



## Short communication

## Maternal separation stress leads to enhanced emotional responses to noxious stimuli in adult rats

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## ABSTRACT

The purpose of the current study was to examine pain processing in adult rats following repeated maternal separation in infancy, a common model of early life stress. Sensory pain processing remained unaltered, as measured using threshold testing of nociception. However, affective pain processing was enhanced as revealed by increased responding during the tonic phase of the formalin test and during the place escape/avoidance test. The pattern of enhanced responses suggests that early life stress alters the emotional response to pain. Further research could determine if this pattern holds true for different pain models, or if post-weaning enrichment could reverse the effects of maternal separation on pain processing.

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Clinical data has suggested that the stress of traumatic events during infancy and childhood can have long-lasting effects and might contribute to a number of mental disorders in adulthood. The underlying mechanisms that are engaged during these stressful events in early life have become an area of intense research interest [10,12]. A well-established animal model of early life stress is maternal separation (EMS) [22,24]. As adults, EMS rats hyper-secrete corticosterone in response to stressors, and this response is abnormally extended due to reduced glucocorticoid receptor binding in the hippocampus and enhanced expression of CRH [19]. These rats also demonstrate higher levels of anxiety in open field and elevated plus mazes and exhibit behavioral similarities to animal models of schizophrenia and depression [12].

Little research has focused on the impact of maternal separation on subsequent pain processing in adulthood. Therefore, the purpose of the current study was to examine pain processing in adult rats following repeated maternal separation in infancy. Maternal separation was carried out as reported elsewhere (see [20] for a

more detailed description). Eighty-six male pups were obtained from sixteen litters. Approval for the maternal separation protocol and testing procedures was obtained from the University of Texas at Arlington Institutional Animal Care and Use Committee, and all animals were treated in accordance with the guidelines set forth by the International Association for the Study of Pain [27]. An overview of the experimental procedures can be seen in Fig. 1.

Experiment 1 was designed to confirm the efficacy of the maternal separation protocol and examined weight gain during the separation period (PND 2–15), eye opening (assessed between PND 13 and 17), and behavior in the elevated plus maze prior to further experimentation in adult rats. A previous report identified EMS-induced alterations in neurodevelopmental milestones [20], including the timing of eye opening, and this aspect of development was assessed in our experiments to demonstrate the effects of EMS during infancy. Analyses of behavior in the elevated plus maze ensured that the effects of maternal separation persisted until early adulthood, as previous studies have reported more anxiety-like behavior in this test [2,12].

Experiment 2 intended to assess the sensory aspect of pain processing. The threshold response to noxious thermal stimulation was evaluated using the hot plate test. Mechanical paw withdrawal thresholds were assessed using the up/down technique [6,16] before and after an intra-plantar injection of an inflammatory agent, carrageenan. Previous studies that have reported sensory thresholds or nociceptive behaviors have provided mixed evidence with regard to the impact of maternal separation on the sensory

*Abbreviations:* PND, post-natal Day; EMS, early maternal separation; EH, early handling; PEAP, place escape/avoidance paradigm; MPWT, mechanical paw withdrawal threshold.

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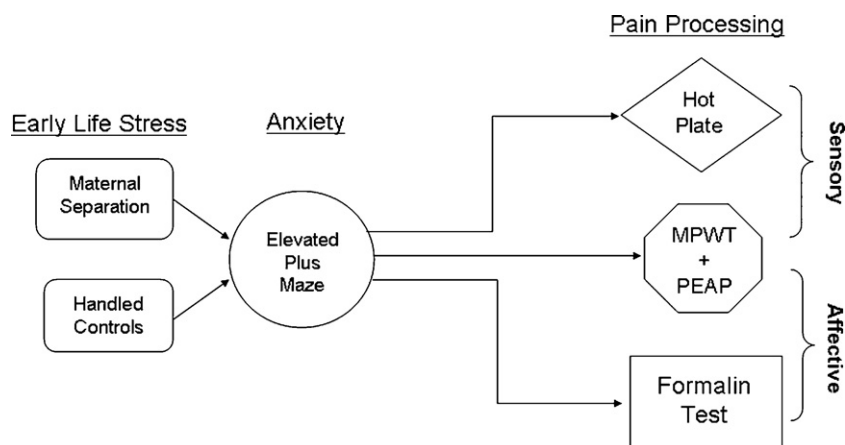


Fig. 1. Overview of experimental procedures.

component of pain processing. Normal responses to baseline tail-flick and hot plate tests have been reported, but EMS animals have also demonstrated a blunted analgesic response to morphine and an enhanced response to noxious visceral stimulation [3,5,13,14,25].

Experiment 3 evaluated the affective/emotional component of pain processing. The formalin test is an established behavioral assay which quantifies observable behaviors directed at the hind paw following an intra-plantar injection of dilute formaldehyde [8]. The tonic, or later period of the formalin test, as well as licking behavior directed to the injected paw involves supraspinal processing and likely reflects activation of brain structures that process pain affect [8,11]. The place escape/avoidance paradigm (PEAP, [16]) is a more recently established test developed in our laboratory that

assesses pain affect by observing whether an animal is willing to actively escape/avoid mechanical stimulation of an injured paw. This paradigm has been vigorously tested and has demonstrated greater sensitivity to changes in nociception than paw withdrawal threshold testing following the administration of low doses of morphine and various anti-depressants [1,16,17]. No previous studies have attempted to quantify the emotional aspect of pain processing in maternal separation animals. Since these animals have demonstrated enhanced neuroendocrine reactivity and increased anxiety-like behaviors in various testing paradigms [2,12], it was hypothesized that maternal separation would result in elevated levels of pain affect in adult rats.

Repeated measures ANOVA was performed on the average pup weights for each litter. There was a significant main effect for time,

Table 1

Confirmation of maternal separation efficacy.

Eye opening <sup>a</sup>	EMS		EH		X <sup>2</sup>		p
PND 13	6		0		4.99		<.05
PND 14	14		1		8.74		<.005
PND 15	48		47		0.28		NS
PND 16	13		24		4.26		<.05
PND 17	9		4		1.15		NS
Total	90		76				
Average pup weight <sup>b</sup>	EMS		EH		Source	F	p
PND 2	8.10	(.29)	7.95	(.55)	Group	<1	NS
PND 3	9.19	(.35)	9.29	(.43)	Time	469.88	<.001
PND 4	10.79	(.49)	10.87	(.51)	Group × Time	<1	NS
PND 5	12.45	(.59)	12.52	(.54)			
PND 6	13.91	(.75)	14.11	(.65)			
PND 7	16.08	(.96)	16.11	(.79)			
PND 8	18.40	(1.09)	18.23	(.83)			
PND 9	20.86	(1.22)	20.65	(.94)			
PND 10	23.23	(1.34)	23.00	(1.06)			
PND 11	25.72	(1.47)	25.49	(1.15)			
PND 12	28.16	(1.63)	28.05	(1.17)			
PND 13	30.46	(1.70)	30.81	(1.28)			
PND 14	33.07	(1.90)	32.92	(1.36)			
PND 15	34.97	(1.93)	35.48	(1.51)			
Elevated plus maze <sup>b</sup>	EMS		EH			F	p
Duration							
Open Arms	80.55	(4.89)	93.09	(6.85)		19.20	<.001
Closed Arms	219.82	(4.80)	206.78	(6.84)		2.45	NS
Non-Mobile	188.32	(2.21)	192.01	(3.25)		<1	NS
Mobile	96.50	(1.92)	95.64	(2.86)		<1	NS
Strongly Mobile	12.38	(.55)	10.40	(.51)		6.95	.01

<sup>a</sup> Number of additional pups with eyes open.

<sup>b</sup> Data expressed as: mean (SEM).

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