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CHILD AND DEVELOPMENTAL PSYCHIATRY (K FITZGERALD, SECTION EDITOR)

Enduring Neural and Behavioral Effects of Early Life Adversity in Infancy: Consequences of Maternal Abuse and Neglect, Trauma and Fear

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Abstract
Purpose of Review Early life experiences have long-lasting influence on a child. For an infant, the quality of caregiving is one of the most critical factors supporting growth and development. Adverse social events in infancy have the potency to alter the child's developmental trajectory and elevate the lifetime risk for a range of psychiatric disorders. Although clinical studies associate early childhood adversities with lifetime risk for mental disorders, the knowledge of underlying neural and molecular alterations leading to these disorders comes mostly from animal studies. In this article, we overview selected animal models of early life social adversity, including maternal abuse and neglect, and maternal trauma and fear.
Recent Findings We first characterize the major behavioral and neural changes normally occurring in early life. We then present several animal models of maternally mediated early life adversity that contribute to reorient the developmental changes toward pathological outcomes. These models yielded to recently identified neurobiological mechanisms, including epigenetic alterations, through which these adversities lead to a lasting dysregulation of the stress response system, aberrant fear learning and memory, and increased anxiety or depression-like behaviors.
Summary We conclude by emphasizing the unique role of the caregiver's influences on the developing brain in infancy. Understanding of the infant's mechanisms of vulnerability and resilience to maltreatment is essential for the advancement of novel therapeutic and preventive approaches.

Keywords Brain development · Infant · Maternal care · Critical period · Stress · Maltreatment

Introduction

Numerous studies have shown that early life adversity may have profound impact on children's psychosocial health and their development. Neglect, abuse, and trauma in infancy and early childhood have been associated with impaired psychological functioning and increased risk for psychiatric disorders in youth and throughout life [1••, 2, 3, 4•]. Understanding the developmental trajectory of the human brain and the mechanisms through which adversities alter this trajectory are thus critical for the advancement of effective preventive and treatment approaches [5]. However, despite accumulating clinical evidence, little is known about the neurobiology of early life adversity.

The use of animal models has been very helpful in characterizing the early life periods critical for neurobehavioral development [6, 7•, 8–11]. Non-human animal models cannot reproduce all aspects of normal and pathological human brain function, but these models have been successful in exhibiting specific neural and behavioral characteristics of

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early life development and effects of adversities. In contrast to human studies, animal models allow experimenters to interfere with the normal development of the central nervous system in a tightly controlled setting. Rodent research has been particularly useful in characterizing the early life development of attachment and safety learning, as well as the emergence of stress and threat responses [12–14]. Although rodent studies have identified distinct critical periods for neurobehavioral development in the prenatal, early postnatal, and adolescent periods, infancy appears to be critically important for the emergence, growth, and maturation of stress and threat response functions [15, 16]. This article will review a rodent model of early postnatal neurobehavioral development and the effects of social adversities on this development. We will specifically focus on the consequences of maternal abuse and neglect, as well as the effects of maternal trauma and fear.

Behavioral and Neural Development in Infancy

The postnatal/preweaning period is characterized by important behavioral changes and brain maturation of the rodent infant (Fig. 1). In terms of sensory maturation, the rodent infant is born at a developmental stage equivalent to the beginning of the third gestational trimester in humans. It is blind, deaf, hairless, and unable to thermoregulate. This characteristic makes an infant rat especially vulnerable and dependent upon the mother for nutrition and nurturing. The newborn pup has functional olfactory, gustatory, and somatosensory modalities which guide the infant's behavior and support early life learning. Sensorimotor functions gradually develop after birth. By postnatal (PN) day 10, the pup develops rudimentary walking, which allows it to step out of the nest by itself [17, 18]. Audition and vision start emerging around PN12–13 and PN13–14, respectively [19], and thermoregulation matures around PN16–18 [20]. About 3 weeks after birth, the pup no longer relies upon the caregiver for survival and is ready to be weaned.

Sensorimotor development of the young rodent is associated with important neuronal maturation that continues after weaning and throughout adolescence as detailed below and in other reviews [21, 22]. The volume of the brain itself increases greatly after birth: for example, between birth and PN30, the volume of the olfactory bulb alone increases sevenfold [23, 24]. This increase in size is associated with the partitioning and maturation of individual brain structures. For example, in the amygdala, a key structure for processing threat [25], the different nuclei become subdivided between PN7 and 14 [26]. The cellular composition of brain structures also changes: for example, mitral cells are set up in the olfactory bulb during embryogenesis (e.g., present at birth), while 89% of the granular cells are integrated to the olfactory bulb after birth [23].

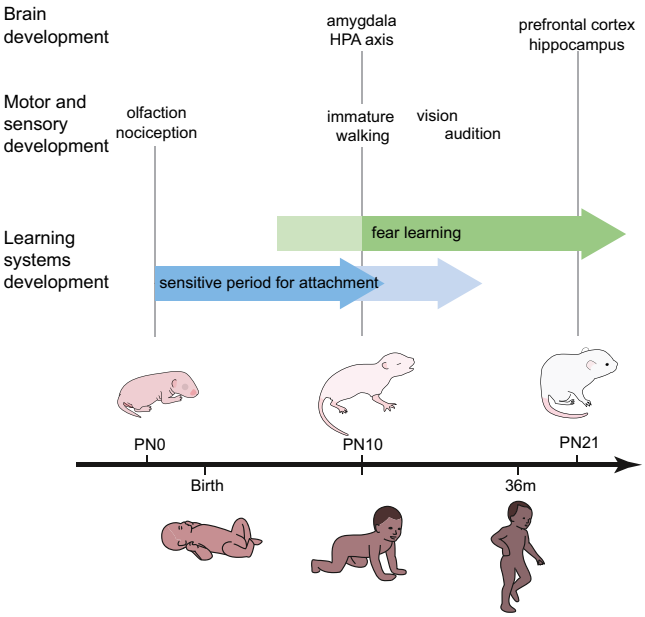

Fig. 1 During infancy, humans and rats undergo analogous stages of behavioral, motor, sensory, and neural development. At birth, rat pups have functional systems for olfaction and nociception, but have very limited locomotor skills and cannot see or hear. It is often considered that rats are born at a maturational age equivalent to the beginning of the third trimester of human gestation. The sensitive period for attachment learning in rodents lasts through postnatal (PN) day 10, although it can be extended to PN15 in some experimental conditions. Around PN10, rats begin to be capable of immature walking, akin to the human toddler phase. In rats, this age also marks the typical emergence of the fear learning system; however, chronic stress during infancy can lead to the early onset of fear learning. This emergence of the fear system is supported by the amygdala and HPA axis becoming functional and involved in the learning. As rats mature from PN10 through PN21, they continue to nurse but also begin to eat solid food. The visual and auditory systems become functional. Rats are typically weaned at PN21, the age at which the hippocampus and prefrontal cortex begin to contribute to learning processes

As brain structures mature during infancy, the connections between these structures refine. Myelination increases after birth [27, 28], axons and dendrites arborize and increase their length [29], and synapses sprout. For example, in a 4-day-old rodent brain, only 1% of the adult dentate gyrus synapses [30] and only 6% of the adult amygdala synapses are present [29]. Some neurotransmitter-specific afferents also change their mode of discharge and/or their postsynaptic effect. For example, norepinephrine-producing neurons originating in the locus coeruleus undergoes drastic modifications of its firing pattern between birth and weaning age [31]: norepinephrine neurons change from exhibiting a very low spontaneous firing rate to displaying a more tonic firing. Accompanying this shift in the spontaneous firing rate, there are developmental changes in the noradrenergic response to sensory stimulation. At birth, tactile stimulation results in a sustained activation of the norepinephrine system which lasts for up to 20 s, while the same stimulation presented at weaning age leads to an

activation shorter than 100 ms [31]. The postsynaptic effects of the neurotransmitters can also change drastically. One of the most investigated examples is the shift of actions of the transmitter gamma-aminobutyric acid (GABA) during early development: while GABA inhibits adult neurons, it excites immature ones [32, 33]. In addition to these modifications in the postsynaptic activity, changes in the neurophysiological properties of these neurons can also be observed. Ehrlich et al. [34] showed significant developmental changes in the electrophysiological properties of amygdala neurons—including their input resistance, spontaneous membrane potential oscillations, train of action potentials in response to direct current injection and afterhyperpolarization, and the shape of the generated action potentials. The maturation of these neurophysiological properties leads to the emergence of adult-like oscillations after PN14 [35]. In summary, between birth and weaning age, the rodent brain undergoes important modifications at molecular, cellular, structural, and systemic levels.

These neurodevelopmental changes are reflected in the changing psychomotor and behavioral functioning of the animal. In particular, this includes the animal's response to threat and safety signals. For example, during the first 10 days of life, the stress response of the rodent infant is minimal to nonexistent in normal rearing conditions; their plasma glucocorticoid levels are low and nociceptive stimuli evoke little to no hypothalamic-pituitary-adrenal (HPA) axis activation (for review, see [36]). Secure attachment and safety learning also develop during this stress hypo-responsive period (SHRP). As mentioned earlier, the altricial infant is highly dependent upon maternal care for survival. It must thus learn to respond to maternal presence by producing approach and prosocial behavior. In rodents, attachment learning occurs during the first 10 days of life and relies on the unique neurobiology of the infant brain. The sustained activation of the norepinephrine system in response to tactile stimulation allows the pup to rapidly learn about the mother and bond with her. At such an early age, rodent infants are still blind and deaf, and they rely mostly on olfaction to locate the dam ventrum and the nipple [37–39]. This dependence upon olfaction to orient the infant and promote behaviors directed toward the mother is shared between rodents and humans. Indeed, several studies have shown that the scent of lactating maternal breasts is a crucial cue that the newborn baby uses to orient toward the nipple and that triggers appetitive oral responses [40–42]. Moreover, both rodents and human infants can form long-lasting memories of olfactory cues associated with suckling [43–45]. During the sensitive period for attachment in rodents, pairing a neutral odor with a stimulus mimicking maternal care, such as stroking with a brush to mimic maternal licking, leads this odor to acquire the valence of a maternal scent. As such, this cue triggers approach and nipple attachment [10, 44, 46–49]. Rodent studies searching for markers of learning-induced plasticity have shown that this learning of a new maternal odor relies upon the olfactory bulb and the anterior piriform cortex [50, 51]. When a neutral odor is repeatedly paired with a stimulation characterizing (or mimicking) maternal care, this stimulation activates the pup's locus coeruleus and causes a strong influx of norepinephrine into the olfactory bulb. The immense rise of norepinephrine levels in the olfactory bulb prevents the mitral cells of the infant from habituating to the odor [52–56]. This olfaction-mediated attachment learning mechanism is specific for the period from birth to PN10, a developmental stage known as a sensitive period for attachment. It enables the rapid attachment of the newborn to the mother and the first learning about safety. From PN10 onwards, due to the maturation of the locus coeruleus and the noradrenergic system, a nurturing stimulation does not produce such high rises in norepinephrine level responses [12]. Thus, animals who do not receive appropriate nurturing prior to PN10 lose the ability to attach normally to the dam, an effect that defines this critical period.

Indeed, secure attachment and the attenuated stress response observed during the SHRP are disrupted if maternal care is deficient or absent, leading to long-term changes in affective functions. There is a natural variation in the amount and quality of care that dams provide to their pups; some dams, termed "low licking/grooming" (LG), spend significantly less time actively caring for their pups than dams termed "high licking/grooming" (HG) [57]. In adulthood, differences in behavior, stress reactivity, and gene expression can be observed between the offspring of LG and HG dams. For example, adult offspring of LG dams tend to exhibit more anxiety-like behavior than offspring of HG dams (e.g., increased startle responses, decreased open field exploration, and longer latencies to eat food provided in a novel environment, reflecting a greater fear of novelty) [57]. In conjunction, adult offspring of LG dams also display stronger plasma adrenocorticotropic hormone (ACTH) and corticosterone (the main corticosteroid in rodent, equivalent to human cortisol) responses to an acute stressor and have increased levels of *corticotropin-releasing factor* (*CRF*) messenger RNA (mRNA) in the hypothalamus [58]. To our knowledge, no research has directly tested whether there are differences between offspring of HG and LG dams in the activation of the norepinephrine system during the sensitive period for attachment. However, the offspring of HG dams have higher α2-adrenoreceptors in the locus coeruleus, which suggests that maternal behavior shapes the trajectory of the norepinephrine system into adulthood [59]. Cross-fostering studies have confirmed that HG and LG effects are explained by differences in parental care rather than differences in genetics [60]. Indeed, this variability in parental care causes epigenetic variability. For example, variations in maternal care lead to long-lasting epigenetic modifications of genes controlling the neuromodulatory and neuroendocrine systems, including the glucocorticoid and oxytocinergic systems [61, 62]. These systems have been shown to be involved in regulating social behavior as well as stress and threat responses, beginning in infancy and

throughout the lifespan. Treatment with a histone deacetylase inhibitor eliminated differences in HPA axis reactivity between offspring of HG and LG dams, suggesting that epigenetic modifications may be a mechanism by which maternal care shapes the stress responsiveness and behavior of offspring [61].

Maternal Abuse and Neglect

A history of early childhood maternal neglect and maltreatment is associated with a wide range of adverse somatic and mental health outcomes in youth and adults [63–66]. Infancy, a phase of dynamic brain development and vulnerability to environmental influences, overlaps with the maternal postpartum period which is characterized by an increased risk for maternal psychological or psychiatric problems, including postpartum psychosis, depression, and anxiety [67, 68•, 69–70]. Recent studies show that the postnatal period is also marked by an increased risk for paternal anxiety and depression [71–74]. These parental mental health risk factors, along with other psychological, social, or economic challenges of parenthood, may contribute to a disruption of parental care or a caregiver's aberrant behaviors, including child abuse and neglect. Although animal models cannot reflect the complexities of human life, they allow experimenters to study the effects of early social adversities on specific neural systems and functions.

Maternal abuse in early infancy is often experimentally modeled in rodents by limiting the amount of bedding in the housing cage from PN2 through 9 [75]. This procedure leads to increased maltreatment by the dam of her pups (stepping on the pups, rough handling) due to the increased difficulty for the dam to build a nest: she spends more time building it and transporting the pups than nursing and nurturing them [49, 76]. Alternatively, during the sensitive period for attachment, between birth and PN10, maltreatment can be modeled by pairing a novel odor to nociceptive stimuli such as tail pinches or mild foot/tail shocks [49, 76]. In this paradigm, pups learn to associate the odor with the dam and exposure to this odor will paradoxically trigger approach and infantile behavior characteristic of interactions with the dam [49, 77], as would an odor paired with a positive maternal cue. Pups exposed to either of these experimental paradigms show decreased body weight and have increased plasma corticosterone inter-animal variability, typical of a state of chronic stress, in early infancy [75]. Maternal maltreatment during infancy has also been associated with epigenetic changes. In adulthood, rats that had been fostered with an "abusive" dam had decreased *brain-derived neurotrophic factor* (*BDNF*) mRNA in the prefrontal cortex and, accordingly, also had increased epigenetic downregulation of the *BDNF* gene at PN8, PN30, and PN90 [78]. Maternal maltreatment during infancy also appears to alter the expression of *BDNF* mRNA [79] and telomere length [80] in the amygdala. These molecular features have also been implicated in the pathology of mood disorders in humans [81].

Maltreatment during infancy also leads to long-lasting changes in affective behavior (see Fig. 2). Pups exposed to chronic stress or maternal abuse in infancy show reduced sucrose consumption suggesting anhedonia and more depressive-like behavior on the forced swim test[1] in adolescence and adulthood [49, 77]. They also exhibit impaired adult social interactions [83••]. Rats that experienced maternal maltreatment show altered fear learning circuits, leading to reduced fear conditioning [84, 85] and stronger reactions to the threat of a predator odor [86] than non-maltreated rats. These effects mirror the findings that are observed in human individuals who experienced maltreatment in childhood, such as enhanced amygdala activation in response to viewing threatening faces, altered development of the circuitry responsible for orchestrating response to threat, and heightened risk for psychopathology [87•].

Another common experimental manipulation that is frequently used to model maternal care deprivation is the maternal separation procedure. Most typically, this paradigm involves separating pups from the dam for 3 h every day from PN2 through 14. This procedure appears to affect fear learning and memory in pups, as well as the extinction of conditioned fear, e.g., the decrease of the behavioral response to the threatening cue following the repeated non-reinforced presentation of that cue. Research shows that maternal separation promotes the retention of fear memories formed in infancy. One study demonstrated that PN17 pups with a prior history of early maternal separation retained the fear memory around 30 days longer than rats that had not been separated from their mother in infancy [88]. In rats aged PN24 and older, fear memories are susceptible to relapse; e.g., the fear response to the threatening cue tends to reappear with time passing after the extinction. This relies on GABAergic inhibition. In infant rats, fear extinction is typically not susceptible to relapse. Experimental evidence shows that PN17 rats that experienced maternal separation during early infancy were susceptible to relapse following extinction of a fear memory, unlike rats reared in standard conditions [89]. This may be due to changes in the inhibitory GABAergic circuitry within the amygdala, as maternally separated rats required GABAergic inhibition for the expression of extinction, a pattern observed in adulthood, while rats reared in standard conditions did not [89]. These findings suggest that the affective stress induced by maternal separation may result in premature

[1] In the forced swim test, rats are placed in a tall container of water while the experimenter records how much time the rat spends swimming and how much time the rat spends passively floating. Swimming is interpreted as an active coping mechanism, whereas floating is interpreted as a sign of "behavioral despair," one component of major depressive disorder. Rats that have higher immobility time on this test are said to be exhibiting more depressive-like behavior [82] (see Fig. 2).

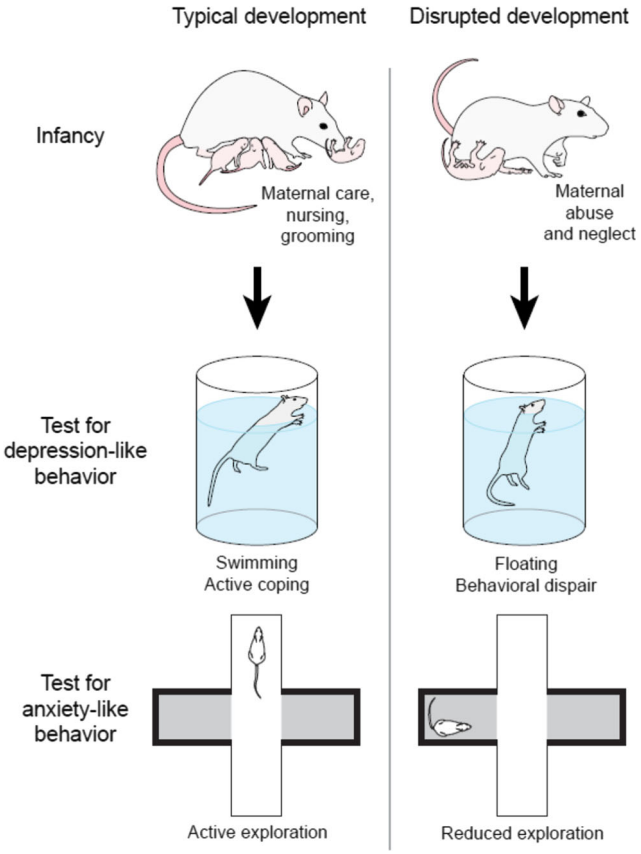

Fig. 2 Maternal maltreatment may take a variety of forms including (but not limited to) neglect of pups, rough handling, low levels of licking and grooming behavior, and stepping on pups. Deficits in the quality of maternal care may arise from phenotypic variation (e.g., higher or lower licking/grooming behavior) or from experimenter manipulation (e.g., maternal separation, reduced bedding). These deficits can have long-lasting consequences on the behavior, endocrine system, and neurobiology of rats. In comparison to normally reared animals, adult rats that experienced maternal maltreatment in infancy exhibit more immobility during the forced swim test, a model of depressive-like behavior. Additionally, rats that experience maternal maltreatment tend to explore the open arms of the elevated plus maze less than normally reared rats, which suggests that rats that experience maternal maltreatment are more anxious

and altered development of the threat processing system, an observation also reported by human studies [90, 91]. Early maternal separation may also affect the development of neural systems involved in depression; for instance, PN15 pups that experienced maternal separation had decreased hippocampal neurogenesis, one of the major neurobiological phenotypes of depression, when compared to pups that were reared in standard conditions [92].

The maternal separation paradigm, similarly to maternal abuse paradigms, exhibits effects on the behavior and neurobiology of rats that can be observed in adulthood. Rats that experienced maternal separation tend to show more depressive-like behavior on the forced swim test [92, 93] and more anxiety-like behavior on the elevated plus maze[2] in adulthood [95] (see Fig. 2). The experience of maternal separation during infancy fundamentally alters the function and regulation of the HPA axis in adulthood. Rats that experienced repeated maternal separation had higher baseline corticosterone levels [93] and higher *CRF* mRNA density in the hypothalamus [93, 96, 97]. Similarly, increased levels of glucocorticoid receptor [98], ACTH precursor [99], and *vasopressin* mRNA [100] have been observed in the hypothalamus of mice that experienced maternal separation relative to mice that were normally reared. These differences in HPA axis function may be due to changes in the epigenetic regulation of genes responsible for controlling the HPA axis. Extraction of DNA from the hypothalamus of non-separated and maternally separated mice revealed that separated mice present epigenetic enhancement of the *vasopressin* gene transcription compared to non-separated mice. Treatment with a vasopressin antagonist normalized the altered HPA axis reactivity in maternally separated mice [99]. Despite some promising preclinical findings, human studies have not yet established the role of the vasopressin receptor antagonism in ameliorating effects of early life stress on HPA reactivity [101]. Maternal separation also appears to result in changes in the epigenetic regulation of the glucocorticoid receptor gene *NR3C1* in the hypothalamus that prevented an increase in CRF following chronic mild stress exposure in maternally separated mice [98]. Finally, some investigators have found no difference in rat baseline HPA axis activity due to maternal separation, but have found differences in ACTH levels [95] and corticosterone levels [100, 102] following exposure to an acute stressor. Although differences between studies may arise because of differences in the separation paradigm, age of the stress hormone assay, and differences in applied stressors, these results suggest that repeated maternal separation during infancy causes long-lasting changes in HPA axis reactivity.

Maternal Trauma and Fear

Clinical studies show that a parental diagnosis of an anxiety disorder increases the risk of pathological anxiety in children, and parental history of posttraumatic stress disorder (PTSD) is associated with an elevated risk for PTSD in their offspring [103, 104]. Parent-child transmission of stress, anxiety, and fear may be explained by various mechanisms, including hereditary mechanisms, experiential factors, or gene-environment interactions [105]. Recent research suggests that

[2] The elevated plus maze is a cross-shaped maze consisting of two arms enclosed by walls and two arms without walls. Rodents normally avoid open spaces where they are more exposed to predators but also have a natural tendency to explore novel environments. When a rat is placed in the center of the maze, it is presented with a conflict between moving into the dimly lit enclosed arms and exploring the exposed arms. The amount of time rats spend in the open arms and in the closed arms is counted; more time spent in the closed arms is indicative of increased anxiety-like behavior [94] (see Fig. 2).

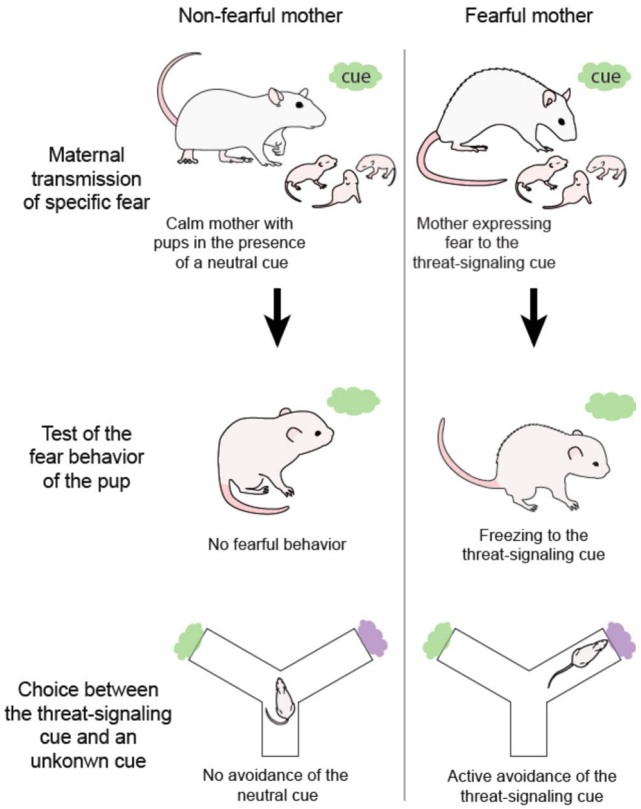

Fig. 3 A mother previously conditioned to associate a cue, such as an odor, to a shock is presented with the cue again in the presence of her offspring. By responding with fear to the presence of the threat-signaling cue, she can transmit her fear of the cue to them. Such transmission relies upon the detection of maternal fear pheromone by the offspring. Once the pups have associated the new cue to maternal fear, they express fear of this cue themselves: when presented with the cue, they freeze to it, i.e., they become fully immobile in a crouched posture with piloerection. Moreover, if they are given the possibility to choose between the fearful cue and another cue in a Y-maze, they will actively avoid the fearful cue and chose the other arm of the Y-maze

parental modeling and children's social fear learning play an important role in the transmission of specific maladaptive fears, such as those occurring in phobias or PTSD [103, 106–108]. Despite abundant clinical and experimental evidence, little is known about neurobiological mechanisms underlying this parent-child fear transmission [109]. Recent animal studies offer insight into the neural underpinnings of the mother-to-infant transmission of fear [110••, 111].

We have shown above that early in infancy, stress responses are typically diminished and classical threat conditioning is quiescent. Maternal neglect and abuse may alter this early quiescence of stress and threat processing systems leading to premature emergence of the stress response and fear learning. However, we have recently found in normally reared pups that maternal stress alone may activate the infant's HPA axis and amygdala threat learning system [110••, 111]. We observed that from birth onwards, infant rats can acquire cue-specific threat responses from their mother through social fear learning [110••, 111] (see Fig. 3). The presence of a frightened mother activates the pup's HPA axis and causes a robust corticosterone rise and an increased activity of the amygdala and other brain areas that are critical for processing threat, stress, and pain [110••, 111]. Pharmacological inactivation of the amygdala prevented the acquisition of maternal fear [110••]. Our findings suggest that maternally transmitted threat responses acquired in infancy may be long-lasting [110••].

An early life emergence of social transmission of specific fears during the stress hypo-responsive period, when learning about environmental dangers through fear conditioning is naturally suppressed (due to low levels of corticosterone which is necessary for fear conditioning), may be adaptive as it allows the offspring to learn promptly from parents about possible threats in the surrounding world. Indeed, human studies show that infants and young children quickly acquire parental fear behaviors [112]. Recent research suggests that parental modeling of anxious and fearful behaviors and children's social learning of fear/anxiety may mediate parent-child transmission of fear and anxiety independently of hereditary factors [103] and that the treatment of parental anxiety may decrease the risk of this transmission [113•].

Concluding Remarks

Although human growth and development occur throughout the whole life, infancy is distinctly marked by critical periods in brain development, which are characterized by a unique sensitivity to social influences. These critical periods enable the maturation and tuning of neural systems that are critical for safe and successful navigation through life. Animal models emphasize the significance of undisrupted caregiver-infant interactions for neurobehavioral development. The models of maternal abuse and neglect, and maternal trauma and fear discussed in this review provide examples of how animal research helps to characterize neural and molecular mechanisms affected by early life social adversities. Understanding of the infant's mechanisms of vulnerability and resilience to maltreatment is essential for the advancement of novel therapeutic and preventive approaches.

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Compliance with Ethical Standards

Conflict of Interest Dr. Julie Boulanger-Bertolus, Amanda M. White, and Dr. Jacek Debiec declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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