



## Review

# Early maternal separation and responsiveness to thermal nociception in rodent offspring: A meta-analytic review



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## HIGHLIGHTS

- Rodent offspring exposed to early maternal separation had lower sensitivity to nociceptive thermal stimulation compared to non-separated controls.
- Tail flick, but not hot plate responses, were associated with changes in pain sensitivity.
- Receipt of injections during separation was associated with changes in pain sensitivity.
- Males, but not females, showed changes in pain sensitivity.
- The effect size was stronger for animals tested at younger ages, and larger effect size differences were found in older than more recent papers.

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## ABSTRACT

Although numerous animal studies have assessed the impact of maternal separation upon pain sensitivity, overall conclusions are difficult to draw about the literature in light of mixed patterns of findings. In this research, a meta-analysis was performed to assess effects of early maternal separation on sensitivity to nociceptive thermal stimulation in rodent offspring and to identify moderators that might explain variable results between studies. Fifteen studies comprising 19 rodent offspring samples ( $N = 1642$ ) fulfilled all selection criteria. Analyses indicated that rodent offspring exposed to early maternal separation had longer response latencies (RLs) reflecting lower sensitivity to nociceptive thermal stimulation compared to non-separated controls. Heightened effect size heterogeneity was also evident. Moderator analyses indicated variable findings between studies were partially or fully explained by operationalizations of maternal separation (early handling vs. maternal separation), type of noxious stimuli, age of testing, receipt of injections during separation, sex composition of samples, and publication year. Biobehavioral underpinnings of overall group differences and moderator effects are posited in the discussion.

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## 1. Introduction

Disrupted early attachment relationships have potentially negative consequences for offspring including the development of anxiety-like behaviors (e.g., [25]), depressive-like responses (e.g., [31]), cognitive deficits (e.g. [35]), and changes of pain sensitivity (e.g., [50,57]). One of the most widely used methods used to assess causal effects of disrupted attachment on responses to painful stimulation has been to separate rodent pups from their dams for specific durations during pre-weaning and to compare their responses to those of non-separated controls.

To date, links between early maternal separation and pain sensitivity have been inconsistent. One of the most common methods of studying pain in rodents has been to evaluate latencies of avoidance responses, particularly withdrawal reflexes of the paw or tail following exposure to nociceptive thermal stimuli [2]. Using such approaches, some researchers have reported reduced pain sensitivity and longer response latencies (RLs) in offspring separated from their dams relative to non-separated controls (e.g., [11]). Others have found a complementary pattern (e.g., [40]), or null effects compared to control conditions (e.g., [27]). Because of findings have been variable, it is difficult to draw conclusions about this literature from individual studies. Meta-analysis, a procedure that supports conclusions through synthesizing data from multiple studies rather than possibly idiosyncratic results of discrete studies, may clarify this issue. Meta-analysis can also help to identify methodological factors and sample characteristics that contribute to effect size variability in studies of maternal separation and pain sensitivity.

With respect to plausible methodological moderators, operationalizations of maternal separation have varied widely between studies. For example, in early handling (EH) paradigms [30], pups experience brief daily separations from the dam during pre-weaning (e.g., 15 min or less). Notably, offspring exposed to early handling have reduced pituitary–adrenal endocrine stress responses and lower levels of anxiety or fear as adults when confronted with environmental demands compared to non-separated, non-handled offspring (see Pryce et al. [59] for a review). Benefits of early handling to stress responding may result from compensatory maternal licking and nursing compared to non-handling, exposure of pups to a different environment, and similarity to natural environments in which separations arise when dams must leave the nest to forage [6,32].

Prolonged maternal separation (MS) has been used in other studies. MS or maternal deprivation have sometimes been used interchangeably in the literature [29] to describe a variety of experimental manipulations, all of which involve removal of pups from the dam for different intervals (single or repeated, 1–24 h) during pre-weaning (e.g., [5,17,40]); such paradigms imply less normative deprivation of maternal care, nutrition, or warmth that may yield anxiety-like behavior similar to that found non-handled offspring. While past narrative reviews [29] contended that operationalizations of maternal separation (e.g., handling versus prolonged separation) contribute to inconsistent findings, quantitative assessments of effect size differences between such paradigms can clarify the extent to which definitions of maternal separation influence effect size heterogeneity. Related features of maternal separation

paradigms including treatment during handling (e.g., receipt or non-receipt of saline injections), number of separation episodes, and cumulative separation time also warrant consideration to clarify specific features of separation paradigms most critical to variability in offspring pain sensitivity.

Timing or age of exposure to nociceptive stimulation is another methodological factor that has varied between studies. Exposure to nociceptive stimuli has occurred during pre-weaning (i.e., within the first 21 postnatal days) (e.g., [14]); during adolescence (1–2 months of age) (e.g., [12]) and during adulthood (e.g., [20,21]). Because newborn mammals of many species are highly dependent on maternal care early in life [37], younger pups should be more sensitive to nociceptive stimulation, albeit it is not clear whether maternal separation has stronger effects for earlier versus later exposure. Effect sizes may also differ as a function of the nature of nociceptive stimulation. For example, the tail flick test, based on spinal tail flick reflex latencies following exposure to heat stimuli [19], is thought to result in shorter RLs than the hot plate test, which assesses latencies of supra-spinal paw licking or other initial responses to heat stimuli [55]. Given that mechanisms underlying pain perception differ between these tasks, the nature of nociceptive stimulation may contribute to inconsistent results.

Maternal separation studies have also diverged on sample characteristics. For example, studies have used various rodent strains including Sprague Dawley rats (e.g., [17]), Long-Evans rats (e.g., [9]), and CD-1 mice (e.g., [34]) which may influence responses due to subtle genetic differences. While a preponderance of studies has used male pups exclusively (e.g., [34]), mixed sex samples (e.g., [9]), and all female samples (e.g., [57]) have also been evaluated. In light of sex differences in neuroendocrine and behavioral responses to stressors [53], maternal separation may have stronger effects on responses of male only rodent offspring.

Based on this overview, a meta-analysis was performed to evaluate the overall impact of early maternal separation on responses to tail-flick or hot plate tests in rodent offspring. From the perspective that early life stress enhances risk for developing anxiety-like behaviors (e.g., [25]), we hypothesized that higher overall pain sensitivity based on shorter (i.e., faster) RLs to nociception would emerge in separated offspring relative to non-separated controls. Assuming significant effect size heterogeneity between studies in this literature, we also evaluated moderating effects of methodological factors and sample characteristics outlined above.

## 2. Method

### 2.1. Literature search

To identify relevant studies, ScienceDirect, PsycINFO and Web of Science database searches were performed between inception dates and October, 2014. Search terms included: “maternal deprivation” OR “maternal separation” OR “postnatal [i.e., early] handling” AND “rat” OR “mice” OR “rodent”; “dam” OR “mother” AND “rat” OR “mice” OR “rodent” AND “pain” OR “nociception” OR “nociceptive” OR “noxious”. All searches the broad field “anywhere” to identify citations. In addition, reference lists of previous narrative reviews and papers identified from database searches were

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