**Interactive and main effects of stress and environmental enrichment on rodent learning and memory: a protocol for a systematic review and meta-analysis**

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**Citation**

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**Questions**

1. Is there an overall effect of stress on learning and memory in rodents?
2. Is there an overall effect of environmental enrichment on learning and memory in rodents?
3. Is there an interaction of stress and environmental enrichment on learning and memory in rodents overall?
4. If there is a significant interaction of stress and environmental enrichment, is this effect antagonistic or synergistic?
5. Are the significant main effects (i.e., of stress and/or environmental enrichment) or interactive effects (i.e., stress x environmental enrichment) mediated by

5a) sex?

5b) the type of stressor?

5c) the type of environmental enrichment?

5d) the type of learning/memory outcome?

**Searches**

Databases to be searched: Scopus, ISI Web of Science, and BASE (Belfield Academic Search Engine) for Grey Literature. We will also conduct backwards and forwards searching of included studies.

Search string Scopus (syntax will be adjusted for ISI Web of Science):

TITLE-ABS-KEY(("environment\* enrich\*" OR "enrich\* environment\*" OR "complex environment\*" OR "environment\* complex\*" OR "complex housing") AND (\*stress\* OR depriv\* OR separat\* OR advers\*) AND (learn\* OR cognit\* OR memor\* OR escap\* OR \*maze\* OR operant\* OR reward\* OR \*discrimination\* OR spatial\*) AND (rodent\* OR rat OR rats OR \*mice OR \*mouse OR vole\* OR "guinea pig\*" OR squirrel\* OR hamster\* OR gerbil\* OR chipmunk\* OR chinchilla\* OR beaver\* OR gopher\* OR lemming\* OR porcupine\*))

[Restrictions: English language]

**Types of studies to be included**

Empirical studies on any captive bred rodent species. The studies need to include a manipulation of stress and abiotic environmental enrichment in a fully- or partially crossed design (i.e., fully-crossed: stress + control, stress + enrichment, control + enrichment, control + control; partially-crossed: stress + control, stress + enrichment, control + enrichment).

**Condition or domain being studied**

This systematic review and meta-analysis will examine interactive effects of stress and environmental enrichment on learning and memory in relation to the main effects of stress and environment enrichment.

**Participants/population**

Inclusion: captive bred rodents.

Exclusion: wild rodents or rodents that have been captured from the wild and brought into captivity. Individuals that have been modified (physically through surgery, injections etc, or through genetic modification and selection).

**Intervention(s)/exposure(s)**

Exposure of a stressor (Table 1) and/or environmental enrichment (Table 2) in a fully- or partially-crossed design.

**Comparator(s)/control**

There must be a control group for both the stressor and the environmental enrichment manipulations (i.e., animals kept in benign, or “standard” lab environment).

**Main outcome(s)**

Common measures of learning or memory (Table 3).

**Additional outcome(s)**

Effect of potentially important moderators:

* sex
* type of stressor
* acute vs chronic stress
* type of environmental enrichment
* age of stress and environmental enrichment exposure
* age at learning / memory assay
* Type of learning / memory assay

**Data extraction**

Title/abstract and full-text screening followed by data extraction from relevant full-texts. Title/abstract and full-text screening will be completed by two researchers. Data extraction will be completed by one researcher and a sub-set (~30%) will be cross checked by a second researcher.

*Data to be extracted:*

Study details

* study ID
* first author
* year published
* experiment id
* animal group id
* effect size id
* species name
* strain
* sex
* type of housing
* age of enrichment exposure
* age of stress exposure
* age of learning/memory assay
* type of environmental enrichment
* type of stressor
* chronic vs acute stress
* type of learning/memory assay
* type of learning/memory measurement
* Unit of type of learning/memory measurement

Data used to calculate effect size and variance

* mean (stress + enrichment)
* error (stress + enrichment)
* sample size (stress + enrichment)
* mean (control + enrichment)
* error (control + enrichment)
* sample size (control + enrichment)
* mean (stress + control)
* error (stress + control)
* sample size (stress + control)
* mean (control + control)
* error (control + control)
* sample size (control + control).

**Risk of Bias**

We will collect data on if the authors were blind to animal treatment prior to collecting response data, and if the animals were randomly assigned to their treatments.

**Strategy for data synthesis**

Meta-analytic means and confidence intervals, heterogeneity, and variance explained by moderator variables will be calculated. Weighted, multi-level mixed-effects meta-analytic/meta-regression models will be used. Results will be reported in text, in tables, and in forest/orchard plots.

**Analysis of subgroups or subsets**

Potentially by sex as indicated by above. Also, moderators for meta-regression analyses can be considered as subgroup / subsets analyses (e.g., the type of stressors or enrichment as well as the types of learning and memory).

**Contact details for further information**

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**Type and method of review**

Systematic review and meta-analysis.

**Anticipated or actual start date**

01 April 2021.

**Anticipated end date**

01 April 2022.

**Funding sources/sponsors**

Australian Research Council Discovery Grant (DP200100367) awarded to Shinichi Nakagawa and Malgorzata Lagisz.

**Conflicts of interest**

Nil.

**Language**

English.

**Country**

Australia.

**Stage of review**

Piloting.

**Subject index terms status**

NA.

**Subject index terms**

NA.

**Date of registration in OSF**

**Date of first submission**

NA.

**Details of any existing review of the same topic by the same authors**

None.

**Stage of the review at the time of this submission**

|  |  |  |
| --- | --- | --- |
| **Stage** | **Started** | **Completed** |
| Preliminary searches | Yes | Yes |
| Piloting of study selection | Yes | Yes |
| Formal screening of search results against eligibility criteria | No | No |
| Data extraction | No | No |
| Data analysis | No | No |

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

**Table 1: Types of stressors**

|  |  |
| --- | --- |
| **Category** | **Description** |
| Density | The number of animals housed together. This includes social isolation. |
| Scent cues | Cues from predators or competitors |
| Shock | Foot shock etc. |
| Exertion | Forced exercise such as forces swim or treadmill |
| Restraint | Restraining the individuals |
| Maternal separation | Neonatal separation from mothers |
| Circadian disruptions | Disruption of light vs dark hours etc. |
| Other | Other types of stress |
| Combination | A combination of multiple stressors |
| Unclear | It is not clear what the type of stressor was |

**Table 2: Types of environmental enrichment**

|  |  |
| --- | --- |
| **Category** | **Description** |
| Nesting material | Nesting material/bedding |
| Objects | Objects used for visual and tactile stimulation. That can include tubes for hiding |
| Complexity of cage | How complex the cage was such as adding multiple levels |
| Wheel | A running wheel used for voluntary exercise |
| Combination | A mixture of multiple forms of enrichment |
| Other | Other types of environmental enrichment |
| Unclear | It is not clear what the type of environmental enrichment was |

**Table 3: Types of learning and memory**

|  |  |
| --- | --- |
| **Category** | **Description** |
| Habituation | Open field, startle response, nose poke etc. |
| Conditioning | Includes appetitive (e.g., contextual and cued conditioning, conditioned place preference), aversive (e.g., contextual and cued fear conditioning, delay and trace eyeblink conditioning, step-down avoidance, step-through active and passive avoidance, conditioned place preference), operant (e.g., skinner-like box, serial reaction time, DNMTP or DMTP tasks; DRL period tests, or any type of conditioning required for memory such as working memory (e.g., T Maze, Y Maze, Radial Maze) and recognition memory (e.g., object recognition, object displacement, social recognition) |
| Recognition | Object recognition, object displacement, social recognition etc. |