nesting materials and a hiding tube or hut. This type of housing restricts the ability of mice to perform natural behaviours, such as segregation of spaces for elimination and nesting. Compared to mice housed in more complex environments, standard-house mice show a higher incidence of stereotypies, alopecia, and aggression (depending on the type of enrichment). There is abundant evidence that indicate that mice exposed to higher cognitive, sensory and motor stimulation cope better with anxiety-eliciting environments and can recuperate better from chronic stress, pain and stress-induced depression. This evidence indicates that environmental enrichment has a positive effect on affective states in mice.

METHODS

Search strategy: To find empirical studies assessing the effects of environmental enrichment on outcomes related to affective states in mice, we searched for literature in two databases (MEDLINE and Web of Science). UBC University librarian, Katherine Miller was consulted to determine the search strategy.

Participant or population: Laboratory mice.

Intervention: Environmental enrichment.

Comparator: Standard housing.

Study designs to be included: No limits on study design were imposed.

Eligibility criteria: The articles included in this review were available in English, described a primary in vivo research trial, used laboratory mice for the study, used environmental enrichment as an intervention, used standard tests for anxiety (i.e., elevated plus maze, open field and light-dark test; Supplementary Information 3: Definitions). We excluded in vitro studies , studies that were carried out on other rodents (e.g. rats, house mice, mole rats etc.), that considered enrichment as the addition of nesting or bedding materials, or that considered "pair housing" as an enrichment intervention, with no detailed description of the type of enrichment used and the way it was provided (e.g., regimen), that lacked a well described control condition (or at least included an image of the control condition) paired to the environmental enrichment , that used pregnant females to assess prenatal effects or transgenerational effects, that assessed outcomes after environmental enrichment was removed and reviews of literature systematic or narrative.

Information sources: MEDLINE and Web of Science.

Main outcome(s): Anxiety-like behavioural responses in the elevated plus maze, open field and/or dark-light box were searched for.

Quality assessment / Risk of bias analysis: Using SYRCLE RoB tool, each study was assessed by two independent individuals . Bias was classified as low if criteria was met, high if criteria was not met and unknown if the information given did not allowed us to make a judgement for risk of bias. The risk of bias assessment was done for each of the following domains:

1. Sequence generation (selection bias) – Were treatments allocated randomly using a sequence generation method? Note that if authors mentioned that treatments were allocated randomly, but did not include the sequence generation process, we noted the study as "unknown" risk of bias for this element.
2. Blinding of personnel (performance bias) – Were the investigators or personnel performing the experiments blind to

treatment when performing the behavioural tests?
3. Blinding of outcome assessors (detection bias) – Were the observers scoring the behaviour blind to treatment and individual identification?
4. Incomplete outcome data (attrition bias) – Is the data for each outcome complete? Are any events of attrition or exclusion from analysis reported? Is there consistency between the numbers in each group reported in the methodology and results?
5. Selective outcome reporting (reporting bias) – Is there alignment and consistency in the outcomes reported between the study predictions, methods, and results? Are most commonly reported outcomes present in the study results?
6. Other bias – Were there any other important issues regarding bias?

Strategy of data synthesis: From each study retained, we extracted 1) article identification: authors information, title, year and journal, 2) study design characteristics: sample size for control and treatment groups), 3) animal model characteristics: strain, genotype, sex, and age, 4) characteristics of the intervention and control conditions: cage size, duration of exposure, age at first introduction, detailed description of structures, items, surface, dimension or substrates considered as enrichment, and 5) the mean and variation (i.e., standard deviation or standard error) for each outcome measure (Supplementary Information 4: Outcome measures). From the latter, we estimated the standardized mean difference (SMD; Cohen's d) and its 95% confidence intervals (CIs).

Subgroup analysis: NA.

Sensitivity analysis: NA.

Language restriction: No limits on language were imposed on the search beyond that of the databases themselves, although only studies in English were included in the review.

Country(ies) involved: Canada.

Keywords: Environmental enrichment; Animal welfare; Anxiety.

Contributions of each author:

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