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Rodent Model of Infant Attachment Learning and Stress

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Abstract

Here we review the neurobiology of infant odor learning in rats, and discuss the unique role of the stress hormone corticosterone (CORT) in the learning necessary for the developing rat. During the first 9 postnatal (PN) days, infants readily learn odor preferences, while aversion and fear learning are attenuated. Such restricted learning may ensure that pups only approach their mother. This sensitive period of preference learning overlaps with the stress hyporesponsive period (SHRP, PN4–14) when pups have a reduced CORT response to most stressors. Neural underpinnings responsible for sensitive-period learning include increased activity within the olfactory bulb and piriform "olfactory" cortex due to heightened release of norepinephrine from the locus coeruleus. After PN10 and with the decline of the SHRP, stress-induced CORT release permits amygdala activation and facilitates learned odor aversions and fear. Remarkably, odor preference and attenuated fear learning can be reestablished in PN10–15 pups if the mother is present, an effect due to her ability to suppress pups' CORT and amygdala activity. Together, these data indicate that functional changes in infant learning are modified by a unique interaction between the developing CORT system, the amygdala, and maternal presence, providing a learning system that becomes more flexible as pups mature.

Keywords

mother–infant interactions; olfactory bulb; norepinephrine; attachment; imprinting; locus coeruleus; amygdala; learning; classical conditioning; corticosterone; stress; fear

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INTRODUCTION

> "There is continuity in development, such that the organization at one stage provides the basis for organization at the next succeeding stage. This does not mean, however, that all processes persist throughout life, nor does it mean that behaviors must remain stable across stages. On the contrary, development is essentially a dynamic process that promotes reorganization and adaptation across time"
>
> (Levine, 1982).

At birth, altricial infant rats are confined to the nest and exquisitely designed to identify, learn, and remember experiences with their caregivers. Indeed, infants readily learn an attraction to their mother's odor, which ensures that infants will exhibit approach behaviors toward the mother in order to receive the food, protection, and warmth needed for survival. Perinatal learning of maternal odor is required for pups to approach the mother and attach to her nipples for nursing (Pedersen & Blass, 1982), though somatosensory cues from the nipple are also required for these behaviors (Polan & Hofer, 1999; Stern, 1997). The maternal odor continues to be learned throughout the postnatal period (Cheslock, Varlinskaya, Petrov, & Spear, 2000; Pedersen, Williams, & Blass, 1982), presumably since the mother's odor can be altered with her diet (Leon, 1992). Overall, infant behavior is centered on maintaining contact with the mother (Galef & Kaner, 1980; Leon, 1992), and, as will be discussed here, this early attachment process is facilitated by infants' enhanced ability to learn preferences and their decreased ability to learn aversions or fear. Presumably, this constrains infants to form only preferences to caretakers.

Such attachment learning has a wide phylogenetic representation and appears to enable altricial animals to easily form a repertoire of proximity-seeking behaviors toward the primary caregiver, regardless of the quality of care they receive. For example, in avian imprinting, a chick will continue to follow its caregiver even while being shocked (Hess, 1962; Salzen, 1970). A similar experiment in dogs has shown that puppies will display strong attachment to a handler who provides rough treatment or neglect (Rajecki, Lamb, & Obmascher, 1978). Additionally, nonhuman primates and human children will also demonstrate strong attachment to an abusive caregiver (Harlow & Harlow, 1965; Helfer, Kempe, & Krugman, 1997; Maestripieri, Tomaszycki, & Carroll, 1999; Sanchez, Ladd, & Plotsky, 2001).

We have hypothesized that the infant rat learning system is designed to ensure that pups will learn an approach response towards and preference for the mother, regardless of whether she is associated with pain or pleasure (Hofer & Sullivan, 2001). We refer to this period of attachment learning as the "sensitive period." Furthermore, it is worthwhile to note that postpartum mothers of various mammalian species also display a sensitive period for learning about offspring (Brennan & Keverne, 1997; Insel & Young, 2001; Keverne & de la Riva, 1982; Marlier, Schaal, & Soussignan, 1998; Moffat, Suh, & Fleming, 1993; Okere & Kaba, 2000; Pissonnier, Thiery, Fabre-Nys, Poindron, & Keverne, 1985). Much like that of the infant, mother learning requires unique neural circuitry to facilitate odor preferences,

approach responses, and nurturing behavior toward offspring (Brennan & Keverne, 1997; Insel & Young, 2001; Lévy, Gervais, Kindermann, Orgeur, & Piketty, 1990).

In just 3 short weeks, rat pups are transformed into independent organisms with the maturation and experience to survive on their own. These 3 weeks represent a time of transition from maternal dependence to independence that uniquely characterizes the dramatic reorganization and adaptation of learning required of the infant. In this review, we discuss the neural basis that enables pups to transition between readily learning preferences within the context of attachment to learning fear. One prominent characteristic of learning after postnatal day (PN) 10 is the amygdala's dependence on stress-induced corticosterone (CORT) release. Indeed, the ontogeny of infant stress responsiveness and the hypothalamic–pituitary–adrenal (HPA) system development were two major foci of Seymour Levine's developmental work. As will be evident below, Levine's contributions to developmental psychobiology have certainly been instrumental in helping us understand the neurobehavioral basis of infant attachment and the ontogeny of fear learning.

NEUROBIOLOGY OF INFANT RAT ODOR PREFERENCE LEARNING

During the infant sensitive period, PN1–9, pups display an enhanced capacity for preference learning. We have shown that learned odor preferences (conditioned via either positive or aversive stimuli paired with an unfamiliar odor) during this period are in part due to strong noradrenergic input to the olfactory bulb from the locus coeruleus (LC). Infant acquisition (learning) is disrupted if norepinephrine (NE) receptors are blocked in the bulb (Sullivan, Zyzak, Skierkowski, & Wilson, 1992) or if the LC is pharmacologically destroyed (Sullivan, Wilson, Lemon, & Gerhardt, 1994). Presentations of an odor with the activation of olfactory bulb NE β-receptors or stimulation of the LC during this period are sufficient to produce odor preference learning (Sullivan, Stackenwalt, Nasr, Lemon, & Wilson, 2000; Yuan, Harley, Darby-King, Neve, & McLean, 2003). Additionally, we have shown that NE is required for the maintenance of the prolonged mitral cell response characteristic of sensitive-period learning (Wilson, Sullivan, & Leon, 1987).

Unique properties of the LC appear to be responsible for infant preference learning. In effect, the LC of a sensitive-period pup is characterized by prolonged stimulus-evoked excitation, which prompts release of an enormous amount of NE (Nakamura, Kimura, & Sakaguchi, 1987). This is in contrast to the LC of an older pup, in which there is a much shorter evoked physiological response and thus smaller release of NE (Nakamura et al., 1987). The dramatic reduction in NE release at the close of the sensitive period is associated with the functional emergence of LC α2 inhibitory autoreceptors and the downregulation of LC α1 excitatory autoreceptors (Nakamura et al., 1987; Pieribone, Nicholas, Dagerlind, & Hokfelt, 1994; Scheinin et al., 1994). To test whether these developmental changes in LC autoreceptors are important for ending pups' rapid preference learning, we recreated neonatal levels of these LC autoreceptors' activity in older pups to reproduce the large NE release of younger pups. Specifically, after stimulating the LC with intra-LC cholinergic infusion, combined with drugs that blocked the autoinhibition (α2 antagonists) and enhanced the autoexcitation (α1 agonists), we successfully reinstated pups' rapid NE-dependent odor preference learning (Moriceau & Sullivan, 2004b). These data suggest that

functional changes in the LC support termination of the rapid and robust preference learning period.

Though early-life learning is characterized by odor preference learning, infants during this developmental period also have a decreased capacity to learn aversions or fear. Specifically, during the sensitive period, neonatal rats readily learn an odor preference even when an unfamiliar odor has been paired with an aversive stimulus, such as .5 mA foot-shock or tail pinch (Camp & Rudy, 1988; Haroutunian & Campbell, 1979; Moriceau & Sullivan, 2006; Moriceau, Wilson, Levine, & Sullivan, 2006; Roth & Sullivan, 2005; Spear, 1978; Sullivan & Hall, 1988; Sullivan, Hofer, & Brake, 1986; Sullivan, Landers, Yeaman, & Wilson, 2000). At the end of the sensitive period, similarly to older animals, pups readily learn to avoid unfamiliar odors paired with the same aversive stimuli (Blozovski & Cudennec, 1980; Camp & Rudy, 1988; Collier, Mast, Meyer, & Jacobs, 1979; Goldman & Tobach, 1967; Haroutunian & Campbell, 1979; Moriceau & Sullivan, 2006; Moriceau et al., 2006; Myslivecek, 1997; Stehouwer & Campbell, 1978; Sullivan, Landers, et al., 2000).

Shock-induced preference learning during the sensitive period is likely not due to the pups' inability to feel pain since unconditioned responses to shock vary little between sensitive-period pups and older pups (Barr, 1995; Collier & Bolles, 1980; Emerich, Scalzo, Enters, Spear, & Spear, 1985; Fitzgerald, 2005; Shair, Masmela, Brunelli, & Hofer, 1997; Stehouwer & Campbell, 1978; Sullivan, Landers, et al., 2000). Also, pups' inability to learn aversions or fear is not limited to olfactory-cued fear conditioning, as other learning paradigms that produce learned fear in older animals (such as passive avoidance and inhibitory conditioning) do not readily do so in infant rats (Bialik, Pappas, & Roberts, 1984; Blozovski & Cudennec, 1980; Camp & Rudy, 1988; Collier & Mast, 1979; Myslivecek, 1997).

Due to the known role of the amygdala in supporting learned fear in older animals (Cahill, Weinberger, Roozendaal, & McGaugh, 1999; Debiec & LeDoux, 2006; Fanselow & Gale, 2003; Fanselow & LeDoux, 1999; Goosens & Maren, 2001; Maren, 2003; Sigurdsson, Doyere, Cain, & LeDoux, 2007), we have examined whether the amygdala mediates the developmental transition that permits pups' emergence of avoidance and fear learning at PN10 (Sullivan, Landers, et al., 2000). Using markers that reflect neural activity (2-deoxyglucose uptake and cfos immunohistochemistry), we have found that the amygdala only appears to be involved in odor-shock conditioning when this conditioning is able to support odor avoidance acquisition—that is, when the sensitive period has ended (Moriceau et al., 2006; Roth & Sullivan, 2005; Sullivan, Landers, et al., 2000; Sullivan & Wilson, 1993, 2003).

As further evidence of its limited role in infant preference learning, amygdala lesions during the sensitive period do not prevent the ability of infants to learn a shock-induced conditioned odor preference (Moriceau et al., 2006; Sullivan & Wilson, 1993). In contrast, amygdala lesions in older pups prevent them from learning a conditioned odor aversion (Maren, 1999; Moriceau et al., 2006; Sullivan, Landers, et al., 2000). Finally, the reduced ability of sensitive-period pups to exhibit amygdala long-term depression (LTD) further suggests that the amygdala is not participating in infant learning (Thompson, Sullivan, & Wilson, 2008).

Altogether, these data suggest that the lack of amygdala participation in circuitry mediating sensitive-period learning is key to an infant's increased capacity to learn a preference. While we first hypothesized that the immaturity of the amygdala (Berdel & Morys, 2000; Berdel, Morys, & Maciejewska, 1997; Bouwmeester, Wolterink, & van Ree, 2002; Cunningham, Bhattacharyya, & Benes, 2002; Morys, Berdel, Jagalska-Majewska, & Luczynska, 1999; Nair & Gonzalez-Lima, 1999) was responsible for its lack of participation, recent studies have since suggested that the amygdala is sufficiently mature to respond to stimuli during the sensitive period (Thompson et al., 2008). Rather, it is increasing CORT levels that play a crucial role in the emergence of fear learning and in the participation of the amygdala after the sensitive period (Barr et al., 2009; Moriceau & Sullivan, 2006; Moriceau et al., 2006; Shionoya, Moriceau, Bradstock, & Sullivan, 2007; Sullivan & Holman, 2010; Sullivan, Landers, et al., 2000).

CORTICOSTERONE, AMYGDALA ACTIVITY, AND THE ONTOGENY OF FEAR

Our interest in CORT was initiated by two areas of research. First, work showing that pups' ontogenetic emergence of fear to predator odor (unlearned fear) occurs at the same age as learned fear (~PN10) and is controlled by the endogenous increase in CORT during development (Takahashi, 1994). Second, pups'sensitive period for odor preference/ attachment learning overlaps with an infant "stress hyporesponsive period" (SHRP, PN4–14), during which pups' CORT levels are lower than normal and remain either unaffected or are minimally increased by stressors (Grino, Paulmyer-Lacroix, Faudon, Renard, & Anglade, 1994; Levine, 2001; Rosenfeld, Suchecki, & Levine, 1992).

Interestingly, CORT response is functional at birth (Arai & Widmaier, 1991; Martin, Cake, Hartmann, & Cook, 1977; Widmaier, 1990) and the sensory stimulation provided by the mother during nursing and grooming seems to control the pups' low CORT levels (Levine, 1962; Stanton & Levine, 1990; Van Oers, De Kloet, Whelan, & Levine, 1998). Indeed, sensitive-period pups show increases in CORT in response to intense stressors such as prolonged maternal deprivation or cold, which can be returned to normal low levels with replacement of maternal sensory stimulation or maternal presence (Avishai-Eliner, Yi, Newth, & Baram, 1995; Levine, 2001; Walker, Scribner, Cascio, & Dallman, 1991). Additionally, functional CORT receptors are already present throughout the brain, including within the amygdala (Alexis, Kitraki, Spanou, Stylianopoulou, & Sekeris, 1990; Diorio, Viau, & Meaney, 1993; Kitraki, Alexis, Papalopoulou, & Stylianopoulou, 1996; Rosenfeld, van Eekelen, Levine, & de Kloet, 1993).

Studies utilizing presentations of predator odor have helped provide a causal link between CORT responsivity, amygdala activation, and the ontogeny of natural or unlearned fear. We and others have shown that during the SHRP, predator-odor presentations fail to elicit a CORT response unless it is a very prolonged presentation (Gould, Tanapat, & Cameron, 1997; Moriceau, Roth, Okotoghaide, & Sullivan, 2004; Takahashi, 1994; Wiedenmayer & Barr, 2001; Wiedenmayer, Magarinos, McEwen, & Barr, 2005). Furthermore, these researchers showed that increasing neonatal CORT levels prior to presentation of the predator odor, however, will engage the amygdala and ultimately permit fear expression.

Alternatively, depletion of CORT in older pups blocks amygdala responsivity to the male odor presentations, and thus fear expression. Together, these data highlight the importance of CORT in the emergence of natural (unlearned) fear and suggest that changes in the developing CORT system facilitate the transition between sensitive-period preference learning and postsensitive-period fear conditioning.

To investigate this relationship, we gave sensitive-period pups either systemic or intra-amygdala CORT injections prior to odor-shock conditioning. We found that either of these approaches enabled sensitive-period pups to learn an odor aversion. As summarized in Table 1, neural assessment of their brains by 2-deoxyglucose uptake indicated that the learning had evoked significant activity within the amygdala (Sullivan, Landers, et al., 2000). In turn, we can extend the age at which odor-shock conditioning produces an odor preference and prevent amygdala activity by eliminating endogenous CORT in older pups, through either removal of its source, the adrenal glands, or administration of the CORT receptor antagonist, RU 38486 (Moriceau & Sullivan, 2004a, 2006). Preventing the increase of CORT by adrenalectomy has also been shown to delay the emergence of learned fear with aversive conditioning (Bialik et al., 1984; Collier et al., 1979). This developmental effect is in sharp contrast to CORT effects on learning in adults, where it only modifies how well a behavior is learned (Corodimas, LeDoux, Gold, & Schulkin, 1994; Pugh, Tremblay, Fleshner, & Rudy, 1997; Roozendaal, Carmi, & McGaugh, 1996).

Based upon the data discussed above, low CORT levels and the consequent lack of significant amygdala activity during the sensitive period appear to prevent pups from learning aversions or avoidances to odors associated with the mother. Levine and his colleagues have demonstrated that sensory stimulation from the mother is responsible for maintaining low CORT levels during the SHRP (Levine, 2001). For example, removal of maternal sensory stimulation during the SHRP, such as that occurring when pups are separated from the mother for a prolonged period of time (24 hr), produces significant elevations in CORT levels (Levine, 2001). Aberrant maternal care in the rat will produce similar effects (Gilles, Schultz, & Baram, 1996). Furthermore, maternal presence in older pups (>PN12) can blunt CORT release to stressful and painful stimuli (Stanton & Levine, 1990; Stanton, Wallstrom, & Levine, 1987; Suchecki, Rosenfeld, & Levine, 1993). Likewise, our own data illustrated in Figure 1 replicate the remarkable ability of the mother to suppress CORT levels even during stress in PN14 and PN21 pups. The sensory cues capable of blunting the stress-induced CORT release appear to be olfactory and somatosensory (Barr et al., 2009; Moriceau & Sullivan, 2006; Shionoya et al., 2007; Stanton & Levine, 1990; Suchecki et al., 1993; Wiedenmayer, Magarinos, McEwen, & Barr, 2003). The decrease in CORT levels due to social sensory cues has since been referred to as “social buffering” (Hennessy, Kaiser, & Sachser, 2009; Kikusui, Winslow, & Mori, 2006), and has been shown to exist in humans and other animals (DeVries, Glasper, & Detillion, 2003; Kirschbaum, Klauer, Filipp, & Hellhammer, 1995; Thorsteinsson & James, 1999).

The finding that maternal presence blunts CORT release to stressful and painful stimuli in older pups (Stanton & Levine, 1990; Stanton et al., 1987; Suchecki et al., 1993), prompted us to examine whether maternal presence in older pups (PN10–15) is capable of suppressing amygdala activity and blocking fear learning. We found that indeed maternal presence

blocked fear learning (aversion) in response to odor-shock conditioning, as well as prevented significant amygdala activation and permitted significant olfactory bulb activation (Moriceau & Sullivan, 2006). Furthermore, systemic or intra-amygdala CORT infusions allowed the pups to learn odor aversions in the presence of the mother (Moriceau & Sullivan, 2006). As depicted in Table 1, our results indicate that maternal presence in PN10–15 pups reengages the attachment circuitry during learning, effectively preventing them from acquiring an odor aversion or fear. The ability of maternal presence to reengage the attachment circuitry appears to end at PN15, as PN16 pups still learn an odor aversion even in the presence of the mother (Upton & Sullivan, 2010). Based upon these data, we now define PN10–15 as a "conditional sensitive period," in which odor preference learning and attenuated fear learning can be reestablished if the mother is present.

To summarize, the brain of the developing infant rat is optimized to facilitate attachment during a developmental period when pups are confined to the nest (until PN9), with circuitry providing remarkable constraints on aversion and fear learning. The ecological significance of this may relate to the possible occurrence of rough handling by the mother during normal mother–infant interactions (i.e., stepping on pups while entering/leaving the nest and rough pup retrieval). From an evolutionary perspective, it would be maladaptive for pups to learn to avoid the maternal odor in a situation where the mother is required for milk and warmth, suggesting that this attenuated avoidance learning ensures that pups continue to only approach/follow the caregiver (Hofer & Sullivan, 2001). During the conditional sensitive period (PN10–15), when pups are still dependent on the mother but can begin expanding their environment beyond the nest, they readily demonstrate avoidance and fear learning to aversive stimuli in the absence of the mother. However, the attachment circuitry and restraint on fear learning can be reengaged during this transitional period if the mother is present. This suggests that older pups have a more sophisticated learning system that enables them to respond appropriately to learning situations dependent on whether the mother is present or not. The data summarized here make it clear that the ontogeny of pups' CORTand amygdala responsivity play a pivotal role in the dramatic reorganization and adaptation of learning necessary for the developing rat.

CONCLUDING REMARKS

Seymour Levine, one of the first to study the role of early experiences in shaping stress responses, has left a lasting legacy regarding the profound influence of the mother on the development of the stress system in numerous species (Levine, 1957, 1967; Lyons, Martel, Levine, Risch, & Schatzberg, 1999; Morgado et al., 2008; Schmidt et al., 2006; Stanton et al., 1987). The data outlined in this review indicate that functional changes in infant learning are modified by a unique interaction between the developing CORT system, the amygdala, and the learning context that depends on whether the mother is present or absent.

While human children show remarkably similar behavior within the realm of attachment (proximity seeking, tolerance of pain), it is unclear if the rat attachment circuitry outlined here exists in human infants. Bowlby's (1965) use of the animal literature in the construction of his attachment theory would argue the likely evolutionary conservation of attachment

circuitry. Following this, it is likely the case that the human infant's brain is similarly organized to ensure rapid, robust attachment to his or her caregiver.

The importance of a healthy and secure attachment in humans is illustrated by the fact that securely attached children have an increased probability of maturing into mentally healthy adults compared to insecurely attached children (Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008; Gunnar & Quevedo, 2008). Conversely, children in abusive attachment relationships have a greater probability of experiencing adult mental problems (Glaser, 2000; Grossman et al., 2003; Sanchez et al., 2001; Teicher et al., 2003). Presumably, this reflects an altered trajectory of brain development, and it is clear that the brains' HPA axis and amygdala are particularly vulnerable to early environmental influences (Dent, Smith, & Levine, 2001; Eghbal-Ahmadi, Avishai-Eliner, Hatalski, & Baram, 1999; Francis, Caldji, Champagne, Plotsky, & Meaney, 1999; Swiergiel, Takahashi, & Kalin, 1993). Based upon the data reviewed here, developmental insults to these systems would certainly have the capacity to disrupt early learning processes responsible for securing attachment, thus increasing the risk for poor mental outcomes.

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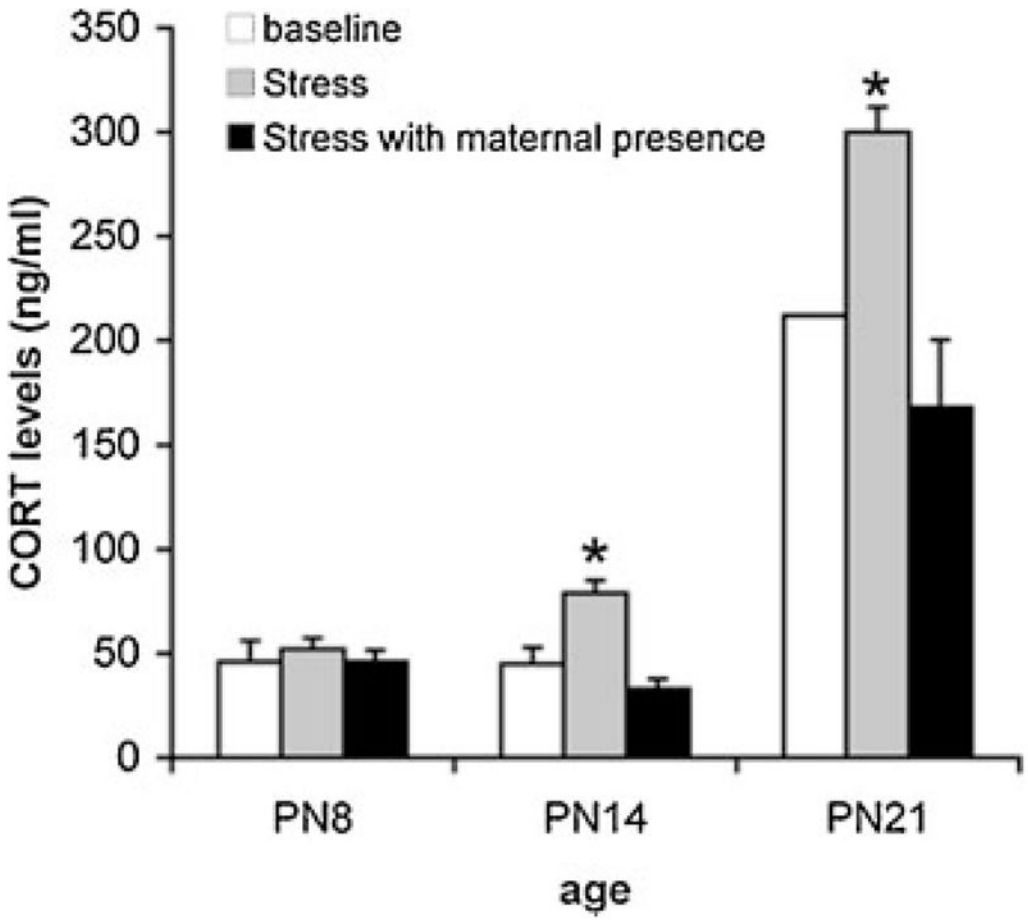

FIGURE 1.

Ontogeny of CORT levels. CORT levels in response to .5 mA foot-shock were measured in PN8, PN14, or PN21 pups with or without maternal presence to assess the ontogeny of social buffering. Immediately following 11 shock presentations with an interval of 4 min (between 12 and 2 pm), pups were anesthetized with pentobarbital and blood was taken from the hearts' ventricle. Shock elicits a significant increase in CORT in PN14 and PN21 pups, but fails to do so in neonatal pups (PN8). Maternal presence in PN14 and PN21 pups prevents the CORT response to shock (Moriceau & Sullivan, 2006; Moriceau et al., 2006). The mother was anesthetized by urethane to prevent her from interfering with the shock administration, as well as to control for maternal behavior and milk letdown. The pups were, however, free to contact the mother. Stress =foot-shock; PN =postnatal day.

Table 1

Odor-Shock Conditioning in Rat Pups

	Sensitive period (PN1–9)		Conditional sensitive period (PN10–15)	
Measure	**Saline**	**CORT increase (systemic or intra-amygdala CORT)**	**Saline**	**CORT reduction (maternal presence, adrenalectomy, amygdala CORT receptor blocker)**
Behavior	Preference	Aversion	Aversion	Preference
Corticosterone level	Low	High	High	Low
2-DG uptake				
Olfactory bulb	Increase	No change	No change	Increase
Anterior piriform cortex	Increase	No change	No change	Increase
Posterior piriform cortex	No change	Increase	Increase	No change
Amygdala	No change	Increase	Increase	No change

Note. The table summarizes our understanding of the brain regions supporting sensitive period (PN1–9) odor preference learning and conditional sensitive period (PN10–15) odor aversion learning. Learned odor preferences during the sensitive period are associated with increased neural activity, as measured by 2-deoxyglucose uptake within the olfactory bulb and anterior piriform “olfactory” cortex. There is no significant activity within the amygdala or posterior piriform cortex. In contrast, when CORTis high endogenously (PN12) or via treatment (PN8), learned odor aversions are associated with significant activity within the amygdala and posterior piriform cortex. Maternal presence during odor-shock conditioning in PN12 pups decreases CORT levels, increases neural activity within the olfactory bulb and anterior piriform “olfactory” cortex, inhibits posterior piriform cortex and amygdala responsivity, and permits odor preference learning. Note, this is the same neural circuitry responsible for PN8 preference learning (Moriceau & Sullivan, 2006; Moriceau et al., 2006; Raineki, Shionoya, Sander, & Sullivan, 2009; Sullivan, Landers, et al., 2000). PN = postnatal day.