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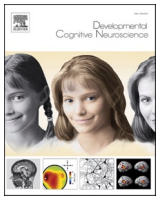

# A meta-analytic study of the effects of early maternal separation on cognitive flexibility in rodent offspring

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ABSTRACT

Adverse early life experiences, such as maternal separation, are associated with an increased risk for several mental health problems. Symptoms induced by maternal separation that mirror clinically relevant aspects of mental problems, such as cognitive inflexibility, open the possibility of testing putative therapeutics prior to clinical development. Although several animal (e.g., rodent) studies have evaluated the effects of early maternal separation on cognitive flexibility, no consistent conclusions have been drawn. To clarify this issue, in this study, a meta-analysis method was used to systematically explore the relationship between early maternal separation and cognitive flexibility in rodent offspring. Results indicate that early maternal separation could significantly impair cognitive flexibility in rodent offspring. Moderator analyses further showed that the relationship between early maternal separation and cognitive flexibility was not consistent in any case, but was moderated by variations in the experimental procedures, such as the deprivation levels, task characteristics, and rodent strains. These clarify the inconsistent effects of maternal separation on cognitive flexibility in rodents and help us better understand the association between early life adversity and cognitive development.

## 1. Introduction

A growing proportion of evidence suggests that early life adversity is associated with neuropsychiatric vulnerability and an increased risk of several mental illnesses, including schizophrenia (Bale et al., 2010; Briefer et al., 2017; Deveney and Deldin, 2006; Floresco et al., 2009; Goldstein and Volkow, 2011; Lovallo, 2013). Many mental disorders are clinically heterogeneous with distinct symptoms that reflect behavioral and cognitive dysfunctions. Cognitive flexibility refers to the cognitive ability of an individual to solve problems with different approaches based on context and the ability to adapt to new environments and achieve goals in flexible manners (Dajani and Uddin, 2015; Hurtubise and Howland, 2017; Powell and Ragozzino, 2017). The impairment of cognitive flexibility is extensively present in neuropsychiatric patients (Morice, 1990; Ottaviani et al., 2016). Identifying the neural and molecular mechanisms that contribute to cognitive inflexibility by analyzing early life adversity will aid in the advancement of treatment for multiple psychiatric disorders. The rodent model is a convenient and valuable tool to experimentally test the causal relationship and underlying mechanisms between early life adversity and cognitive flexibility, as well as to conduct life-span longitudinal studies to understand the changes in behavioral and physiological traits due to early life adversity.

Researchers have used rodents as a model system to investigate the potential role of early life adversity in cognitive inflexibility (Hedges and Woon, 2011; Spann et al., 2012). Many of these models focused on disrupting the attachment in relationships between pups and their dams, which is considered to be the most important relationship in early life. In these studies, the rodent pups were separated from the dams before weaning, and the cognitive flexibility tasks were completed after weaning. Then, the pups would be compared to the non-separated control group. However, the results from these studies showed inconsistency regarding the effects of early maternal separation on cognitive flexibility. Some researchers found that the cognitive flexibility of rodent pups that had been separated from their dams was impaired compared with the non-separated control group (Oitzl et al., 2000; Wang et al., 2011), while other researchers found improvement in the cognitive flexibility of rodent pups (Lehmann et al., 1999; Wong and Jamieson, 1968). These inconsistencies may be a result of experimental procedural variations in the maternal separation processes or differences in the assessments of cognitive flexibility (Kosten et al., 2012).

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Meta-analysis, a process that supports conclusions by combining data from multiple studies rather than a single result, may clarify this issue. In our study, the meta-analysis method was used to systematically explore the relationship between early maternal separation and cognitive flexibility in rodent offspring, as well as the moderators influencing the relationship between them.

In previous studies, experimental manipulations of maternal separation were varied. For example, in the early handing (EH) paradigm, pups were briefly removed from the dams and the cage during pre-weaning (Levine et al., 1956). This length of time is similar to the amount of time a dam leaves the nest to inspect surroundings. The pups would get more of the mother's "licks" when they returned to their dams, thus not constituting serious deprivation (Liu et al., 1997). However, in the maternal separation (MS) or maternal deprivation (MD) paradigms, pups were separated from the dams for a long time (1–24 h) in the pre-weaning period. The longer length of separation induced a helpless state of less caring and could therefore cause stress to the pups (Lovic and Fleming, 2004; Pryce and Feldon, 2003). The most invasive separation manipulation is artificial rearing (AR). In these cases, the pups were completely separated from the dams for days, weeks, or even months (Levy et al., 2003; Lovic and Fleming, 2004), and their body temperature and nutrition were strictly controlled. Such complete deficits of maternal linking can cause severe neural stress in the periphery and the brain, which may influence the cognitive performance of rodent pups (van Oers et al., 1998; Weaver et al., 2004, 2006). The different studies adopted different types of separation with different time durations, and these differences in methodological operation may therefore lead to inconsistencies in the reported results in literature.

In most cases, the experimental manipulations of maternal separation were that the pups were separated only from the dams, but it was also possible that they were concurrently isolated from their littermates. Some researchers employed early handling or maternal separation, regardless of whether the pups were separated from their dams only or also from their littermates (Kosten et al., 2012). Such manipulation differences may also lead to inconsistencies in the reported results because the pups could receive tactile and olfactory stimuli from littermates, which may mitigate the effects of separation from their dams (Alberts, 2007; Moreno et al., 2018; Simpson et al., 2019), therefore influencing cognitive performance. Therefore, we have distinguished "separation" and "isolation" in the present study. Separation means that the pups are separated only from their dams, but not from their littermates. Isolation means that the pups are not only separated from their dams, but also isolated from their littermates.

In a series of studies, the cognitive flexibility tasks generally involve rodents learning a set of reward and punishment rules which are then changed into new rules after acquisition. Then, the rodents are required to solve problems by using the new rules. However, there are differences in the types of tasks used to assess rodents' cognitive flexibility. Some studies use spatial learning tasks involving escaping from aversion situations, such as the Morris water maze (MWM) and Barnes maze (Barnes, 1979; Marszalek-Grabska et al., 2018; Mills et al., 2014; Morris, 1981). There are also studies that use spatial learning tasks or odor-based digging tasks to obtain food rewards based on location information, such as the T maze, Y maze, behavioral sequencing tasks (BST), four-choice tasks, and attentional set-shifting tasks (ASST) (Endo et al., 2012; Thomas et al., 2016). In these tasks, in order to respond to or benefit from the challenges in the environment, animals must adjust their behaviors to receive rewards or avoid punishment (aversion) (Hu, 2016; Zhang et al., 2019). The tasks' opposing characteristics probably involve and assess cognitive performance as governed by different neural circuits of the brain (Den Ouden et al., 2013; Lammel et al., 2012). Therefore, in view of the fact that the underlying assessment patterns and mechanisms differ between these tasks, the different types and characteristics of tasks may contribute to the inconsistency of the results reported in previous literature.

In addition, studies of maternal separation also showed differences in sample characteristics. For example, rodent strains used in the studies include Wistar rats (Noschang et al., 2012), Long-Evans rats (Baudin et al., 2012), C57B1/6 mice (Thomas et al., 2016), Sprague-Dawley rats (Lovic and Fleming, 2004), and BALB/cJ mice (Mehta and Schmauss, 2011). Differences in sample characteristics could also be due, in part, to the sample sex. Most studies used male samples only (Oitzl et al., 2000) or a mixed sample with males and females (Fabricius et al., 2008), and a few used female samples only (Banqueri et al., 2018;Lovic and Fleming, 2004). Given there are sex differences in neuroendocrine and behavioral responses to stressors, maternal separation may have different effects on male and female rodent offspring in regard to cognitive performance (Taylor et al., 2000; Sangenstedt et al., 2018). For instance, studies of the hippocampus, a center for stress and sex hormones and also known as a neural substrate for cognition (Cheng et al., 2011, 2014, 2016; Lisman et al., 2017), have shown that structural plasticity and remodeling in the adult brain varies greatly between the sexes following experiences of stress (McEwen, 2002). The corpus callosum, another brain structure involved in cognition processes, can be affected in a specific sexed manner due to early stress (Berrebi et al., 1988). Therefore, differences in sample sexes may also affect the relationship between maternal separation and cognitive flexibility. Additionally, timing or age for the tests is the methodological factor that varies between studies and may contribute to the inconsistency of previous studies. In these previous studies, tasks assessing cognitive flexibility were performed during different age stages from adolescence (Thomas et al., 2016; Wang et al., 2015a), adulthood (Benner et al., 2014; Lehmann et al., 1999), to aged (Levy et al., 2003; Oitzl et al., 2000).

On this basis, we perform meta-analysis to determine the effects of early maternal separation on cognitive flexibility in rodent offspring. Moreover, we perform a series of subgroup analyses to explore the moderating effects of the above-mentioned methodological factors and sample characteristics.

## 2. Method

### 2.1. Study selection

A comprehensive literature search of maternal separation and cognitive flexibility in rodent offspring up to Aug. 31, 2021, was conducted using three databases, namely ScienceDirect, PsycINFO, Web of Science. We also used Google Scholar to find additional related articles which were not contained in these databases. The keywords used were: ("early life stress" or "postnatal stress" or "maternal separation" or "maternal deprivation" or "early handling") And ("cognitive flexibility" or "Behavioral flexibility" or "set-shifting" or "reversal learning") And ("rat" or "mice" or "rodent"). The references and related reviews of the identified articles were reviewed to detect additional studies that were found to have met the topic of the present study.

Next, we screened each article according to the following inclusion criteria (see flow chart of the article selection process in Fig. 1): (1) comprised rodent offspring; (2) used experimental manipulations of mother-pup separation during the pre-weaning phase (i.e., before postnatal day 21), and assigned to the experimental conditions or control conditions; (3) provided specific data of evaluating cognitive flexibility in order to calculate the amount of effect size by transforming the formula. For studies that effect sizes could not be calculated, corresponding authors were contacted for necessary details; otherwise, these studies were excluded from the meta-analysis. Finally, according to the above criteria, 23 studies comprising 32 samples (N = 848) were included in the main meta-analysis (online Supplementary Table S1).

### 2.2. Data extraction

In order to conduct our preliminary analysis and evaluate potential moderators, we extracted (by two coders independently, see Supplement for details) all data required to calculate the effect sizes (e.g., means,

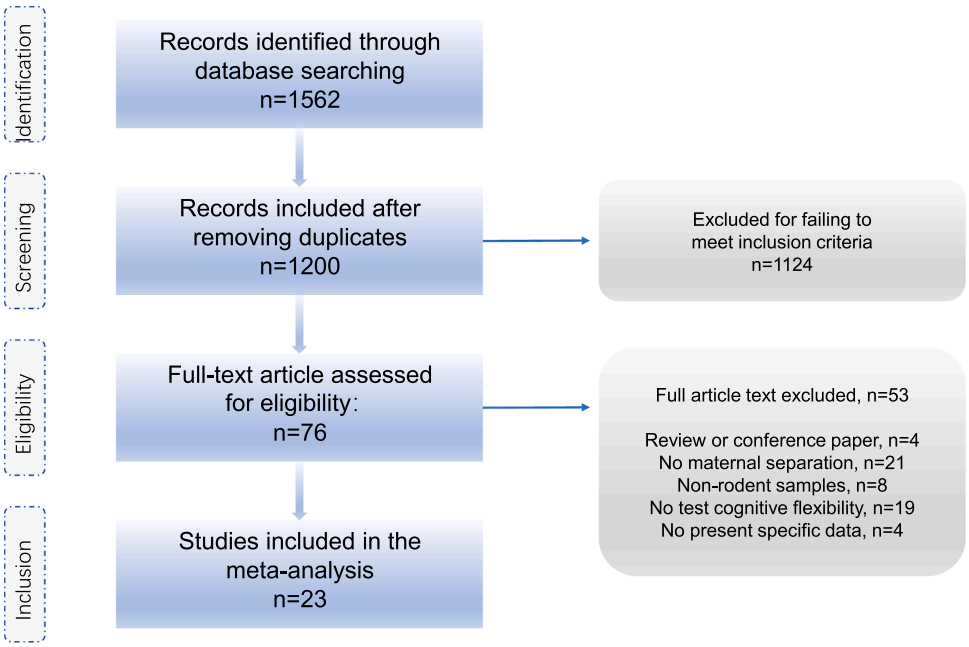


**Fig. 1.** Flow diagram of studies selection process. We screened 1562 records and included 23 publications in this meta-analysis review.

standard deviations, and sample size), as well as data on eight characteristics in studies. Three sample characteristics were extracted: (1) sample size; (2) sample sex composition (i.e. male (M) vs. female (F) vs. mixed (M/F)); (3) rodent strain (Wistar, C57B1/6, Long-Evans, Sprague-Dawley, BALB/cJ, Brown-Norway, CD1); five methodological characteristics were extracted, including: (1) maternal separation type (i.e., EH vs. MS or MD vs. AR); (2) social deprivation level (separation vs. isolation); (3) age of exposure to the task of cognitive flexibility (e.g., on postnatal day 60); (4) task type (T or Y, MWM, ASST, five/four-choices tasks, BST, Barnes maze); (5) task characteristic (reward vs. aversion). According to these sample and study methodological characteristics, the following were evaluated as potential moderators: rodent strain, sample sex composition, maternal separation type, social deprivation level, task type, task characteristics, and age of exposure to tasks.

### 2.3. Data analysis

All analyses were performed with Comprehensive Meta-Analysis Version 2.0 (CMAV2; Borenstein et al., 2005). In order to integrate the effect of maternal separation on cognitive flexibility, we used Hedges' g as the effect size measure to reflect the inter-group differences in cognitive flexibility. Different effect size measure that could be converted into Hedges' g was also available. A random-effect model was used in the present study, which assumes that the selected studies are random samples from a larger population and seek to generalize the findings(Borenstein et al., 2010). Based on Cohen (1992) standards, the effect size Hedges' g is explained by the following method: small effect ($g = 0.2$), medium effect ($g = 0.5$), and large effect ($g = 0.8$).

Cochran's Q was used to assess the heterogeneity of effect sizes, and this was supplemented by the $I^2$ index that represents the percentage of variation across studies that is due to heterogeneity rather than chance. According to Higgins et al. (2003), $I^2$ values of 25 %, 50 %, and 75 % represent low, moderate, and high heterogeneity respectively. Substantial heterogeneity in the effect size indicates the potential for moderation effects. Then, moderator analyses were conducted to account for potential sources of the heterogeneity. For the categorical moderators, i.e., rodent strain, sample sex composition, maternal separation type, social deprivation level, task type, and task characteristics, weighted random-effects ANOVAs were calculated, and $Q_{between}$ were used for testing the statistical significance of the moderator variables. For the continuous moderator, age of exposure to task, univariate random-effects meta-regression analysis was applied, and $Q_{regression}$ was used for testing the statistical significance of the moderator effect (Chen and Jackson, 2016).

### 2.4. Evaluation of publication bias

Statistically significant studies tend to be more likely to be published. Therefore, post-publication studies are more likely to be included in the meta-analysis. This may lead to systematic errors between the actually included studies and those that should be included, and thus publication bias, affecting the results of meta-analysis (Çoğaltay and Karadağ, 2015). Publication bias was assessed by using the funnel plot approach and checking the significance of Egger's test that quantifies the estimated bias as reflected in the funnel plot, with a non-significant $p$ value indicating insufficient evidence for publication bias. The trim and fill method also was used to evaluate possible publication bias (Duval and Tweedie, 2000).

### 2.5. Risk of bias assessment

Risk of bias assessment was performed according to SYRCLE guidelines to evaluate the methodological quality of included studies (Hooijmans and Ritskes-Hoitinga, 2013; Bonapersona et al., 2019). See Supplement for details.

## 3. Result

### 3.1. Overall effect sizes of the outcomes

The outcomes of meta-analysis showed that there was significant difference in cognitive flexibility between the maternal separation and control groups, Hedges' $g = 0.493$ ($S = 0.153$, 95 % CI = 0.193–0.794), and $p < 0.01$ (Fig. 2). Based on the average effect size, the results suggest that early maternal separation will necessarily impair the cognitive flexibility of rodents in general. Note that significant heterogeneity was observed for the distribution of effect sizes as the Q-value (1, 31) = 135.886, $p < 0.001$, and $I^2 = 77.187$ %. Therefore, moderator analyses were necessary to explore potential moderators that could have contributed to such heterogeneity.

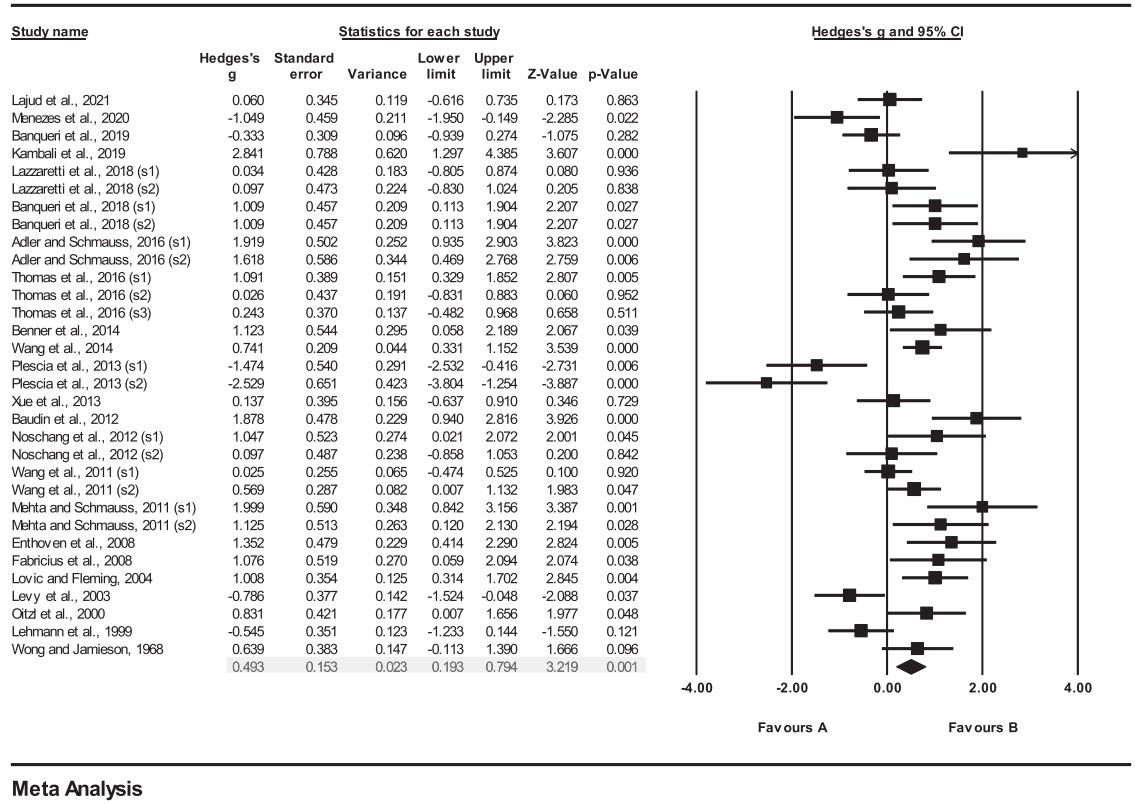


**Fig. 2.** Forest-plot showing the effects of maternal separation on cognitive flexibility across all studies. Box size represents study weighting. The diamond represents the overall effect size and 95 % confidence intervals. The gray shadow shows the outcomes of meta-analysis with a random-effect model.

### *3.2. Moderator effects on maternal separation-cognitive flexibility associations*

The categorical moderator variables and continuous moderator variables were tested to assess the impact of moderating effects on the association between maternal separation and cognitive flexibility. Subgroup analyses of the hypothesized categorical moderators (i.e., rodent strain, maternal separation type, sample sex composition, task type, social deprivation level, task characteristics) are presented in Table 1.

*Strain and sex.* As shown in Table 1, the rodent strain could moderate the effect sizes of maternal separation on cognitive flexibility between studies ($Q_{between} = 12.312$, $p < 0.05$). In the studies using C57B1/6, BALB/cJ, CD1 mice and Brown Norway, Long-Evans rats, the cognitive flexibility of the maternal separation groups was significantly lower than

**Table 1**
Effect of categorical moderators on maternal separation-cognitive flexibility effect sizes.

| Moderator | Q $_{between}$ | Subgroup | K[a] | N[b] | Hedges'g | SE | LL | UL |
|---|---|---|---|---|---|---|---|---|
| **Strain** | 12.312 * | BALB/cJ | 3 | 4 | 1.014 * | 0.453 | 0.126 | 1.902 |
| | | C57Bl/6 | 5 | 7 | 0.822 *** | 0.216 | 0.399 | 1.245 |
| | | Sprague-Dawley | 3 | 3 | 0.100 | 0.509 | -0.898 | 1.097 |
| | | Wistar | 11 | 15 | 0.099 | 0.243 | -0.377 | 0.906 |
| | | Other[c] | 3 | 3 | 1.320 *** | 0.308 | 0.717 | 1.923 |
| **Maternal separation type** | 4.095 | Early handing | 4 | 7 | -0.306 | 0.483 | -1.253 | 0.641 |
| | | Maternal separation | 17 | 23 | 0.689 *** | 0.159 | 0.377 | 1.001 |
| | | Artificial rearing | 2 | 2 | 0.115 | 0.897 | -1.643 | 1.873 |
| **Sex** | 1.904 | Males | 13 | 14 | 0.599 ** | 0.222 | 0.163 | 1.034 |
| | | Females | 8 | 10 | 0.135 | 0.337 | -0.525 | 0.795 |
| | | Males and Females | 5 | 8 | 0.707 ** | 0.267 | 0.184 | 1.230 |
| **Task type** | 13.130 * | Five/Four-choice | 2 | 4 | 0.874 | 0.467 | -0.042 | 1.789 |
| | | ASST | 6 | 8 | 1.141 *** | 0.296 | 0.560 | 1.722 |
| | | MWM | 10 | 12 | -0.087 | 0.284 | -0.644 | 0.470 |
| | | T or Y | 4 | 6 | 0.351 * | 0.148 | 0.060 | 0.642 |
| | | Other[d] | 2 | 2 | 1.099 ** | 0.375 | 0.363 | 1.835 |
| **Social deprivation level** | 4.770 * | Isolaition | 10 | 11 | 0.868 *** | 0.182 | 0.511 | 1.224 |
| | | Separation | 13 | 21 | 0.272 | 0.204 | -0.127 | 0.671 |
| **Task characteristics** | 8.590 * * | Aversive | 12 | 15 | 0.049 | 0.224 | -0.390 | 0.487 |
| | | Reward | 11 | 17 | 0.895 *** | 0.182 | 0.537 | 1.252 |

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
[a] number of studies.
[b] number of effect sizes.
[c] "Other" included CD1 mice and Brown Norway and Long-Evans rats due to the number limitation.
[d] "Other" included BST and Barnes maze tasks due to the number limitation.

that of the control group. However, no significant difference was found in the studies using Wistar and Sprague Dawley rats. The sex composition of the sample did not moderate the relationship between maternal separation and cognitive flexibility ($Q_{between} = 1.904$, $p > 0.05$).

*Maternal separation type and social deprivation level.* The maternal separation type (EH, MS/MD and AR) did not moderate the relationship between maternal separation and cognitive flexibility ($Q_{between} = 0.282$, $p > 0.05$). However, the social deprivation level during maternal separation could moderate effect sizes ($Q_{between} = 4.770$, $p < 0.05$); to elaborate, the offspring isolated from both the dams and littermates had significantly lower cognitive flexibility than the control group's offspring, while offspring only separated from their dams showed no difference compared to the controls.

*Task type and task characteristics.* Our results show that the effect sizes of maternal separation on cognitive flexibility were moderated by task types ($Q_{between} = 13.130$, $p < 0.05$), with significantly larger group differences in studies that used ASST, BST, T/Y maze and Barnes tasks as opposed to the five/four-choice and MWM. That is, maternally separated offspring performed significantly lower on cognitive flexibility tasks than controls when the ASST, BST, T/Y maze and Barnes tasks were used, whereas no significant difference was found in five/four-choice and MWM. We also found that task characteristics could influence the effect sizes as another moderator ($Q_{between} = 8.590$, $p < 0.01$). Specifically, for the measurement tasks involving reward stimulation, the cognitive flexibility of the separation groups was significantly lower than that of the controls. In contrast, for the tasks involving aversive stimulation, there was no difference between the separation and control groups.

Analyses of the hypothesized continuous moderator (i.e., age of exposure to test) are presented in Table 2. As shown, the method of moments analyses indicates that cognitive flexibility was not moderated by the age of exposure to test ($Q_{regression} = 0.668$, $p = 0.414$).

### 3.3. Publication bias

In our assessment of potential publication bias, Egger's regression test indicated that significant publication bias was not present (intercept = 1.245, 95 % CI = −1.452 to 3.941, t (30) = 0.943, $p > 0.05$). Additionally, the asymmetrical distribution of effect sizes of maternal separation on cognitive flexibility was determined based on the trim and fill analysis method of the random-effects models (Fig. 3). Four studies that show less than the average effect sizes were omitted from this distribution. Their addition would have resulted in a decrease from the observed Hedges' g = 0.493 to an adjusted Hedges' g = 0.262 (95 % CI = −0.053 to 0.577).

### 3.4. Risk of bias assessment

No publication reported information on all SYRCLE potential bias items, and "unclear" was the most common score (54.7 %) (online Supplementary Fig. S1). However, in 87.0 % of the cases, measures to prevent bias were reported, including computerized approaches. 20 studies reported being blinded or randomized. Overall, we estimated a risk of bias of 3 [1] (median [IQR]) on a 10 points scale.

**Table 2**
Effect of continuous moderators on maternal separation-cognitive flexibility effect sizes.

| moderator | Effect size and 95 % confidence interval | | | | Heterogeneity Q regression |
|---|---|---|---|---|---|
| | Slope | SE | LL | UL | |
| **Age of exposure to test** | -0.002 | 0.002 | -0.006 | 0.002 | 0.668 |

## 4. Discussion

In general, our meta-analysis showed that there was a significant difference in the performance of rodent offspring in the cognitive flexibility tasks between the maternal separation groups and non-separate control groups. The results suggest that experimental manipulations of maternal separation necessarily impair the cognitive flexibility of rodent offspring. However, in view of the large heterogeneity between the studies, we conducted a series of moderator analyses to investigate the impact of methodological factors and sample characteristics on the relationship between maternal separation and cognitive flexibility.

In the experimental operations on the type of maternal separation, the social deprivation level was a key methodological influence on the heterogeneity of effect sizes, while the maternal separation type had a null effect. This suggests that the social deprivation degree, but not the deprivation time, significantly moderates the effects of maternal separation on the flexibility performance of rodents. Although different deprivation times could induce stresses to different degrees, such as psychological, physiological, or even neural stresses (Cirulli et al., 1992; Pryce and Feldon, 2003; van Oers et al., 1998), it seems that stresses occurring at different levels/degrees are likely not the key inducer of heterogeneity regarding the effect size of flexibility performance. However, we think that the stress responses in certain stress targets (e.g., neural factors or hormones) associated with flexible cognition in the brain might be involved in inducing the heterogeneity. For example, the brain-derived neurotrophic factor (BDNF), a potential indicator related to neural stress (McEwen et al., 2015), has been found to show different alterations in the prefrontal cortex in rats separated from their dams only versus from both dams and littermates (Reus et al., 2011; Wang et al., 2015b); no difference was detected in isolation for different daily amounts before weaning (Greisen et al., 2005). BDNF is an important brain protein that supports the structure and function of the brain, including the prefrontal cortex that governs cognitive flexibility (Liston et al., 2006; McEwen et al., 2015; Sakata et al., 2013; Wang et al., 2015b; Xue et al., 2013). Thus, differences in BDNF levels are a potential basis that governs the influence of maternal separation on the heterogeneity of effect sizes. In general, these results suggest that stress responses are a possible reason underlying the heterogeneity of flexibility performance due to maternal separation. Thus far, few studies have examined the different moderating effects of experimental operations on the cognitive flexibility of rodents according to maternal and peer factors, but some studies have focused on other cognitive functions such as learning and memory abilities. We have reviewed these previous studies and found that the experimental operations of separation and isolation, however, had no different effects on the outcomes of learning and memory (Kosten et al., 2012), which is inconsistent with our results. This might be due to the different cognitive types for learning, memory, and cognitive flexibility. Learning and memory are cognitive functions that depend mainly on hippocampal regulation, whereas cognitive flexibility is more dependent on the prefrontal cortex (Lupien et al., 2009; McEwen and Morrison, 2013).

Task characteristics were found to be another methodological influence on heterogeneity in the effect sizes of flexibility performance due to maternal separation. Our results showed that cognitive flexibility of the separation groups was significantly lower than the control groups when the tasks involved reward stimulation, while no differences were found in tasks involving aversive stimulation. Consistent with our findings, Noschang et al. (2012) compared the effects of early handling on different reversal learning tasks, and also found that the rats performed worse in the Y maze, a spatial task with a food reward, while the reversal learning ability was not damaged in MWM, a spatial task involving escape from aversive situations. All these results suggest that the task characteristics could moderate cognitive flexibility and should be considered in future studies. Adaptive alteration could be the reason for the finding that task characteristics moderate rodent behavior and flexibility performance. In order for the mice that had undergone early

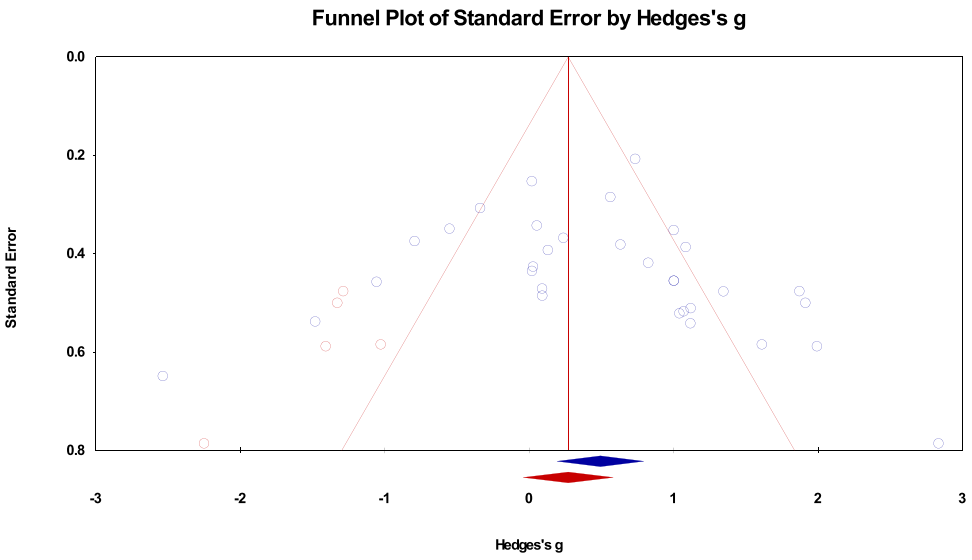


**Fig. 3.** Funnel plot for the effect sizes in the meta-analysis. The vertical line indicates the weighted mean effect. Blue circles indicate observed effects for actual studies, and red circles indicate imputed effects for studies believed to be missing due to publication bias. The blue diamond reflects the unadjusted weighted mean effect size, whereas the red diamond reflects the weighted mean effect size after adjusting for publication bias. (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

maternal separation to survive in an adverse environment, they must quickly identify and response to risk factors in that environment by adaptively tipping the balance of approach-avoidance situations towards avoidance (Irvine, 2018; Teicher et al., 2016). Such balance adaptive alterations will enhance, to some extent, the performance of mice in tasks involving aversion, which could compensate for the cognitive impairment caused by maternal separation and thus making separated groups no different from the controls. Differences in the motivation behind tasks with distinct characteristics are another possible reason causing these moderation effect results. The tasks involving aversion, such as the MWM, usually force mice to escape from hurt and even death, which are a greater motivation to finish the tasks (Kelley, 2004). Therefore, the performance of mice in aversive tasks would be increased compared to reward tasks, hence mitigating and even counteracting the effects of maternal separation on cognitive flexibility. Additionally, previous studies demonstrated that early maternal separation could induce dysfunctions in the dopamine (DA) and serotonin (5-HT) systems associated with rewards and aversive cognitive processing, respectively (Cools et al., 2009; Crockett et al., 2009; Den Ouden et al., 2013). Such dysfunction in the DA and 5-HT systems with doubly dissociable effects on cognition may explain the finding that task characteristics moderate rodent performance following separation (Cools et al., 2009; Crockett et al., 2009; Den Ouden et al., 2013; Teicher et al., 2006). Specifically, the reward tasks depend highly on the mice's DA system (Boureau and Dayan, 2011). Hence, it is conceivable that the dysfunction of the DA system caused by maternal separation would damage cognitive flexibility performance in reward tasks (Chocyk et al., 2010; Tamborski et al., 1990). On the contrary, tasks using aversive stimulation to model cognitive flexibility do not depend only on the 5-HT system and importantly, the reduction of 5-HT levels by separation as previously shown can enhance aversive cognitive processing (Burghardt et al., 2004; Cools et al., 2008; Crockett et al., 2009). Such enhancement could benefit the mice in solving tasks featuring aversion, which would compensate for the flexibility impairment caused by maternal separation and thus make the separation groups no different from the control groups. Interestingly, when determining the influence of task type as a moderator on the heterogeneity of effect size, an inconsistent result in regard to the task characteristics was found. For instance, the Barnes task involves aversion and it was significantly influential. However, no significance was found in four-choice tasks involving rewards. This suggests that the task type as moderator influencing the effect size of flexibility performance is independent and probably has interaction effects with other moderators such as social deprivation levels or the maternal separation types. However, because only 23 studies comprising 32 samples were eligible for this meta-analytical study, it was difficult to further analyze the interaction effects between these potential moderators. Certainly, it is necessary in the future to conduct a full investigation when enough studies are available for analysis. Overall, the cognitive deficits shown by the rodents that had experienced early adverse experiences (maternal separation) may depend on the nature of the stimulus itself regarding the type of cognitive flexibility tasks.

Among the hypothesized moderating factors of sample characteristics, the sex composition and age of exposure to tasks within the samples were found to have a null effect. The rodent strain emerged as a significant moderator. In terms of the impact of rodent strain, we found that C57B1/6 and BALB/cJ mice and Brown Norway and Long-Evans rats pups were more sensitive to the effects of maternal separation than other rodents. This might be due to the strains' different responses to stress or trauma, including the rodent pups and dams (Moloney et al., 2015; Mundorf et al., 2022; Snyder et al., 2018; Tan et al., 2009). Although the sex and age difference in response to stress have been previously studied (Berrebi et al., 1988; McEwen, 2002; Shansky, 2019; Taylor et al., 2000; Reincke and Hanganu-Opatz, 2017), these factors might not be involved in governing the flexibility of cognition. Although these conclusions are tentative, they suggest to some extent that the cognitive deficits developed in rodents that have experienced early life stress are due to a combination of genetic background and environmental factors.

Despite our findings that some factors affect the relationship between maternal separation and cognitive flexibility in rodent offspring, there are several practical constraints. First, because there are a few references that meet the inclusion criteria, the conclusions may be tentative and therefore cannot be generalized to the entire literature on the relationship between maternal separation and cognitive flexibility. These results may not extend to other cognitive flexibility tasks or species other than rodents. In addition, the tasks used in the mentioned studies did not use a uniform unit of measurement (e.g., reaction time, number of times), which may also lead to inaccuracies in the results. Finally, there may be some factors beyond the scope of this study that affect the relationship between maternal separation and cognitive flexibility (e.g. room temperature during separation, number of separation episodes, etc.). Future research can study these potential factors. In the present study, although the methods and approach we adopted are rigorous and reasonably conservative, the quality of the conclusions depends critically on the quality of the studies and data included. From our qualitative bias assessment, the risk for potential bias is comparatively small, and lower than previously reported in some behavioral

neuroscience studies (Antonic et al., 2013; Bonapersona et al., 2018). Furthermore, our models did not display evidence of significant publication bias based on the analysis for the studies included. Although we cannot fully exclude that the above-mentioned limitations may affect the outcome, it is unlikely that the conclusions drawn would be substantially impacted. Nevertheless, we have attempted to address these methodological issues as comprehensively as possible in our analysis study.

Our meta-analysis found that the differences in the study results on the impact of maternal and infant separation on cognitive flexibility were influenced by the experimental manipulations of maternal separation, the evaluation of cognitive flexibility tasks, and sample characteristics. Therefore, in future studies, it is critical to clarify the mechanisms underlying the effects of these moderators on the relationship between maternal separation and cognitive flexibility in rodent offspring.

## Declaration of Interest

The authors declared no competing financial interests.

## Data Availability

Data will be made available on request. Neither of the experiments reported in this article was formally preregistered. Neither the data nor the materials have been made available on a permanent third-party archive; requests for the data or materials can be sent via email to the author at chengl@ccnu.edu.cn.

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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.dcn.2022.101126.

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