



Review article

The relative benefits of environmental enrichment on learning and memory are greater when stressed: A meta-analysis of interactions in rodents

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ABSTRACT

Environmental enrichment ("EE") is expected to alleviate the negative effects of stress on cognitive performance. However, there are complexities associated with interpreting interactions that obscure determining the benefit EE may play in mitigating the negative effects of stress. To clarify these complexities, we conducted a systematic review with meta-analysis on the main and interactive effects of EE and stress on learning and memory in rodents. We show that EE and stress interact "synergetically" where EE provides a greater relative benefit to stressed individuals compared to those reared in conventional housing. Importantly, EE can fully-compensate for the negative effects of stress where stressed individuals with EE performed equally to enriched individuals without a stress manipulation. Additionally, we show the importance of other mediating factors, including the order of treatment exposure, duration and type of stress, type of EE, and type of cognitive assays used. This study not only quantifies the interactions between EE and stress, but also provides a clear example for how to conduct and interpret a meta-analysis of interactions.

1. Introduction

Environmental enrichment (hereafter "EE"), broadly defined as an increase in the complexity and novelty of the physical and social environment (Rosenzweig et al., 1978), has been widely shown to have many benefits to individual health and fitness since it was first described by Hebb (1949). EE has been shown to alter brain structure and function, including increasing neurogenesis and brain weight, and such changes have been associated with reduced neurological disorders like anxiety and depression, decreased neuronal aging, and improved learning and memory (Kozorovitskiy et al., 2005; Mohammed et al., 2002; Singhal et al., 2014; van Praag et al., 2000). These benefits of EE have been mainly reported in rodents but have also been described in other study systems including invertebrates (e.g., Lomassese et al. 2000; Bertapelle et al. 2017), fish (e.g., Batzina et al. 2014; Zhang et al. 2020), and primates (including humans) (e.g., Kozorovitskiy et al. 2005; Rogers et al. 2019). Due to the seemingly conserved and substantial benefits of EE, interest in understanding such effects is widespread across disciplines: from neurobiology and psychology aiming at ameliorating the

detrimental effects of neurological disorders and diseases (e.g., Fischer et al. 2007; Baroncelli et al. 2010) to improving animal welfare in captive animals (e.g., Coleman and Novak, 2017; Zhang et al., 2020) and increasing our understanding of animal behavior in ecology and evolution, including improving the ecological relevance of experimental outcomes (e.g., Dukas and Mooers, 2003; Mason et al. 2007).

A key benefit of EE is that it can attenuate the negative effects of stress by either acting on the same neurological pathways concurrently or acting on different pathways in parallel (Du et al., 2012; Morley-Fletcher et al., 2003; Schrijver et al., 2002; Smail et al., 2020; van Praag et al., 2000). While stress can be beneficial and considered adaptive in certain circumstances by inducing the 'fight or flight' response, excessive stress can be highly detrimental to brain structure and function (McEwen, 2004). For example, chronic stress can reduce synaptic plasticity, neurogenesis, and impair neurotransmitter responsiveness (Joëls et al., 2004; Sapolsky, 1999), but even acute stress can have negative effects such as dendritic spine loss (Chen et al., 2010). Stress-induced changes in the brain are linked to neurological disorders such as anxiety and depression as well as reduced cognitive performance in learning

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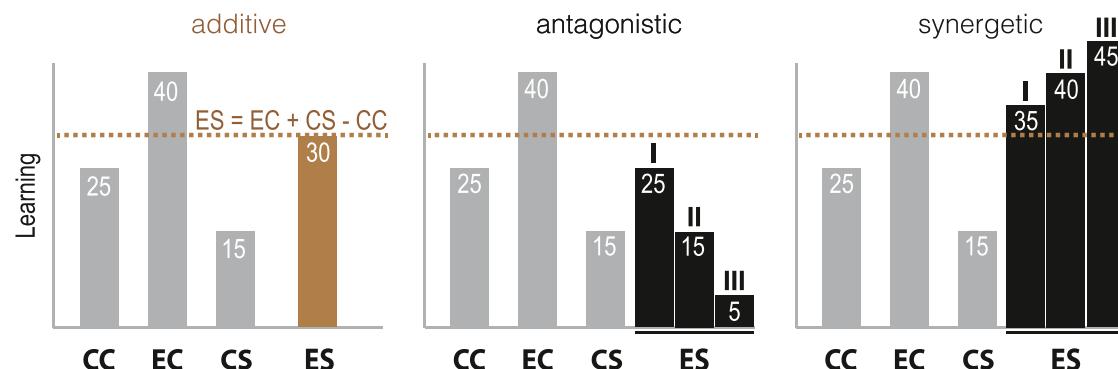
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and memory (Conrad, 2010). Indeed, the lack of EE can also be a stressor in and of itself such as the barren environments often used as conventional housing in many laboratories and animal rearing facilities (e.g., Chourbaji et al., 2005; MacLellan et al., 2021). However, EE can not only attenuate stress-induced effects caused by a barren environment but it can also mitigate the negative effects of other environmental stressors through cognitive reserve and increased neuroplasticity (Petrosini et al., 2009) which can increase resiliency and recovery from stress (Crofton et al., 2015; Fox et al., 2006; Morley-Fletcher et al., 2003; Schrijver et al., 2002; van Praag et al., 2000; Wright and Conrad, 2008).

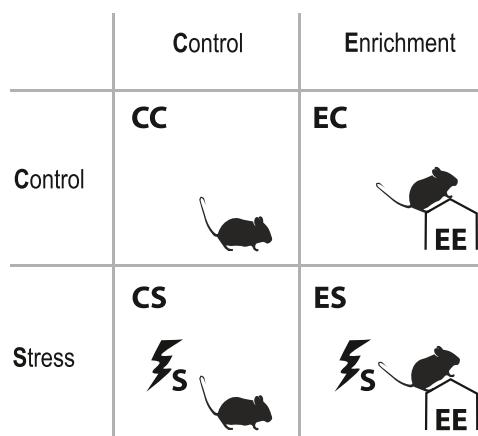
While the literature generally shows that EE can be beneficial for reducing anxiety and depression and increasing cognitive performance (see van Praag et al., 2000), and that stress can negatively impact the same traits (see Joëls et al., 2006, 2004), there is still ambiguity surrounding the ‘interaction’ between EE and stress on such responses. Many studies show that EE can alleviate the negative effects of stress (e.g., Crofton et al., 2015; Fox et al., 2006; Wright and Conrad, 2008) and broadly define this as an ‘interaction’ between EE and stress (see Smail et al., 2020). However, the use of the term ‘interaction’ within the literature does not necessarily refer to a statistical interaction (see Fig. 1A). Furthermore, the current literature does not provide any clear

hypotheses regarding if there is indeed expected to be a statistical interaction between the two, nor the direction and scenarios within a statistical interaction (Fig. 1A). For example, EE may alleviate the negative effects of stress, but the statistical interaction term may not significantly differ from zero, meaning that the effect of EE and stress is ‘additive’ where the relative benefit of EE is equal in both stressed and unstressed individuals (Fig. 1A) (note that we are using the term ‘unstressed’ here to refer to individuals that are exposed to additional environmental stressors above that of conventional housing in many animal studies). Alternatively, there may indeed be a significant interaction between EE and stress where the relative benefit of EE is either greater (i.e., synergistic; Fig. 1A) or smaller (i.e., antagonistic; Fig. 1A) in stressed individuals compared to unstressed individuals. Further, within antagonistic or synergistic interactions, it is also difficult to predict the degree that EE can compensate for stress (i.e., I, II, & III in Fig. 1A). For example, within a synergistic interaction, one of three scenarios may apply: (I) EE may still undercompensate for the effects of stress, (II) EE may fully-compensate for the effects of stress, or (III) EE may overcompensate for the effects of stress. Thus, there is substantial need to disentangle such effects to more clearly understand how EE can mitigate the negative effects of stress.

A Interaction effect scenarios

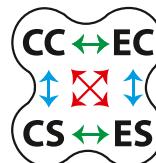


B Fully-crossed experiment



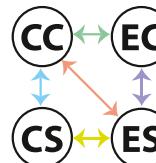
C Effect sizes

1) Focal comparisons – 3 effect sizes:



- Main effect of EE
- Main effect of Stress
- Interaction of EE x Stress

2) Pairwise comparisons – 5 effect sizes:



- EC vs CC
- CS vs CC
- ES vs CC
- ES vs CS
- ES vs EC

Fig. 1. Schematics showing (A) the patterns of interaction scenarios with four experimental groups (CC = ‘full’ controls from conventional housing, EC = EE with no stress manipulation/controlled for stress, CS = stress manipulation with no EE manipulation/controlled for EE, ES = EE and stress manipulations; also see panel B) and an arbitrary cognitive performance unit where (1) there is an additive effect with no interaction, as the effect of ES = EC + CS - CC (e.g. 30 = 40 + 15 - 25), (2) there is an antagonistic interaction is a significantly negative deviation from the additive effect with 3 scenarios (I, II, & III) in reference to CS, and (3) there is synergistic interaction is a significantly positive deviation from the additive effect with 3 scenarios (I, II, & III), (B) the type of fully-crossed experimental design required for primary studies to be included in our meta-analysis where C = control, E = EE, S = stress and (C) the two groups of effect sizes (i.e., the ‘focal’ and ‘pairwise’ effect sizes) used in the meta-analysis.

Quantifying interactions requires a sample size that is approximately four times larger than that needed to detect main effects (Gelman et al., 2020). Therefore, individual experimental studies may be underpowered to quantitatively determine which interaction scenario occurs (i.e., if there is an additive, synergistic, or antagonistic interaction, and to what degree EE can compensate for stress; Fig. 1A). Furthermore, the difficulty in synthesizing the interaction between EE and stress is also likely due to differences in study designs (Smail et al., 2020; see also Joëls et al., 2006; Toth et al., 2011). For example, stress (both acute and chronic) can sometimes result in increases in learning and memory (e.g., Diamond et al., 2007; Shors, 2001), but this is dependent on many factors, including the timing and duration of stress relative to the learning and memory tasks as well as the type of cognitive measure (Conrad, 2010). Responses can also differ based on demographic factors such as sex (e.g., Welberg et al. 2006; Girbovan and Plamondon, 2013) and age of exposure to stress and/or EE (e.g., Mora et al. 2007). Additionally, the benefits of EE are thought to be due to complex relationships between the abiotic environment, social interactions, and exercise, rather than independent effects (Hall, 1998; van Praag et al., 2000), but studies often vary in the combination of factors manipulated. Studies also use different types of stressors, including both physical and psychological, which can affect different parts of the brain and induce different responses (e.g., Herman and Cullinan, 1997). Therefore, while it is important to understand the broad patterns mentioned above and in Fig. 1A, it is also necessary to consider other mediating factors; something that is often difficult when reading independent experimental studies or qualitative reviews.

Here, we used rigorous statistical and meta-analytic methods to clarify the interaction between EE and stress on learning and memory (i.e., cognitive performance) as well as considered potentially important mediating factors by conducting a series of meta-analyses and meta-regression analyses using the experimental rodent literature. We used studies that had conducted fully-crossed 2-by-2 factorial experiments (Fig. 1B) between EE and stress (see Section 2 for more details including justification). We then estimated the main and interactive effects of EE and stress on learning and memory, as well as conducted a series of 'pairwise' comparisons between the four different treatment combinations from the 2-by-2 experiments (Fig. 1C). This allowed us to address five key questions: (1) What are the main effects of EE and stress on learning and memory? (2) Do EE and stress interact to affect learning and memory (i.e., see Fig. 1A), or are the effects additive where EE benefits both stressed and unstressed individuals equally? (3) If there is an interaction, is it synergistic (i.e., the benefit of EE is greater in stressed individuals) or antagonistic (i.e., the benefit of EE is lower in stressed individuals)? (4) To what degree does EE mitigate the negative effects of stress on learning and memory (e.g., does EE fully-compensate, under- or over-compensate for the effects of stress)? (5) What moderating factors that differ between studies and effect sizes are important in determining both main and interactive effects of EE and stress on learning and memory? Addressing these questions using powerful quantitative methods is key for furthering our understanding of the role that EE can play as a non-pharmaceutical approach to alleviating the negative effects of stress, with implications across disciplines: from neurobiology and psychology to animal welfare, ecology and evolution. Furthermore, our methods used in this study provide an important example on how to conduct and interpret meta-analyses and meta-regression analyses of interactive effects – something that has rarely, if ever, been done in the neuroscientific and behavioral literature.

2. Methods

This meta-analysis is reported according to the items for systematic review and meta-analysis established in PRISMA (Moher et al., 2009) modified for Ecology and Evolution, PRISMA-Eco Evo (O'Dea et al., 2021) (Appendix S1); PRISMA-Eco Evo is also suited for a systematic review and meta-analysis of animal model data. We also followed the

guidelines set out in (Foo et al., 2021) for question formulation, literature searching and screening. We pre-registered our main aims and our study outline at the Open Science Framework (<https://osf.io/r328g>).

2.1. Literature searching and screening

We used the PECO (Population, Exposure, Comparator, Outcome) framework (Morgan et al., 2018) to define the scope of our questions and to aid in our literature searching and screening (see Table 1). Then, we performed a comprehensive systematic search for peer-reviewed studies, including published manuscripts, pre-prints, and theses, that met our selection criteria (see Appendix S3, Fig. S1 for abstract and full-text screening decision trees, and Fig. S2 for PRISMA-type diagram of screening process). Broadly, included studies must have been experimental studies on rodents using a fully-crossed 2-by-2 design with individuals exposed to EE alone (EC), stress alone (CS), EE and stress (ES), or unexposed 'full' controls reared in conventional housing (CC) (Fig. 1B) and reported at least one measure of learning and memory after treatment exposure. Briefly, we did not include studies that were partially-crossed (i.e., did not include all four treatment combinations) as this prevented the calculation of our interaction effect size, used physical alterations of the animals as a stressor (e.g., teeth removal, diseases, etc.), or that used contextual fear memory such as PTSD as a response. We also did not include studies that only manipulated social environment as a form of EE as some manipulations of the social environment without additional forms of enrichment can be classed as a stress manipulation (e.g., Monteiro et al., 2014), which may confound EE and stress manipulations (see Appendix S3, Fig. S2). All abstracts and full-texts were each screened using Rayyan QCRI (Ouzzani et al., 2016) by two independent researchers (ELM and ML). Any conflicts in decisions were discussed and resolved by referring to the decision tree (Appendix S3, Fig. S1) until consensus was reached.

First, we searched titles, abstracts, and keywords of papers published between January 1900 and June 2021 in *ISI Web of Science Core Collection*, *Scopus*, *Medline*, and *Embase* using the following search string modified for each database (see Appendix S3, Table S1 for exact search strings for each database): ("("environment* enrich*" OR "enrich* environment*" OR "complex environment*" OR "environment* complex*" OR "complex housing") AND (*stress* OR depriv* OR standard* 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))". Searches on these databases resulted in 1763 unique bibliographic records for screening (Appendix S3, Fig. S2). Abstract screening identified 87 papers that met our title and abstract screening criteria and 27 met our full-text screening criteria (Appendix S3, Fig. S1; Fig. S2).

Next, we conducted a gray literature search with the Bielefeld

Table 1

Descriptions of the population, exposure, control and outcome (PECO) used in this study. See Appendix S3, Fig. S1 for decision tree of inclusion and exclusion criteria and Fig. 1B for the experimental design required to be included in this meta-analysis.

PECO	Description
Population	Rodents (non-genetically or physically modified)
Exposure	Must have three treatment combinations:
	• EE without a stress manipulation (i.e., controlled for stress) (EC)
	• Stress without an EE manipulation (i.e., controlled for EE) (CS)
	• EE and stress (ES)
Control	Animals reared in conventional housing without an EE or stress manipulation (i.e., 'full' controls) (CC)
Outcome	Any measure of learning (i.e., acquisition of information) or memory (i.e., retention of information). Collectively referred to as "cognitive performance"

Table 2

Included papers in our analyses as well as a description of the EE and stress manipulations and the animals used in each study.

Reference	Manipulation of EE	Manipulation of stress	Study animals
Aghighi Bidgoli et al., 2020	Toys replaced weekly for novelty.	Noise stress.	Male Wistar rats
Berardo et al., 2016	Multilevel cage, toys, and running wheels. Location of items changed for novelty.	Maternal separation.	Male Wistar rats
Bhagya et al., 2017	Increased number of conspecifics with larger cage, and toys. Toys replaced for novelty.	Restraint.	Male Wistar rats
Blanco et al., 2017	Multilevel cage with chambers, toys, and shelter. Toys replaced for novelty	Foot shock.	Male Swiss Mice
Castelhano-Carlos et al., 2014	'Phenoword': Corn cob bedding, running wheels, drinking and feeding boxes, and an automated gate.	Unpredictable stress randomly selected from: confinement to a restricted space, cage tilt, sudden noise, wet bedding, overnight illumination, cage change with new conspecifics, water deprivation, food deprivation, cold water instead of bedding, reversed light and dark cycle.	Male Wistar Han IGS rats
Chen et al., 2010	Toys, running wheels, and nesting material. Toys moved for novelty.	Restraint.	Male ICR Mice
Cordier et al., 2021	Increased number of conspecifics, toys, climbing platform, and running wheels. Toys and cage layout changed for novelty.	Maternal separation.	Male Wistar rats
Cui et al., 2006	Larger cage with multiple levels, shelter, running wheel, wood shavings, and toys. Toys changed for novelty.	Limited nesting/bedding materials.	Male rats (strain unreported)
Dandi et al., 2018	Increased number of conspecifics, toys, climbing platforms, and running wheels. Toys and cage layout changed for novelty.	Maternal separation.	Mixed sex (sexes not separated) Wistar rats
do Prado et al., 2016	Increased number of conspecifics, toys, climbing platforms, and bedding.	Maternal separation.	Male and female Sprague-Dawley rats
Guan et al., 2021	Increased number of conspecifics, larger cage with additional level, wood shavings, running wheels, shelter, and toys. Toys changed for novelty.	Unpredictable stress randomly selected from: water deprivation, food deprivation noise, cage tilt, forced swimming, squeezing tail, restriction, shaking, soiled cage, and heat stress.	Mixed sex (sexes not separated) Wistar rats
González-Pardo et al., 2019	Increased number of conspecifics, larger cage, toys, platforms, and running wheels.	Maternal separation.	Male Wistar rats
Grace et al., 2009	Running wheels.	Maternal separation.	Male Sprague-Dawley rats
Hui et al., 2011	Increased number of conspecifics in larger cages, containers, platforms, running wheels. Objects changed weekly and water and food locations moved for novelty.	Maternal separation.	Mixed sex (sexed not separated) Sprague-Dawley rats
Lui et al., 2011	Increased number of conspecifics in larger cages, toys, platforms, shelter, and running wheels.	Restraint.	Male Sprague-Dawley rats
Menezes et al., 2020	Larger cage, toys, and shelter. toys changed for novelty.	Maternal separation.	Male Wistar rats
Mitra and Sapsolsky, 2009	Larger cage, nesting material, toys, fruit-flavored chews, food mixed with flavored cereal, and sunflower seeds. Objects rearranged for novelty.	Restraint.	Male Wistar rats
Mohammadian et al., 2019	Larger cage, shelter, toys, and running wheels. Objects changed for novelty.	Maternal separation.	Male and female Wistar rats
Molina et al., 2019	Increased number of conspecifics in larger cages, multiple levels, ramps, toys, running wheels, and flavored cereal. Toys changed for novelty.	Noise.	Male Wistar rats
Molina et al., 2016	Larger cage, multiple levels, ramps, toys, running wheels, and flavored cereal. Toys changed for novelty.	Noise.	Male Wistar rats
Monteiro et al., 2014	Increased number of conspecifics in larger cages, shelter, and toys.	Social isolation.	Male Swiss mice
Nawaz et al., 2018	Larger cage, shelter, toys, and running wheels. Toys changed for novelty.	Restraint.	Male Wistar rats
Novaes et al., 2021	Larger cage, toys, and platforms. Toys changed for novelty.	Restraint.	Male Wistar rats
Rule et al., 2021	Increased number of conspecifics in larger cages, sawdust bedding, platforms, toys, hammocks. Toys changed for novelty.	Combination of forced swim, restraint, and elevated platform.	Male Lister hooded rats
Shilpa et al., 2017	Increased number of conspecifics in larger cages, nesting material, and toys. Toys changed and rearranged for novelty.	Restraint.	Male Wistar rats
Sun et al., 2016	Larger cage, toys, and running wheels. Toys changed for novelty.	Foot shock.	Male Sprague-Dawley rats
van der Veen et al., 2015	Increased number of conspecifics in larger cages with multiple levels, running wheels, shelter, ladders, maze and tubes leading to food.	Maternal separation.	Male Wistar rats
Veena et al., 2009	Increased number of conspecifics in larger cages, and toys. Toys changed and rearranged for novelty.	Restraint.	Male Wistar rats
Vivinetto et al., 2013	Increased number of conspecifics in larger cages, toys, and running wheels. Toys changed and rearranged for novelty.	Maternal separation.	Male Wistar rats
Zubedat et al., 2015	Increased number of conspecifics in larger cages, running wheels, toys, and platforms with sand boxes. Toys changed for novelty.	Forced swim, mirror box, restraint.	Male Wistar rats

Academic Search Engine (BASE) using the search string “tit:stress* tit:enrich* doctype:(15 18 * 19)”. This resulted in 25 documents. Two documents met our title and abstract screening criteria, but no documents met our full-text screening criteria (Appendix S3, Fig. S1; Fig S2).

Lastly, we conducted backwards and forwards searching of the bibliographies and citing literature of the 27 relevant papers that met our full-text requirements. This resulted in a further 2055 unique references after removing duplicates from our previous searches. Of these 2055 references, 7 met our title and abstract screening criteria and 4 met our full-text requirements. In total, this originally resulted in the inclusion of 31 papers. However, one paper consistently reported negative values for one of their treatment groups which prevented the calculation of our effect size, the logarithm response ratio (see Eqs. 1–8 below). Therefore, this study was excluded from our analysis, resulting in the final inclusion of 30 papers and 92 effect sizes (see Table 2 for included studies).

2.2. Dataset compilation

We compiled a dataset with all relevant paper and effect size identifiers, descriptive statistics, and relevant moderator variables to be included in the meta-regression analysis (see <https://osf.io/fb38q/> for raw and processed data; see Appendix S2 for codebook/metadata). If descriptive statistics were not provided in text or in a table, we extracted these from figures using Web Plot Digitizer (Rohatgi, 2021). Where we were unable to extract descriptive statistics from figures, we contacted the authors for further details. All error measures (i.e., standard errors, confidence intervals, and percentiles) were converted to standard deviations (SD); medians were converted to means (Hozo et al., 2005). Table 3 presents the potentially relevant moderators that were included in our meta-regression analyses (see Section 2.4) that could help explain variation in learning and memory responses to EE and stress. All data extractions were conducted by ELM and 50% of extractions were checked by ML for accuracy, without blinding authors or institutions of the included studies as no investigators were authors of the included papers or had conflicts of interests with any of the included studies.

2.3. Effect-size calculation

To quantify differences in individual performance in the cognitive assays, we employed the logarithm of response ratio, hereafter, lnRR (Hedges et al. 1999; see also Lajeunesse, 2011; Senior et al. 2020). We note that Standardised Mean Difference (SMD) is often used as an effect size index in meta-analyses across different fields (see Section 2.5 and 3.4 for a sensitivity analysis using SMD), but lnRR has several advantages compared to SMD, including no assumption regarding heteroscedasticity between different groups and often having higher statistical power (Nakagawa et al., 2015; Yang et al., 2022). The point estimate and sampling variance (var) of lnRR are (Eqs. 1 and 2):

$$\ln RR = \ln\left(\frac{M_T}{M_C}\right) = \ln(M_T) - \ln(M_C) \quad (1)$$

$$\text{var}(\ln RR) = \frac{SD_T^2}{N_T M_T^2} + \frac{SD_C^2}{N_C M_C^2} \quad (2)$$

where M_T and M_C are averages of treatment (T) and control (C) groups, respectively, SD and N are (sample) standard deviations and sample size. We had 4 groups in the 2-by-2 factorial design: (1) ‘full’ control group from conventional housing (CC), (2) group with only EE (i.e., were not exposed to a stress manipulation/were controlled for stress) (EC), (3) group with only stress (i.e., were not exposed to an EE manipulation/were controlled for EE) (CS), and (4) group with both EE and stress (ES) (Fig. 1B). Therefore, we were able to calculate five different treatment and control ‘pairwise’ effect sizes (lnRR), which are $\ln(M_{EC}/M_{CC})$, $\ln(M_{CS}/M_{CC})$, $\ln(M_{ES}/M_{CC})$, $\ln(M_{ES}/M_{EC})$, $\ln(M_{ES}/M_{CS})$ and $\ln(M_{ES}/M_{EC})$

(Fig. 1C).

Further, we calculated three ‘focal’ effect sizes: 1) the main effect of EE, 2) the main effect of stress and 3) the interaction effect between EE and stress (Morris et al., 2007; see also Lajeunesse, 2011). The main effect for EE and its sampling variance can be expressed in Eqs. 3 and 4, where all the symbols and subscripts are as above:

$$\ln RR_{EE} = \ln\left(\frac{M_{ES} + M_{EC}}{2}\right) - \ln\left(\frac{M_{CS} + M_{CC}}{2}\right) = \ln\left(\frac{M_{ES} + M_{EC}}{M_{CS} + M_{CC}}\right) \quad (3)$$

$$\begin{aligned} \text{var}(\ln RR_{EE}) = & \left(\frac{1}{M_{ES} + M_{EC}}\right)^2 \left(\frac{SD_{ES}^2}{N_{ES}} + \frac{SD_{EC}^2}{N_{EC}}\right) \\ & + \left(\frac{1}{M_{CS} + M_{CC}}\right)^2 \left(\frac{SD_{CS}^2}{N_{CS}} + \frac{SD_{CC}^2}{N_{CC}}\right) \end{aligned} \quad (4)$$

Similarly, the main effect of stress, along with the sampling variance, is expressed in Eqs. 5 and 6:

$$\ln RR_{\text{stress}} = \ln\left(\frac{M_{ES} + M_{CS}}{2}\right) - \ln\left(\frac{M_{EC} + M_{CC}}{2}\right) = \ln\left(\frac{M_{ES} + M_{CS}}{M_{EC} + M_{CC}}\right) \quad (5)$$

$$\begin{aligned} \text{var}(\ln RR_{\text{stress}}) = & \left(\frac{1}{M_{ES} + M_{CS}}\right)^2 \left(\frac{SD_{ES}^2}{N_{ES}} + \frac{SD_{CS}^2}{N_{CS}}\right) \\ & + \left(\frac{1}{M_{EC} + M_{CC}}\right)^2 \left(\frac{SD_{EC}^2}{N_{EC}} + \frac{SD_{CC}^2}{N_{CC}}\right) \end{aligned} \quad (6)$$

Finally, the interaction and its sampling variance can be expressed in Eqs. 7 and 8, where a positive value indicates a synergistic interaction (Fig. 1A) where the effect of EE is greater in individuals with a stress manipulation compared to individuals without a stress manipulation, negative values indicate an antagonistic interaction (Fig. 1A) where the effect of EE is smaller in individuals with a stress manipulation compared to individuals without a stress manipulation, and values of zero indicate an additive effect (Fig. 1A) where EE has an equal effect in individuals with a stress manipulation and individuals without a stress manipulation:

$$\ln RR_{EE \times \text{stress}} = (\ln M_{ES} - \ln M_{CS}) - (\ln M_{EC} - \ln M_{CC}) = \ln\left(\frac{M_{ES}/M_{CS}}{M_{EC}/M_{CC}}\right) \quad (7)$$

$$\text{var}(\ln RR_{EE \times \text{stress}}) = \frac{SD_{ES}^2}{N_{ES} M_{ES}^2} + \frac{SD_{EC}^2}{N_{EC} M_{EC}^2} + \frac{SD_{CS}^2}{N_{CS} M_{CS}^2} + \frac{SD_{CC}^2}{N_{CC} M_{CC}^2} \quad (8)$$

We used these three main and interactive effects as our ‘focal’ effect sizes for the meta-analyses and meta-regression analyses (see below; Fig. 1C) to address questions 1, 2, 3 and 5, and the five ‘pairwise’ effect sizes to demonstrate the relative difference in learning and memory of each treatment compared to controls to determine the degree that EE can compensate for the effects of stress (used to address question 4) (Fig. 1C). Both analyses are required to disentangle different scenarios of interactions (Fig. 1A; for more see Section 4.4).

We note that our dataset included proportion (percentage) data (e.g., the percent of correct responses made by individuals in choice tests), which are bounded at 0 (0%) and 1 (100%). Therefore, we transformed group means (M) and group standard deviations (SD) for proportion data using Eq. 9 and 10 before applying Eqs. 1–8 to calculate lnRR and the sampling variance:

$$f(M) = \text{arcsine}\left(\sqrt{M}\right) \quad (9)$$

$$\text{var}\left(f(M)\right) = \frac{SD^2}{4M(1-M)} \quad (10)$$

where f indicates a function, in our case, the arcsine transformation, and the variance (var) associated with the arcsine transformation that was derived using the delta method (e.g., Nakagawa et al., 2017). We also obtained effect sizes using untransformed percentage data for a

Table 3

Moderator variables included in the meta-regression analyses that were predicted to mediate effects of EE and stress on learning and memory. Categories in bold represent the moderator groups with ≥ 5 effect sizes (k) so were included in the meta-regression analyses. Also see Appendix S2 for codebook/metadata with more detailed descriptions and justifications of each moderator.

Moderator	Categories	Models
Learning vs memory	<ul style="list-style-type: none"> • Learning (i.e., acquisition of information) • Memory (retrieval of information) 	<ul style="list-style-type: none"> • Main effect of EE • Main effect of Stress • Interaction
Type of assay	<ul style="list-style-type: none"> • Recognition • Habituation • Conditioning 	<ul style="list-style-type: none"> • Main effect of EE • Main effect of Stress • Interaction
Type of reinforcement	<ul style="list-style-type: none"> • Aversive • Appetitive • Not applicable (i.e., in habituation and recognition assays) 	<ul style="list-style-type: none"> • Main effect of EE • Main effect of Stress • Interaction
Age at EE	<ul style="list-style-type: none"> • Prenatal (mother was exposed during pregnancy) • Early post-natal (PND < 21) • Adolescent (PND 21 – 60) • Adult (PND > 60) 	<ul style="list-style-type: none"> • Main effect EE • Interaction
Exercise EE	<ul style="list-style-type: none"> • Exercise • No exercise 	<ul style="list-style-type: none"> • Main effect of EE • Interaction
Social EE	<ul style="list-style-type: none"> • Social EE • No social EE 	<ul style="list-style-type: none"> • Main effect of EE • Interaction
Age at Stress	<ul style="list-style-type: none"> • Prenatal (mother was exposed during pregnancy) • Early post-natal (PND < 21) • Adolescent (PND 21 – 60) • Adult (PND > 60) 	<ul style="list-style-type: none"> • Main effect of Stress • Interaction
Type of stress	<ul style="list-style-type: none"> • Restraint • Noise • Maternal separation • Combined stressors • Shock • Density 	<ul style="list-style-type: none"> • Main effect of Stress • Interaction
Stress duration	<ul style="list-style-type: none"> • Acute (< 7 days exposure) • Chronic (≥ 7 days exposure) • Intermittent (alternating days of exposure vs no exposure) 	<ul style="list-style-type: none"> • Main effect of Stress • Interaction
Order of treatment exposure	<ul style="list-style-type: none"> • Stress before EE • EE before stress • Concurrently 	<ul style="list-style-type: none"> • Interaction

sensitivity analysis (see Section 2.5 and Section 3.4).

2.4. Meta-analysis and meta-regression

We carried out all relevant calculations and analyses in the R environment using Rstudio version 1.4.1106 (RStudio Team, 2021). The R scripts and raw and processed data used in this study are all openly available on the Open Science Framework at <https://osf.io/fb38q/>.

We conducted eight multilevel, mixed-effects meta-analytic models: three using our three ‘focal’ effect sizes that averaged across treatments to get the main effects of EE, stress, and the interactive effect of EE and stress (these three models were later used for the meta-regression analyses), and five ‘pairwise’ effect sizes used as comparisons between treatment combinations (Fig. 1C). For each meta-analytic model, we also estimated a multilevel version of heterogeneity (I^2) which quantifies unexplained variation after accounting for sampling variance (Borenstein et al., 2021; Higgins et al., 2003; Nakagawa and Santos, 2012).

To explain some of the unexplained variation in the three ‘focal’ models, we conducted a series of uni-moderator meta-regression analyses (see Section 2.5 and Section 3.4 for multi-moderator meta-

regressions). We ran uni-moderator models with each of the relevant factors as moderators (see Table 3) and estimated the variance explained by the moderators by calculating marginal R^2 (Nakagawa and Schielzeth, 2013). We also performed contrast analyses to test for significant differences in mean effect sizes between each category within moderators. Moderator categories with k (the number of effect sizes) < 5 were excluded due to limited power of these levels (cf. O’Dea et al., 2021). We note that we used uni-moderator models as our main meta-regression models for two reasons: (1) k would be substantially smaller in the multi-moderator ‘full’ model due to missing data in some moderators as not all details were reported in some of the included manuscripts, and $k < 5$ for some moderator levels (see Section 3.1); and (2) co-linearity or nestedness of some of our moderators (see Fig. 2) which can result in difficulty partitioning Akaike weights between moderators (see Section 2.5 for more details on Akaike weights). For these reasons, discrepancies can occur between uni-moderator and multi-moderator models which is especially true when sample sizes differ between uni-moderator and multi-moderator models (Grueber et al., 2011).

All meta-analytic and meta-regression models were run using the *rma.mv* function from the *metafor* package version 3.0.2 (Viechtbauer, 2010) with study ID (due to multiple effect sizes obtained from the same studies), effect size ID, and rodent strain as random effects. We also controlled for non-independence in sampling variance from the same study individuals by including a variance-covariance matrix of the sampling variance in the model. For each model estimate, we also report 95% confidence intervals (CI) and 95% prediction intervals (PI). Prediction intervals show the probability that a new effect size from a new study will fall within the PI range (IntHout et al., 2016; Nakagawa et al., 2020).

2.5. Publication bias tests and sensitivity analyses

We used the three ‘focal’ meta-analytic models (i.e., the main effects of EE and stress, and the interaction model) to test for publication bias and the ‘robustness’ of the reported results through sensitivity analyses. To test for publication bias, we used three approaches. First, we carried out visual inspection for asymmetry in funnel plots which can indicate a ‘small-study effect’ where studies with small sample sizes tend to have large effects in magnitude (Sterne et al., 2005). However, a funnel plot does not provide a statistical test of asymmetry. Therefore, secondly, we conducted an inferential method using regression analyses, often referred to as Egger’s regression, that is often used to test for a statistical significance of funnel asymmetry (Egger et al., 1997). A multilevel meta-analytic version of Egger’s regression can be conducted by fitting sampling standard errors (i.e., the square-root of sampling variance) as a moderator. However, this method can be biased because there is an inherent correlation between effect size and sampling variance in lnRR (e.g., see Eqs. 1 and 2). Therefore, we fitted the following instead (Eq. 11; cf Nakagawa et al., 2022):

$$\sqrt{\frac{1}{\tilde{N}}} = \sqrt{\frac{1}{N_{ES}} + \frac{1}{N_{EC}} + \frac{1}{N_{CS}} + \frac{1}{N_{CC}}} \quad (11)$$

where \tilde{N} is sometimes referred to as ‘effective sample size’. Third, we tested for a time-lag bias where the magnitude of effect declines in more recent publication years by fitting the mean-centered Publication Year as a moderator along with $\sqrt{1/\tilde{N}}$ in the full models (this method is detailed in Nakagawa et al., 2022). The time-lag bias is also known as a decline effect; one of the main reasons for such a decline in the magnitude of effect sizes over time is due to earlier publications of significant results than those of non-significant results (Koricheva and Kulinskaya, 2019; Trikalinos and Ioannidis, 2005).

To test the robustness of the three ‘focal’ effect sizes, we conducted ‘leave-one-group-out’ sensitivity analyses where one animal group (in this case, this corresponded to one study) was removed from the dataset

at a time and a new meta-analytic mean and 95% CI were calculated. This allowed us to assess if a singular study was having a disproportionately strong effect on the meta-analytic mean. We also reran the three focal models using a comparable effect size, standardized mean difference (SMD; also known as Cohen's *d* or Hedge's *g*; formulas are described in Gurevitch et al., 2000), as well as using untransformed percentage data as transformations can sometimes reveal or hide interactions (Knol et al., 2011).

Lastly, we ran multi-moderator 'full' models for the three focal effects with all potentially relevant moderators (Table 3) in the model. We ran model selection based on AIC (Akaike's Information Criterion), using the R package *MuMin* version 1.43.17 (Barton and Barton, 2015). AIC represents a parsimony method where model fit and the number of parameters is balanced, with a smaller AIC value indicating the most parsimonious model. We selected the top set of models within delta AIC of 6 (for a review of AIC-based model selection, see Grueber et al., 2011) and calculated the importance of each moderator (i.e., Akaike weights) within this top model set. Akaike weight is the percentage a particular moderator appears within the top set of models and, therefore, the weight indicates the relative importance of a particular moderator compared to the other moderators within a given dataset (Galipaud et al., 2017). We expected that if uni-moderator models and multi-moderator models are consistent with each other, R^2 from uni-moderator models and Akaike weights from the multi-moderator model selection predictors would be comparable. However, as stated in Section 2.4, when correlations exist between those moderators (co-linearity, overlaps, or nestedness, for categorical moderators), these statistical indices become inconsistent with each other; this may be especially so when sample sizes differ between uni-moderator and multi-moderator full models. In such cases, caution is required in interpretation of the meta-regression results.

2.6. Risk of bias

We recorded if studies randomly allocated their subjects into treatments ('randomization') and if measures of learning and memory were conducted blind to treatment ('blinding') then calculated the proportion of studies that explicitly stated if they did or did not use randomization/blinding or if it was not reported. We then included if a study used randomization or blinding as moderators in separate uni-moderator meta-regressions for each 'focal' model. We then analysed contrasts between mean effect sizes to test if effect sizes were smaller in studies that used randomization or blinding (sensu Holman et al., 2015). In addition, we also recorded the unit of replication (i.e., if the study used individuals or cage number) as their unit of replication. We then reported the proportion of studies that used cage as their unit of replication (note that no contrast analysis was done as most studies used the same unit of replication).

2.7. Deviation from pre-registration

We followed the pre-registration (<https://osf.io/r328g>) as closely as possible, except for four minor deviations. First, we were unable to test for sex differences in responses due to the lack of data on females (see Section 4.3). Second, we included fully-crossed studies, but not partially-crossed studies, as we could not calculate effect sizes for the interactions from partially-crossed studies (see Eqs. 7 and 8). Third, we conducted a series of uni-moderator meta-regression analyses rather than subgroup analyses which enabled us to calculate the variation explained by each moderator (marginal R^2), although we note these two types of analyses are equivalent except that meta-regression analyses have more statistical power. Fourth, some of our moderator categories for the type of stressor and type of EE differed slightly based on the types of manipulations used in the studies that met our selection criteria (Table 3).

3. Results

3.1. Data overview

Out of the 30 papers that met our inclusion criteria (Table 2), we obtained 92 effect sizes for each meta-analysis. A majority of studies were on rats (*Rattus norvegicus*) (Wistar strain) (Fig. 2A), with 79 effect sizes on males and only 3 effect sizes on females (the remaining 10 effect sizes were from data reported with both sexes combined) (Fig. 2A).

For the EE treatments, most manipulated EE during adolescence, and included a manipulation of both voluntary exercise and social environment (Fig. 2B) along with the addition of other objects/toys and increased cage size and/or complexity (see Table 2). For the stress treatments, the most common manipulation was maternal separation (Fig. 2C) and thus, the most common age of exposure to stress was at the early post-natal stage (Fig. 2C). Therefore, most individuals were exposed to stress prior to EE (Fig. 2E). Additionally, most stress was chronic stress (exposure > 7 days) compared to acute stress (Fig. 2C).

Most studies measured memory responses (i.e., retention of information) compared to learning responses (i.e., acquisition of information) and used aversive reinforcement in conditioning assays (Fig. 2D). The majority of studies also measured learning and memory in adults (Fig. 2E), since most EE and stress manipulations occurred prior to adulthood (Fig. 2E).

3.2. Meta-analysis

In the 'focal' meta-analytic models, EE significantly improved learning and memory by an average of 19% (95% confidence interval, hereafter, CI = [12%, 25%]; note these are the back-transformed values of lnRR; see Table 4 for untransformed values) and stress significantly impaired learning and memory by an average of 10% (CI = [-17%, -4%]) (Table 4; Fig. 3A). We also detected a significantly positive average effect size for the EE × stress interaction meaning that there is a significant synergistic interaction (refer to Fig. 1A) where EE improved learning and memory by 12% (CI = [0.4%, 24%]) more in stressed individuals compared to individuals not exposed to a stress manipulation (Table 4; Fig. 3A).

The 'pairwise' comparison models corroborated the patterns found in the three focal models and demonstrated that EE fully-compensated for the negative effect of stress (Table 4). EE individuals performed 11% (CI = [5%, 16%]) better in learning and memory assays compared to 'full' controls from conventional housing (EC/CC), and stressed individuals performed 18% (CI = [-29%, -8%]) worse in learning and memory assays compared to 'full' controls from conventional housing (CS/CC) (Table 4; Fig. 3B). Additionally, stressed individuals with EE performed 25% (CI = [5%, 45%]) better in learning and memory assays compared to stressed individuals without EE (ES/CS) and 8% (CI = [0.3%, 16%]) better compared to 'full' controls from conventional housing (ES/CC) (Table 4; Fig. 3B). Finally, we did not detect a significant difference between stressed individuals with EE compared to individuals with EE that were not exposed to a stress manipulation (ES/EC), with only an average of 1% (CI = [-8%, 6%]) difference detected between the two groups (Table 4; Fig. 3B) – consistent with scenario II under the 'synergistic' panel in Fig. 1A which demonstrates full-compensation of the negative effects of stress.

Heterogeneity was high for all meta-analytic models ($I^2 > 81\%$ in all models; Table 4). Most of this heterogeneity was due to differences among effect sizes and among studies (Table 4). Therefore, the observed high heterogeneities justify our meta-regression analyses below, where we investigate moderators that vary between studies and effect sizes.

3.3. Meta-regression

3.3.1. Moderators of (main) EE effects

Of all the moderators examined that might account for some of the

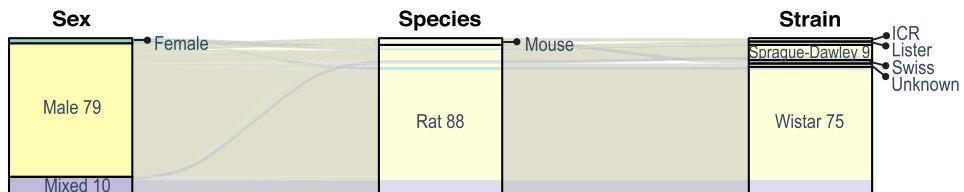
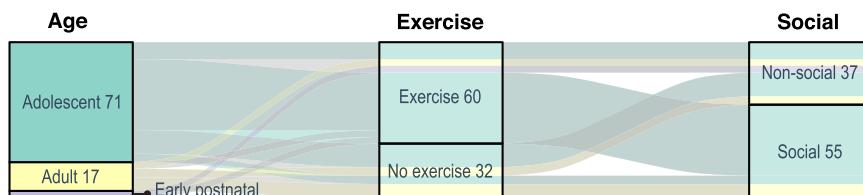
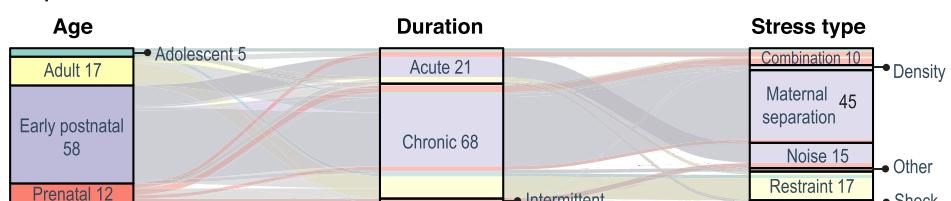
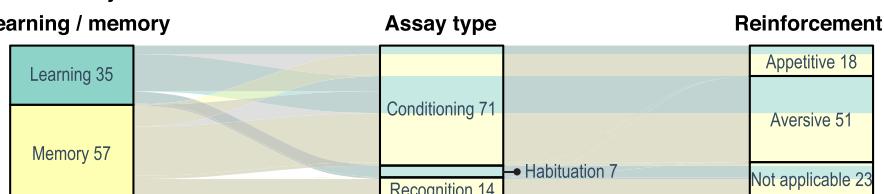
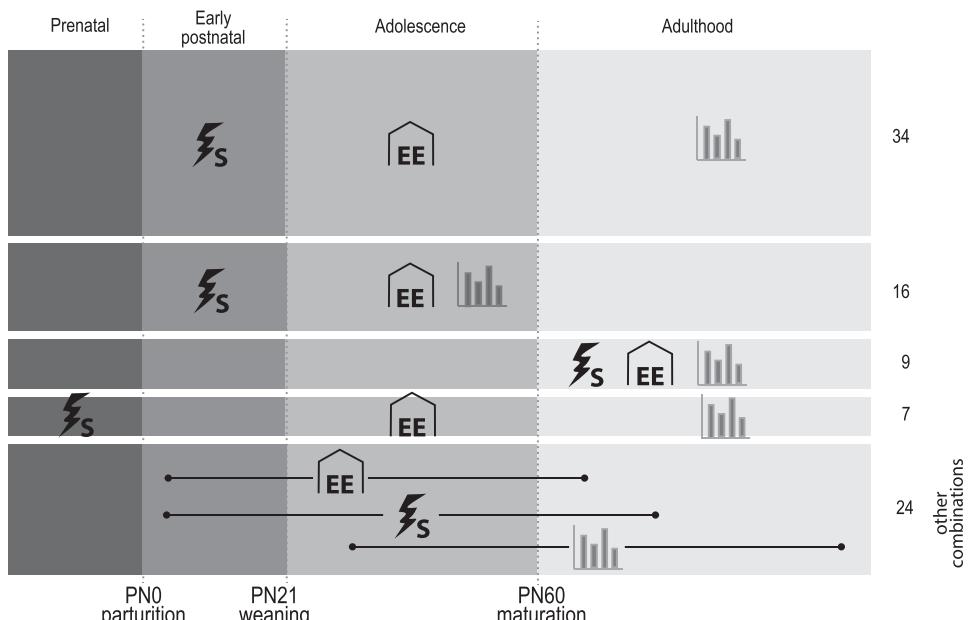
A study subjects**B environmental enrichment****C stress exposure****D cognitive assay****E experimental timelines**

Fig. 2. Overview of the distributions of effect sizes in the main groups of moderator variables. (A) study subjects overview, (B) EE overview, (C) stress overview, (D) assay overview, (E) experimental timeline where S symbol represents the stress treatment, EE represents environmental enrichment, and the bar chart symbol represents the cognitive performance assay. Number of effect sizes (k) are shown for moderator levels/categories with $k \geq 5$.

variation in learning and memory due to EE, the type of assay and the type of reinforcement used within assays explained the most variation ($R^2 = 7.38\%$ and 7.72% respectively; **Table 5**). There was no statistically significant difference in the average effect size between learning responses versus memory responses ($R^2 = 2.57\%$, **Table 5**; **Fig. 4A**). Improvements in learning and memory responses (collectively) were significantly higher when measured in the conditioning assays than in the recognition assays (**Fig. 4B**). The average effect sizes were similar between habituation and conditioning assays but the small number of available effect sizes for habituation responses ($k = 7$) resulted in broad confidence interval for the point estimate (**Fig. 4B**). Learning and memory responses to EE were clear (i.e., significantly different from zero) in assays that used appetitive or aversive reinforcement (with similar average effect sizes for both types of reinforcement), but not in assays that did not use reinforcement (**Fig. 4C**). All other moderators accounted for little of the total variation in learning and memory responses due to EE (< 3.5%), with no significant difference in average effect sizes between moderator categories (**Fig. 4**).

3.3.2. Moderators of (main) stress effects

Of all the moderators examined that might account for some of the variation in learning and memory responses to stress, the type of assay used to measure cognitive performance explained the most variation ($R^2 = 18.53\%$; **Table 5**). There was no difference in the average effect size between learning responses versus memory responses ($R^2 = 0.28\%$, **Table 5**; **Fig. 5A**). Stress significantly impaired learning and memory (collectively) in the habituation and conditioning assays, but not in the recognition assays, with a significant difference in average effects

Table 4

Overall meta-analytic mean (lnRR and 95% confidence intervals, CI), heterogeneity (I^2), and variance explained by the random effects for each of the eight meta-analytic models: the three ‘focal’ analyses of the main effects and interaction of EE and stress, and the five ‘pairwise’ comparisons between the different treatments and controls. Bold values represent estimates that are significantly different from zero.

	Meta-analytic model	lnRR	95% CI	I^2	Variance explained by random effects
Focal analyses	Main effect of EE	0.19	0.12, 0.25	93.11%	Study: 17.87% Strain: < 0.1% Effect size: 75.24%
	Main effect of Stress	-0.10	-0.17, -0.04	93.76%	Study: 19.46% Strain: < 0.1% Effect size: 74.30%
	Interaction of EE × stress	0.12	0.004, 0.24	81.70%	Study: 44.91% Strain: 4.21% Effect size: 32.58%
Pairwise analyses	EC/CC	0.11	0.05, 0.16	86.11%	Study: 10.11% Strain: < 0.01% Effect size: 76.00%
	CS/CC	-0.18	-0.29, -0.08	94.90%	Study: 27.34% Strain: < 0.01% Effect size: 67.55%
	ES/CC	0.08	0.003, 0.16	81.51%	Study: 11.35% Strain: 4.13% Effect size: 66.03%
ES/CS	ES/CS	0.25	0.05, 0.45	94.57%	Study: 21.32% Strain: 23.92% Effect size: 49.33%
	ES/EC	-0.01	-0.08, 0.06	84.15%	Study: < 0.01% Strain: 2.52% Effect size: 81.63%

detected between habituation assays and recognition assays (**Fig. 5B**). The other moderators explained between ~3.5 and ~10% of total variation (**Table 5**) with a trend for an impairment of learning and memory for most moderator categories, although not all moderator categories significantly differed from zero (**Fig. 5**). Performance in assays with appetitive reinforcement significantly decreased after stress but did not significantly decrease in assays that used aversive reinforcement or no reinforcement, although the average effect sizes did not differ between any of the reinforcement categories (**Fig. 5C**). Learning and memory was impaired most clearly when individuals were exposed to stress as adults, but not at the other life stages, with a significant difference in the average effect sizes detected between adult and early postnatal stress exposures (**Fig. 5D**). Restraint stress and chronic stress clearly negatively affected learning and memory, but not acute stress or the other stress categories (**Fig. 5E, F**). No significant differences were detected in the average effect sizes between any of the stress categories or between chronic versus acute stress (**Fig. 5E, F**).

3.3.3. Moderators of the interactive effect between EE and stress

Of all the moderators examined that might account for some of the variation in learning and memory responses to the interaction of EE and stress, the duration of stress exposure and the order of treatment exposure explained the most variation ($R^2 = 15.98\%$ and 10.27% , respectively; **Table 5**). There was a significant difference in the average effect sizes between individuals exposed to chronic versus acute stress, with individuals exposed to chronic stress showing a significant synergistic interaction but an additive effect for acute stress (**Fig. 6J**). Additionally, we detected a significant synergistic interaction when individuals were exposed to EE after exposure to stress, but not when individuals were exposed to EE prior to stress or concurrently with stress (**Fig. 6F**). However, the difference in the average effect sizes for the treatment order categories were not significant, potentially due to the low sample size ($k = 6$) in studies that exposed individuals to EE prior to stress (**Fig. 6F**).

All other moderators explained between ~< 1% and ~10% of total variation in the interaction model (**Table 5**). We detected few significant differences in average effect sizes between moderator categories, but some moderator categories were significantly positive (i.e., indicating a significant synergistic interaction) (**Fig. 6**). Learning responses (as opposed to memory responses), assays that used aversive reinforcement, EE exposure during adolescence, prenatal stress exposure, and EE that involved voluntary exercise or did not involve an increase in social interactions all showed significant synergistic interactions where EE resulted in a greater improvement in learning and memory in stressed individuals compared to individuals with that were not exposed to a stress manipulation. However, it must be taken into consideration that the number of effect sizes per moderator category (k) may affect the ability to detect significant effects in some moderator categories.

3.4. Publication bias, sensitivity analyses, and risk of bias

There was no statistical evidence for publication bias for any of our focal models. Visual inspection of funnel plots did not indicate any clear funnel asymmetry (**Fig. 7**), nor was there an effect of ‘effective sample size’ in our multi-level full-models indicating that studies with smaller sample sizes did not tend to have larger effect sizes (lnRR [EE] = -0.06, 95% CI = [-0.87, 0.74]; lnRR [stress] = 0.11, 95% CI = [-0.91, 1.13]; lnRR [interaction] = -0.38, 95% CI = [-2.35, 1.59]). We also found no evidence of a time-lag bias where the strength of the effect declines in more recent publication years (lnRR [EE] = 0.04×10^{-1} , 95% CI = [-0.01, 0.02]; lnRR [stress] = -0.01, 95% CI = [-0.03, 0.01]; lnRR [interaction] = -0.03×10^{-1} , 95% CI = [-0.03, 0.02]).

Using SMD as the effect size instead of lnRR for the three focal models produced qualitatively similar results, with a significantly positive effect of EE (SMD [EE] = 0.72, 95% CI = 0.47, 0.98, $I^2 = 86.73\%$), a significantly negative effect of stress (SMD [stress] = -0.42, 95% CI =

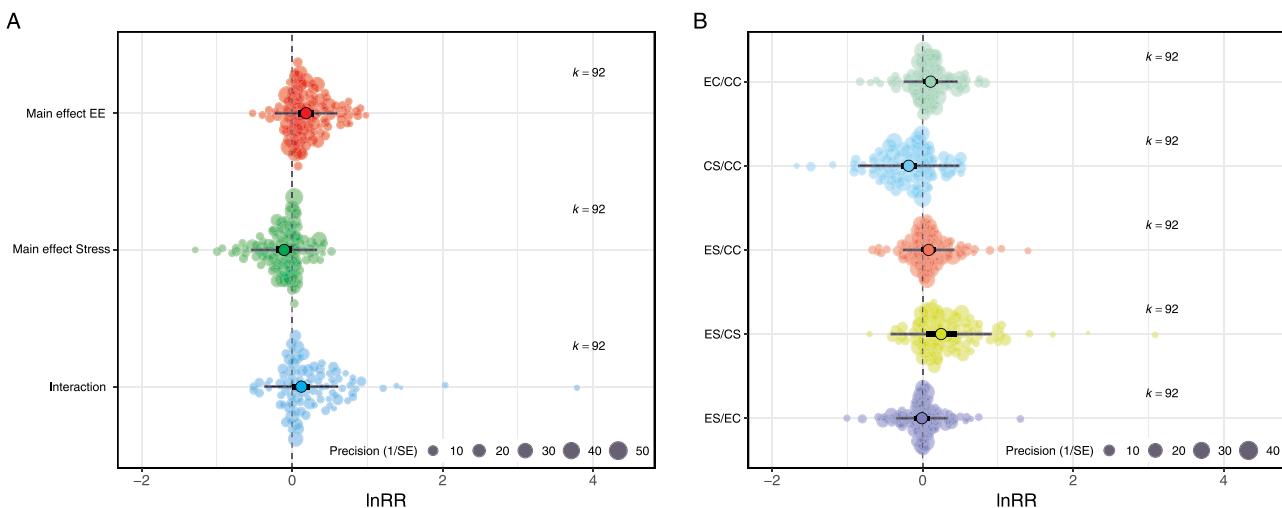


Fig. 3. Orchard plots showing the eight meta-analytic models. (A) main effects of EE and stress, and interaction of EE and stress, (B) ‘pairwise’ comparisons between treatments and controls. Each circle represents an individual effect size with the size of the circle representing the precision of the effect size (i.e., the inverse of standard error). Thick black lines are 95% CI (confidence intervals), thin black lines are 95% PI (prediction intervals). Positive values indicate that learning and memory increased in the treatments relative to the controls for the main effects and pairwise models, and that there was a synergistic interaction where the effect of EE was greater in stressed individuals compared to individuals without a stress manipulation in the interaction model. Negative values indicate learning and memory decreased in treatments compared to the controls for the main effects and pairwise models, and that there was an antagonistic interaction where the effect of EE is lower in stressed individuals compared to individuals without a stress manipulation in the interaction model. Effect sizes of zero indicate that there was no difference in learning and memory between treatments and controls in the main effects models, and that EE had an equal effect (i.e., additive) in both stressed individuals and individuals without a stress manipulation in the interaction model.

Table 5

Marginal R^2 for each moderator used in the uni-moderator meta-regression analyses for each of our three focal meta-analyses: EE main effect, stress main effect, and the EE \times stress interaction.

Moderator	EE main effect	Stress main effect	Interaction effect
	R^2	R^2	R^2
Learning vs memory	2.57%	0.28%	1.97%
Type of assay	7.38%	18.53%	5.77%
Type of reinforcement	7.72%	3.66%	5.87%
Age at EE	1.12%	NA	< 0.01%
Exercise EE	< 0.01%	NA	1.47%
Social EE	3.37%	NA	3.75%
Age at Stress	NA	9.99%	9.27%
Type of stress	NA	7.03%	0.44%
Stress duration	NA	8.24%	15.98%
Order of treatment exposure	NA	NA	10.27%

$-0.72, -0.13, I^2 = 89.59\%$), and a significantly positive ‘synergistic’ interaction of EE and stress on learning and memory ($SMD_{[interaction]} = 0.69, 95\% CI = 0.34, 1.04, I^2 = 66.57\%$). Repeating the three focal analyses using untransformed percentage data also produced qualitatively and quantitatively similar results (Appendix S3, Table S2).

The ‘leave-one-group-out’ sensitivity analysis did not indicate that any one study was driving the effects found in our models, although the removal of some studies resulted in slightly non-significant, but similar average effect sizes, for the interaction model (see Appendix S3, Figs. S3–S5). However, there were some inconsistencies between the Akaike (AIC) weights from the multi-moderator ‘full’ model meta-regression and the R^2 values from our uni-moderator meta-regression analyses (Appendix S3, Table S3). Such inconsistencies were expected due to an unequal number of effect sizes between the uni-moderator and multi-moderator models and correlations/nestedness between some of our moderators which results in difficulties partitioning AIC weights (Fig. 2). Therefore, the results of our meta-regression analyses should be interpreted with caution bearing this limitation in mind.

Of the 30 included studies, 50% explicitly stated that they randomly

allocated individuals into treatments and only 20% of studies claimed they recorded responses blind to treatment. Details regarding randomization and blinding were unclear or not reported for the remaining 50% and 80% of studies, respectively, with no studies explicitly stating that they did not use randomization or blinding. The pairwise comparisons between studies that did or did not report using randomization and blinding showed no statistically significant differences in mean effect sizes for any of the focal models (Appendix S3, Table S4). None of the included studies stated that they used cage as their unit of replication, nor did any of the studies report controlling for cage effects in any other way (e.g., including cage as a random effect, or only selecting one individual per cage).

4. Discussion

4.1. The main and interactive effects of EE and stress on learning and memory

In this study, we aimed to quantify the degree that EE can ameliorate the negative effects of stress on learning and memory (“cognitive performance”) in rodents (see Fig. 1A for a schematic of potential scenarios). We did so by conducting a meta-analysis on the main and interactive effects of EE and stress as well as on five different ‘pairwise’ comparisons between treatments and controls. We found that EE improved learning and memory by an average of 19% and that stress impaired learning and memory by an average of 10%, as shown by the two main effect models. We also found that there was a significant synergistic interaction between EE and stress where EE improved learning and memory by an average of 12% more in individuals exposed to a stress manipulation compared to individuals without stress manipulation. Additionally, as revealed in the pairwise comparisons, EE fully-compensated for the negative effects of stress on learning and memory as indicated by no detectable difference in cognitive performance between individuals exposed to both EE and a stress manipulation compared to individuals only exposed to EE (‘ES/EC’ pairwise comparison). Individuals with EE and a stress manipulation also showed an 8% average improvement in cognitive performance above that of

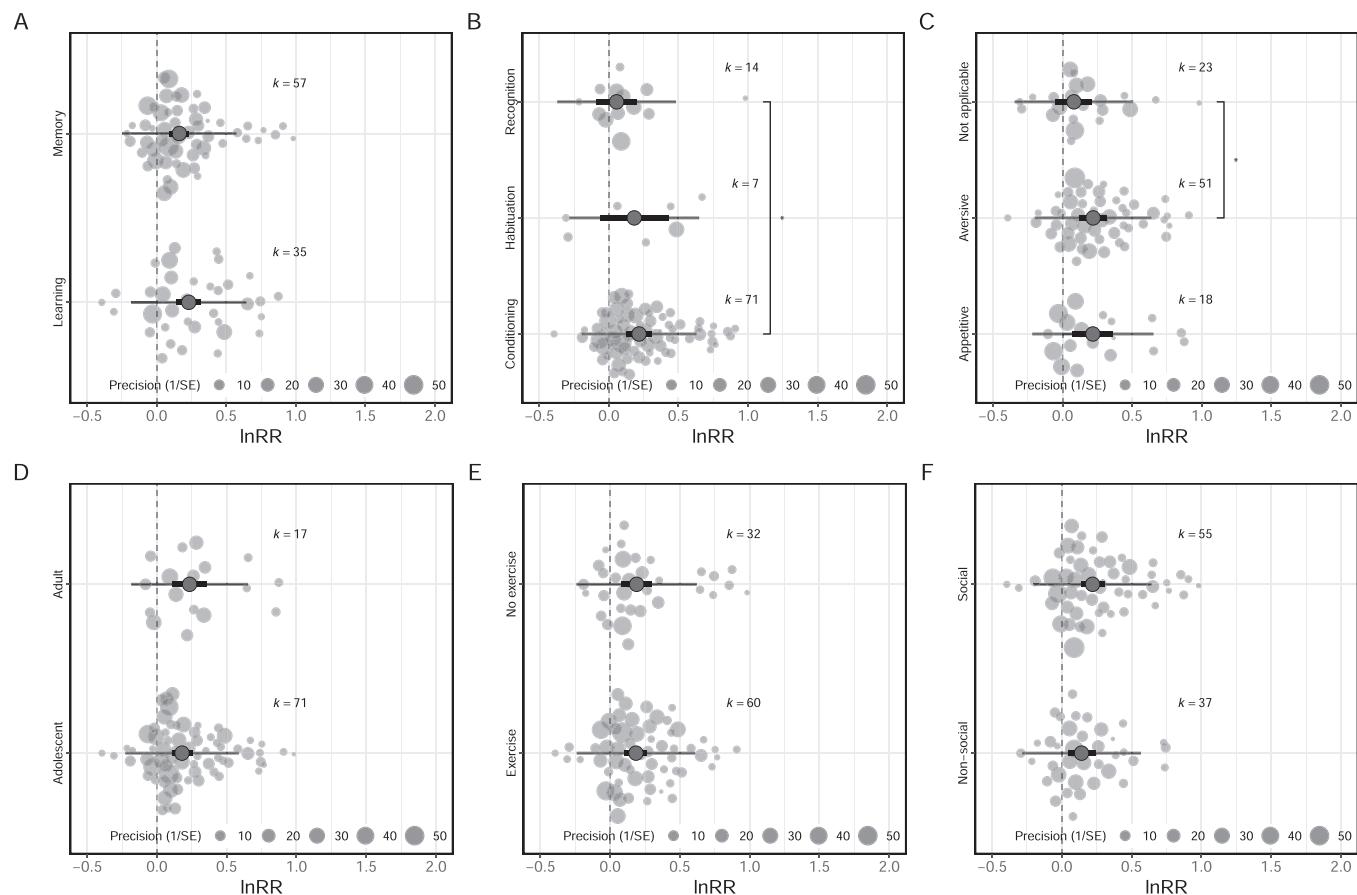


Fig. 4. Orchard plots showing the six different meta-regressions on the main effect of EE on learning and memory. (A) learning versus memory response, (B) the type of assay, (C) the type of reinforcement, (D) the age at EE, (E) type of manipulation of exercise during EE, (F) manipulation of the social environment during EE. Each circle represents an individual effect size with the size of the circle representing the precision of the effect size (i.e., the inverse of standard error). Thick black lines are 95% CI (confidence intervals), thin black lines are 95% PI (prediction intervals). Asterisks represent significance from contrasts with *** $p \leq 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$.

animals from conventional housing (i.e., ‘full controls’; ‘CC’).

While the primary literature examining the effects of EE and stress alone is very diverse (Girbovan and Plamondon, 2013; Joëls et al., 2006; Wells, 2009), it may be unsurprising that we detected an overall improvement in learning and memory with EE and an overall impairment from stress, given the large number of primary studies that have claimed such effects (reviewed in Conrad, 2010; van Praag et al., 2000). However, it is substantially more difficult to discern broad patterns of interactive effects from individual studies and qualitative reviews. This is partly due to the inherent complexity associated with examining interactions, especially when the pathways mediating the traits, such as the Hypothalamic-Pituitary-Axis, are highly complex (Smail et al., 2020) and behavioral traits are often highly variable (Cauchoux et al., 2018; Dingemanse and Dochtermann, 2013). Further, a single experiment is often under-powered to detect any interaction. Therefore, using a powerful meta-analysis of interactions, novel to the field of neuroscience and animal behavior, we clearly highlight the benefit of EE for learning and memory in stressed individuals. While the results reported here do not provide information regarding the complex mechanisms driving the positive synergistic interaction (see Smail et al., 2020; also see Singhal et al. (2014) for reviews of the underlying mechanisms), our analyses demonstrate that EE can indeed be effective at mitigating the negative effects of stress which has implications for our understanding of neuroplasticity and cognitive reserve. Our analysis also indicates which moderators (see Sections 3.2.3 and 4.2) are the most effective at compensating for stress-induced reductions in learning and memory and thus, which situations EE can be best employed to prevent or treat

reductions in cognitive performance.

The main and interactive effects presented here have broad implications for many research areas. For example, EE can sometimes be considered a treatment or prophylactic to ameliorate the negative effects of stress, not only on cognitive performance (e.g., Fischer et al., 2007; Menezes et al., 2020; Shilpa et al., 2017), but on other stress-induced conditions such as anxiety, depression, and post-traumatic stress disorder (e.g., Fox et al., 2006; Gong et al., 2018; Hendriksen et al., 2010). It can also have potential benefits for other neurological disorders such as Alzheimer’s, dementia, and Huntington’s disease (e.g., Du et al., 2012; Hockly et al., 2002; Jeong et al., 2011; Nithianantharajah and Hannan, 2006; van Dellen et al., 2000; Young et al., 1999). While we cannot generalize the results reported here to other stress-induced conditions or neurological disorders, it would also be beneficial to investigate non-additive effects of EE in other contexts through dedicated quantitative syntheses.

Furthermore, impacts on learning and memory can be important for a range of ecologically relevant behaviors (e.g., Cole et al., 2012; Maille and Schradin, 2016; Raine and Chittka, 2008), and studies have shown that EE can alter behaviors beyond direct measures of cognitive performance (e.g., Dukas and Mooers, 2003; Rogers et al., 2019; Zhang et al., 2020). Indeed, EE may mimic a more natural environment (e.g., Hutchinson et al., 2005; Näslund and Johnsson, 2016; also see Lambert et al., 2016), yet many laboratory studies, including those examining the effects of stress, are conducted in otherwise barren environments. Therefore, the use of barren laboratory conditions is likely to alter conclusions drawn from such studies (e.g., Hutchinson et al., 2005;

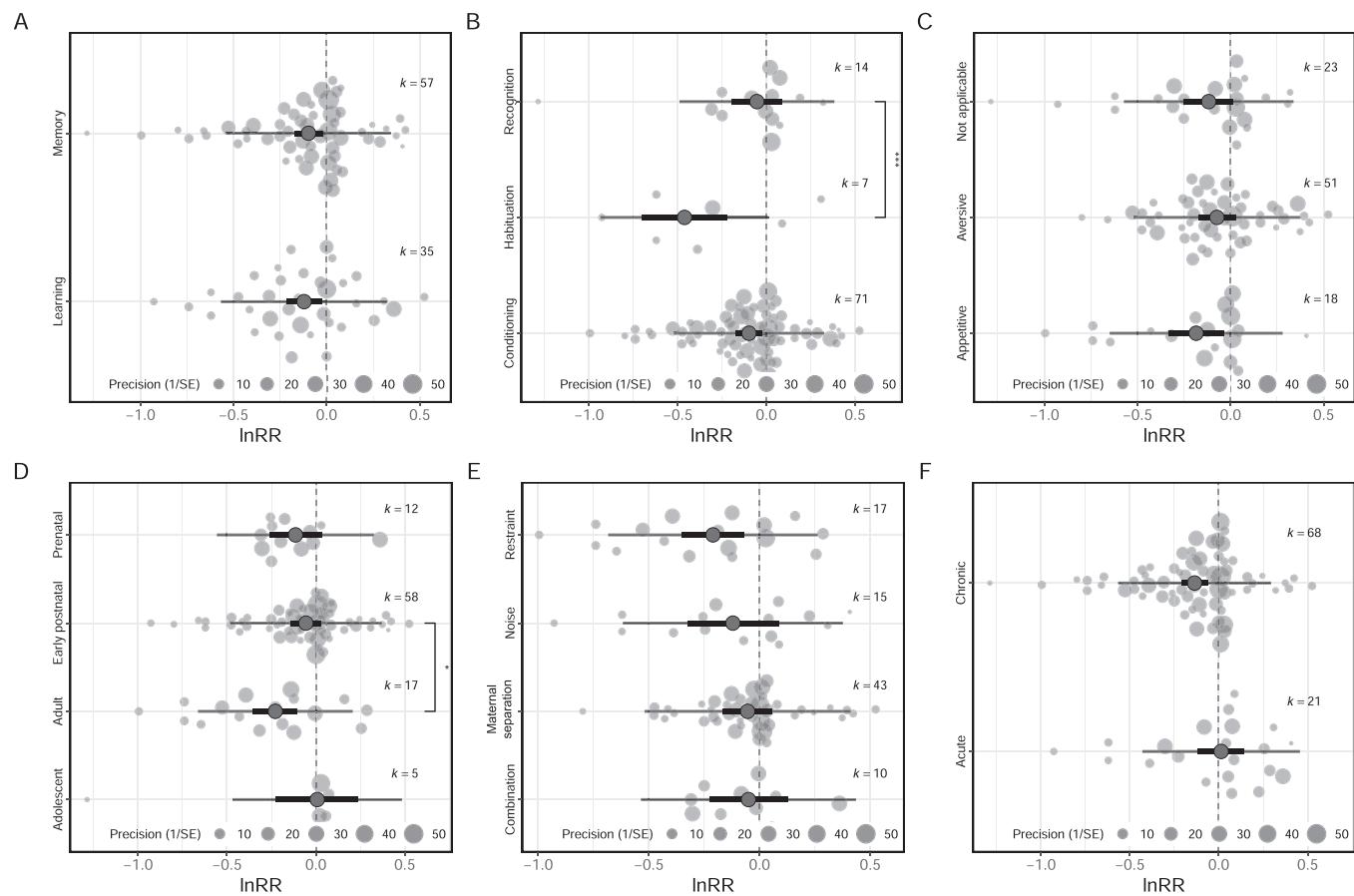


Fig. 5. Orchard plots showing the six different meta-regressions on the main effect of stress on learning and memory. (A) learning versus memory response, (B) the type of assay, (C) the type of reinforcement, (D) the age at stress, (E) the type of stressor, (F) chronic or acute stress. Each circle represents an individual effect size with the size of the circle representing the precision of the effect size (i.e., the inverse of standard error). Thick black lines are 95% CI (confidence intervals), thin black lines are 95% PI (prediction intervals). Asterisks represent significance from contrasts with *** $p \leq 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$.

Näslund and Johnsson, 2016; also see Lambert et al., 2016). Additionally, many other animals, such as agriculturally important species and some animals in zoological parks, are also kept in conventionally barren environments (Mason, 2006). Such barren environments can be considered stressful and the use of EE as the ‘default’ environment may not only be beneficial for animal welfare but may also confer benefits to other aspects of health and fitness such as improved reproductive success (e.g., Díez-León et al., 2013).

Overall, we show that EE can provide a greater benefit when stressed and that EE can fully-compensate for stress induced reductions in learning and memory, at least in laboratory rodents. This robust finding has implications for many research areas, including biomedical science and psychology, animal welfare, and ecology and evolution. Importantly, the methods employed in this meta-analysis can certainly be applied to examine other combinations of environments and treatments, as well as other types of outcomes.

4.2. Explaining heterogeneity in the main and interactive effects

As is expected in studies that vary in design and outcomes, we found high levels of heterogeneity in all meta-analyses ($I^2 > 80\%$) (Higgins et al., 2003; Senior et al., 2016). Most of this variation was due to differences among studies and effect sizes. Therefore, using meta-regression analyses, we aimed to explain some of this variation by assessing the importance of potentially mediating variables related to differences among studies and effect sizes in the main effect and interaction ('focal') models. In the main effect models, all moderator categories showed at least a slight improvement in learning and memory

with EE and at least a slight impairment of learning and memory with stress. In the interaction model, all moderator categories showed at least an additive benefit of EE on stress. This is shown by an effect size non-significantly different from zero (additive effect of EE) or a significantly positive effect size (a synergistic interaction showing a greater benefit of EE in stressed individuals relative to individuals without a stress manipulation). Therefore, in the circumstances considered here, EE can be expected to provide at least the same benefit to learning and memory in stressed individuals relative to individuals without a stress manipulation.

Interestingly, the interaction model shows that EE may be more effective as a treatment for stress-induced reductions in cognitive performance rather than as a prevention (i.e., as a prophylactic). This is shown by the significant positive (synergistic) interaction when EE was provided after stress, but not when EE was provided prior or concurrently to stress (i.e., all other treatment orders show an additive effect). Furthermore, the order of treatment exposure explained some of the most variation in the interaction model ($R^2 = 10.27\%$). However, it must be noted that we did not detect any significant differences between the average effect sizes of each ‘order of treatment’ category, which may be due to a small number of effect sizes in the other categories (i.e., when EE was provided before stress or concurrently to stress). The positive synergistic interaction when stress occurred prior to EE but not in the other treatment order categories has implications for our understanding of cognitive reserve and individual resiliency to adversity. Previous research has suggested that early life EE can reduce stress responses later in life (Llorens-Martín et al., 2011), and while we do show that EE can provide some benefit when stress occurs after EE, there is a trend

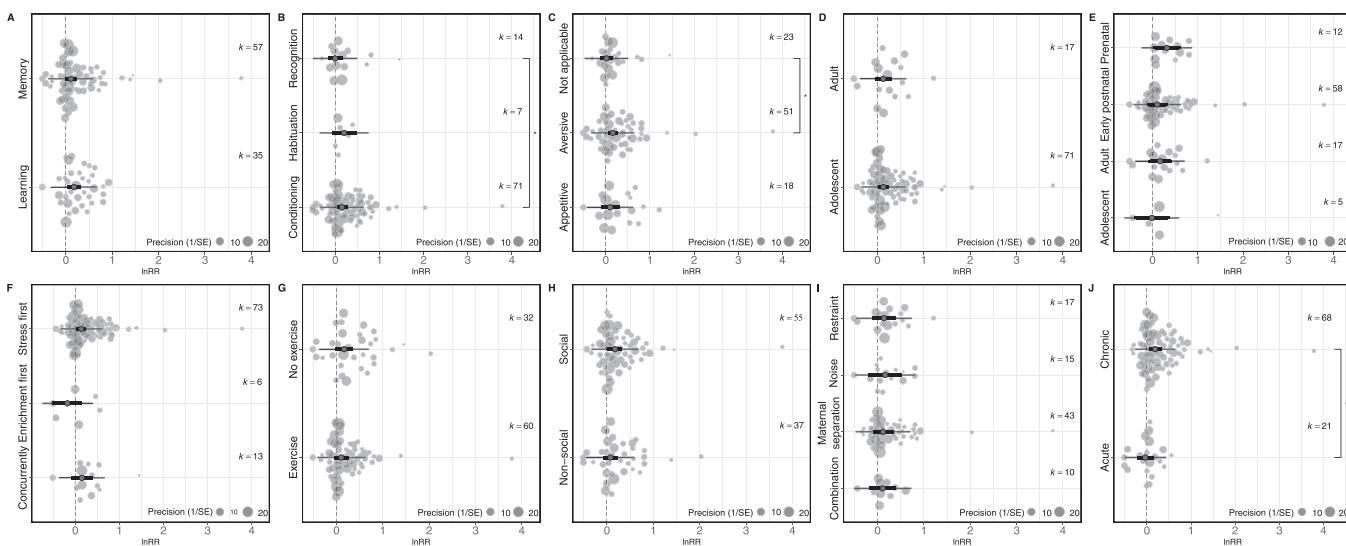


Fig. 6. Orchard plots showing the 10 different meta-regressions of moderators on the interaction between EE and stress on learning and memory. (A) learning versus memory response, (B) the type of assay, (C) the type of reinforcement used, (D) the age at EE, (E) the age at stress, (F) the order of treatment exposure, (G) if EE involved a manipulation of exercise, (H) manipulation of the social environment during EE, (I) the type of stressor, (F) stress was chronic or acute. Each circle represents an individual effect size with the size of the circle representing the precision of the effect size (i.e., the inverse of standard error). Thick black lines are 95% CI (confidence intervals), thin black lines are 95% PI (prediction intervals). Asterisks represent significance from contrasts with *** $p \leq 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$.

towards an antagonistic interaction (i.e., the benefit of EE is lower in stressed groups compared to individuals without a stress manipulation). This trend towards an antagonistic interaction may also be due to the removal of the EE prior to the stress manipulations which may cause additional stress on top of the stress manipulation (e.g., Latham and Mason, 2010).

Such differences in effectiveness of EE at compensating for stress based on the order of treatment exposure opens questions regarding the underlying biological mechanisms that may result in a lower protective effect compared to a compensatory effect (see Smail et al., 2020). While we are not aware of any studies that have directly tried to tease apart the effectiveness of EE as a treatment versus as a prevention, EE has been shown to be effective in both situations for other conditions such as addiction and autism (e.g., Guilarte et al., 2003; Solinas et al., 2008; Stairs and Bardo, 2009; Woo and Leon, 2013; also see Llorens-Martín et al., 2011). However, the synergistic effect of EE when EE exposure occurs after the stress manipulation may also be due to the proximity of the stressor to the assay and confounding effects of age (also see Section 4.3). For example, in the relevant papers included in this meta-analysis, most stress exposures occurred prior to adolescence, most of the EE exposures were conducted during adolescence or early adulthood, and most assays were performed in adults. Consequently, very few studies exposed older individuals (i.e., during adolescence or adulthood) to stress prior to EE. Also, very young individuals exposed to stress prior to EE have the longest time to recover prior to assessment in the assays. Similarly, in the main effect of stress model, we found that individuals exposed to prenatal stress showed the greatest improvement in cognitive performance with EE, but adults showed the greatest impairment of cognitive performance. This suggests that proximity to the cognitive assay, age, and order of treatment exposure may be confounded. While it is difficult to separate these effects (also see Solinas et al., 2010), other studies have shown that adults and adolescents can indeed be more susceptible to the negative effects of stress compared to younger individuals (e.g., Hodes and Shors, 2005) and that the timing of the stressor relative to the assay can affect performance (e.g., Diamond et al., 2006; Dominique et al., 1998). Therefore, future studies should aim to disentangle such effects by manipulating the order of EE and stress exposure while controlling for age and/or proximity to the

cognitive performance assay.

Additionally, individuals exposed to chronic stress experienced the greatest benefit to learning and memory from EE compared to individuals exposed to acute stress in the interaction model, and this explained the most variation in the interaction model ($R^2 = 15.98\%$). Such an effect is consistent with the significant reduction in cognitive performance with chronic, but not acute stress, in the main effect of stress model. Some studies have shown that acute stress in certain contexts can be neutral or even beneficial (Hidalgo et al., 2012; Joëls et al., 2006). Thus, acute stress may not be subject to a strong ‘mitigating’ effect of EE, similar to that of ‘full’ controls kept in conventional housing. Surprisingly, the type of stressor used in the experiments explained minimal variation in the interaction model ($R^2 = 0.4\%$) and there was no significant interaction detected for any individual stressor category (i.e., the benefit was always additive). This result contrasts with the main effect of stress model that explained substantially more variation ($R^2 = 7.03\%$). Thus, the magnitude of the impairment of learning and memory could vary between individual stressors, with restraint stress being the most detrimental, whereas the relative benefit of EE is similar across all types of stressors.

Finally, in the meta-regression analyses of the main effect of EE and the interaction models, differences between social environment and voluntary exercise explained very little variation. This result is consistent with former studies that have shown that the effect of EE is comprised of a complex interplay between multiple environmental factors rather than a single factor (Hall, 1998; van Praag et al., 2000). However, it must be noted that all EE treatments may provide increased exercise due to increased physical play and utilisation of the added objects in the enclosures. Therefore, while our definition of exercise was the inclusion a running wheel, the minimal variation accounted for by the provision of a running wheel may be due to increased exercise experienced by animals in all EE manipulations. Nevertheless, a study by Birch et al. (2013) found that individual activity in enriched cages without a running wheel was not higher than that of unenriched cages, yet an increase in memory was still observed. Thus, Birch et al. (2013) claim that the increase in memory was due to cognitive and sensory stimulation alone. Furthermore, the minimal variation explained by differences in the age at EE is more likely due to a limited diversity of

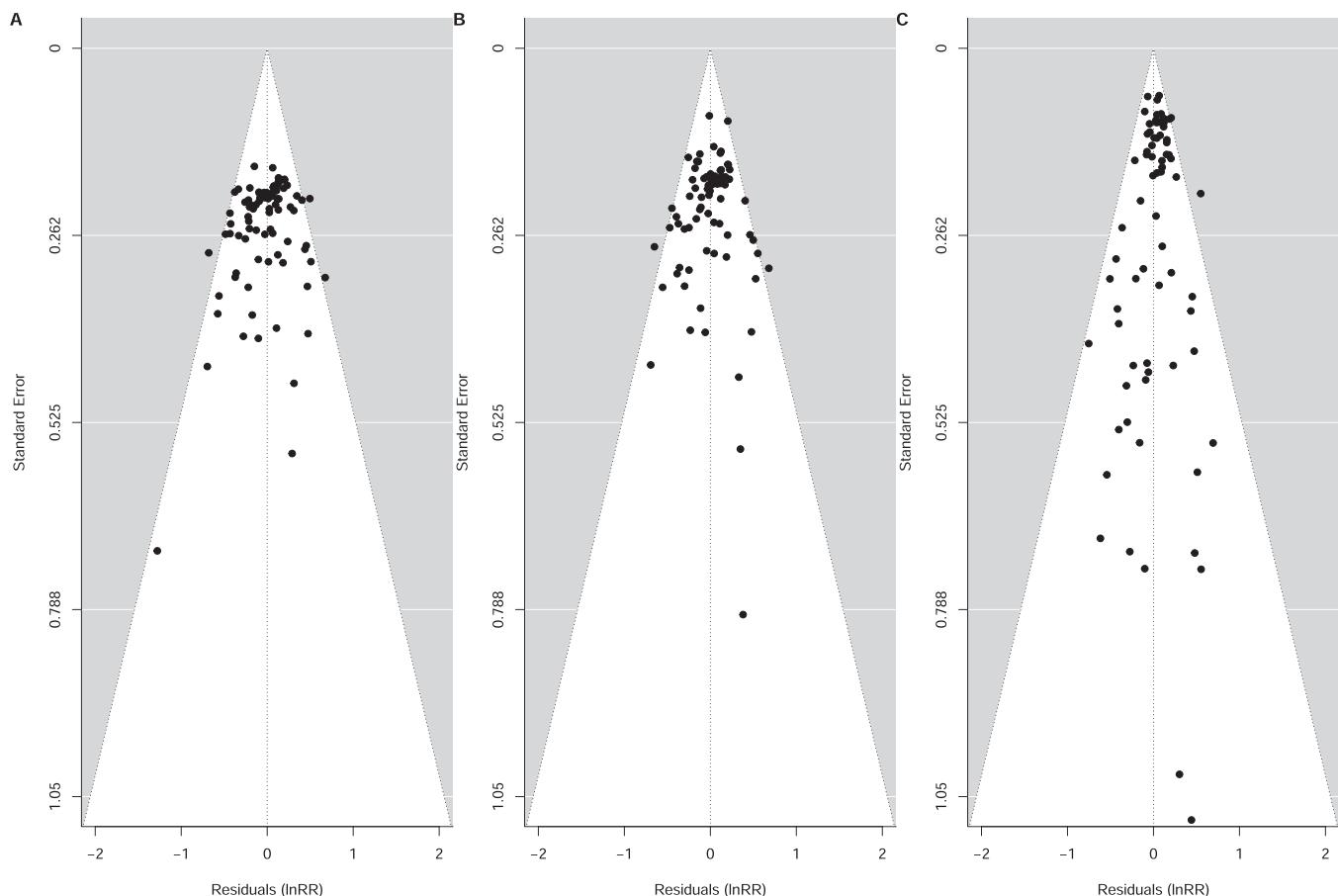


Fig. 7. Funnel plots of the standard error and residuals (lnRR) from the full models to show the relationship between the (residual) effect sizes and precision. (A) EE main effect, (B) stress main effect, (C) EE \times stress interaction.

ages used in the studies; all studies manipulated EE during adolescence or adulthood, with 79.5% of studies manipulating EE in adults. Therefore, *apropos* of our suggestion regarding the order of treatment exposures, future studies should examine the effects of EE at younger ages.

4.3. Potential limitations, publication bias, and risk of bias

We did not detect any evidence for publication bias in the literature as we did not find evidence for a small-study effect, nor evidence for a 'time-lag' bias (also known as decline effect). Further, our leave-one-group-out sensitivity analysis did not show clear evidence that any one study was biasing our results, there was not a qualitative difference between using the logarithm response ratio (lnRR) or the standardised mean difference (SMD) effect sizes, nor was there a qualitative or quantitative difference between using transformed versus untransformed percentage data. However, the marginal R^2 of the uni-moderator models did not always match the Akaike weights from the multi-moderator meta-regression due to strong correlations and nestedness between moderators which can result in difficulty partitioning Akaike weights between the moderators. Therefore, the correlations and nestedness (i.e., overlaps) between the moderators are a limitation that should be considered when interpreting the meta-regression results. These overlaps should be resolved where possible in future experiments to separate the effects of the moderators. For example, as mentioned, the age that individuals were exposed to the treatments is highly correlated with order or treatment exposure, and – while unavoidable – aversive and appetitive reinforcement is nested within conditioning assays.

Additionally, a key limitation in any meta-analysis is that we are constrained by the type of studies currently available for synthesis.

Particularly, the results of this meta-analysis are largely male-biased as only 3.26% of effect sizes were on females. Because of this, we were unable to assess sex differences in the effects of EE and stress on learning and memory. Thus, the results reported here may not be generalizable to females. Being able to assess sex-specific effects is highly important as females are expected to respond differently to stress (e.g., Andreano and Cahill, 2009; Mitsushima et al., 2006) and EE (e.g., Girbovan and Plamondon, 2013; Grech et al., 2018; Welberg et al., 2006) compared to males. For example, male mice can become territorial and develop social hierarchies which may become a stressor for low-ranking males when social environment is manipulated as part of EE (McQuaid et al., 2012; Toth et al., 2011). Negative effects of high density have also been shown in male rats (Brown and Grunberg, 1995). We therefore emphasize that future studies should incorporate both sexes into their study design (also see Tannenbaum et al., 2019; Zajitschek et al., 2020). We also suggest that more mice (*Mus musculus*) studies within the rodent literature are needed given our dataset contains mostly rat-based (*Rattus norvegicus*) studies. Additionally, consideration of the potential stress effects of conventional laboratory housing is needed when interpreting results. We therefore suggest that future studies should use more 'natural' environments as opposed to barren environments as controls.

Finally, only 50% and 20% of studies, respectively, explicitly reported that study individuals were randomly allocated to treatments and that the investigators were blind to treatment during the cognitive assay. While no studies explicitly stated that they did not use randomization or blinding, we cannot clearly determine if such practices were used in at least 50% of the studies. Nevertheless, we did not detect any differences in average effect sizes between studies that reported using randomization and blinding compared to studies that did not report using these

practices. We also found that no studies included in this analysis used cage (as opposed to individual) as their unit or replication, nor did they appear to control for cage effects in other ways, such as including cage as a random effect in their analyses. Thus, such studies may be at risk of pseudo-replication (Lazic, 2010). Future studies should aim to ensure that their study designs include both randomization and blinding as well as reduce pseudo-replication to reduce potential biases (see Holman et al., 2015; Lazic, 2010). Studies should also ensure that all procedures are clearly reported in the manuscript.

4.4. Notes for the meta-analysis of interactions

As we did in our study, it is essential for future meta-analyses of interactions to consider and conduct both the 3-effect-size ‘focal analysis’ and the 5-effect-size ‘pairwise’ analysis to fully understand the nature of interactions. Meta-analyses using effect sizes such as SMD or lnRR are so-called ‘contrast-based’ methods where estimated effects represent comparisons between 2 (or more) groups (Fig. 3; White et al., 2019). Therefore, it is usually not possible to get average effects for each of the four groups (as in the bar graphs in Fig. 1A). However, the three focal effect sizes calculated in Eqs. 3–7 allow us to resolve this issue by taking the average of each treatment and control to calculate the main and interactive effects of EE and stress. Nevertheless, a significantly positive interaction (as found in our analysis) from the focal analysis only tells us that we have a synergistic interaction (see Fig. 1A; while a significantly negative interaction effect would indicate an antagonistic interaction). But, determining that we have a significant synergistic interaction does not tell us which of the 3 scenarios applies where EE can either under-compensate, fully-compensate, or over-compensate for the effects of stress (i.e., scenarios I, II and III in Fig. 1A). Only by conducting the pairwise analyses, can we tell that our results support scenario II in the syngenetic interaction (i.e., there is no difference between the group ES and EC) where we show that EE fully-compensates for the effects of stress. This process seems somewhat complicated, but the focal analysis is equivalent to conducting a 2-way ANOVA and the pairwise analysis is like post-hoc comparisons. As mentioned earlier, to detect the same degree of interaction effect as that of main effects, one needs four times more subjects (Gelman et al., 2020). Therefore, the analyses using the ‘focal’ effect sizes may be one of few ways to detect an interaction effect in a robust manner.

It is beyond the scope of this paper to cover all potential combinations of interaction patterns (i.e., Fig. 1A is a simple schematic of potential scenarios), but detailed discussions of different patterns can be found elsewhere, although mainly in the field of ecology (Côté et al., 2016; Piggott et al., 2015). However, it is also notable that the effect of interactions can be masked or be unintentionally created when applying statistical transformation to data (e.g., Knol et al., 2011). For example, we transformed percentage data to escape bounding between 0 and 100 (Section 2.4). Therefore, we were testing interactions on the transformed scale, not the original percentage scale (although non-transformed data gave qualitatively and quantitatively similar results; see Appendix S3, Table S2). The point here is that such a sensitivity analysis should be a routine part of meta-analyses of interactions (Noble et al., 2017) to confirm the robustness of results.

Most notably, we provide a fully annotated R code that includes calculating all eight effect sizes and their variances, quantifying heterogeneity, publication bias tests, sensitivity analyses, and the visualisation of results using orchard plots (*sensu* Nakagawa et al., 2022) as a HTML file on the Open Science Framework (<https://osf.io/fb38q/>) that can be adopted by any researcher interested in conducting a meta-analysis of interactions.

5. Conclusions

Through a series of meta-analyses and meta-regressions on the experimental rodent literature, we quantitatively demonstrate for the

first time that EE and stress synergistically interact where EE provides a significantly greater benefit to learning and memory in stressed individuals compared to individuals not exposed to a stress manipulation. We also show that EE can fully-compensate for the negative effects of stress as we detected no difference in cognitive performance between individuals exposed to EE and a stress manipulation compared to individuals provided with EE and no stress manipulation. Furthermore, a variety of factors that vary between studies and effect sizes can explain some of the variation in responses, with factors relating to the type of assays and stress explaining more variation in the models compared to factors relating to EE. This meta-analytic study not only has implications for the use of EE as a non-pharmaceutical approach to ameliorating stress-induced reductions in learning and memory, but also provides insights for other stress-induced conditions and neurological disorders, animal welfare, and laboratory/captivity based behavioral studies. Moreover, the interplay between EE and stress has provided an excellent example on how to quantify, understand, and interpret interaction effects, where the methods used here can be extended to interactions beyond the scope of this study.

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Data availability

All data and code are available at <https://osf.io/fb38q/>.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:[10.1016/j.neubiorev.2022.104554](https://doi.org/10.1016/j.neubiorev.2022.104554).

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