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Unique infant neurobiology produces distinctive trauma processing

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ABSTRACT

Trauma experienced in early life has unique neurobehavioral outcomes related to later life psychiatric sequelae. Recent evidence has further highlighted the context of infant trauma as critical, with trauma experienced within species-atypical aberrations in caregiving quality as particularly detrimental. Using data from primarily rodent models, we review the literature on the interaction between trauma and attachment in early life, which highlights the role of the caregiver's presence in engagement of attachment brain circuitry and suppressing threat processing by the amygdala. Together these data suggest that infant trauma processing and its enduring effects are impacted by both the immaturity of brain areas for processing trauma and the unique functioning of the early-life brain, which is biased towards forming robust attachments regardless of the quality of care. Understanding the critical role of the caregiver in further altering early life brain processing of trauma is important for developing age-relevant treatment and interventions.

1. Introduction

For decades, it has been known that the brains of altricial species, such as humans and rodents, continue to develop after birth (Sanchez et al., 2001; De Bellis and Thomas, 2003; Levine, 2005; Plotsky, Thrivikraman et al., 2005; Andersen and Teicher, 2008; Roth et al., 2011; Landers and Sullivan, 2012). Environment and genetics sculpt the developing brain to more closely fit diverse environments to enhance survival. However, this open system is vulnerable to environmental perturbation, and early-life experiences have an increased saliency to affect cognitive and emotional development. Extreme and species-atypical environmental perturbations can initiate a developmental pathway that results in maladaptive cognitive or emotional behavior, or even mental illness. However, understanding environmental influences on brain development has been challenging because the process of building a brain is complex. Moreover, many of the effects of early life trauma are revealed only in certain circumstances, such as during periods of high stress or are not expressed until a later stage of development (Ainsworth, 1969; Gunnar et al., 2007; Landers and Sullivan, 2012; Raineki et al., 2012b). Although mechanisms mediating these early-life environmental effects are poorly understood, the quality of caregiving has been identified as a critical variable in initiating trajectories of cognitive and emotional development.

For altricial species, the caregiver provides the main salient sensory stimuli within the early nest environment. As such, caregiver behavior and caregiving quality are paramount in defining the early experience of the infant pup and the attachment formed between the infant and the caregiver. Researchers studying multiple species, including Konrad Lorenz, Niko Tinbergen, Harry Harlow, John Bowlby, and Mary Ainsworth, (Hess, 1962; Harlow and Harlow, 1965; Ainsworth, 1969; Bowlby, 1978; Harmon et al., 1984) demonstrated the importance of attachment quality in defining cognitive and emotional development across multiple species. Although variations in caregiving naturally occur within species, these researchers highlighted the detrimental effects of species-atypical experiences, such as prolonged separation or physical abuse from the caregiver (Gunnar et al., 2007), considered to be trauma models of abuse and neglect. This research quickly linked poor attachment quality with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis as one effector for disrupting development following aberrant early-nest experience (Sanchez, 2006; Gunnar et al., 2007; Rincon-Cortes and Sullivan, 2014), although other factors are also likely important (Sullivan and Dufresne, 2006). In particular, integration of human and animal research has shown that chronic overactivation of the HPA axis in response to early-life trauma can produce long-term adaptations in the HPA response to stress, and these changes are thought to be involved in the pathogenesis of disorders such as PTSD, depression and anxiety (Graham et al., 1999). Although this research has begun to identify causal relationships between early-life

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trauma with the caregiver and deficits in cognitive-emotional development, the inherent complexity of abuse requires elegant animal models that balance translational potential with the ability to determine mechanisms.

2. Trauma processing in early life is different

2.1. Some brain areas that process adult trauma are not yet mature

The substrate of early life experience on the brain involves changes at nearly every level of analysis, from cellular signaling to behavioral expression. Indeed, through the decades, almost every neurotransmitter system and a multitude of brain regions have been implicated as mediating or impacted by early life experiences, including changes in receptors, neurotransmitter levels, brain structure, epigenetics, the microbiome, immune system and homeostasis maintenance (Knudsen, 2004; Andersen and Teicher, 2008; Drury et al., 2012; Heim and Binder, 2012; Blakemore and Mills, 2014; Buran et al., 2014; Coria-Avila et al., 2014; Nelson et al., 2014; Pechtel et al., 2014; Penhune and de Villers-Sidani, 2014; Poulos et al., 2014; Yu et al., 2014; Zannas and Binder, 2014; Bale, 2015; Hartley and Lee, 2015; Tost et al., 2015; Umemori et al., 2015; Werker and Hensch, 2015). It is beyond the scope of this review to describe brain development in detail (Casey et al., 2005; Houston et al., 2014). However, a few basic concepts are helpful for the present discussion, which can apply to human, primate, and rodent models. First, the brain develops throughout early life and adolescence, with different brain areas each having their own developmental trajectory and maturation; these developmental trajectories can involve changes in neural connectivity, receptor function, and structure (Wakefield and Levine, 1985; Berdel et al., 1997; Cunningham et al., 2002; Jagalska-Majewska et al., 2003; Knudsen, 2004; Van Eden and Uylings, 2004; Brummelte and Teuchert-Noodt, 2006; Chareyron et al., 2012a,b; Ehrlich et al., 2012). Furthermore, all brain areas are involved in myriad behaviors, and each brain area's microcircuits supporting each behavior have their own developmental trajectory; this makes it nearly impossible to say a particular brain area becomes functional at a specific age. However, careful functional studies have helped identify species-typical milestones in brain development and how these milestones are compromised following environmental perturbations in infancy.

In order to understand how early-life abuse trauma impacts the child, it is necessary to consider whether brain areas implicated in adult trauma processing are functional in the infant. Although brain regions involved in basic physiological functions are certainly mature at birth, they continue to mature and develop more complex connections throughout postnatal development. Areas involved in higher order functioning and complex behaviors are more delayed in maturation, including the amygdala, hippocampus, and prefrontal cortex (PFC), with evidence suggesting specific functions of each of these brain areas emerge at different ages. For instance, plasticity in the form of long-term potentiation (LTP) emerges in the hippocampus around the second postnatal week in rodents (Harris and Teyler, 1983; Wilson, 1984; Swann et al., 1990; Bekenstein and Lothman, 1991), while contextual learning comes online around postnatal (PN) day 23 (Raineki et al., 2010a). Furthermore, some brain areas likely encode information at one age but influence behavioral expression at a later age (Pattwell et al., 2012; Poulos et al., 2014). Emerging evidence also suggests age-specific functions for some brain areas, such as the important role of the rodent locus coeruleus (LC) in attachment, described below (Landers and Sullivan, 2012). Finally, patterns of connectivity between brain regions have distinct developmental trajectories that can be further perturbed by abuse trauma.

Although trauma in early life has ubiquitous effects on brain development, the amygdala, hippocampus and prefrontal cortex have been identified as critical loci of dysfunction following trauma with a caregiver. These regions are critical for processing trauma in adulthood and maturation of these brain areas and their connectivity occurs slowly over early life in humans, nonhuman primates, and rodents (Graham et al., 1999; Sanchez et al., 2001; Skuse et al., 2003; Holland and Gallagher, 2004; Casey et al., 2005; Bachevalier and Loveland, 2006; Brummelte and Teuchert-Noodt, 2006; Tottenham and Sheridan, 2009; Tottenham, 2012; Gee et al., 2013; Lavenex and Banta Lavenex, 2013; Malter Cohen et al., 2013). The amygdala is considered to be the critical structure involved in the formation and storage of learned threat associations (Davis et al., 1994; Phelps and LeDoux, 2005), with the lateral nucleus as the site of storage and plasticity for threat memories and the central nucleus acting as the threat output center through its projections to downstream structures involved in expression of threat responses, such as freezing (eg. paraventricular nucleus(Krettek and Price, 1978; LeDoux et al., 1988; Phelps and LeDoux, 2005)). The basic neuroanatomical architecture of the human amygdala is present by birth (Humphrey, 1968; Ulfig et al., 2003) and in females, amygdala growth is complete by four years old (Giedd et al., 1996). It has been suggested that amygdala function emerges around 6–7 months of age in human infants, using the visual cue of fearsome faces (Jones et al., 2009; Jessen and Grossmann, 2015). This assessment is concordant with behavioral measures of amygdala emergence in children, including separation anxiety and fear of heights (Jones et al., 2009; Strawn et al., 2014; Jessen and Grossmann, 2015; Strawn et al., 2015). In typically-developing rodents, this region becomes engaged in threat learning at PN10 (Sullivan et al., 2000a; Sullivan and Holman, 2010).

The hippocampus is critically important in many diverse functions, including the ability to remember specific information about events, such as where and when events occurred. Research in humans suggests that functional connectivity between the amygdala and hippocampus appears to be delayed in children (Gee et al., 2013, 2014; Gee, 2016). As a child's hippocampus is difficult to image using brain scanning techniques, there is scant data on hippocampal functional emergence, although hippocampal growth rates greatly slow down as a child approaches 2 years old (Qin et al., 2014). Evidence from rodent studies on development of the hippocampus shows that the region demonstrates considerable growth during the initial postnatal period, coming online at PN23 in species-typical rearing conditions (Raineki et al., 2010a; Chareyron et al., 2012a,b).

Finally, the developmental trajectory of the prefrontal cortex remains poorly understood. For example, evidence from human fMRI studies suggests that the anterior cingulate cortex (ACC) and medial PFC (mPFC) come online around 4 months and as early as 4 years in children, respectively (Allman et al., 2001; Gee et al., 2013; Graham et al., 2015). On the other hand, the PFC subarea orbitofrontal cortex (OFC), which has an important role in processing the valence of odors (Zald and Pardo, 1997; Gottfried et al., 2002; Anderson et al., 2003; Rolls, 2015) is thought to be functional by 2–3 years of age. Although the PFC, hippocampus and amygdala are robustly involved in trauma processing during adulthood, their involvement in processing early-life trauma is poorly understood, due to their limited maturity and/or functional unavailability. Research in human and animal models has added a new layer of complexity to this work by showing that traumatic experience itself can affect the developmental trajectory of these brain regions as well as their connectivity with one another (Gee et al. 2013).

2.2. The infant attachment circuit

In order to understand how early life abuse trauma perturbs brain development, it is critical to consider the unique ecological niche of the altricial infant. Indeed, the infant brain is not an immature version of the adult brain, but rather, exhibits specific functional adaptations suited for the demands of early life. As altricial infants are unable to fight predators, find mates or acquire resources, they must rely on caregivers for protection, warmth and food during a temporally constrained sensitive period in early life (Bowlby, 1978; Spear and Rudy, 1991); forming attachments to caregivers ensures these demands are

met. Thus, the infant brain exhibits distinct functional adaptations for robust attachment formation to ensure survival.

The neurobiology of infant attachment has mostly been described using rodents, though a unique attachment learning circuit has been posited across a variety of species. Just as imprinting in avian species occurs wherein the chick quickly learns to express approach behaviors toward the caregiver, rodents also use a unique learning circuit within the brain to support forming attachments. This attachment circuit involves the olfactory system, the piriform cortex, and the locus coeruleus, as will be discussed below. Infant rodents (pups) make an excellent model for understanding attachment learning because, similarly to humans and other primates, they must learn to attach to the caregiver, which can be a male or female. As pups can neither see nor hear until the third week of life, olfaction is the main sensory system used for interactions with the caregiver; in contrast, newborn humans use all of their sensory systems (Ehret, 1976; Weber and Olsson, 2008). The caregiver odor is of paramount importance to survival, as pups rely on this cue for proximity seeking, nipple attachment for nursing, and social behavior; without these, pups cannot access nourishment, thermoregulation, or maternal care (Sullivan et al., 1990).

For many years, pup approach behavior towards the caregiver (henceforth, maternal) odor was considered to be innate or guided by pheromones. However, we now know that the maternal odor is learned (Sullivan and Leon, 1986; Sullivan and Wilson, 1991; Leon, 1992). This learning ensures that pups, like children, can form robust attachments to adoptive caregivers of either sex. In the rodent, this learning process begins in the prenatal environment, where amniotic odors acquire a preferred valence and direct nipple attachment at birth (Landers and Sullivan, 2012). The odor itself is arbitrary, as neutral odor placed into the amniotic fluid a few days before birth can become salient (Pedersen and Blass, 1982; Smotherman and Robinson, 1987; Hepper and Cleland, 1998). A new maternal odor can also be rapidly learned outside of the womb; given the fact that a dam's odor can change with her diet, this flexibility is especially important to ensure a robust attachment. For example, a novel odor (e.g. peppermint) placed either on or in the vicinity of the mother will readily take on the orienting properties of maternal odor (Sullivan et al., 1990; Cheslock et al., 2000; Roth and Sullivan, 2005). Outside the nest, if a novel odor is paired with a stimulus that mimics maternal behavior, such as milk, warmth, or stroking (grooming), this odor acquires the value of a new maternal odor that is not only preferred, but can support nipple attachment and social behavior in the absence of a natural maternal odor (Sullivan et al., 1986a; Roth and Sullivan, 2005, 2006; Roth et al., 2013).

The neurobiology supporting robust attachment towards maternal odor is remarkably simple during the first nine days of life in rodents (see Fig. 1). At this age, the first relay station for olfactory processing is the olfactory bulb, the site of learning-associated odor plasticity. This learning requires that the odor is paired with copious amounts of NE from the LC, the sole source of norepinephrine NE to the olfactory bulb (Sullivan et al., 1992; Sullivan et al., 2000b; Yuan et al., 2000). Because the infant LC fails to show habituation or show auto-inhibition, the large amounts of NE required for attachment-related plasticity are available (Nakamura et al., 1987; Winzer-Serhan et al., 1996). In addition, the olfactory bulb exhibits enhanced responding to the learned maternal odor (Sullivan et al., 1990; Yuan et al., 2002; Roth and Sullivan, 2006; Raineki et al., 2009). The olfactory bulb axons of mitral cells project directly to the piriform cortex (Schwob and Price, 1984; Swanson and Petrovich, 1998; Haberly, 2001; Wilson and Stevenson, 2003); this region plays an important role in assigning the hedonic value to a learned odor in a region-specific manner. In particular, the anterior piriform is engaged by odors learned during this sensitive period learning, while the posterior piriform is engaged in response to learned odor aversions in older pups and adults (Roth and Sullivan, 2005; Moriceau and Sullivan, 2006; Moriceau et al., 2006). The sensitive period ends when pups are around 10 days old, as the LC becomes more adult-like. At this time, NE release is greatly restricted and specific and takes on a modulatory role in odor learning that is more similar to what has been described in adult rats (Ferry and McGaugh, 2000). As mentioned above, PN10 is also the age when the amygdala begins to facilitate learned avoidance responses to cues associated with threat; as will be discussed below, this may explain why pups fail to learn aversions to abusive caregivers associated with painful stimuli.

Human children also exhibit robust learning about the caregiver (DeCasper and Fifer, 1980; Sullivan et al., 2011), which enables an infant to attach to adoptive parents of either sex. Although we are unsure if the mechanism supporting this learning in human infants is the same as the rodent, NE plays a critical role in bond formation across multiple species (Nelson and Panksepp, 1998; Numan and Young, 2016). Furthermore, NE levels are very high at birth and over the first two years of life in children (Lagercrantz and Bistoletti, 1977), suggesting it is a phylogenetically conserved system.

2.3. Infant trauma processing and regulation by the caregiver

The unique effects of abusive or neglectful caregiving must be understood within the conceptual framework of the caregiver as a regulator of altricial infant emotion and physiology. This regulation has been shown to be critical for a child's response to trauma but also interaction with the world, such as infant response to novelty (Nachmias et al., 1996; Gunnar et al., 1996). Caregiver regulation of the infant is seen during perfunctory caregiving, e.g. soothing a crying infant or by smiling at or tickling a baby to increase arousal. This stimulation of baby's sensory systems changes the baby's physiology; for example, soothing a stressed baby can lower stress hormone levels as well as regulate the baby's brain (Hofer, 1973; Hofer et al., 1976; Stone et al., 1976; Hofer, 1984; Sullivan et al., 1986a,b; Hofer, 1994). While many different people can help regulate the baby, the caregiver gains special access to this regulation as the baby learns about the caregiver from birth. This unique access also renders the caregiver most salient in perturbing infant emotional development resulting from poor regulation within low-quality attachments.

Although there are natural variations in maternal care, extremely stressful circumstances can push these normal variations into trauma-associated maternal care; these can engender a disordered attachment, which is associated with a decreased regulatory capability of the infant by the caregiver (Carlson et al., 2014; Hostinar et al., 2014). In humans, disordered attachment related to trauma is linked with social behavioral problems in later life (Caron et al., 2015; Bryant, 2016) and there is some evidence for a link with depressive symptoms (Shevlin et al., 2014, but see Fearon et al., 2010); however, the mechanisms for these changes remain poorly understood. Animal research has shown that abuse trauma in early life produces structural and functional changes in the amygdala and a changed threat system (Caldji et al., 1998; Maestripieri et al., 1999; Sanchez et al., 2001; Elzinga et al., 2003; Teicher et al., 2003; Roth and Sullivan, 2005; Ivy et al., 2008; Bagot et al., 2009; Raineki et al., 2012b; Tang et al., 2014; Sullivan and Opendak, 2018). By modeling attachment in normal and traumatic circumstances in infant rats, we can explore some of the neural mechanisms by which early life attachment programs cognition and emotional processing throughout the lifespan.

2.4. Disordered attachments form to abusive caregivers due to unique infant neurobiology

In species throughout the animal kingdom, including humans, young form attachment to abusive caregivers (Hess, 1962; Stanley, 1962; Harlow and Harlow, 1965; Salzen, 1970; Rajecki et al., 1978). Attachments to an abusive or negligent caregiver may have short-term advantages, e.g. there is neonatal access to care, despite long-term consequences associated with compromised threat processing and emotion expression. Indeed, this abuse-related attachment appears phylogenetically conserved and occurs across species, including chicks

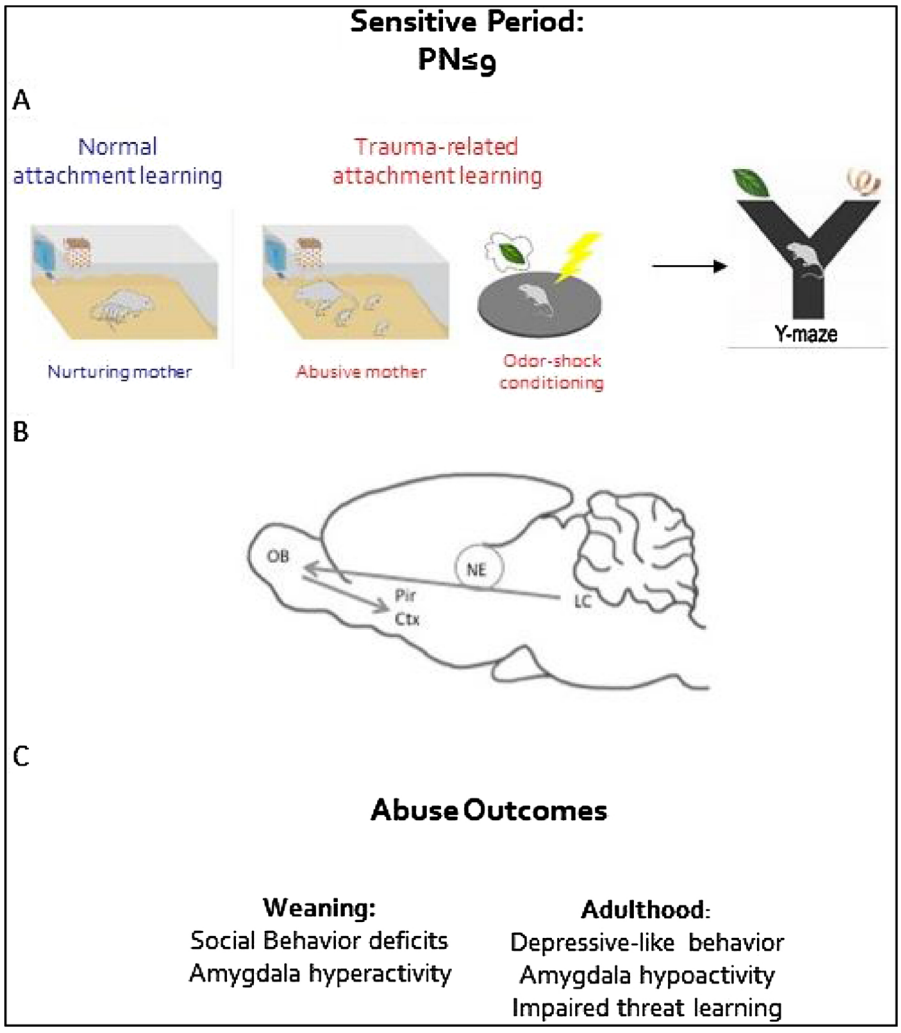

Fig. 1. Unique characteristics of the infant brain. A, During a sensitive period, which ends when pups are PN9, infant neurobiology is biased towards attachment learning, regardless of the quality of care, including attaching to abusive caregivers (Roth and Sullivan, 2005). We mimicked attachment learning to an abusive caregiver by using an odor-shock conditioning paradigm, which enabled us to uncover a developmentally unique learning system in pups that typically supports attachment learning. Notably, when aversive stimuli are presented the pup's attachment learning network is engaged, rather than the adult amygdala-dependent fear learning (Sullivan et al., 2000a). Indeed, following either abusive rearing or odor shock conditioning, pups tested in a Y-maze approach the odor paired with infant adversity. B, This specialized attachment learning system occurs during a sensitive period for attachment learning (PN < 9), with this learning supported by an attachment learning neural circuit involving norepinephrine (NE) from the locus coeruleus (LC) to produce approach responses to the odor (Moriceau et al., 2006). It is noteworthy that this newly learned odor is not simply approached, but the odor also takes on qualities of the maternal odor to support nipple attachment and enhance prosocial behaviors to the mother, even if she is physically abusive. Thus, infants during a sensitive period for attachment will learn attachment regardless of the quality of care, showing a preference for the maternal odor following abuse as well as repeatedly pairing the maternal odor with a tail shock. C, There are short-term benefits from this robust attachment learning network as it ensures pups remain with the abusive caregiver and receive some food and water required for survival. However, there are long-term costs that become salient at weaning, including social behavior deficits, disrupted fear/threat system and a hyperactive amygdala (Sullivan et al., 2000a; Raineki et al., 2010a,b,c; Sevelinges et al., 2011; Raineki et al., 2012a,b). In adolescence and adulthood, rats with a history of abuse will exhibit decreased preference for a social stimulus over a non-social stimulus in Crawley's three chamber test, depressive-like behavior in the forced swim test and impaired fear conditioning (Rincon-Cortes and Sullivan, 2014; Sarro et al., 2014).

that form attachments after being shocked during imprinting (Hess, 1962; Salzen, 1970; Rajecki, Lamb et al. 1978), dogs (Stanley, 1962) and monkeys raised with a wire surrogate that inflicts pain (Harlow and Harlow, 1965). More recent work has modeled abusive caregiving in nonhuman primates and again shows that infants retain strong preference for the abusive caregiver (Maestripieri et al., 1999; Sanchez et al., 2001; Suomi, 2003; O'Connor and Cameron, 2006). Low quality or inconsistent caregiving can be reflected in the quality of attachments, with abusive or disordered attachments associated with impaired social and emotional behavior throughout the lifespan (Gunnar et al., 1996; Nachmias et al., 1996; Gunnar et al., 1996). As will be discussed below, these robust attachments form despite low quality care because of the unique circuitry of the infant brain.

The rodent literature provides some clues to understanding the unique response of the infant brain to traumatic cues. In adulthood, rats typically engage the amygdala, hippocampus, and PFC when learning about threatening stimuli. While these brain areas facilitate threat learning and avoidance in adulthood, immaturity of these brain areas in infancy and a brain biased towards forming attachments prevents the acquisition of aversion to a caregiver during a sensitive window. This process of learning to attach to an abusive caregiver occurs in pups within the nest and can be modeled in the laboratory. To effectively model disordered attachment in non-human animals, we can capitalize on the phylogenetically conserved abuse resulting from stress and low resources in most species. In rats, this abuse can be induced by constraining nest-building resources available to the dam. Provided with insufficient nest-building materials, the dam repetitively nest builds, steps on and drags pups across the cage floor, causing pain-related vocalizations. Despite this painful experience with the mother, pups still show a robust preference for the maternal odor in a Y-maze choice test (Raineki et al., 2010b) (see figure for summary). Furthermore, infusing a novel peppermint odor into the cage environment during this abusive maternal care fails to activate amygdala-dependent learned odor aversion towards the peppermint. Instead, pups show a preference for the odor and the odor takes on the qualities of maternal odor to support nipple attachment and prosocial behaviors (Sullivan et al., 1986b; Roth and Sullivan, 2005). It is important to note that, in this low resources model of abusive care, the mother still cares for pups, and pups gain weight normally, but this care is tempered with rough treatment (Roth and Sullivan, 2005). As such, this low bedding model may be even more informative about real-life conditions of abuse-related trauma where typical care is punctuated with bouts of abuse and maturation occurs at a typical rate. These results complement other infant models of early life experience that range from low care within a normal range of maternal care (Meaney, 2001), to maternal separation and novelty (Plotsky et al., 2005; Callaghan and Richardson, 2014;

Tang et al., 2014), to the more extreme reduction in nest building material combined with an aversive wire mesh floor, producing a highly abusive mother (Ivy et al., 2008). Together, these and other models have shown that the type, intensity, duration and timing of the variations in infant care can produce a host of distinct neurobehavioral phenotypes in later-life.

While demonstrating that rat pups maintain a robust attachment to an abusive mother is important to show cross-species validity, this complex model is difficult to parse for brain mechanisms responsible for this paradoxical pain-associated attachment. Since attachment is learned and pups rely on the olfactory system for attachment, we can complement the low resources model with a simpler model that relies on the olfactory classical conditioning learning paradigm. Just as new maternal odors can be learned when a previously neutral odor is paired with stimuli evoking maternal care, such as milk or stroking, in this paradigm, odor is repeatedly paired with a moderately painful foot-shock (0.5 mA) or tail-pinch. Although it has been shown that pairing moderate pain with a neutral odor produces an odor preference in young pups (Spear, 1978; Haroutunian and Campbell, 1979; Sullivan et al., 1986b; Camp and Rudy, 1988), this procedure also produces a new maternal odor (Raineki et al., 2012a). Specifically, the previously neutral odor paired with mild pain can induce nipple attachment as well as social approach behavior if infused into a nest environment where the dam has been washed of her own odor (Perry et al., 2016). Later in development, pups exposed to this repeated odor-shock treatment recapitulate the functional impairments observed following maternal abuse trauma, including impaired threat conditioning, atypical social behavior and depressive-like behavior. Importantly, shock treatment in the absence of an odor cue fails to produce these impairments (Raineki et al., 2010a; Sevelinges et al., 2011). The combined approach of using an ecologically-relevant model of low resources-induced maternal abuse and the experimentally controllable situation of odor-shock proxy abuse outside the nest provides unique insight into why abuse-related attachments are formed and maintained.

The inability of the paired odor-pain procedure to produce odor avoidance is not due to pups' inability to detect the aversive stimulus or feel pain. Noxious stimuli readily elicit < PN9 pup escape responses and the pain threshold does not appear to change as shock switches from supporting preference to supporting aversion learning (Stehouwer and Campbell, 1978; Collier and Bolles, 1980; Emerich et al., 1985; Barr, 1995). As described above, the pup's olfactory bulb, anterior piriform cortex, and a hyper-functioning LC work together to generate enhanced odor preference learning to produce an attachment. Furthermore, low endogenous levels of circulating CORT in pups' immature stress system prevent experience-dependent plasticity in the amygdala to support robust attachment toward odor cues associated with pain (Sullivan et al., 2000a; Moriceau et al., 2006; Barr et al., 2009). However, repeated trauma in the form of maternal abuse and odor-shock pairings upsets the tenuous balance between attachment bias and stress buffering to produce lasting effects on the developing attachment and threat circuits.

2.5. Uncovering abuse trauma effects in early life

While the effects of infant abuse trauma can be identified, in general these effects are not always readily detectable (Pollak et al., 2000). Indeed, rat pups exposed to either the odor-shock model of early-life trauma or low resources-induced maternal abuse from PN3-PN8 fail to demonstrate aversion towards the maternal odor: their social behavior towards the mother is normal in measures of nipple-attachment and choices towards her odor in a Y-maze (Raineki et al., 2012b; Rincon-Cortes et al., 2015). However, an injection of CORT (modeling a high stress environment) to PN8 pups following either abuse paradigm produced fewer choices towards the maternal odor and less time nipple-attached, as well as amygdala hyperactivity (Raineki et al., 2012b). Again, pups reared in typical (non-abusive) conditions fail to demonstrate amygdala activation before PN10. In addition, CORT injection fails to activate the amygdala or disrupt attachment behaviors in pups reared with a control nurturing mother, pups subjected to shock alone, or pups exposed to repeated odor-stroke pairings. These results parallel data in humans, wherein stress uncovered latent neurobehavioral deficits in children with disordered attachment following abuse and/or neglect (Ainsworth, 1969; Gunnar et al., 1996). In addition, pups reared with an abusive mother from PN3-8 were shown to have increased CORT, heightened amygdala reactivity, and impaired attachment behaviors with the mother, suggesting that chronic stress induced premature amygdala engagement (Raineki et al., 2010b). This suggests that normal and abusive attachments, while appearing to have similar supporting neural circuits in infancy, have divergent neural circuits that can be uncovered by CORT administration (Raineki et al., 2012b). Specifically, CORT administration activates the amygdala in abused pups only, suggesting that abuse induces latent plasticity in this brain area at a time when it is functionally dormant in normally-reared pups. Importantly, these data from CORT injection studies suggest that trauma by an abusive caregiver or experience with repeated pairing of traumatic shock with attachment circuitry changes amygdala development so that stress produces a hyperactive amygdala that halts normal social behavior (Ainsworth, 1969; Gunnar et al., 1996); pharmacological inactivation of the amygdala prevents these deficits, indicating a causal role for the amygdala in these behaviors (Raineki et al., 2012a).

As individuals mature, stress is no longer necessary to uncover the effects of early life adversity. Stress-induced neurobehavioral deficits in infants with a history of trauma predicted later life depressive-like behaviors and amygdala, hippocampus, and PFC dysfunction (Raineki et al., 2012b; Perry et al., 2016). Specifically, rats with a history of abuse trauma exhibited social behavior deficits with peers as early as PN20, marked by decreased exploration of a conspecific in a three-chamber test of sociability(Crawley, 2004); this preceded depressive-like symptoms in sucrose consumption and forced swim tests beginning in adolescence (PN45) and persisting through adulthood, accompanied by task-dependent amygdala functional changes (see Fig. 1) (Sevelinges et al., 2007, 2008, 2011; Raineki et al., 2012a). These results mirror results in humans, where childhood dysfunctional social behavior occurs prior to onset of depression in adolescence (Mason et al., 2004; Letcher et al., 2009; Mazza et al., 2010).

2.6. Enduring impact of infant trauma with the caregiver

Trauma associated with the early caregiving environment compromises emotional and cognitive development and heightens vulnerability to later life mental health difficulties; these phenomena have been modeled using a variety of animal species for decades (Levine, 1957; Denenberg, 1963; Harlow and Harlow, 1965; Levine et al., 1985; Famularo et al., 1992; Hofer, 1994; Teicher et al., 2003; Andersen and Teicher, 2008). This is also shown in our complementary models: rearing by an abusive mother or experiencing repeated paired odor-shock during a sensitive period in early development results in amygdala-prefrontal cortex (PFC) deficits, anxiety and depressive-like behavior and social behavior impairments that emerge around weaning age (Sevelinges et al., 2007; Sevelinges et al., 2008; Raineki et al., 2010b,c; Sevelinges et al., 2011; Roth et al., 2014; Raineki et al., 2015; Rincón-Cortés and Sullivan, 2016). As mentioned above, these impairments can be uncovered before adolescence if infants are stressed following the trauma.

While the effects of early life caregiver abuse are ubiquitous throughout the brain, we have focused on the amygdala in our rodent model and have identified a causal role for the amygdala in attachment-related trauma. Although pups with a history of maternal abuse in a low-resources model as well as the repeated odor-shock proxy abuse paradigm failed to demonstrate amygdala-dependent learned aversion towards the maternal odor, CORT injection in these pups uncovered amygdala hyperactivity. This amygdala activation could be observed

before PN10, the species-typical age at which amygdala-dependent learning becomes engaged, suggesting that early-life abusive attachment recruited the amygdala despite pups failing to learn the amygdala-dependent aversion to the maternal odor (Raineki et al., 2010b). Long-term changes to amygdala function following repeated odor-shock conditioning and/or low resources-induced maternal abuse were observed in a task-specific manner: odors paired with pain attenuated amygdala neural activity supporting adult odor-fear learning, while social behavior and depressive-like behavior were accompanied by amygdala hyperactivity (see Fig. 1) (Sevelinges et al., 2007, 2008). These results suggest that abuse trauma in early life may produce latent changes in the amygdala, potentially underlying some of the long-term behavioral effects associated with abuse, including the development of psychiatric disorders.

3. Concluding remarks

Evolution has ensured that the infant brain of altricial species is designed to support attachment to the caregiver, even when the quality of care is compromised or even abusive. This relies upon the unique neurobiology of the altricial infant brain, which processes even traumatic information by the attachment circuitry (LC-OB-Anterior Piriform), rather than the regions used to process trauma in adulthood (Amygdala-HPC-PFC). Through the use of two complementary rodent models of early-life abuse, we have shown that when trauma is repeatedly paired with olfactory learning within the sensitive window for attachment, the attachment circuitry can prematurely engage the immature amygdala, a key player within adult-like threat-processing circuitry. This can produce latent amygdala hyperactivity followed by impairments in emotionality and social behavior lasting into adulthood.

Although a growing literature has linked the amygdala, attachment quality, and stress axis development in humans, little is known regarding the specific mechanisms by which trauma acts on these systems. Furthermore, no consensus has been reached on the mapping of human and rodent age; data on the ontogeny of threat learning in children draws parallels between weaning, the age at which rats prepare for independence outside the nest, and various developmental milestones in children, including beginning school, entering adolescence, or leaving home as young adults (Poulton et al., 1999; Gunnar and Donzella, 2002; Tottenham and Sheridan, 2009; Tottenham, 2012; Gee et al., 2013; Callaghan and Tottenham, 2016). Although early life has been shown as a sensitive period for caregiver modulation of children's stress responses (Nachmias et al., 1996; Gunnar et al., 1996; Gunnar and Donzella, 2002), the neurobiology and developmental timing of this social buffering remain unknown. Further work will be necessary to determine whether humans engage the same neural circuitry as rodents in forming attachments to a caregiver and whether the child's brain is predisposed towards forming attachments at this age.

Our results complement a vast array of other infant experience models, including removing the source of pups' sensory stimuli by separating them from the mother (maternal separation/deprivation), exposure to trauma or novelty outside the nest, CORT manipulation, and neonatal handling. Taken together, these manipulations have identified a vast array of mechanisms mediating the enduring impact of abuse trauma, ranging from molecular events to systems-level changes. Understanding how the diverse types of infant experiences relate to the myriad disorders expressed across the lifespan requires appreciation of the unique neurobiology of the infant brain and the ecological niche of the altricial infant.

Author contributions

MO and RMS wrote the review.

Conflict of Interest

None.

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