



Published in final edited form as:

Dev Neurosci. 2012 ; 34(2-3): 101–114. doi:10.1159/000336732.

The Development and Neurobiology of Infant Attachment and Fear

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Abstract

Survival of altricial infants depends on attachment to the caregiver – a process that requires infants to identify, learn, remember, and approach their attachment figure. Here we review the neurobiology of attachment in infant rats where learning about the caregiver is supported by a specialized attachment neural circuitry to promote the infant-caregiver relationship. Specifically, the attachment circuit relies on infants acquiring learned preferences to the maternal odor, and this behavior is supported by the hyper-functioning locus coeruleus and generous amounts of norepinephrine to produce experience-induced changes in the olfactory bulb and anterior piriform cortex. Infants also possess a reduced ability to acquire learned aversions or fear, and this behavior is facilitated through attenuated amygdala plasticity to block fear learning. Presumably, this attachment circuitry constrains the infant animal to express only learned preferences regardless of the quality of care received. As pups mature, and begin to travel in and out of the nest, the specialized attachment learning becomes contextually confined to when pups are with the mother. Thus, when outside the nest, these older pups show learning more typical of adult learning, presumably to prepare for independent life outside the nest. The quality of attachment can alter this circuitry, with early life stress prematurely terminating the pups' access to the attachment system through premature functional activation of the amygdala. Overall, the attachment circuit appears to have a dual function: keeping pups close to the caregiver but also to shape pups' behavior to match the environment and define long-term emotion and cognition.

Keywords

social behavior; mother-infant interactions; olfactory bulb; norepinephrine; attachment; imprinting; locus coeruleus; amygdala; learning; classical conditioning; corticosterone; stress

INTRODUCTION

“Hidden within the observable interactions of parent and offspring are sensorimotor, thermal, and nutrient-based events which have unexpected and widespread regulatory effects on infant behavior and physiology. ... These regulatory processes also appear to mediate long-term shaping effects exerted by early relationships.” (Hofer, 1994)

Attachment, the enduring bond between individual animals or humans [1], has a wide phylogenetic representation. Attachment also occurs throughout the lifespan and includes the mother attaching to her offspring, the offspring attaching to the caregiver, and mates attaching to one another. Considerable work has begun to document how the human brain

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forms attachment, with focus primarily limited to adult pair bonding and romantic love [2-9]. In other species, attachment research has focused on both infant and adults, with decades of research characterizing its neural basis at molecular, cellular, and systems levels [10-16]. In this review, we focus on infant attachment and integrate neurobiological attachment research in infant mammalian species.

Human infants exhibit attachment behaviors to their caregiver within minutes of birth. This occurs despite the birth process and transitioning from the familiar rhythmic and warm intrauterine environment to a world filled with new sensory experiences. This appears to be a daunting process since infants are required to identify their caregiver, form a memory about the experience with the caregiver, and continuously seek closeness to their caregiver for survival. Indeed, it seems that evolution has shaped the infant's social and emotional behavior to learn about and maintain proximity to the caregiver through this attachment process. The caregiver becomes the target for social behaviors and proximity-seeking behaviors and provides the food, protection, and warmth necessary for survival. Pre-programmed behaviors that are practiced in utero together with prenatal learning of the caregiver's smells and sounds greatly facilitate this transition and attachment. This is combined with the infant's exceptional postnatal learning, where other features of the mother and other caregivers are rapidly learned. For instance, within hours of birth, newborns orient towards and prefer their mother's voice, which is due to both prenatal and postnatal experience with the mother's voice [17]. Similar prenatal and postnatal experience seems to underlie newborns response to maternal odor. Indeed, at birth, an infant placed on the mother's ventrum will crawl to a breast scented with amniotic fluid in preference to the untreated breast [18]. Importantly, maternal diet, which scents the amniotic fluid, directly influences this preferential response [19-21]. This odor also influences the infant's response to the mother, as expressed by orienting to the odor source and the odor's ability to attenuate crying [21,22]. Together, these studies illustrate that complex attachment behaviors of human attachment and bonding can be analyzed at the sensory system level to provide insight into how sensory stimuli can regulate behavior and physiology [23,24].

Due to the limitation in the assessment of the neurobiology of attachment in humans, most of our understanding of the neurobiology of early life learning is based on animal research. Similar to humans, this survival-dependent learning is realized by exceptional learning processes early in life in other animal species. Early life attachment learning known as "imprinting" is temporally limited to a window of time as first demonstrated following hatching in chicks [23, 26-30]. The rapid learning and some of its neural support has been identified in mammals [12,13]. Importantly, while this animal work provides understanding and insights into human attachment, children show far more flexibility in forming attachment, including attachment to multiple caregivers throughout development [30] with continual learning occurring during awake and sleep [31].

Here, we will review the literature on the neurobiology of rodent infant attachment learning and how it is reorganized during development to presumably meet the changing needs of the infant as it transitions to independence. Such developmental transitions in behavior include a complex interplay between experience, learning, and neural changes and are thought to represent periods of vulnerability [32-35] although this process becomes the foundation for normal brain and behavior [36-39].

Rodent attachment learning

Attachment learning has been identified across many species, including rats [40-45], rabbits [46-49], mice [50-52], and non-human primates [53-56]. During this time of dependency upon the mother, the infants' behaviors are focused on keeping physical contact with the mother. The sensory stimuli controlling this attachment vary with each species, but in the

infant rat, this behavior is guided and controlled by maternal odor [57,58]. Specifically, maternal odor controls infants' approach responses to the mother. Once pups make contact with the mother's ventrum, perioral somatosensory cues combined with maternal odor become the proximal maternal stimuli essential for nipple attachment [59,60].

Infant rat pups, born blind and deaf, orient toward mother's odor naturally within the nest, and decades of research have now shown the maternal odor is not a pheromone, as originally proposed, but is learned [57-70]. The maternal odor elicits approach, physical contact with the mother, and nipple attachment, and without the maternal odor, pups show greatly diminished contact with the mother, failure to nipple attach, and exhibit low survival rates [71,72]. This has been demonstrated in naturalistic paradigms with the specific sensory qualities of the attachment figure (scent, texture, color, sound) during infant-caregiver interaction [15,26,43,44,52]. Any neutral odor can become the maternal odor simply by placing a novel odor (i.e. peppermint or citral) on the mother during mother-infant interactions or in the amniotic fluid during the last days of gestation [41,57,65,73-76], although sensitive period olfactory learning also occurs in controlled classical conditioning experiments performed outside the nest without the mother [64,77-84]. Indeed, pairing a novel odor with a reward is sufficient to produce both learned odor preferences (demonstrated by an approach to the odor) and nipple attachment. However, perhaps the most striking feature of this early learning is the variety of stimuli that have been shown to function as a reward for young pups. Indeed, pairing a novel odor with milk, warmth, nursing, and tactile stimulation or stroking to mimic grooming all support odor learning [41,63,64,70,73,76,82-88]. As will be discussed below, painful stimuli can also support this odor attachment learning. Finally, the maternal odor continues to be learned repetitively throughout the early postnatal period, presumably to accommodate the changes induced in the maternal odor by the mother's diet.

Somatosensory input is a component of early approach behaviors in rat pups and supports early learning. Manipulations of somatosensory input from the first day of life throughout development have now been done to examine the role of early somatosensory inputs, specifically involving the perioral area and whiskers, in infant attachment behavior. For example, sectioning of the infraorbital nerve, the sensory nerve that innervates the whiskers, was found to result in increased infant mortality due to inability of pups to nipple attach normally, by disrupting nipple searching behaviors such as sweeping the snout over the ventrum just prior to grasping the nipple [89]. Furthermore, de-whiskering throughout development, which affects tactile learning and whisker behavior in adulthood [90], delays pups' nipple attachment in early life [91]. The importance of perioral somatosensory information to pups is also evident in pups' early life somatosensory learning. Specifically, passive whisker stimulation paired with reward results in stimulation-evoked head and oromotor activity in pups as early as 1 day old, which is similar to the behavioral activation required for nipple attachment [92]. The most dramatic effects of early life whisker deafferentation occur when whiskers begin to move (whisking) at postnatal day (PN) 12 just prior to eye and ear opening. Specifically, upon examination of early exploratory behaviors, studies showed that deafferentation of the infant whiskers results in abnormal head turns in pups, latencies to explore and contact novel objects using the whiskers, increased contact with other sensory surfaces during tactile exploration such as paws and mouth, and delayed whisking emergence and development [93, 94].

Together, this research indicates that the maternal odor is used for early attachment but is experienced among an array of sensory stimuli in the nest. Learning within any sensory system is likely a continuous and reciprocal process as pups mature and maternal behavior decreases. That is, as we place these behavioral learning results into the natural environment of pups, it is important to consider the myriad of sensory stimuli that are activated as pups

interact with the mother and that learning likely co-occurs in all sensory systems. Specifically, as pups experience the maternal odor, it is accompanied by touch and warmth (somatosensory system) and the taste of milk (gustatory system), which are likely combined by pups as the maternal representation. These maternal stimuli each have a role in facilitating interactions with the mother: the odor orients pups to the mother, but at the nipple it is a combined signal of maternal odor plus stimulation of the perioral area (snout, whiskers) induced by pup's own motor responses (lateral head movements along the ventrum) that permit nipple location and grasping for nursing. Moreover, pups are likely to be simultaneously learning about the mother, siblings, and nest. Passive stimulation of the whiskers, for instance, may be a sensory cue that is used within the context of the nest while the pup is huddling with siblings or competing for access to a nipple.

Neurobiology of infant attachment

As illustrated in Figure 1, this robust olfactory-based attachment learning system in rats is supported by a unique learning neural circuitry: infants' noradrenergic locus coeruleus (LC) and its abundant release of norepinephrine (NE) into the olfactory bulb induces the plasticity required for learning. Indeed, neural plasticity within the olfactory bulb is the critical site for physiological and anatomical changes within the brain to support the maternal odor learning [95-107]. Learning-induced plasticity has been well documented in naturalistic learning experiments [24,80], and in conditioning experiments conducted outside the nest [79, 80, 97-107]. The maternal odor, whether natural or artificial (placed on the mother or ingested), as well as odors learned through controlled classical conditioning studies all produce a similar enhancement of olfactory bulb neural responding. Neural assessments have been done using a variety of techniques including 2-deoxyglucose (2-DG) uptake, c-Fos immunohistochemistry, electrophysiology, CREB phosphorylation (pCREB), and optical imaging, and the effects observed with these techniques are all confined to early life.

Norepinephrine (NE) appears to be both necessary and sufficient for the learning-induced behavioral and neural changes seen in pups. NE-dependent olfactory bulb learning-induced changes are dependent upon NE released from the LC [108-118]. NE appears to evoke olfactory bulb plasticity by preventing the olfactory bulb's primary output neurons (mitral cells) from habituating to continual olfactory stimulation [100]. At the molecular level, NE also increases pCREB via cyclic AMP stimulation that likely underlies transcription of immediate-early and late-response genes involved in synapse formation, neurogenesis, and learning [110]. Thus far, it seems that rat pups use the same intracellular cascades used in adult learning and memory [119-123].

One unique feature of infant learning is that the infant LC releases substantially more NE into the olfactory bulb during the sensitive period than during adulthood [118]. This appears due to pups' lack of the recurrent collateral inhibition from α -2 inhibitory autoreceptors, which in adults and older pups inhibits LC firing and NE release into the olfactory bulb [124-127]. The LC α -2 receptors' autoinhibition becomes functional around 10 days of age [123,127], which changes the LC's stimulus-induced responding and greatly reduces the amount of NE release. Indeed, the functional emergence of the LC's α -2 inhibitory autoreceptors signals the end of the pups' sensitive period of heightened ability to learn odors. At this point, NE begins to play a more modulatory role (versus the necessary and sufficient role), which has been repeatedly demonstrated in adult learning [128,129].

Thus far we have discussed the experience-induced changes in the olfactory bulb and LC that are responsible for early-life learned-odor associations. While cellular and physiological changes in the olfactory bulb play a prominent role in the early learning process, the olfactory piriform cortex (part of the olfactory cortex) appears to have an important role in assigning the hedonic value to a learned odor. Primary sensory axons of mitral cells of the

olfactory bulb directly project to the piriform cortex [130,131]. The piriform cortex can be divided, both anatomically and physiologically, into two distinct structures: 1) the anterior piriform cortex, which is influenced by direct olfactory bulb input; and 2) the posterior piriform cortex, which is more influenced by input from limbic structures and intracortical connections [132-134]. Early-life learned odor preferences engage the anterior piriform cortex (with no detectable activity in the posterior piriform), while learned odor aversions in older pups and adults support posterior piriform cortical activity [80].

Since naturalistic early attachment learning likely produces simultaneous learning in multiple sensory systems, we also questioned whether the NE was important for pup learning within the somatosensory system. Indeed, the noradrenergic LC innervates the somatosensory system along the ascending somatosensory pathway [135]. We found that NE is necessary and sufficient to induce early associative learning during the first days of life. Specifically, newborn rat pups can be conditioned to whisker stimulation paired with increased systemic NE [135]. We were unable to detect learning-associated changes in the immature barrel cortex [91, 92]. Thus, NE is implicated in plasticity within the whisker system in adulthood [136] and during development [137] and complements the role of NE in the olfactory system discussed above. This suggests that NE-associated early classical conditioning may represent a common principle across sensory system development.

Neurobiology of pain-associated attachment

Another unusual feature of pup attachment learning is that it persists regardless of the quality of care that is received. That is, pups with an abusive mother also form a strong attachment [24,80]. This pain-related attachment could be mimicked outside the nest, where pups can learn a new maternal odor, even when that odor is paired with a 0.5mA shock or tailpinch [69,70]. This paradoxical attachment learning suggests that there is suppression of avoidance and fear learning, perhaps to protect pups from learning to fear the mother. Since the conceptualization of attachment theory, the attenuation of fear and avoidance is known to be a critically important characteristic of attachment learning [1,23-24]. Early imprinting studies demonstrated that shocking young chicks in the presence of the surrogate caregiver elicits an approach response to the caregiver rather than an aversion [27-28]. Abusive caregiving also elicits attachment in non-human primates [138-141].

The ability of young pups to learn an attachment to an abusive caregiver is likely related to the suppression of learning systems that would enable pups to fear or avoid their caregiver. For example, fear of predators, cued-fear conditioning, inhibitory conditioning, and passive avoidance do not functionally emerge until after the sensitive period has terminated at PN10 [69,77-80,142-154]. For example, the fear-conditioning paradigm of odor-shock (0.5mA shock) conditioning produces a paradoxical odor preference in young rat pups (less than 10 days of age, i.e. sensitive period) despite an apparent pain response [45,147-151]. The same paradigm produces an odor aversion in pups older than PN10 signaling the end of the sensitive period for attachment learning and the emergence of adult-like fear learning [45,69,79,148].

Evidence suggests that the absence of amygdala plasticity is responsible for the paradoxical response to aversive stimuli during the sensitive period [15,45,79,148,153,154]. In adult animals, the amygdala is the brain area responsible for fear learning in both conditioning and natural fear paradigms [155-168]. In contrast, the amygdala does not exhibit learning associated plasticity during laboratory or natural fear paradigms in infant rat pups less than PN10 [79,80,153,169,170]. In these sensitive-period pups, odor-0.5mA shock conditioning supporting odor preference learning is unaltered by pharmacological suppression of the amygdala and initially suggested to us that the amygdala may simply be too immature to support fear learning. Indeed, peak neurogenesis in the amygdala begins in the first week of

life, yet the functional development of the amygdala extends into adolescence [171-179]. Synaptic development begins around PN5, with a protracted increase between PN10-20, and an adult-like synaptic profile is not reached until early adolescence [163,171]. Long-term synaptic plasticity (LTP) induced in the adult basolateral amygdala does not emerge until the end of the attachment learning sensitive period [180].

Thus, infant odor-shock conditioning activates the same brain circuitry as appetitive learning paradigms using milk, warmth, or stroke (olfactory bulb, anterior piriform cortex, LC), and requires the absence of amygdala plasticity, unlike in the adult. These data suggest that instead of being an immature adult prototype, the unique infant learning circuitry has been conserved by evolution to support attachment to the caregiver. Many animals including humans form attachments to abusive caregivers at all costs in order to survive [181,182].

It may be important to mention that infants can learn aversions under some circumstances. Infant rats are able to learn to avoid odors if paired with malaise, such as that produced by a lithium chloride (LiCl) injection or 1.2 mA shock [183-204]. Interestingly, while in adult and pre-weaning rats the amygdala responds to odor-malaise conditioning [205], but in infants, odor-malaise uses a non-amygdala neural circuit for odor aversion learning [200,201]. Another remarkable constraint exists on aversion learning during infancy: if neonatal rats are nursing during odor/taste-LiCl conditioning, this produces a learned odor preference or blocks taste learning [200,201,206-208].

In summary, data indicate that infants do not readily learn aversions, and we attribute this to unique neural circuitry optimized to facilitate attachment to the caregiver. In Figure 1, we illustrate our current understanding of this early social attachment circuit. Next, we review how this circuitry changes to transition the developing animal from attachment learning to learning that can accommodate both learned preferences and aversions. Indeed, as will be discussed in the next sections, the sensitive period can be altered to support fear learning simply by elevating corticosterone (CORT), and older pups can have their sensitive period learning reinstated by lowering CORT, which can be done naturalistically dependent upon the mother's presence or absence.

CORT controls the age limits for the sensitive period for attachment learning

The emergence of fear learning signals the end of the attachment sensitive period and coincides with delayed stress-induced CORT release in infants. Before we describe the role of CORT in pup attachment learning, some unique features of their stress system will be described. Early in the rat pups' life CORT basal levels are relatively low and most stressors do not induce CORT release, a development period known as the stress hyporesponsive period (SHRP) [209-218]. Maternal sensory stimulation during nursing or grooming maintains pups' low CORT levels [39,219-222]. In fact, maternal separation (greater than a few hours) deprives the pup of the regulating sensory stimuli from the mother and increases CORT levels, while return of maternal stimulation is able to return pups CORT to normal low levels. As pups' SHRP ends around PN10, stressful stimuli increase pups' CORT levels, although the presence of the mother can greatly attenuate CORT levels. This attenuation of CORT levels by maternal presence is referred to as 'social buffering' and occurs in many different animal species, including humans [52-56,221,222]. This reduced stress reactivity is hypothesized to protect the developing organism from stress hormones' negative effects [223-229]. Indeed, high levels of CORT administered to the neonatal rat affects growth, brain size, neuroendocrine function, and cellular structure and formation.

CORT plays a modulatory role in adult fear and avoidance conditioning by increasing or decreasing learning strength [229-230]. However, CORT has a direct impact on infant conditioning by switching whether infants will learn avoidance or attachment. Specifically,

increasing CORT by systemic injections or by intra-amygdala infusions in pup during either fear conditioning or presentation of a predator odor is sufficient to produce an amygdala-dependent fear response, further indicating pain threshold is not a variable in pups' emergence of fear learning [45,72,147-149,151,153,231]. At PN10, pups have a sufficient endogenous level of stress-induced CORT to permit amygdala plasticity and fear. In these older pups (PN10 to PN15), reducing CORT levels through social buffering (maternal presence) or intra-amygdala receptor CORT blocker prevents fear learning and reinstates attachment learning through prevention of the participation of the amygdala in learning [105,148,200]. Since this effect of maternal presence lowering CORT to prevent fear learning is only possible through PN15, this limit defines a transitional sensitive period that follows the sensitive period for attachment learning [105]. Thus, the age range for increase in CORT to terminate attachment learning in the infant rat pup is 6 through 15 days of age [105]. We suggest that this age limit protects pups from learning an aversion to the maternal odor while pups are dependent on maternal care and ends after weaning when survival outside the nest is possible. We also suggest that 5 day old pups and younger do not have an amygdala sufficiently mature to support avoidance learning [171-179].

As illustrated in Figure 2, the mechanism for the mother's presence (social buffering) to change pup learning appears to be at the level of the hypothalamic paraventricular nucleus (PVN), a brain area critical for initiating the action of the Hypothalamic-Pituitary-Adrenal (HPA) axis. Specifically, the PVN appears to coordinate the diverse neural input from different types of stressors. While the PVN receives input from different neurotransmitters, from different brain areas, NE is a major player in controlling this brain area [232-233]. Social buffering, at least in rats, results in attenuation of PVN neural activity and suppression of PVN NE release. This was demonstrated in pups during the Transitional Sensitive Period age (PN12-14) where suppression of PVN NE release blocked CORT to promote attachment learning even during fear conditioning [45]. Additionally, microinfusions of NE into the PVN initiates fear learning even in the presence of the mother [45]. In an adult rat during stress, the main source of the NE in the PVN is derived from ascending brain stem pathways (A1, A2, with smaller amounts from the LC), however we do not yet have this information in infant rat pups. Together these data represent a transitional period of pups' continued dependence upon maternal presence inside the nest, while enabling fear as an adaptive mechanism to transition to life outside the nest.

The relationship between the mother and pup is reciprocal and the pups can also influence the mother's CORT level, although in the opposite direction [234-236]. That is, the mother has a robust stress response with the pups and a stress hyporesponsive state while away from her pups. The ability of social stimuli to control CORT is similar in both the mother and infant via modulation of NE in the PVN. The robust stress response mounted by the mother presumably enables the mother to protect her pups, such as occurs with maternal aggression.

To summarize, during the early attachment period or in older pups with maternal presence, pups do not mount a CORT response to pain (i.e., shock), which prevents amygdala plasticity, and ultimately prevents the pups learning fear. The ability of CORT levels to turn on and off the pups' fear system may inhibit fear when in the nest, but permit fear when pups are old enough to explore outside the nest. Indeed, crawling transitions to walking just at the age pups begin to mount a CORT response (PN10).

Long-term consequences of early-life environment

Learning during early life is important to subsequent behavior in the adult rat. For example, the learned maternal odor leaves a lasting trace throughout the lifespan, although the role of the conditioned odor in modifying behavior changes from that used during infancy (attachment to the mother) to that used during adulthood (adult mate preference and

parenting) [95,237,238]. Furthermore, recent work from our lab suggests that similar enduring, depressive-like effects and social behavior deficits are produced by repeated odor-shock conditioning and by rearing pups with a maltreating mother, although these effects are most pronounced in adulthood [24,72,237]. The conditioned odors (the odor used in odor-shock conditioning) also evoke enhanced neural responses in the olfactory bulb and attenuated amygdala activation in the adult, which are aspects of pups' unique neural response to the maternal odor [237,238].

This early life learning compliments the more general effects of the early environment in the regulation of behavior throughout the lifespan, which has long been recognized in clinical and experimental studies [239-251]. Indeed, sensory stimulation from the mother during development is a necessary component in shaping healthy adult cognition and emotion in rodents, nonhuman primates, and humans [36-40,140,141]. More recent studies, including our own, which involve manipulations of the early environment are providing a clear understanding of how early stress and trauma may have a lasting effect on adult behavior. For example, the maternal deprivation or maternal separation paradigm, which is a model of infant neglect, removes pups from the nest for an extended period of time (3 to 24 hours) either once or multiple times during the first and second postnatal weeks. The maternal separation procedure - also viewed as deprivation of multiple sensory stimuli from the mother - has been shown to regulate pups' CORT, although it has ubiquitous effects. Rat pups' initial behavioral responses to maternal separation consist of increased behavioral activity and vocalizations, including ultrasonic vocalization and increased activity, which likely attract the mother [252-254]. The initial responses can be greatly attenuated if pups are provided with adequate warmth and a source of maternal odor. However, within a few hours of separation, the HPA axis is engaged and CORT increases as a result of increases in adrenocorticotropic hormone (ACTH) that control the stress response at the level of the pituitary, although there are additional ubiquitous effects throughout the brain. This disruption in the HPA axis and its immediate and enduring effects on the brain and behavior has clearly indicated the important role of stress hormones in organizing emotional and cognitive development, although there are likely multiple ways of altering normal brain development. Specifically, maternal separation effects gene expression, glucocorticoid receptors, neural function (i.e., LTP), and the long-term susceptibility to stress-related diseases [239-251]. Thus, research using naturalistic environmental stimuli has greatly expanded our understanding of the potential CORT related mechanisms using different levels of analysis and has provided a stronger link between clinical and basic research.

Clinical implications of early attachment learning

The clinical literature suggests that the infant's relationship to the caregiver is important in shaping human behavior and the trajectory of brain development. The individual that experiences early abuse or neglect has a greater probability of psychopathological disorders, although access to at least one strong positive figure has been shown to dramatically decrease this risk [1,255]. For example, the Bucharest Early Intervention Project provides a long-term study on the effects of institutionalization on cognitive abilities and brain function in young children and the benefits of early intervention (less than 2 years old). These studies have highlighted a sensitive period for attachment in early life and the unique window of opportunity to repair early life effects of a deprived, harsh environment [255-260]. These results greatly enhance our understanding of clinical and basic research studies, although the effects of social deprivation and abuse within the attachment dyad and non-attachment related trauma may have different clinical outcomes [261]. The long-term effects of these clinical studies have been highlighted with brain imaging research showing that these early adverse events are correlated with aberrant adult brain functioning, most notably in the limbic system, frontal cortex, and cerebellum [262-271]. Although the neurobiological

effects of abuse from the caregiver are still not well understood, especially with respect to neural circuitry, overall the clinical work suggests that both mental and physical health during childhood are affected with strong convergence of data across species and studies, and this pattern continues through adolescence into adulthood.

In this review, we have outlined some neural and behavioral properties of infant attachment that go beyond its support of proximity-seeking and attachment behaviors. These unique features suggest that the infant rat's attachment circuit is not simply due to the absence or immaturity of neural structures but rather to its unique characteristics, producing an infant brain that has optimized attachment to the caregiver. There is some evidence that an attachment circuit may exist in the child's brain, which was originally discussed by Bowlby [1] but this may be difficult to identify and test in children. Bowlby's original attachment theory was strongly based on a vast integration of clinical observations and pioneering research on mother-infant relations in animals and imprinting [25-27,138,272-274]. It should be noted that the paradigm shifting work in the Bucharest Early Intervention Project [255-260] and its use of rigorous controls, has provided evidence of a sensitive period for attachment ranging from the first to third year of life depending on the behavioral neural system being studied and the age measured. While the details of the neural circuitry and timing of attachment are still unclear in human children, the rat pup model system may provide a greater understanding of the neurobiology of attachment and secure a foundation for the exploration of unique qualities of neural structures during early life. Additionally, the rat pup model of attachment can be used to identify the critical role of social interactions in infancy for the ability to test normal processing of sensory stimuli and learning at the earliest moments of postnatal life.

Acknowledgments

This work was supported by grants NIH-DC009910, NIH-MH091451, NSF-IOB0850527/0544406 to RMS.

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Sensitive Period for ATTACHMENT Learning
birth to PN9

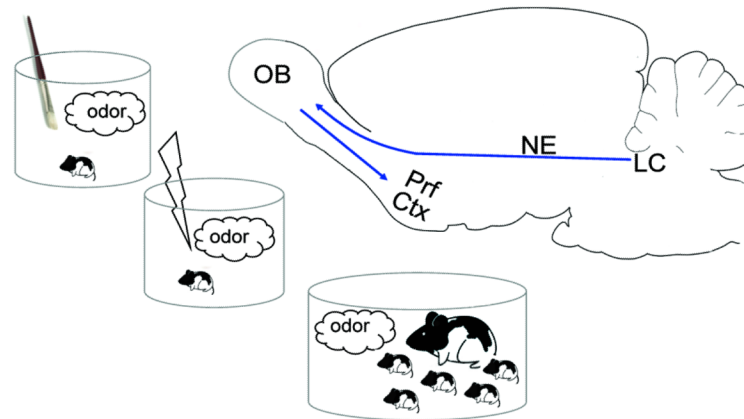


Figure 1.

Young infant rat pups very rapidly learn a new maternal odor. This learning is supported by a wide range of stimuli functioning as a reward that when paired with an odor results in the acquisition of a new maternal odor. For example, a novel odor paired with either tactile stimulation (mimics maternal licking), a mildly painful 0.5 mA shock/tailpinch (mimic mother stepping on pups/handling them roughly), or maternal care produces a new maternal odor. This learning is supported by a simplistic neural circuit (blue arrows) that requires the pairing of the novel odor with increased locus coeruleus (LC) norepinephrine (NE) release into the olfactory bulb (OB). Learning induced changes are found in the OB and anterior piriform cortex (Prf Ctx). At around PN (postnatal day) 10, functional emergence of the LC recurrent collaterals stimulate alpha-2 postsynaptic receptors, which terminate LC firing and provide insufficient levels of NE to the olfactory bulb to support the plasticity required for learning the new maternal odor [64,65,79-81,85,100-118,148].

Transitional Sensitive Period for ATTACHMENT Learning PN10 to PN15

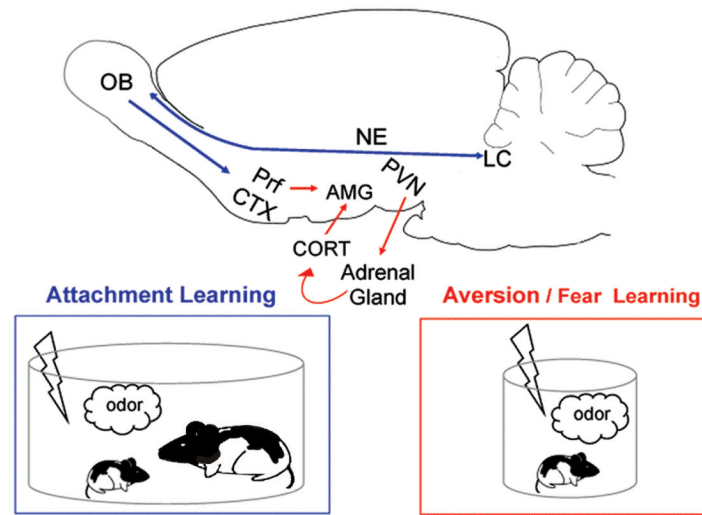


Figure 2.

As pups mature and begin to make brief trips outside the nest, attachment learning only occurs if the mother is present. Pups appear to use the same attachment learning circuitry used during the sensitive period when with the mother. Away from the mother, the more adult-like amygdala-dependent (AMG) fear learning system emerges. Pups' ability to switch between these two learning systems is due to emerging systems: 1) shock begins to induce increased release of the stress hormone corticosterone (CORT) at around PN10, which supports aversion/fear learning and 2) maternal presence blocks this shock-induced CORT release, which prevents amygdala plasticity and reinstates the attachment learning. Maternal presence (anesthetized) blocks adrenal gland CORT release by blocking NE into the paraventricular nucleus (PVN). By 16 days old, maternal presence does not block amygdala-dependent fear learning. The attachment neural circuitry is illustrated in blue and the aversion/fear learning circuitry is illustrated in red [15,24,45,79,137,148,169,153,180,200,201].