Published in final edited form as:
Dev Psychobiol. 2005 November ; 47(3): 230–242.

Neurobiology of Infant Attachment

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Abstract

A strong attachment to the caregiver is critical for survival in altricial species, including humans. While some behavioral aspects of attachment have been characterized, its neurobiology has only recently received attention. Using a mammalian imprinting model, we are assessing the neural circuitry that enables infant rats to attach quickly to a caregiver, thus enhancing survival in the nest. Specifically, the hyper-functioning noradrenergic locus coeruleus (LC) enables pups to learn rapid, robust preference for the caregiver. Conversely, a hypo-functional amygdala appears to prevent the infant from learning aversions to the caregiver. Adult LC and amygdala functional emergence correlates with sensitive period termination. This study suggests the neonatal brain is not an immature version of the adult brain but is uniquely designed to optimize attachment to the caregiver. Although human attachment may not rely on identical circuitry, the work reviewed here suggests a new conceptual framework in which to explore human attachments, particularly attachments to abusive caregivers.

Keywords

mother-infant interactions; olfactory bulb; norepinephrine; attachment; imprinting; locus coeruleus; amygdala; learning; classical conditioning; abuse; corticosterone; sensitive period; stress

INTRODUCTION

The powerful influences of infant experiences on adult life are well established with strong support from both clinical and basic research, beginning with Freud. More recently, the psychiatrist John Bowlby proposed that infant relationships define future relationships and stressed the importance of understanding early attachment to the mother (Bowlby, 1965). He characterized human infant attachment in a specific, defined framework that permitted testing in an experimentally refined protocol easily applied to humans. Beyond that, his characterization of attachment is relevant throughout the animal kingdom. First, Bowlby noted that infants rapidly form an attachment to the caregiver. The classic example is imprinting in chicks, although human infants can also rapidly learn about the mother during the hours following birth (DeCasper & Fifer, 1980). Second, Bowlby noted infants undergo considerable abuse while remaining attached to the caretaker. In the avian model of imprinting, chicks will continue to follow their mother during the imprinting period even while being shocked (Hess, 1962; Salzen, 1970). Naive post-critical period chicks (only hours older) are quickly able to learn an aversion to a surrogate mother when given similar shock presentations. A similar experiment in young dogs showed that puppies will learn a strong attachment to a handler providing shock or rough treatment (Fisher, 1955; cited in Rajecki, Lamb, & Obmascher, 1978). This phenomenon extends to primates. The Harlows (1965) showed that nonhuman

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Contract grant sponsor: NICHD-HD33402
Contract grant sponsor: NSF-IBN0117234

primate infants of abusive mothers still exhibited strong attachment, and recent work on a colony of abusive nonhuman primates shows similar results (Maestripieri, Tomaszycki, & Carroll, 1999; Sanchez, Ladd, & Plotsky, 2001). Moreover, human children, even those abused by their caregiver, generally exhibit a strong attachment to that caregiver (review—Helfer, Kempe, & Krugman, 1997). We have hypothesized that this attachment system may have evolved to ensure that altricial animals easily form a repertoire of proximity-seeking behaviors to the primary caregiver, regardless of the quality of the care they receive (Hofer & Sullivan, 2001).

In general, altricial species rely, at least to some extent, on learning about the mother to form attachment. This is exemplified in the avian imprinting model with its temporally defined sensitive period when the learning process is rapid and robust, although sensitive periods can be found in many species during developmental stages critical for survival. For example, postpartum animals quickly learn about their offspring; animals learn to identify their mate and, and as described here, infants learn about their caregiver (Brennen & Keverne, 1997; Insel & Young, 2001; Marlier, Schaal, & Soussignan, 1998; Moffat, Suh, & Fleming, 1993; Okere & Kaba, 2000).

Mammalian Imprinting Model

To assess the neurobiology of infant attachment, we have developed an infant rat model that conforms to the characteristics of attachment initially described by Bowlby. First, Bowlby stated that the infant rapidly forms an attachment to the caregiver. As illustrated in Figure 1 (top), neonatal rats very rapidly and easily learn an odor preference, although learning becomes more adult-like after postnatal day (PN) 10 (lower Fig. 1). We modeled this rapid odor learning outside the nest using a classical conditioning paradigm in which a novel odor was paired with a positive stimulus such as stroking (left Fig. 1; Pedersen, Williams, & Blass, 1982;Sullivan, Brake, Hofer, & Williams, 1986a;Sullivan, Hofer, & Brake, 1986b). This learning occurs naturally in the nest to the maternal odor, although the preference can also be acquired to a novel odor applied to the mother (Galef & Kaner, 1980;Roth & Sullivan, 2005;Sullivan, Wilson, Wong, Correa, & Leon, 1990;Terry & Johanson, 1996). Rapid odor learning may be a critical component of the altricial rat's survival because a newborn rat has limited sensory input (olfactory, somatosensory) and depends on learning its mother's odor for approach to the mother and nipple attachment (Polan & Hofer, 1999;Shair, Masmela, Brunelli, & Hofer, 1997). This period of unique odor learning ends at PN 10 and is called the sensitive period (Sullivan, Landers, Yeaman, & Wilson, 2000a; see lower Fig. 1 where learning is more adult-like). The second attachment characteristic defined by Bowlby is that infants will undergo considerable abuse while remaining attached to the caretaker. As is illustrated in Figure 1 (right, top), neonatal (PN6) rat pups learn to approach an odor even after pairing that odor with a painful stimulus (0.5 mA shock), although older (PN12; lower right) pups easily learn to avoid an odor paired with shock on the previous day (Sullivan et al., 2000a). Specifically, using a classical conditioning paradigm, pups exposed to an odor while receiving either a shock (0.5 mA) or tail pinch subsequently express a preference for that odor (Camp & Rudy, 1988;Moriceau & Sullivan, 2004b;Sullivan et al., 1986a,b,2000a). This shock-induced learning and preference acquisition is not due to pups' inability to feel pain, since shock threshold varies little during this period of development (Barr, 1995;Emerich, Scalzo, Enters, Spear, & Spear, 1985;Stehouwer & Campbell, 1978;Sullivan et al., 2000a).

While shock-induced preference acquisition may appear paradoxical, it may have developed to prevent pups from learning an aversion to the mother when being handled roughly in the nest. Indeed, rough treatment of pups by the mother is common in the nest. Mothers frequently step on pups when entering and leaving the nest or retrieve pups by a leg rather than at the nape of the neck. During these painful interactions, pups emit vocalizations associated with pain

(Hofer, 1996). The benefits of a system preventing pups from learning an aversion to the mother are obvious since pups need to exhibit approach behaviors to procure the mother's milk, warmth, and protection. Thus, in the altricial rat pup, the neonatal learning system seems specifically designed for attachment and is expressed behaviorally as an enhanced ability to acquire learned odor preferences and a decreased ability to acquire learned odor aversions (reviews—Hofer & Sullivan, 2001; Sullivan, 2001, 2003).

It should be noted that neonatal rats are able to learn aversive conditionings if an odor is paired with malaise (> 1.0 mA-strong shock or LiCl), since pups easily learn about interoceptive but not exteroceptive cues (Campbell, 1984; Haroutunian & Campbell, 1979; Miller, Molina, & Spear, 1990; Rudy & Cheatle, 1977, 1978; Spear, 1978; Spear & Rudy, 1991). However, while odor illness associations are easily learned by pups away from the mother, this learning is diminished if LiCl conditioning is done while pups are suckling (Martin & Alberts, 1979; Melcer, Alberts, & Gubernick, 1985).

During the sensitive period (PN1–9, age when pups show enhanced preference learning and attenuated aversion learning), neonatal rats are confined to the nest. It is appropriate to learn only preferences, not aversions, in a situation where only the mother and other pups are encountered. However, as the sensitive period terminates around PN10, walking develops and the probability of leaving the nest greatly increases (Bolles & Woods, 1965). At this stage of development, pups require a more complex learning system more suited to the extra-nest environment. As illustrated in Figure 1 (lower, PN12), the more mobile pup is more adult-like, with a discriminating learning system to deal with the increasingly complex environment. Specifically, aversions are more easily learned and odor preferences are less easily learned, enabling pups to deal more appropriately with stimuli outside the nest. As is reviewed below, the pup's learning circuitry appears to show remarkable correspondence to its changing behavioral needs as its mobility increases.

Long-Term Importance of Odors Learned in Infancy

In rats, early attachment-related odors appear to retain value into adulthood, although the role of the odor in modifying behavior changes from that used during infancy (attachment to the mother) to that used in adulthood (reproduction). Work done independently in the labs of Celia Moore (Moore, Jordan, & Wong, 1996) and Elliot Blass (Fillion & Blass, 1986) demonstrated that adult male rats exhibited enhanced sexual performance when exposed to the odors experienced in infancy. These results are consistent with observations in other species on the influence of early experience on adult mate preference, such as avian imprinting (Slagsvold, Hansen, Johannessen, & Lifjeld, 2002; Ten Gate & Vos, 1999).

Neural Circuitry Underlying Neonatal Attachment Learning

It is curious that neonatal rats can be classically conditioned, since brain areas known to be important in adult learning may not yet be functional (e.g., amygdala, hippocampus, frontal cortex; Fanselow & Rudy, 1998; Nair & Gonzalez-Lima, 1999; Rudy & Morledge, 1994; Sananes & Campbell, 1989; Stanton, 2000; Sullivan et al., 2000a; Verwer, Van Vulpen, & Van Uum, 1996). Thus, the infant rat must use a different learning circuit from adults, presumably one designed through evolution to provide rat pups with the neural circuitry required to survive and optimize attachment to a caregiver (Hofer & Sullivan, 2001). Three brain structures have been shown to have a role in the neonatal rat's sensitive period for heightened odor learning: the olfactory bulb, the noradrenergic locus coeruleus (LC), and the amygdala. The adult circuit for odor learning appears more complex and includes the olfactory bulb, piriform cortex, hippocampus, amygdala, and orbitofrontal cortex (Hess, Gall, Granger, & Lynch, 1997; Ramus & Eichenbaum, 2000; Roullet, Datiche, Lienard, & Cattarelli, 2004; Schettino & Otto, 2001;

Schoenbaum, Chiba, & Gallagher, 1999; Sevelinges, Gervais, Messaoudi, Granjon, & Mouly, 2004; Tronel & Sara, 2002).

Olfactory Bulb

In sharp contrast to learning in adult rats, neonatal odor learning produces changes in the olfactory bulb. The bulb is a simple structure with functional cell groupings called glomeruli that are intermediary between the input from the receptors on the olfactory nerve and the output via mitral cell dendrites. The glomerulus response in neonatal rats to an odor is modified after learning, with a corresponding change in the output signal of the olfactory bulb via the mitral cells. Importantly, this learning-induced olfactory bulb change occurs both naturally in the nest and in controlled learning experiments (McLean, Harley, Darby-King, & Yuan, 1999; Moriceau & Sullivan, 2004b; Sullivan & Leon, 1986; Sullivan et al., 1990; Wilson, Sullivan, & Leon, 1987; Yuan, Harley, & McLean, 2003; Yuan, Harley, McLean, & Knopfel, 2003; Yuan, Mutoh, Debardieux, & Knopfel, 2004; Zhang, Okutani, Inoue, & Kaba, 2003). As with the behavioral changes in attachment, the olfactory bulb neural changes described here are retained into adulthood and their acquisition is dependent upon experiences during infancy (Pager, 1974; Woo & Leon, 1988).

Recordings of mitral cells during learning indicate that the excitatory response of mitral cells to the CS odor continues throughout learning in the paired group (odor-reward), but habituation occurs in the control groups (Wilson & Sullivan, 1992). Molecular events within mitral cells during learning may provide insight into how the olfactory bulb response to the learned odor is permanently changed (McLean et al., 1999; Yuan et al., 2003; Zhang et al., 2003). Within minutes of acquisition, cAMP levels, induced by neurotransmitters binding, increase CREB phosphorylation (pCREB) and lead to changes in protein synthesis that allow a long-term CS-UCS association trace to form in mitral cells (Fig. 2). Research by the McLean and Harley group shows that manipulation of CREB directly alters learning induced molecular events; mutant CREB mice (too little CREB) fail to learn. This learning-induced cascade of molecular events has been identified in a wide variety of species across development, suggesting that the molecular biology underlying memory storage is highly conserved across both development and species (Carew, 1996; Carew & Sutton, 2001; Kandel, 2001; Rankin, 2002). However, while learning-induced intracellular events appear unchanged with development, as outlined here, the neural circuitry involved in olfactory memory shows marked changes with development.

Locus Coeruleus (LC)

The LC is a pontine nucleus and the sole source of norepinephrine (NE) for the olfactory bulb (McLean & Shipley, 1991; Shipley, Halloran, & De la Torre, 1985). In sharp contrast to the role of NE in neonatal learning, the LC is not necessary for adult learning, although NE enhances or attenuates memories during consolidation in adults (Roozendaal, Nguyen, Power, & McGaugh, 1999). In the neonate, the NE from the LC is both necessary and sufficient for neonatal learning. Related experiments found that an odor preference can be rapidly acquired by activation of olfactory bulb NE β-receptors with isoproterenol paired with odor stimulation (Langdon, Harley, & McLean, 1997; Sullivan, Zyzak, Skierkowski, & Wilson, 1992) or by direct stimulation of the LC, the source of olfactory bulb NE (Sullivan, Wilson, Lemon, & Gerhardt, 1994; Sullivan, Stackenwalt, Nasr, Lemon, & Wilson, 2000b). Moreover, destroying the LC or preventing olfactory bulb NE receptor binding prevents neonatal odor learning (Sullivan et al., 1992, 2000b). While many other neurotransmitters have a role in neonatal rat learning, NE appears particularly important in learning-induced neural plasticity in development (dopamine-Weldon, Travis, & Kennedy, 1991; Zhang, Okutani, Yagi, Inoue, & Kaba, 2000; serotonin-McLean, Darby-King, Sullivan, & King, 1993;McLean et al., 1999;

Yuan et al., 2003; GABA-Okutani, Zhang, Yagi, & Kaba, 2002; Okutani, Zhang, Otsuka, Yagi, & Kaba, 2003; and opiates-Barr & Rossi, 1992; Kehoe & Blass, 1986; Roth & Sullivan, 2001, 2003). For example, within the olfactory bulb, NE is required for the maintenance of the prolonged mitral cell response necessary for acquisition of an odor preference and olfactory bulb learning-induced changes (Wilson & Sullivan, 1991). A similar role for NE appears to reemerge in adult olfactory learning critical for survival, such as mating and infant care (Brennen & Keverne, 1997; Fleming, O'Day, & Kraemer, 1999; Moffat et al., 1993; Okere & Kaba, 2000).

The LC's changing role in learning appears to be caused by developmental changes in the LC. Neonates show prolonged excitation of the LC and it releases enormous amounts of NE compared to the level released after the sensitive period (Rangel & Leon, 1995). This decrease in NE release is controlled by functional changes in the maturing LC: (1) inhibitory α2 noradrenergic autoreceptors become functional and quickly terminate the LC's excitatory responses to stimuli; (2) LC excitatory α1 autoreceptor function becomes limited and no longer temporally extends the LC's response to sensory stimuli; and (3) decreases in electronic coupling of LC neurons limits the coordination of LC neuron firing (Marshall, Christi, Finlayson, & Williams, 1991; Nakamura & Sakaguchi, 1990; Nakamura, Kimura, & Sakaguchi, 1987; Winzer-Serhan & Leslie, 1999). Given these observations, we hypothesize that the hyperactivation of the LC before PN10 is responsible for enhanced odor preference learning, and that maturation of the LC signals the termination of the sensitive period for learning in rat pups.

Support for the role of the maturing LC terminating the sensitive period comes from a recent experiment from our lab (Moriceau & Sullivan, 2004a). As illustrated in Figure 3, the sensitive period for olfactory learning was reinstated after the sensitive period had terminated by recreating the autoreceptor characteristics of the neonatal LC. Specifically, a relative odor preference was acquired by PN 14 pups (post-sensitive period) when an odor was paired with LC pharmacological manipulations that reinstated the LC's sensitive period low autoinhibition and high autoexcitation. This was done through activation of the LC by acetylcholine concurrently with the blockade of LC inhibitory autoreceptors (α2 antagonist, idazoxan) and activation of the LC excitatory autoreceptors (α1 agonist, phenylephrine) during an odor presentation. These data strongly suggest that the sensitive period, at least in part, is terminated through functional autoreceptor changes within the LC. Furthermore, these data also suggested that the olfactory bulb remains plastic in post-sensitive period pups since simply changing the LC autoreceptors (i.e., changing endogenous NE levels) was sufficient to induce an odor preference. We addressed this issue further by directly increasing olfactory bulb NE in post-sensitive period pups and again found odor preference conditioning. Specifically, an odor associated with bilateral olfactory bulb infusions of an NE β-receptor agonist produced a conditioned approach to that odor even after the end of the normal sensitive period. It should be noted that the olfactory bulb is still developing during the neonatal period (Guthrie & Gall, 2003; Malun & Brunjes, 1996).

Amygdala

In the adult rat, the amygdala is important for the acquisition of the odor-shock induced odor aversion called conditioned fear (Cahill, McGaugh, & Weinberger, 2001; Fanselow & Gale, 2003; Fanselow & LeDoux, 1999; Fendt & Fanselow, 1999; Maren, 2003; McGaugh, Cahill, & Roozendaal, 1999; Pape & Stork, 2003; Pare, Quirk, & LeDoux, 2004). Evidence suggests that the lack of a functional amygdala during neonatal odor-shock conditioning may underlie pups' difficulty in learning fear. First, behaviors associated with amygdala function emerge around PN10: inhibitory conditioning, passive avoidance and olfactory-conditioned aversions (Blozovski & Cudennec, 1980; Collier, Mast, Meyer, & Jacobs, 1979; Myslivecek, 1997;

Sullivan et al., 2000b). Second, amygdala lesions during the neonatal sensitive period (PN1–9) do not prevent the acquisition of an odor preference, although slightly longer training is required (Sullivan & Wilson, 1993). A similar lesion in the adult greatly retards fear conditioning, and the unique recovery traits of a neonatal amygdala cannot account for the dramatic differences in neonatal and adult amygdala lesions (Higley, Hermer-Vazquez, Levitsky, & Strupp, 2001; Maren, 1999). Third, the amygdala does not appear to participate in acquisition of odor-shock induced odor preference during the sensitive period (Fig. 4; Sullivan, 2001; Sullivan et al., 2000b). However, following the termination of the sensitive period, when odor-shock conditioning produces an odor aversion, the amygdala is involved in learning. Fourth, similarly to conditioned fear, unconditioned fear of natural odors does not emerge until PN10 when the amygdala begins to participate in the odor response (Takahashi, 1994; Wiedenmayer & Barr, 2001).

Immaturity of the amygdala may account for its lack of participation in neonatal sensitive period learning. Amygdala neurogenesis continues until PN14, although major nuclei subdivision occurs around PN7 (Bayer, 1980; Berdel & Morys, 2000; Berdel, Morys, & Maciejewska, 1997; Morys, Berdel, Jagalska-Majewska, & Luczynska, 1999). Synaptic development begins to appear around PN5 with a dramatic increase between PN10–20, reaching adult levels by PN30 (Mizukawa, Tseng, & Otsuka, 1989). Behavioral data on the development of amygdala-dependent behaviors suggest that sequential maturation of specific amygdala microcircuits may be important (Hunt & Campbell, 1999; Richardson, Paxinos, & Lee, 2002; Sananes, Gaddy, & Campbell, 1988). Specifically, freezing first emerges in the olfactory, auditory, and visual systems at PN10, 16, and 18 respectively. Learning ability for specific fear-related behaviors within a sensory system also emerges sequentially. In odor-fear conditioning, pups learn freezing, heart rate and startle at PN10, 15, and 21 respectively, whereas in visual fear conditioning, pups exhibit learned freezing, heart rate and startle at PN18, 23, and 30 respectively. Ontogenetic connectivity of the amygdala with motor-related neural areas may also play a role in the ontogenetic emergence of these learned behaviors.

The attenuation of odor aversion conditioning during the sensitive period may also be due to immature major neural connections between the amygdala and other brain areas important in conditioning. For example, amygdala-hippocampus connections are still undeveloped, and the primary cortical input to the hippocampus from the entorhinal cortex is still developing (Crain, Cotman, Taylor, & Lynch, 1973; Fanselow & Rudy, 1998; Nair & Gonzalez-Lima, 1999; Rudy & Morledge, 1994; Stanton, 2000). Furthermore, neonatal learning may not involve the cortex, and the frontal cortex is still undeveloped during this early neonatal period (Landers & Sullivan, 1999a,b; Verwer et al., 1996).

Sensitive Period Learning and the Hypothalamic-Pituitary-Adrenal Axis (HPA)

During stress, the adrenal gland can release corticosterone (CORT), but the early HPA system is limited in function, resulting in attenuated CORT release in response to shock during the neonatal sensitive period (Levine, 1962a). For example, while the adult rat responds to shock with a robust CORT response, the neonatal rat does not (Levine, 1962a, 2001; Van Oers, De Kloet, Whelan, & Levine, 1998). The attenuated neonatal CORT response appears to limit pups' ability to express unlearned fear (predator odor), learned odor aversions (also called conditioned fear), passive avoidance and inhibitory conditioning. These behaviors normally emerge at PN10–11 (the end of the sensitive period) but can be delayed or advanced ontogenetically simply by removing the source of CORT or by prematurely elevating CORT levels (Bialik, Pappas, & Roberts, 1984; Blozovski & Cudennec, 1980; Collier et al., 1979; review—Myslivecek, 1997;Takahashi, 1994; Takahashi & Rubin, 1993; Takahashi, Turner, & Kalin, 1991). Previous work has shown potent CORT effects on the neonatal LC, amygdala,

hippocampus, frontal cortex and HPA axis that last until adulthood using the maternal deprivation paradigm (Dent, Smith, & Levine, 2001; Eghbal-Ahmadi, Avishai-Eliner, Hatalski, & Baram, 1999; Francis, Caldji, Champagne, Plotsky, & Meaney, 1999; Swiergiel, Takahashi, & Kalin, 1993). While CORT has strong effects on adult memory formation, its role in adult learning appears to be modulatory (McGaugh & Roozendaal, 2002). These data suggest that stress during early infancy may be capable of modifying the neural systems underlying attachment and hence the adult functioning of these brain areas.

Recent data from our laboratory support the hypothesis that CORT levels are critical in determining characteristics of early odor learning. We used our paradoxical odor-shock (0.5 mA) conditioning paradigm that produces an odor preference during the sensitive period (Moriceau & Sullivan, 2004b). Specifically, we assessed the effects of manipulating CORT levels on learning during the sensitive period (PN8 pups had their normally low CORT levels increased) or post-sensitive period (PN12 pups had their CORT levels decreased by adrenal gland removal at PN8). As is illustrated in Figure 5, injections of CORT (3 mg/kg, ip) 30 min prior to PN8 conditioning prevented the learning of a shock-induced odor preference and prevented the acquisition of the olfactory bulb learning-induced neural (enhanced 2-DG uptake) changes. Moreover, PN12 CORT-depleted (by adrenalectomy) pups demonstrated shock-induced odor preference learning and acquisition of the olfactory bulb neural changes. CORT replacement in ADX PN12 pups enabled pups to learn a shock-induced odor aversion and prevented the olfactory bulb learning-induced changes. These data suggest that low levels of CORT are critical to ensure neonatal rat pups' attachment to their mother and that neonatal rat pups have unique learning abilities to ensure the olfactory-based attachment to the mother.

Furthermore, we were able to alter the developmental expression of unlearned fear (predator odor) through manipulations of the CORT system similar to those described previously (Moriceau, Roth, Okotoghaide, & Sullivan, 2004). As is illustrated in Figure 6, PN8 pups injected with CORT (3 mg/kg, ip) 30 min prior to presentation of adult male odor showed behavioral expression of fear through freezing and demonstrated activation of the basolateral complex of the amygdala (measured by Fos-positive cells). Also, PN12 CORT-depleting PN12 pups retard the normal expression of fear and the basolateral complex of the amygdalal does not appear to participate. These data suggest that low CORT levels block pups expression of fear (freezing) and attenuate amygdala activation.

Consequences for Adult Behavior

Early life experiences, including early attachment experiences, have an enormous impact on adult life in rodents, nonhuman primates, and humans (Denenberg, 1963; Harlow & Harlow, 1965; Levine, 1962b; Rosenzweig, Bennett, Diamond, Wu, Slagle, & Saffran, 1969; Schore, 2001). The documented overlap in brain areas associated with our attachment model, general early experiences, and later psychiatric problems strongly suggests that the neonatal effects are mediated through the LC, amygdala, cerebellum and HPA axis, as well as presumably nonfunctional neonatal rat brain areas such as the hippocampus and frontal cortex (Dent et al., 2001; Francis et al., 1999; Gutman & Nemeroff, 2002; Heim & Nemeroff, 2001; Kaufman, Plotsky, Nemeroff, & Charney, 2002; Levine, 2001; Perry, Pollard, Blakely, Baker, & Vigilante, 1995; Teicher et al, 1997). Together, these data suggest a potential mechanism for the enduring effects of early attachment on adult psychiatric wellness.

In summary, the present review outlines unique characteristics of neonatal learning that facilitate the infant rat's attachment to the mother. Specifically, pups exhibit enhanced preference learning and attenuated aversion learning. Considering the necessity of infant maternal odor preference learning for survival (nipple attachment, huddling, orientation), it is

beneficial for pups to quickly learn a preference for the maternal odor and block aversion learning that would interfere with pups' attachment to the mother.

This review also suggests that pups' unique neural circuitry underlying infant learning may have evolved to ensure infants rapid attachment to the mother. This circuitry is not simply due to the absence or immaturity of brain structures but rather to the brain having unique characteristics: the olfactory bulbs encode learning, the noradrenergic LC is both necessary and sufficient for the preference learning, and lack of amygdala participation underlies pups' attenuated aversion learning. This NE dependent learning is similar to the neural basis of other survival dependent behaviors in reproduction across species.

References

Barr GA. Ontogeny of nociception and antinociception. NIDA Research Monograph 1995;158:172–201. [PubMed: 8594484]

Barr GA, Rossi G. Conditioned place preference from ventral tegmental injections of morphine in neonatal rats. Developmental Brain Research 1992;66:133–136. [PubMed: 1600627]

Bayer SA. Quantitative 3H-thymidine radiographic analysis of neurogenesis in the rat amygdala. The Journal of Comparative Neurology 1980;194:845–875. [PubMed: 7204644]

Berdel B, Morys J. Expression of calbindin-D28k and parvalbumin during development of rat's basolateral amygdaloid complex. International Journal of Developmental Neuroscience 2000;18:501–513. [PubMed: 10884595]

Berdel B, Morys J, Maciejewska B. Neuronal changes in the basolateral complex during development of the amygdala of the rat. International Journal of Developmental Neuroscience 1997;15:755–765. [PubMed: 9402226]

Bialik RJ, Pappas BA, Roberts DC. Neonatal 6-hydroxydopamine prevents adaptation to chemical disruption of the pituitary-adrenal system in the rat. Hormones and Behavior 1984;18:12–21. [PubMed: 6323301]

Blozovski D, Cudennec A. Passive avoidance learning in the young rat. Developmental Psychobiology 1980;13:513–518. [PubMed: 7409331]

Bolles RC, Woods PJ. The ontogeny of behavior in the albino rat. Animal Behavior 1965;12:427–441.

Bowlby, J. Attachment. New York: Basic Books; 1965.

Brennen PA, Keverne EB. Neural mechanisms of mammalian olfactory learning. Progress in Neurobiology 1997;51:457–481. [PubMed: 9106902]

Cahill L, McGaugh JL, Weinberger NM. The neurobiology of learning and memory: Some reminders to remember. Trends in Neurosciences 2001;24:578–581. [PubMed: 11576671]

Camp LL, Rudy JW. Changes in the categorization of appetitive and aversive events during postnatal development of the rat. Developmental Psychobiology 1988;21:25–42. [PubMed: 3338626]

Campbell, BA. Reflections on the ontogeny of learning and memory. In: Kail, R.; Spear, NE., editors. Comparative perspectives on the development of memory. Hillsdale, NJ: Lawrence Erlbaum Associates; 1984. p. 23-35.

Carew TJ. Molecular enhancement of memory formation. Neuron 1996;16:5–8. [PubMed: 8562090]

Carew TJ, Sutton MA. Molecular stepping stones in memory consolidation. Nature Neuroscience 2001;4:769–771.

Collier AC, Mast J, Meyer DR, Jacobs CE. Approach-avoidance conflict in preweanling rats: A developmental study. Animal Learning and Behavior 1979;7:514–520.

Crain B, Cotman C, Taylor D, Lynch G. A quantitative electron microscopic study of synaptogenesis in the dentate gyrus of the rat. Brain Research 1973;63:195–204. [PubMed: 4764297]

DeCasper AJ, Fifer WP. Of human bonding: newborns prefer their mothers' voices. Science 1980;208:1174–1176. [PubMed: 7375928]

Denenberg VH. Early experience and emotional development. Scientific American 1963;208:138–146. [PubMed: 14026976]

Dent GW, Smith MA, Levine S. Stress-induced alterations in locus coeruleus gene expression during ontogeny. Developmental Brain Research 2001;127:23–30. [PubMed: 11287061]

Eghbal-Ahmadi M, Avishai-Eliner S, Hatalski CG, Baram TZ. Differential regulation of the expression of corticotropin-releasing factor receptor type 2 (CRF2) in hypothalamus and amygdala of the immature rat by sensory input and food intake. Journal of Neuroscience 1999;19:3982–3991. [PubMed: 10234028]

Emerich DE, Scalzo FM, Enters EK, Spear N, Spear L. Effects of 6-hydroxydopamine-induced catecholamine depletion on shock-precipitated wall climbing of infant rat pups. Developmental Psychobiology 1985;18:215–227. [PubMed: 3921418]

Fanselow MS, LeDoux JE. Why we think plasticity underlying Pavlovian fear conditioning occurs in the basolateral amygdala. Neuron 1999;23:229–232. [PubMed: 10399930]

Fanselow, MS.; Rudy, JW. Convergence of experimental and developmental approaches to animal learning and memory processes. In: Carew, TJ.; Menzel, R.; Shatz, CJ., editors. Mechanistic relationships between development and learning. New York: J. Wiley & Sons; 1998. p. 15-28.

Fanselow MS, Gale GD. The amygdala, fear, and memory. Annals of the New York Academy of Sciences 2003;985:125–134. [PubMed: 12724154]

Fendt M, Fanselow MS. The neuroanatomical and neurochemical basis of conditioned fear. Neuroscience Biobehavioral Review 1999;23:743–760.

Fillion TJ, Blass EM. Infantile experience with suckling odors determined adult sexual behavior in male rats. Science 1986;231:729–731. [PubMed: 3945807]

Fisher, AE. The effects of differential early treatment on the social and exploratory behavior of puppies. Doctoral Dissertation; Pennsylvania State University: 1955.

Fleming AS, O'Day DH, Kraemer GW. Neurobiology of mother-infant interactions: Experience and central nervous system plasticity across development and generations. Neuroscience and Biobehavioral Reviews 1999;23:673–685. [PubMed: 10392659]

Francis DD, Caldji C, Champagne F, Plotsky PM, Meaney MJ. The role of corticotropin-releasing factor-norepinephrine systems in mediating the effects of early experience on the development of behavioral and endocrine responses to stress. Biological Psychiatry 1999;46:1153–1166. [PubMed: 10560022]

Galef GG, Kaner HC. Establishment & maintenance of preference for natural and artificial olfactory stimuli in juvenile rats. Journal of Comparative and Physiological Psychology 1980;94:588–595. [PubMed: 7410624]

Guthrie KM, Gall C. Anatomic mapping of neuronal odor responses in the developing rat olfactory bulb. Journal of Comparative Neurology 2003;455:56–71. [PubMed: 12454996]

Gutman DA, Nemeroff CB. Neurobiology of early life stress: Rodent studies. Seminars in Clinical Neuropsychiatry 2002;7:89–95. [PubMed: 11953932]

Harlow, HF.; Harlow, MK. The affectional systems. In: Schrier, A.; Harlow, HF.; Stollnitz, F., editors. Behavior of nonhuman primates. 2. New York: Academic Press; 1965.

Haroutunian V, Campbell BA. Emergence of interoceptive and exteroceptive control of behavior in rats. Science 1979;205:927–929. [PubMed: 472715]

Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. Biological Psychiatry 2001;49:1023–1039. [PubMed: 11430844]

Helfer, ME.; Kempe, RS.; Krugman, RD. The battered child. Chicago: University of Chicago Press; 1997.

Hess, EH. Ethology: An approach to the complete analysis of behavior. In: Brown, R.; Galanter, E.; Hess, EH.; Mendler, G., editors. New directions in psychology. New York: Holt, Rinehart and Winston; 1962.

Hess US, Gall CM, Granger R, Lynch G. Differential patterns of c-fos mRNA expression in amygdala during successive stages of odor discrimination learning. Learning and Memory 1997;4:262–283. [PubMed: 10456068]

Higley MJ, Hermer-Vazquez L, Levitsky DA, Strupp BJ. Recovery of associative function following early amygdala lesions in rats. Behavioral Neuroscience 2001;115:154–164. [PubMed: 11256439]

Hofer MA. Multiple regulators of ultrasonic vocalization in the infant rat. Psychoneuroendocrinology 1996;21:203–217. [PubMed: 8774063]

Hofer, MA.; Sullivan, RM. Toward a neurobiology of attachment. In: Nelson, CA.; Luciana, M., editors. Handbook of developmental cognitive neuroscience. Cambridge, MA: MIT Press; 2001. p. 599-616.

Hunt, P.; Campbell, BA. Developmental dissociation of the components of conditioned fear. In: Bouton, ME.; Fanselow, MS., editors. Learning, motivation, and cognition: The functional behaviorism of Robert C Bolles. Washington, DC: American Psychological Association; 1999.

Insel TR, Young LJ. The neurobiology of attachment. Nature Reviews Neuroscience 2001;2:129–136.

Kandel ER. The molecular biology of memory storage: A dialogue between genes and Synapses. Science 2001;294:1030–1038. [PubMed: 11691980]

Kaufman J, Plotsky PM, Nemeroff CB, Charney DS. Effects of early adverse experiences on brain structure and function: Clinical implications. Biological Psychiatry 2002;48:778–790. [PubMed: 11063974]

Kehoe P, Blass E. Central nervous system mediation of positive and negative reinforcement in neonatal albino rats. Developmental Brain Research 1986;27:69–75.

Landers M, Sullivan RM. Vibrissae evoked behavior and conditioning before functional ontogeny of somatosensory vibrissae cortex. Journal of Neuroscience 1999a;19:5131–5137. [PubMed: 10366646]

Landers M, Sullivan RM. Norepinephrine and associative conditioning in the neonatal rat somatosensory system. Developmental Brain Research 1999b;114:261–264. [PubMed: 10320765]

Langdon PE, Harley CW, McLean JH. Increased 6 adrenoceptor activation overcomes conditioned olfactory learning induced by serotonin depletion. Developmental Brain Research 1997;114:261–264.

Levine S. Plasma-free corticosterone response to electric shock in rats stimulated in infancy. Science 1962a;135:795–796. [PubMed: 14464660]

Levine, S. The effects of infantile experience on adult behavior. In: Bachrach, AJ., editor. Experimental foundations of clinical psychology. New York: Basic Books; 1962b. p. 118-169.

Levine S. Primary social relationships influence the development of the hypothalamic-pituitary-adrenal axis in the rat. Physiology and Behavior 2001;73:255–260. [PubMed: 11438350]

Maestripieri D, Tomaszycki M, Carroll KA. Consistency and change in the behavior of rhesus macaque abusive mothers with successive infants. Developmental Psychobiology 1999;34:29–35. [PubMed: 9919431]

Malun D, Brunjes PC. development of olfactory glomeruli: Temporal and spatial interactions between olfactory receptor axons and mitral cells in opssums and rats. Journal of Comparative Neurology 1996;22:1–16. [PubMed: 8725290]

Maren S. Neurotoxic basolateral amygdala lesions impair learning and memory but not performance of conditioned fear in rats. Journal of Neuroscience 1999;19:8696–8703. [PubMed: 10493770]

Maren S. The amygdala, synaptic plasticity, and fear memory. Annals of the New York Academy of Sciences 2003;985:106–113. [PubMed: 12724152]

Marlier L, Schaal B, Soussignan R. Bottle-fed neonates prefer an odor experienced in utero to an odor experienced postnatally in the feeding context. Developmental Psychobiology 1998;33:133–145. [PubMed: 9742408]

Marshall KC, Christi MM, Finlayson PG, Williams JT. Developmental aspects of the locus coeruleus-noradrenaline system. Progress in Brain Research 1991;88:173–185. [PubMed: 1687618]

Martin LT, Alberts JR. Taste aversion to mother's milk: The age-related role of nursing in acquisition and expression of a learned association. Journal of Comparative and Physiological Psychology 1979;93:430–445. [PubMed: 479392]

McGaugh JL, Roozendaal B. The role of adrenal stress hormone in forming lasting memories in the brain. Current Opinions in Neurobiology 2002;12:205–210.

McGaugh, JL.; Roozendaal, B.; Cahill, L. Modulation of memory storage by stress hormones and the amygdaloid complex. In: Gazzaniga, M., editor. Cognitive neuroscience. 2. Cambridge: MIT Press; 1999.

McLean JH, Shipley MT. Postnatal development of the noradrenergic projection from the locus coeruleus to the olfactory bulb in the rat. Journal of Comparative Neurology 1991;304:469–477.

McLean JH, Darby-King A, Sullivan RM, King SR. Serotonergic influences on olfactory learning in the neonatal rat. Behavioral and Neural Biology 1993;60:152–162. [PubMed: 7906939]

McLean JH, Harley CW, Darby-King A, Yuan Q. pCREB in the neonate rat olfactory bulb is selectively and transiently increased by odor preference-conditioned training. Learning and Memory 1999;6:608–618. [PubMed: 10641765]

Melcer T, Alberts JR, Gubernick DJ. Early weaning does not accelerate the expression of nursing-related taste aversions. Developmental Psychobiology 1985;18:375–381. [PubMed: 4065427]

Miller JS, Molina JC, Spear NE. Ontogenetic differences in the expression of odor-aversion learning in 4- and 8-day-old rats. Developmental Psychobiology 1990;23:319–330. [PubMed: 2170214]

Mizukawa K, Tseng I-Ming, Otsuka N. Quantitative electron microscopic analysis of postnatal development of zinc-positive nerve endings in the rat amygdala using Timm's sulphide silver technique. Developmental Brain Research 1989;50:197–203. [PubMed: 2482140]

Moffat SD, Suh EJ, Fleming A. Noradrenergic involvement in the consolidation of maternal experience in postpartum rats. Physiology and Behavior 1993;53:805–811. [PubMed: 8390059]

Moore CL, Jordan L, Wong L. Early olfactory experience, novelty and choice of sexual partner by male rats. Physiology and Behavior 1996;60:1361–1367. [PubMed: 8916195]

Moriceau S, Sullivan RM. Unique neural circuit for neonatal olfactory learning. Journal of Neuroscience 2004a;24:1182–1189. [PubMed: 14762136]

Moriceau S, Sullivan RM. Corticosterone influences on mammalian neonatal sensitive period learning. Behavioral Neuroscience 2004b;118:274–281. [PubMed: 15113251]

Moriceau S, Roth TL, Okotoghaide T, Sullivan RM. Corticosterone controls the developmental emergence of fear and amygdala function to predator odors in infant rat pups. International Journal of Developmental Neuroscience 2004;22:415–422. [PubMed: 15380840]

Morys J, Berdel B, Jagalska-Majewska H, Luczynska A. The basolateral amygdaloid complex—Its development, morphology and functions. Folia Morphology 1999;58:29–46.

Myslivecek J. Inhibitory learning and memory in newborn rats. Progress in Neurobiology 1997;53:399–430. [PubMed: 9421830]

Nair HP, Gonzalez-Lima F. Extinction of behavior in infant rats: Development of functional coupling between septal, hippocampal, and ventral tegmental regions. Journal of Neuroscience 1999;19:8646–8655. [PubMed: 10493765]

Nakamura S, Kimura F, Sakaguchi T. Postnatal development of electrical activity in the locus coeruleus. Journal of Neurophysiology 1987;58:510–524. [PubMed: 3655880]

Nakamura ST, Sakaguchi T. Development and plasticity of the locus coeruleus. A review of recent physiological and pharmacological experimentation. Progress in Neurobiology 1990;34:505–526. [PubMed: 2202018]

Okere CO, Kaba H. Increased expression of neuronal nitric oxide synthase mRNA in the accessory olfactory bulb during the formation of olfactory recognition memory in mice. European Journal of Neuroscience 2000;12:4552–4556. [PubMed: 11122367]

Okutani F, Zhang JJ, Yagi F, Kaba H. Nonspecific olfactory aversion induced by intrabulbar infusion of the GABA(A) receptor antagonist bicuculline in young rats. Neuroscience 2002;112:901–906. [PubMed: 12088749]

Okutani F, Zhang JJ, Otsuka T, Yagi F, Kaba H. Modulation of olfactory learning in young rats through intrabulbar GABA(B) receptors. European Journal of Neuroscience 2003;18:2031–2036. [PubMed: 14622236]

Pager J. A selective modulation of olfactory bulb electrical activity in relation to the learning of palatability in hungry and satiated rats. Physiology and Behavior 1974;12:189–195. [PubMed: 4816076]

Pape HC, Stork O. Genes and mechanisms in the amygdala involved in the formation of fear memory. Annals of the New York Academy of Sciences 2003;985:92–105. [PubMed: 12724151]

Pare D, Quirk GJ, LeDoux JE. New vistas on amygdala networks in conditioned fear. Journal of Neurophysiology 2004;92:1–9. [PubMed: 15212433]

Pedersen P, Williams CL, Blass EM. Activation and odor conditioning of suckling behavior in 3-day-old albino rats. Journal of Experimental Psychology: Animal Behavior Process 1982;8:329–341.

Perry BD, Pollard R, Blakely T, Baker W, Vigilante D. Childhood trauma, the neurobiology of adaptation and 'use-dependent' development of the brain: How "states" become "traits". Infant Mental Health Journal 1995;16:271–291.

Polan, HJ.; Hofer, MA. Psychobiological origins of infant attachment and separation responses. In: Cassidy, J.; Shaver, PR., editors. Handbook of attachment: Theory, research, and clinical application. New York: Guilford Press; 1999. p. 162-180.

Rajecki DW, Lamb ME, Obmascher P. Towards a general theory of infantile attachment: A comparative review of aspects of the social bond. The Behavioral and Brain Sciences 1978;3:417–464.

Ramus SJ, Eichenbaum H. Neural correlates of olfactory recognition memory in the rat orbitofrontal cortex. Journal of Neuroscience 2000;20:8199–8208. [PubMed: 11050143]

Rangel S, Leon M. Early odor preference training increases olfactory bulb norepinephrine. Developmental Brain Research 1995;85:187–191. [PubMed: 7600666]

Rankin CH. A bite to remember. Science 2002;296:1624–1625. [PubMed: 12040169]

Richardson R, Paxinos G, Lee J. The ontogeny of conditioned odor potentiation of startle. Behavioral Neuroscience 2002;114:1167–1173. [PubMed: 11142648]

Roozendaal B, Nguyen BT, Power AE, McGaugh JL. Basolateral amygdala noradrenergic influence enables enhancement of memory consolidation induced by hippocampal glucocorticoid receptor activation. Proceedings of the National Academy of Sciences 1999;96:11642–11647.

Rosenzweig MR, Bennett EL, Diamond MC, Wu Y, Slagle RW, Saffran E. Influences of environmental complexity and visual stimulation on development of occipital cortex in rat. Brain Research 1969;14:427–445. [PubMed: 5794917]

Roth T, Sullivan RM. Endogenous opioids and their role in odor preference acquisition and consolidation following odor-shock conditioning in infant rats. Developmental Psychobiology 2001;39:188–198. [PubMed: 11745312]

Roth T, Sullivan RM. Consolidation and expression of a shock-induced odor preference in rat pups is facilitated by opioids. Physiology and Behavior 2003;78:135–142. [PubMed: 12536020]

Roth T, Sullivan RM. Memory of early maltreatment: Neonatal behavioral and neural correlates of maternal maltreatment within the context of classical conditioning. Biology Psychiatry 2005;57:823–831.

Roullet F, Datiche F, Lienard F, Cattarelli M. Cue valence representation studied by Pos immunocytochemistry after acquisition of a discrimination learning task. Brain Research Bulletin 2004;64:31–38. [PubMed: 15275954]

Rudy JW, Cheatle MD. Odor aversion learning in neonatal rats. Science 1977;198:845–846. [PubMed: 918668]

Rudy JW, Cheatle MD. A role for conditioned stimulus duration in toxiphobia conditioning. Journal of Experimental Psychology: Animal Behavior Process 1978;4:399–411.

Rudy JW, Morledge P. The ontogeny of contextual fear conditioning: Implications for consolidation, infantile amnesia, and hippocampal system function. Behavioral Neuroscience 1994;108:227–234. [PubMed: 8037868]

Salzen, EA. Imprinting and environmental learning. In: Aronson, LR.; Tobach, E.; Lehrman, DS.; Rosensblatt, J., editors. Development and evolution of behavior. San Prancisco: W.H. Preeman; 1970.

Sananes CB, Campbell BA. Role of the central nucleus of the amygdala in olfactory heart rate conditioning. Behavioral Neuroscience 1989;103:519–525. [PubMed: 2736066]

Sananes CB, Gaddy JR, Campbell BA. Ontogeny of conditioned heart rate to an olfactory stimulus. Developmental Psychobiology 1988;21:117–133. [PubMed: 3345865]

Sanchez MM, Ladd CO, Plotsky PM. Early adverse experience as a developmental risk factor for later psychopathology: Evidence from rodent and primate models. Developmental Psychopathology 2001;13:419–449.

Schettino LF, Otto T. Patterns of Fos expression in the amygdala and ventral perirhinal cortex induced by training in an olfactory fear-conditioning paradigm. Behavioral Neuroscience 2001;115:1257–1272. [PubMed: 11770057]

Schore AN. The effects of early relational trauma on right brain development, affect regulation, and infant mental health. Infant Mental Health Journal 2001;22:201–269.

Schoenbaum G, Chiba AA, Gallagher M. Neural encoding in orbitofrontal cortex and basolateral amygdala during olfactory discrimination learning. Journal of Neuroscience 1999;19:1876–1884. [PubMed: 10024371]

Sevelinges Y, Gervais R, Messaoudi B, Granjon L, Mouly AM. Olfactory fear conditioning induces field potential potentiation in rat olfactory cortex and amygdala. Learning and Memory 2004;11:761–769. [PubMed: 15537739]

Shair NH, Masmela JR, Brunelli SA, Hofer MA. Potentiation and inhibition of ultrasonic vocalization of rat pups: Regulation by social cues. Developmental Psychobiology 1997;30:195–200. [PubMed: 9104550]

Shipley MT, Halloran FJ, De la Torre J. Surprisingly rich projection from locus coeruleus to the olfactory bulb in the rat. Brain Research 1985;239:294–299. [PubMed: 3978450]

Slagsvold T, Hansen BT, Johannessen LE, Lifjeld JT. Mate choice and imprinting in birds studied by cross-fostering in the wild. Proceedings of the Royal Society of London Series B 2002;269:1449–1455. [PubMed: 12137574]

Spear, NE. Processing memories: Forgetting and retention. Hillsdale, NJ: Erlbaum; 1978.

Spear, NE.; Rudy, JW. Tests of the ontogeny of learning and memory: Issues, methods, and results. In: Shair, HN.; Barr, GA.; Hofer, MA., editors. Developmental psychobiology: New methods and changing concepts. New York, NY, USA: Oxford University Press; 1991. p. 84-113.

Stanton ME. Multiple memory systems, development and conditioning. Behavioural Brain Research 2000;110:25–37. [PubMed: 10802301]

Stehouwer DJ, Campbell BA. Habituation of the forelimb-withdrawal response in neonatal rats. Journal of Experimental Psychology: Animal Behavior Processes 1978;4:104–119. [PubMed: 670888]

Sullivan RM. Unique characteristics of neonatal classical conditioning: The role of the amygdala and locus coeruleus. Integrative Physiological and Behavioral Science 2001;36:293–307. [PubMed: 17476313]

Sullivan, RM. Roots of Mental Illness in Children. 1008. New York: New York Academy of Science; 2003. Developing a sense of safety: the Neurobiology of neonatal attachment; p. 122-132.

Sullivan RM, Leon M. Early olfactory learning induces an enhanced olfactory bulb response in young rats. Developmental Brain Research 1986;27:278–282.

Sullivan RM, Wilson DA. Role of the amygdala complex in early olfactory associative learning. Behavioral Neuroscience 1993;107:254–263. [PubMed: 8484891]

Sullivan RM, Brake SC, Hofer MA, Williams CL. Huddling and independent feeding of neonatal rats can be facilitated by a conditioned change in behavioral state. Developmental Psychobiology 1986a; 19:625–635. [PubMed: 3803730]

Sullivan RM, Hofer MA, Brake SC. Olfactory-guided orientation in neonatal rats is enhanced by a conditioned change in behavioral state. Developmental Psychobiology 1986b;19:615–623. [PubMed: 3803729]

Sullivan RM, Wilson DA, Wong R, Correa A, Leon M. Modified behavioral olfactory bulb responses to maternal odors in preweanling rats. Developmental Brain Research 1990;53:243–247. [PubMed: 2357798]

Sullivan RM, Zyzak D, Skierkowski P, Wilson DA. The role of olfactory bulb norepinephrine in early olfactory learning. Developmental Brain Research 1992;70:279–282. [PubMed: 1477962]

Sullivan RM, Wilson DA, Lemon C, Gerhardt GA. Bilateral 6-OHDA lesions of the locus coeruleus impair associative olfactory learning in newborn rats. Brain Research 1994;643:306–309. [PubMed: 8032925]

Sullivan RM, Landers M, Yeaman B, Wilson DA. Good memories of bad events in infancy: Ontogeny of conditioned fear and the amygdala. Nature 2000a;407:38–39. [PubMed: 10993064]

Sullivan RM, Stackenwalt G, Nasr R, Lemon C, Wilson DA. Association of an odor with activation of olfactory bulb noradrenergic β-receptors or locus coeruleus stimulation is sufficient to produce learned approach response to that odor in neonatal rats. Behavioral Neuroscience 2000b;114:957–962. [PubMed: 11085610]

Swiergiel AH, Takahashi LK, Kalin NH. Attenuation of stress-induced behavior by antagonism of corticotropin-releasing factor receptors in the central amygdala of the rat. Brain Research 1993;2:229–234. [PubMed: 8221104]

Takahashi LK. Organizing action of corticosterone on the development of behavioral inhibition in the preweanling rat. Developmental Brain Research 1994;81:121–127. [PubMed: 7805277]

Takahashi LK, Rubin WW. Corticosterone induction of threat-induced behavioral inhibition in preweanling rats. Behavioral Neuroscience 1993;107:860–866. [PubMed: 8280395]

Takahashi LK, Turner JG, Kalin NH. Development of stress-induced responses in preweanling rats. Developmental Psychobiology 1991;24:241–360.

Teicher MH, Ito Y, Gold CA, Andersen SL, Dumont N, Ackerman E. Preliminary evidence for abnormal cortical development in physically and sexually abused children using EEG coherence and MRI. Annals of the New York Academy of Sciences 1997;821:160–175. [PubMed: 9238202]

Ten Gate C, Vos DR. Sexual imprinting and evolutionary processes in birds: A reassessment. Advances in the Study of Behavior 1999;28:1–31.

Terry LM, Johanson IB. Effects of altered olfactory experiences on the development of infant rats' responses to odors. Developmental Psychobiology 1996;29:353–377. [PubMed: 8732808]

Tronel S, Sara SJ. Mapping of olfactory memory circuits: Region-specific c-fos activation after odor-reward associative learning or after its retrieval. Learning and Memory 2002;9:105–111. [PubMed: 12074998]

Van Oers HJJ, de Kloet ER, Whelan T, Levine S. Maternal deprivation effect on the infant's neural stress markers is reversed by tactile stimulation and feeding but by suppressing corticosterone. Journal of Neuroscience 1998;18:10171–10179. [PubMed: 9822770]

Verwer RW, Van Vulpen EH, Van Uum JF. Prefrontal development of amygdaloid projections to the prefrontal cortex in the rat studied with retrograde and anterograde tracers. Journal of Comparative Neurology 1996;376:75–96. [PubMed: 8946285]

Weldon DA, Travis ML, Kennedy DA. Post-training D1 receptor blockade impairs odor conditioning in neonatal rats. Behavioral Neuroscience 1991;105:450–458. [PubMed: 1863365]

Wiedenmayer CP, Barr GA. Developmental changes in c-fos expression to an age-specific social stressor in infant rats. Behavioural Brain Research 2001;126:147–157. [PubMed: 11704260]

Wilson DA, Sullivan RM. Olfactory associative conditioning in infant rats with brain stimulation as reward. II. Norepinephrine mediates a specific component of the bulb response to reward. Behavioral Neuroscience 1991;105:843–849. [PubMed: 1663758]

Wilson DA, Sullivan RM. Blockade of mitral/tufted cell habituation to odors by association with reward: A preliminary note. Brain Research 1992;594:143–145. [PubMed: 1467934]

Wilson DA, Sullivan RM, Leon M. Single-unit analysis of postnatal olfactory learning: Modified olfactory bulb output response patterns to learned attractive odors. Journal of Neuroscience 1987;7:3154–3162. [PubMed: 3668621]

Winzer-Serhan UH, Leslie FM. Expression of α_{2A} adrenoceptors during rat neocortical development. Journal of Neurobiology 1999;38:259–269. [PubMed: 10022571]

Woo CC, Leon M. Sensitive period for neural and behavioral responses to learned odors. Developmental Brain Research 1988;36:309–313.

Yuan Q, Harley CW, McLean JH, Knopfel T. Optical imaging of odor preference memory in the rat olfactory bulb. Journal of Neurophysiology 2003;87:3156–3159. [PubMed: 12037216]

Yuan Q, Harley CW, McLean JH. Mitral cell β_1 and 5-HT_{2A} receptor co-localization and cAMP co-regulation: A new model of norepinephrine-induced learning in the olfactory bulb. Learning and Memory 2003;10:5–15. [PubMed: 12551959]

Yuan Q, Mutoh H, Debardieux F, Knopfel T. Calcium signaling in mitral cell dendrites of olfactory bulbs of neonatal rats and mice during olfactory nerve stimulation and {beta}-adrenoceptor activation. Learning and Memory 2004;11:406–411. [PubMed: 15286182]

Zhang JJ, Okutani F, Yagi F, Inoue S, Kaba H. Facilitatory effect of ritanserin is mediated by dopamine D(1) receptors on olfactory learning in young rats. Developmental Psychobiology 2000;37:246–252. [PubMed: 11084606]

Zhang JJ, Okutani F, Inoue S, Kaba H. Activation of the cyclic AMP response element-binding protein signaling pathway in the olfactory bulb is required for the acquisition of olfactory aversive learning in young rats. Neuroscience 2003;117:707–713. [PubMed: 12617974]

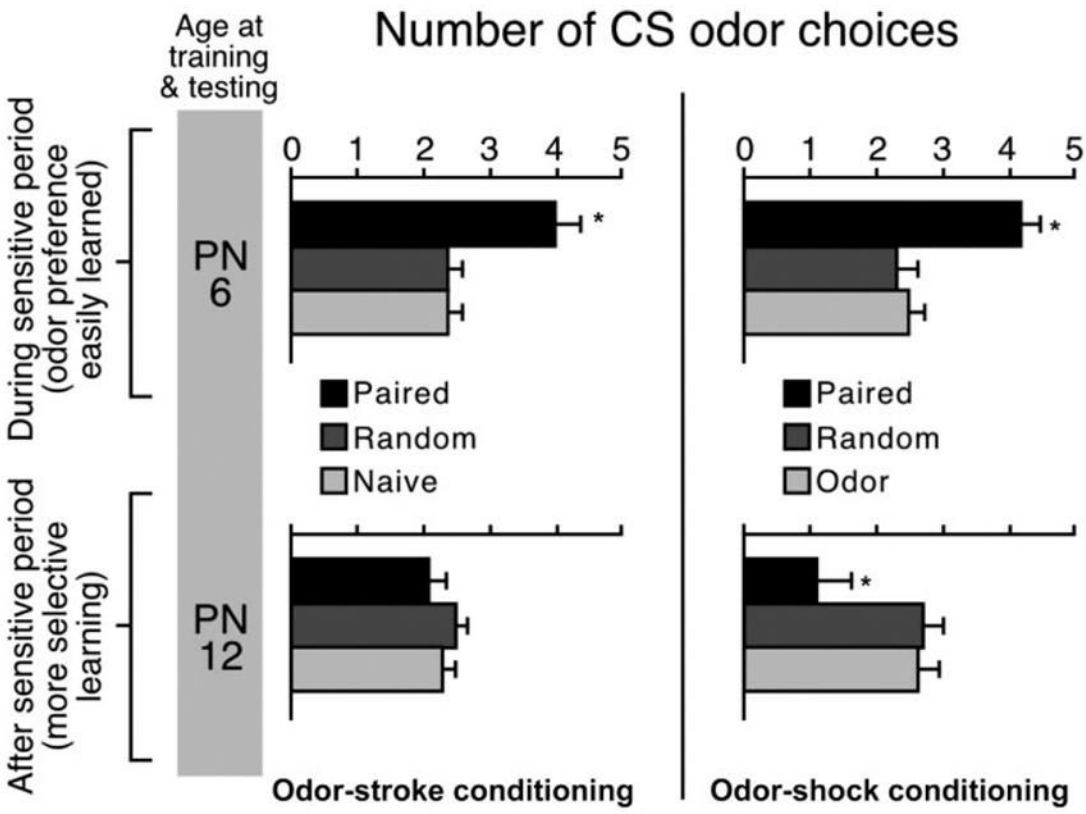

FIGURE 1.

Mean number of CS odor choices (±SEM) in an olfactory Y-maze test. Pups were trained during the sensitive period (PN6) with pleasant odor-stroke conditioning (upper left) or aversive odor-shock (0.5 mA) conditioning (upper right), although pairings of either reward produced a subsequent odor preference at his early age. Older pups (lower), after the sensitive period (PN12), show more discriminating conditioning characteristic of adult animals; odor-stroke conditioning (lower left) was ineffective at producing an odor preference and odor-shock conditioning (lower right) produced a subsequent odor aversion.

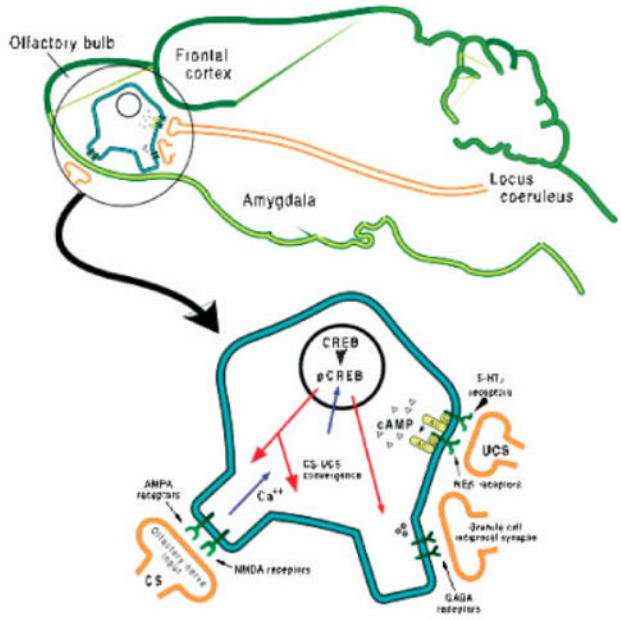

FIGURE 2.

Schematic representation of olfactory bulb input from the noradrenergic locus coeruleus, which is important in inducing early olfactory learning. If the odor is paired with a reward, activation of NE (β-receptors increases cAMP levels, which combined with the high levels of Ca^{++}, activates a cascade resulting in pCREB-mediated changes in gene transcription. These changes could result in odor-specific changes in mitral cell odor coding that would reflect the learned significance of the odor to the animal (Sullivan et al., 2000b; Yuan et al., 2003).

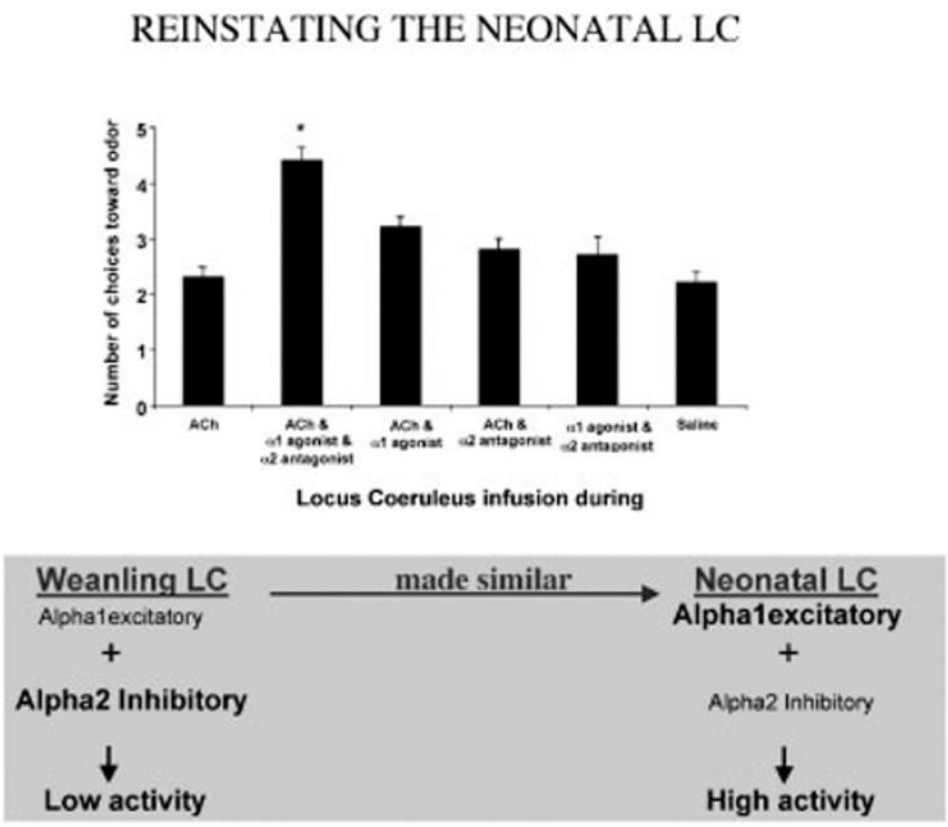

FIGURE 3.

Mean number of choices toward the CS odor (±SEM) during the Y-Maze test. To revert the older LC to the neonatal LC, during acquisition we infused the LC with acetylcholine (ACh) concurrently with α1 agonist (potentiates autoexcitation; phenylephrine) and α2 antagonist (prevents autoinhibition; idazoxan) during an odor presentation. This caused pups to subsequently express a learned odor preference compared with each of the control groups.

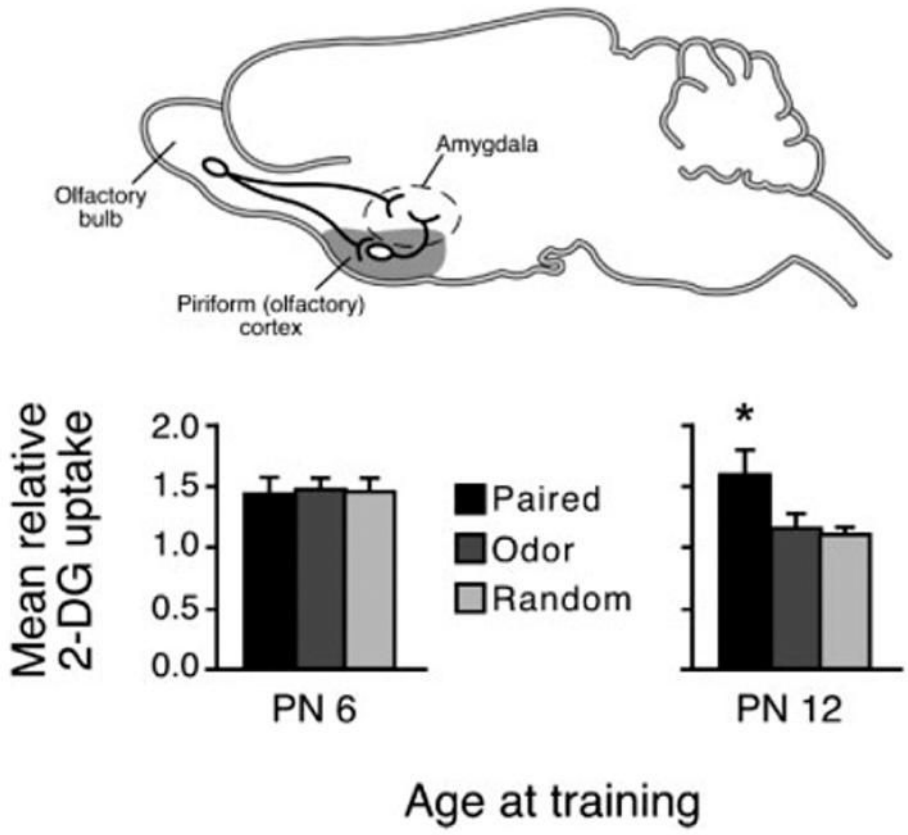

FIGURE 4.

Amygdala activity, as measured by 14C auto-radiography, of sensitive period pups (PN8) does not appear to participate in odor-shock conditioning and may underlie pups' difficulty in learning odor aversions. Older pups, past the sensitive period, have an amygdala that participates in learning and easily form odor aversions (Sullivan et al., 2000a).

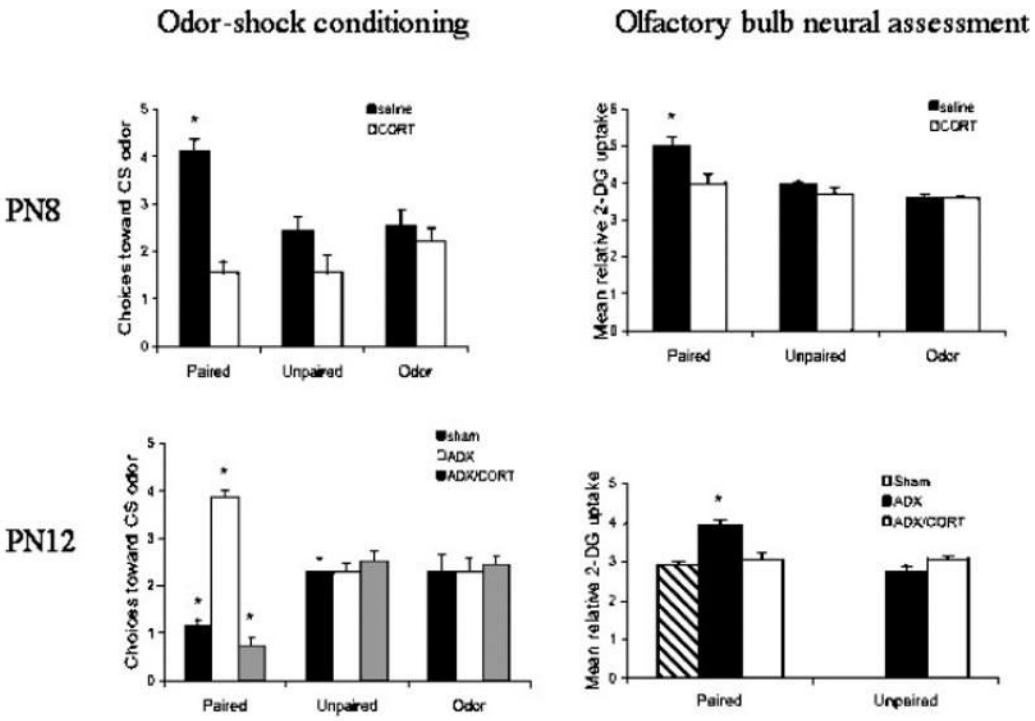

FIGURE 5.

Mean number of CS odor choices (±SEM) in an olfactory Y-maze test (left) and mean level of odor-induced olfactory bulb focal ^{14}C 2-deoxyglucose uptake (±SEM; right). Pups were trained during the sensitive period (PN8; top) or after the sensitive period (PN12; lower) with odor-shock conditioning.

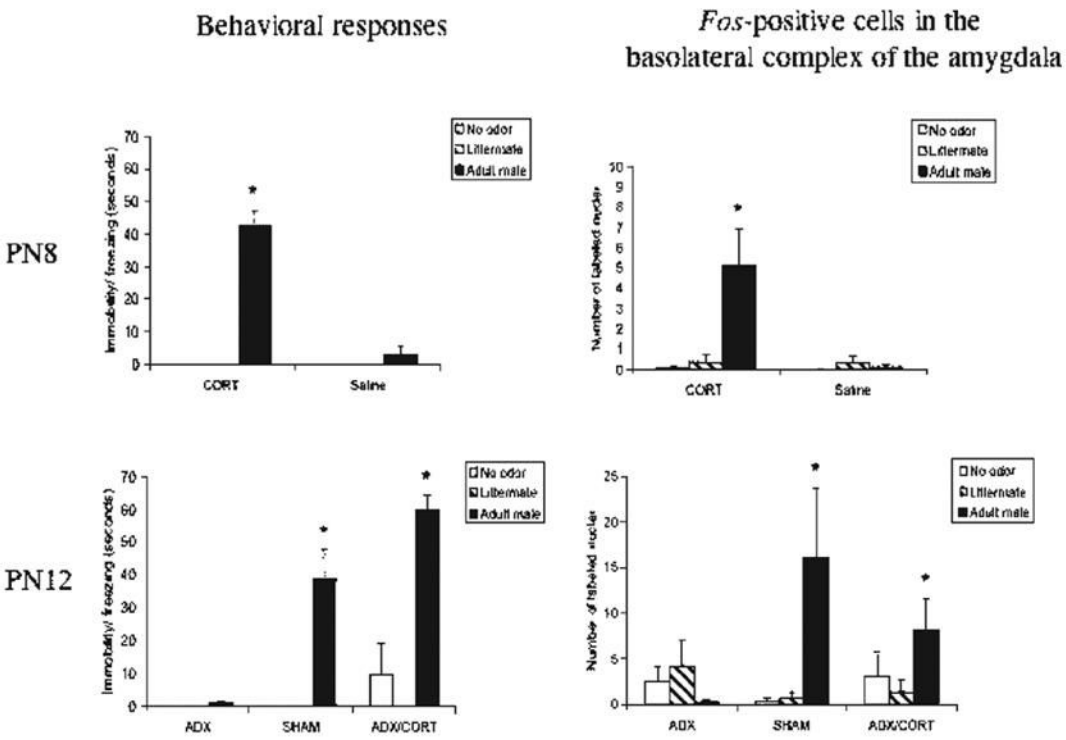

FIGURE 6.

Mean number of immobility/freezing responses (±SEM; left) and mean number of Fos-positive cells in the basolateral complex of the amygdala (±SEM; right). Pups were trained during the sensitive period (PN8; top) or after the sensitive period (PN12; lower).