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Reconsidering the nature of threat in infancy: Integrating animal and human studies on neurobiological effects of infant stress

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ABSTRACT

Early life stress has been associated with elevated risk for later psychopathology. One mechanism that may contribute to such long-term risk is alterations in amygdala development, a brain region critical to stress responsivity. Yet effects of stress on the amygdala during human infancy, a period of particularly rapid brain development, remain largely unstudied. In order to model how early stressors may affect infant amygdala development, several discrepancies across the existing literatures on early life stress among rodents and early threat versus deprivation among older human children and adults need to be reconciled. We briefly review the key findings of each of these literatures. We then consider them in light of emerging findings from studies of human infants regarding relations among maternal caregiving, infant cortisol response, and infant amygdala volume. Finally, we advance a developmental salience model of how early threat may impact the rapidly developing infant brain, a model with the potential to integrate across these divergent literatures. Future work to assess the value of this model is also proposed.

Early life stress has been associated with elevated risk for depression, suicide attempts, anxiety disorders, and substance abuse (Teicher and Samson, 2013). One mechanism that may contribute to such long-term associations is alterations in developmental trajectories of stress-sensitive brain regions. Yet, the potential beginnings of these trajectories in infancy, a period of particularly rapid brain development (Gilmore et al., 2012), remain largely unstudied. In the current paper, we review the literatures on early stress and amygdala development in both animal and human studies, including the few emerging studies in human infancy, to develop a model of how very early life stress may affect early neurobiological development.

Several literatures need to be considered to arrive at a more integrated view of how early stressors may affect infant neurobiology. First, an extensive rodent literature has explored the effects of low maternal nurturance/maternal unpredictability on early offspring stress regulation and brain development (e.g. Baram et al., 2012; Drury et al., 2016; Meaney et al., 1985). Second, Sullivan and her colleagues have presented evidence for a hyporesponsive period to maternal aversive stimuli in early rodent development (Moriceau et al., 2010; Moriceau and Sullivan, 2006; Sullivan and Holman, 2010; Sullivan and Opendak, 2020). Third, in the human literature, McLaughlin and Sheridan's threat/deprivation framework integrates a large body of work differentiating the effects of early threat versus deprivation on brain volumes and neural activity in later childhood and adulthood (Machlin et al., 2023; McLaughlin et al., 2019, 2021). All of these areas of study are relevant to considering how early stress may affect limbic brain development during human infancy, but the different literatures generate somewhat diverging models regarding expected relations between limbic brain development in human infancy and aversive maternal care versus low-nurturing/depriving maternal care that are difficult to integrate.

One model with the potential to integrate across these divergent findings from animal and human research is a Developmental Salience Model of Threat. In a Developmental Salience Model, the nature of salient threat cues changes with development, such that the most potent threat signals in infancy are cues to the caregiver's absence or unavailability, with a shift later in development to the greater salience of threat of bodily injury. An important further corollary in this model is

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that these developmentally layered forms of threat also require fundamentally different adaptive/defensive responses, with threat of caregiver unavailability requiring the infant to increase their calling and contact-seeking, while threat of attack or injury evokes the well-delineated defensive responses of fight, flight, or freeze (Barlow, 2002; Cannon, 1927).

In the body of the paper below, we first review the relevant animal and human literatures that converge on a developmental salience model and then integrate the model with these literatures in more detail.

Given the wide scope of the concept of early adversity, this review will focus on caregiver-related adversity, consistent with a recent meta-analysis that found different neurobiological effects of socioeconomic adversity, such as poverty, and caregiver-related adversity, such as abuse or deprivation of care (Vannucci et al., 2023). In addition, we will focus on effects of adverse care on the hypothalamic-pituitary-adrenal (HPA) axis and on limbic regions involved in the stress-response network, particularly the amygdala (Teicher et al., 2016; Fig. 1). The amygdala is a key region involved in responding to threat, and both the animal and human literatures have extensively explored amygdala alterations in response to caregiver-related threat. The amygdala is particularly rich in cortisol-binding receptors (Avishai-Eliner et al., 1996; Gilmore et al., 2012; Payne et al., 2010; Vázquez-Roque et al., 2012), and the amygdala plays a crucial role in providing regulatory feedback to the HPA axis (Herman et al., 2012, 2016). Thus, altered amygdala volume and function are likely to occur in the context of altered HPA-axis function (Vyas et al., 2004, 2006). (For detail on HPA-axis function, see Hostinar et al., 2014; for detail on amygdala function, see Tottenham, 2012; Vyas et al., 2004).

There is also an expanding literature on the intergenerational transmission of effects of the mother's exposure to childhood abuse or neglect to her infant. Proposed mechanisms of effect include alternations in maternal gestational hormones (Buss, 2017) and alterations in maternal and infant gene expression (Scorza et al., 2020; Turecki and Meaney, 2016), as well as alterations in postnatal maternal behavior (Guyon-Harris et al., 2021; Khoury et al., 2021). Potential effects of prenatal gestational hormones and epigenetic changes on development of the infant threat (salience) network are beyond the scope of this review. However, studies specifically linking mother's childhood abuse or neglect exposure to development of her infant's stress response network are cited where relevant.

Below, we briefly review the key findings of the relevant animal and human literatures, highlighting the somewhat divergent findings within the rodent literature, as well as the contrasting findings in the human literature. We then review the limited emerging findings on development of the threat response system among human infants during the first two years of life. Finally, we describe the integrative value of a Development Salience Model in more detail in relation to the reviewed literatures, and we draw out future directions for studies to assess the utility of the proposed model.

1. Animal Models: Offspring Stress Response and Caregiver-Related Adversity

1.1. Rodent models: Infant stress network response to low nurturance/unpredictability

An extensive literature from randomized rodent studies demonstrates that both maternal separation and low maternal nurturance/unpredictability[2] during the neonatal period produce an increase in basal corticosterone secretion (Kuhn et al., 1990; Levine, 1994) and elevated corticosterone/adrenocorticotropic hormone (ACTH) levels in response to acute stress (Avishai-Eliner et al., 1995; Hofer et al., 1994; Levine, 1994). These effects of maternal low nurturance/unpredictability have been confirmed both in the context of genetic breeding paradigms for low-nurturing behavior, as well as in the context of limited bedding paradigms that stress the mother (Avishai-Eliner et al., 2001; Baram et al., 2012; Drury et al., 2016; Gilles et al., 1996; Raineki et al., 2010; Roth and Sullivan, 2005; Caldji et al., 1998). Furthermore, low maternal nurturance/unpredictability has been linked to epigenetic modifications that augment HPA activity through methylation of the promoter region of the AVP gene which increases hypothalamic arginine vasopressin synthesis (Caldji et al., 1998; Murgatroyd et al., 2009; Plotsky and Meaney, 1993; Turecki and Meaney, 2016). Importantly, these modifications resulting from low nurturance/unpredictability in Generation 1 are passed on to Generation 2 and generate similar patterns of low nurturance in Generation 2 and increased offspring stress in Generation 3.

1.2. Rodent models: Hyporesponsive period to aversive maternal stimuli

The above extensive literature on maternal low nurturance/unpredictability coexists with a second literature demonstrating that the corticosterone response in neonatal rodents (before postnatal day [PND] 10) differs significantly from that of older rodents due to hyporesponsiveness of the HPA axis (Colombel et al., 2023; Levine, 1994; Naeem et al., 2022; Rincón-Cortés and Sullivan, 2014; Sullivan and Opendak, 2021; Walker and Vrana, 1993). The basolateral amygdala is difficult to activate during the hyporesponsive period in young pups, but pharmacologically increasing corticosterone levels can induce threat learning, via corticosterone-amygdala activation (Sullivan and Opendak, 2021). Sullivan and colleagues have further shown that the hyporesponsive period of HPA activity for neonatal rodents is specific to aversive stimuli associated with the mother (Moriceau and Sullivan, 2006; Sullivan and Opendak, 2021), given that the neonatal rat HPA axis is fully capable of responding to stressful stimuli external to the caregiving system, such as cold exposure or saline injection (Dent et al., 2000; Yi and Baram, 1994). Thus, Sullivan and colleagues have theorized that the hyporesponsive period to maternal aversive stimuli may exist to facilitate the formation of an attachment bond to the caregiver, even in the context of harsh or abusive caregiver behavior. This hyporesponsive period to aversive maternal behavior, then, may serve as a sensitive period for attachment learning (Moriceau et al., 2010; Sullivan and Holman, 2010).

Attachment learning in rodents is centered around the pup's acquisition of a preference for the maternal odor (Kojima and Alberts, 2009; Leon, 1992; Sullivan and Opendak, 2021). In order to study abusive attachment dynamics in a rodent model, Sullivan and colleagues developed an odor-shock paradigm in which an artificial odor (e.g., peppermint) is paired with the maternal odor so that rat pups display an odor preference and actively approach the conditioned odor (Roth and Sullivan, 2005; Sullivan et al., 2000). This learned odor is then paired with a 0.5 mA shock. Unlike adult rats, neonatal rats (<PND 10) do not exhibit amygdala activation or a robust corticosterone response to the shock when it is paired with the learned maternal odor, and they continue to approach the learned odor despite the repeated shock (Moriceau and Sullivan, 2005; Sullivan et al., 2000; Fig. 2). This is not due to the inability of pups to perceive pain, as their pain threshold remains relatively consistent during the neonatal period, and they emit vocalizations indicative of distress in response to the shock (Sullivan et al., 2000).

Importantly, the quality of maternal care impacts the duration of the hypo-responsive period. Maternal separation, in particular, is a potent stressor for the pup (removal of the pups from the mother for 3 hours per day; Sánchez et al., 2001). This separation procedure is sufficient to evoke a corticosterone response in pups within the hyporesponsive

[2] Different rodent labs use different summary terms to characterize maternal behaviors, with low nurturance used in the context of differential breeding paradigms (Caldji et al., 1998) and unpredictability used in the context of limited nesting paradigms (Baram et al., 2012). Here, we use the combined designation to refer to this body of rodent research.

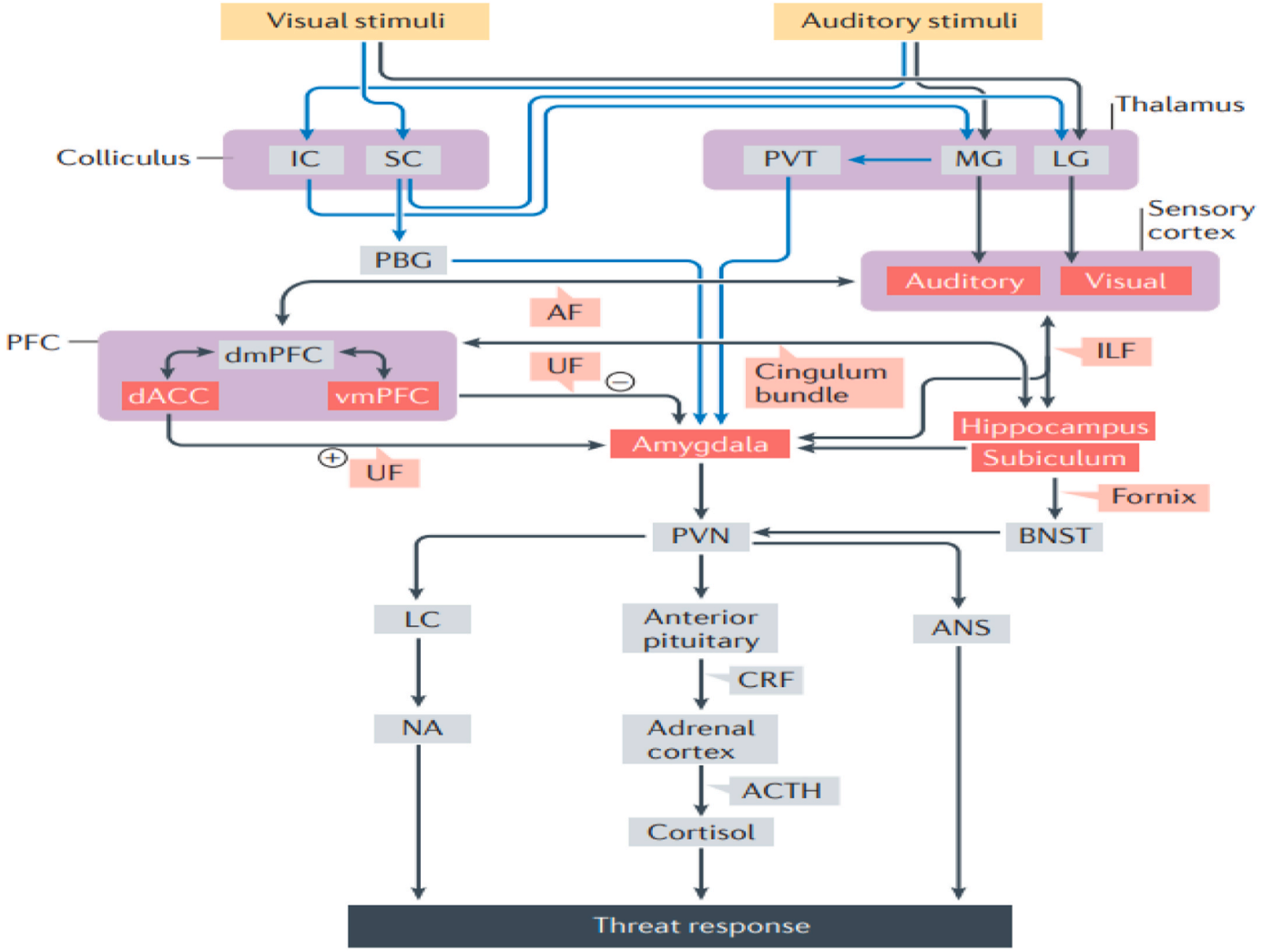

Fig. 1. Diagram delineating brain regions involved in detecting and responding to threat.Note. Reprinted with permission from Teicher et al., *Nature Reviews Neuroscience*, 2016.

period (Huot, 2004), and the separation procedure also appears to disrupt maternal behavior, with dams exhibiting delays in retrieving pups and in initiating licking and grooming upon reunion (Sánchez et al., 2001). In addition, Callaghan and Richardson (2011), (2012) exposed pups to the separation paradigm from postnatal days 2–14, which resulted in an early transition to the adult fear learning system, involving both elevated corticosterone and amygdala responses (see Callaghan et al., 2014, for more detail).

While the hyporesponsive period provides a short-term protective buffer against caregiver-related aversive learning in neonatal rodents, aversive caregiver-related experiences toward the end of that period can leave a lasting imprint on amygdala function and social behavior in adulthood (Raineki et al., 2012), resulting in a marked reduction in approach behavior (Perry et al., 2016) and sociability (Rincón-Cortés and Sullivan, 2016) and an increase in depressive-like behavior in the Forced Swim Test (FST) (Pollak et al., 2010; Porsolt et al., 2001).

1.3. Non-human primate models: Infant stress response network and caregiver-related adversity

Non-human primates (NHP) offer another valuable opportunity to explore how deviations in early care affect the developing stress response system. Non-human primates are closer in their evolutionary relation to humans, with more similarity in early developmental timetables (e.g. more extended dependence on the caregiver) and caregiving experiences (e.g., single offspring; Drury et al., 2016).

Infant maltreatment is a phenomenon documented in both wild and captive NHP populations (Brent et al., 2002; Johnson et al., 1996; Maestripieri and Carroll, 1998). During the initial three months post-partum, two behaviors resembling forms of infant maltreatment have been observed, leading to overt signs of infant distress, including screams and tantrums. First, physically abusive behavior is observed, consisting of violent behaviors toward the infant that cause pain and distress, such as dragging, crushing, or throwing the infant (Maestripieri, 1998; McCormack et al., 2006). Second, infant rejection is observed, which involves behaviors such as pushing the infant away when it seeks maternal contact (Maestripieri, 1998; McCormack et al., 2006). Such early maltreatment has developmental consequences comparable to those seen in maltreated human children, including increased anxiety, emotional reactivity, social deficits, increased cortisol levels (Drury et al., 2017; McCormack et al., 2022), and peripheral inflammation (Howell et al., 2013; K. McCormack et al., 2006, 2009; Sanchez et al., 2010). In addition, alterations are seen in brain systems that impact emotional and stress responses, including impaired serotonin function, reductions in white matter structural integrity, larger amygdala volumes, and alterations in cortico-limbic connectivity (Howell et al., 2013, 2014; Morin et al., 2020), with early higher cortisol levels predicting some of these alterations (Howell et al., 2013; Morin

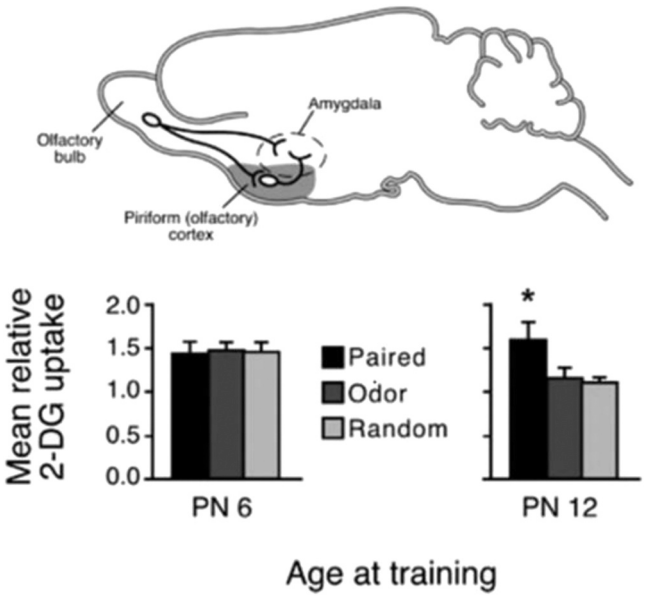

Fig. 2. Rodent pup amygdala responses at postnatal day 6 and postnatal day 12 to odor-shock pairing Note. PN = Postnatal Day; PN6 = Postnatal day 6; PN12 = Postnatal day 12. Reprinted with permission from Moriceau & Sullivan, *Developmental Psychobiology*, 2005.

et al., 2020).

However, in NHP research to date, there has been more emphasis on studying the developmental effects of infant maltreatment overall, potentially due to the co-occurrence of maternal abuse and rejection in NHP's, so that differentiating effects associated with aversive/abusive caregiving and effects associated with low-nurturing/unpredictable care has not been a focus of research. The NHP literature associating early maltreatment with HPA function is mixed. Many primate studies show blunted HPA (cortisol and ACTH) responses to stress in peer-reared infants (Barr et al., 2004; Capitanio et al., 2005; Clarke, 1993), as well as primates exposed to neglect (Dettling et al., 1998) and parental deprivation (Dettling et al., 2002a, 2002b). However, other NHP research shows elevated HPA activity in response to early maltreatment (Fahlke et al., 2000; Higley et al., 1992; Kraemer et al., 1983, 1984; Sánchez et al., 2005). This variability may be accounted for by methodological heterogeneity (differences in procedures/manipulations), as well as genetic and temperamental differences among NHP species (Zhang et al., 2017). In addition, there is not yet a body of research that explores the possibility of an early hyporesponsive period to maternal aversive stimuli among non-human primates (Zhang, 2017).

1.4. Summary and integration: Animal models

One hypothesis that might integrate the apparently conflicting findings in the animal literature is that there may be developmental changes in the types of stressors that are most salient to the stress response network at different points in early development. While a large rodent literature has demonstrated that low maternal nurturance/unpredictability is a reliable stressor for the neonatal rodent pup, Sullivan and colleagues (e.g., Moriceau and Sullivan, 2006; Opendak and Sullivan, 2016) have also shown that there is an early hyporesponsive period to caregiver-related aversive stimuli. Taken together, these literatures suggest that maternal unresponsiveness may be more developmentally salient to the stress network very early in life, while aversive maternal behavior may become more salient after the early period of consolidation of the attachment relationship.

2. Human Studies Among Older Children and Adults

Rodent models have focussed on very young pups in the first days of life, while human studies have primarily focussed on limbic brain development later in childhood and adulthood (Cuartas et al., 2021; McLaughlin et al., 2017, 2019). In addition, animal models consistently find that low nurturance/unpredictability is associated with increased HPA-axis activity and with increased amygdala volume and activity in offspring. In contrast, human studies find that early threat is related to *reduced* amygdala volume later in childhood, while indices of deprivation (institutional care, neglect, low maternal engagement) have not been consistently associated with alterations in amygdala volume or activity (Machlin et al., 2023; McLaughlin et al., 2014, 2019; Sheridan, 2023). Finally, threat/deprivation models consider experiences of both threat and deprivation as likely to engage the HPA axis and cortisol response (McLaughlin et al., 2015), but only experiences of threat of attack or injury are viewed as linked to activation of the amygdala (McLaughlin et al., 2021). This model contrasts with the animal literature, in which corticosterone elevation has been causally linked to increased amygdala volume, with amygdala growth demonstrated at the cellular level following chronic corticosterone administration (Vyas et al., 2004, 2006).

2.1. Caregiver-related adversity and amygdala volume among human children and adults

The threat/deprivation framework posits that experiences of threat and deprivation have different influences on human neurobiological development (McLaughlin et al., 2014, 2019). Threat involves harm or potential harm to the child and includes experiences such as sexual abuse, physical or psychological abuse, witnessing domestic violence, and exposure to community violence. Deprivation experiences, in contrast, involve an absence of expected inputs from the environment, including nurturance and stimulation, as in neglectful environments (McLaughlin et al., 2017, 2019).

Among children exposed to early adversity but assessed for neurobiological outcomes later in childhood, experiences of childhood abuse (threat) have been associated with reduced amygdala volume, particularly in the right hemisphere (McLaughlin et al., 2019; Schaefer et al., 2022; Teicher et al., 2016). In contrast, deprivation, but not threat, has been associated with reductions in cortical grey matter thickness and alterations in frontoparietal circuits linked to cognitive ability, language skills, and executive function (McLaughlin et al., 2017, 2019; Schaefer et al., 2022). Deprivation has not been consistently associated with amygdala volume or activity in studies of older children and adults (McLaughlin et al., 2019). Thus, one point of divergence between animal research in infancy and the threat/deprivation literature on older children and adults is that the animal literature links low maternal nurturance/unpredictability to *increases* in stress responding and *increases* in amygdala volume and activity, while threat of attack or injury in the threat/deprivation framework has been repeatedly related to *reduced* amygdala volume, particularly in the right hemisphere.

The link between indices of neglect or deprivation and amygdala volume among human children and adults is less consistent. Studies of amygdala volume among children and adolescents raised in institutional care during infancy and subsequently adopted have yielded mixed results, with several showing larger volumes (Mehta et al., 2009; Tottenham, 2012; Tottenham et al., 2010; Van Tieghem et al., 2021), others showing smaller volumes (Hanson et al., 2015; Hodel et al., 2015), and others showing no differences (Edmiston, 2011; Sheridan et al., 2012). Results reported by Van Tieghem et al. (2021) may provide a way of understanding these discrepancies. Using an overlapping cohort design, they examined the longitudinal developmental trajectories of amygdala volumes among post-institutionally reared (PI) children and family-reared (FR) comparison children from age 4 years to age 20 years. The PI group exhibited *larger* amygdala volumes than FR children

before age 6.5 years, but significantly *smaller* amygdala volumes between ages 11 years and 16.5 years. This pattern occurred because the comparison children demonstrated age-related amygdala growth throughout childhood, plateauing at a higher volume than PI children around the ages of 9 years to 10 years. Consequently, even though the PI group had larger estimated amygdala volumes at younger ages, their lack of subsequent age-related growth during childhood led to smaller amygdala volumes relative to the FR group from ages 11 years to 16.5 years (Fig. 3; Van Tieghem et al., 2021).

Notably, human studies that have assessed less severe forms of deprivation *during infancy,* such as low maternal nurturance or low sensitivity, have also generally found increased limbic volumes later in

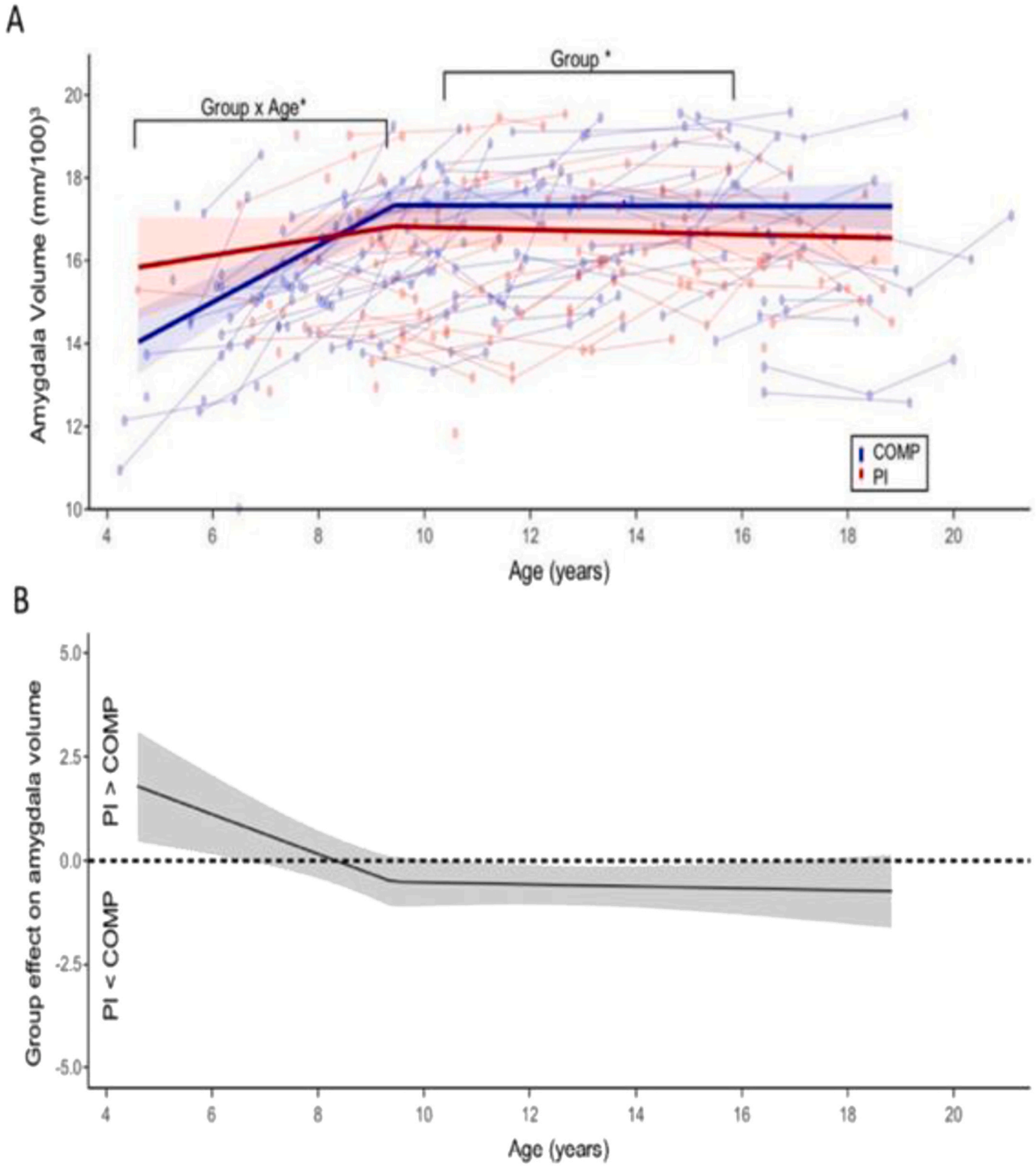

Fig. 3. Effects of previous institutional care on child amygdala volume depend on age at assessment. Note. PI = Previous Institutional care; COMP = Family Reared Comparison Group. Reprinted with permission from Van Tiegham et al., *Cognitive Developmental Neuroscience,* 2021.

childhood or adulthood (amygdala and hippocampus: Bernier et al., 2019; Cortes Hidalgo et al., 2019; Khoury et al., 2019; Lyons-Ruth et al., 2016; Rao et al., 2010; Rifkin-Graboi et al., 2015). In contrast, lower maternal nurturance and sensitivity assessed *after infancy* have shown inconsistent effects on limbic volumes in childhood (Kok et al., 2015; Luby et al., 2012). Thus, studies of caregiver low nurturance/insensitivity, as assessed in early life, more closely parallel the rodent studies, both in methods (age of exposure/type of stressor) and in amygdala findings (increased volume).

These increased amygdala volumes associated with lower maternal nurturance in human infancy contrast with the *decreased* child and adult amygdala volumes related to exposure to childhood abuse (McLaughlin et al., 2019; Teicher et al., 2016). Thus, both developmental timing (infancy versus childhood/adolescence) and type of stressor (deprivation/low maternal nurturance versus threat of physical harm) may influence how adversity affects human limbic development, with deprivation/low nurturance initially resulting in increases in amygdala volume.

It remains unclear whether experiences of abuse in the first two years of life might generate a similar developmental trajectory, characterized by initially increased amygdala volumes compared to typically developing children that then plateau and fail to show developmentally normative increases, leading to reduced amygdala volumes in comparison to normative patterns by adolescence (e.g. Whittle et al., 2014). This might account for why individuals experiencing childhood abuse but who are assessed in adolescence or adulthood typically exhibit smaller amygdala volumes compared to controls (Butterworth et al., 2012; Calem et al., 2017; Dannlowski et al., 2012; Driessen et al., 2000; Riem et al., 2015; Schmahl et al., 2003; Van Velzen et al., 2016). Studies evaluating the long-term effects of abuse versus deprivation on amygdala volume during human infancy are needed.

2.2. Caregiver-related adversity and HPA-axis response

In the first few years of life, the animal literature clearly demonstrates that experiences of deprivation of care are potent triggers for the HPA axis. However, under conditions of chronic stress, counter-regulatory mechanisms result in the downregulation of the HPA axis (Heim et al., 2004; Makino et al., 1994; McEwen, 2008). Thus, although hyper-responsiveness of the HPA axis is often a response to acute stress, hypo-cortisolism has been linked to experiences of chronic stress (Fries et al., 2005; Gunnar et al., 2006; McEwen, 2001).

Among human children, HPA-axis hypo-responsiveness has been related to early experiences of neglect (Gunnar, 2020, 2021; Koss et al., 2016). Low early morning cortisol levels were observed among young children in institutional care (Gunnar and Vazquez, 2001), among toddlers adopted from orphanages (Bruce et al., 2013), and among young children placed in foster care (Dozier et al., 2006; Fisher et al., 2005), with almost 40 % of maltreated foster children exhibiting low morning cortisol (Fisher, 2005). Furthermore, the best predictor of low morning cortisol was a measure of neglectful care, rather than physical or sexual abuse (Fisher, 2005). These patterns appear to persist long after the cessation of early neglect (Gunnar, 2020; Koss et al., 2016; McLaughlin et al., 2015).

Converging with these HPA-axis effects of severe caregiving deprivation, Doom et al. (2022) investigated parent-reported disengaged parenting and parental harshness from infancy to age 15 years in the Fragile Families and Child Well-being study (Reichman et al., 2001). Parental disengagement, particularly during the first year of life, was associated with lower hair cortisol concentrations (HCC) at age 15 years, while parental harshness at age 15 years, but not in infancy, was linked to higher HCC at age 15 years. Finally, patients with varied psychiatric disorders reporting high levels of neglect at age three years exhibited lower HCC levels in adulthood than individuals with low levels of early neglect (Schalinski et al., 2019).

However, early abuse may also be related to blunted cortisol patterns, given that some meta-analyses find blunted cortisol reactivity in youth exposed to early life stress (Bunea et al., 2017; Schär et al., 2022). In addition, Bernard et al. (2017) showed that maltreatment (abuse and neglect combined) was associated with lower wake-up cortisol levels, and Peckins et al., (2023) found that maltreated youth had blunted cortisol reactivity at age 9 years relative to comparison youth, with sexually and physically abused youth showing blunted cortisol reactivity and recovery trajectories relative to emotionally abused youth and neglected youth. Thus, the relations between types of child maltreatment and cortisol hyper- or hypo-activity remain unclear. Many factors are likely to contribute to inconsistencies in the literature, such as developmental timing and the type and severity of adversity (Ouellet-Morin et al., 2019; Young et al., 2021).

In summary, both early neglect and later abuse may be related to down-regulation of cortisol responses as the child matures. However, it is unclear when such downregulation might begin developmentally, with the majority of studies assessing HPA activity in childhood or adulthood rather than during the first two years of life. Given that down-regulation is expected to follow a period of chronically heightened cortisol activity, prolonged elevation of cortisol levels in infancy may lead to down-regulation of cortisol by early childhood.

3. Human Studies in Infancy

Because the human infant is born with experience-expectant capacities to engage in continuous mutual regulatory interactions with caregivers (Jaffe et al., 2001; Feldman, 2003), lack of adequate responsive regulation by the caregiver may impact the brain's stress response network differently in the first two years of life than during later developmental periods. The infant brain develops rapidly over the first two years of life, with grey matter volume (GMV) reaching 80 % of adult volume in that time (Gilmore et al., 2012; Groeschel et al., 2010). White matter axonal connections also develop rapidly prenatally, with pruning and myelination largely beginning after birth (Dubois et al., 2014; Knickmeyer et al., 2008) and continuing to be refined into adulthood (Groeschel et al., 2010). The amygdala, in particular, increases steeply in volume postnatally over the first 3 years of life (Alex et al., 2023; Uematsu et al., 2012). Such periods of rapid growth are hypothesized to signal experience-expectant sensitivity to environmental inputs, which fosters early adaptation to the affordances in one's environment (Turecki and Meaney, 2016).

However, the study of neurobiological development in the first two years of human life has been limited, first by the difficulty of scanning the infant without sedation under natural sleep in a strange environment, and, second, by the likelihood of motion artifact due to infant movement in the scanner. Therefore, the study of infant brain morphology and functional connectivity over the first two years of life is an area of investigation that is likely to proceed slowly and with modest sample sizes. We first overview the emerging studies on caregiver-related adversity, HPA-axis functioning, and amygdala development among human infants. We then propose a developmental salience model with the potential to integrate findings across human and animal literatures.

3.1. Caregiver-related adversity and stress regulation in infancy

A large body of work indicates that maternal sensitive and responsive behavior in infancy is linked to more optimal patterns of infant cortisol regulation, particularly faster recovery to a mild stressor, whereas less sensitive caregiving is linked to more prolonged activation of the HPA axis (e.g., Atkinson et al., 2016, for review). Notably, for human infants as well as rodent pups, the most reliable stress paradigms have involved manipulation of the presence and responsiveness of the mother rather than the manipulation of external stressors. Among human infants, the most widely used stress paradigms have been the Still-Face Paradigm (4–8 months; Tronick et al., 1978) and the Strange Situation Procedure

(12–18 months; Ainsworth et al., 1978). Thus, more sensitive maternal behavior is associated with more optimal recovery to stressors that involve manipulation of maternal responsiveness (Still Face Paradigm) or repeated brief maternal separations (Strange Situation Procedure).

A separate literature on maternal buffering, including both human and animal studies, has explored the important role of the caregiver's sensitive presence as a buffer for the infant stress response system to stressors *external to the caregiving relationship*, such as inoculation, unfamiliar adults, or mildly frightening toys (see Hostinar et al., 2014, for review). This important body of work finds that caregiver presence and/or sensitive quality of caregiver regulation has an important muting effect on child stress responses to threats outside the caregiving system. However, there is a crucial difference between the caregiver's effectiveness as a buffer against threats *external to the caregiving relationship* and how the caregiver's own low responsiveness, unpredictability, or attack is directly experienced by the infant threat response system, which is the subject of the present paper. As reviewed above, research across species indicates that stresses within the caregiving relationship itself, such as low maternal care/unpredictability and abuse/aversive handling, function as direct sources of both behavioral distress and physiological threat. Because the focus of the present paper is on stress *within the caregiving relationship itself*, the work on maternal buffering is not reviewed further here.

While maternal sensitive and responsive behavior in human infancy has been linked to more optimal patterns of infant cortisol regulation, less attention has been paid to differentiating among aspects of maternal insensitivity and how different aspects of insensitivity may have different relations to the infant stress response at different developmental points. Importantly, insensitive caregiving can vary widely from harsh/intrusive behavior to a pronounced lack of engagement. Given the differential salience for neonatal rodent pups of maternal low nurturance/unpredictability compared to aversive behavior, it will be important to differentiate low nurturance/unpredictability versus aversive dimensions of caregiving in future studies during human infancy.

3.2. Caregiver-related adversity and amygdala volume and connectivity in human infancy

In human developmental research, few studies have assessed aspects of parenting in infancy in relation to brain volumes in infancy (Ilyka et al., 2021). Sethna et al. (2017), in a sample of 38 infants, found that maternal low positivity (positive communication and engagement) was associated with decreased total brain volumes among 4-month-olds, whereas lower maternal sensitivity, defined as timely, consistent responsive behavior, was associated with smaller subcortical GMV (putamen, thalamus, globus pallidus, caudate). In addition, in a sample of 17 infants, Rifkin-Graboi et al. (2015) reported that lower maternal sensitivity was related to larger hippocampal volume, but not amygdala volume, among 6-month-olds.

Two additional studies have examined the mother's childhood history of maltreatment in relation to limbic volumes or connectivity during the neonatal period. Moog et al. (2018) found that maternal childhood maltreatment was associated with reduced newborn GMV but was not related to newborn amygdala or hippocampal volume. Hendrix et al. (2021) found that the mother's history of emotional neglect was related to increased newborn connectivity between amygdala and prefrontal cortex, which may be an index of accelerated brain development in the face of adversity (Callaghan et al., 2014).

3.3. Infant HPA-axis activity and amygdala volumes in human infancy

Among human infants and children, the theoretically important relation between cortisol output and amygdala volume has barely been studied. Among school-aged children, two studies reported that higher cortisol levels in response to a frustration-based laboratory stressor were associated with smaller amygdala volumes (Fowler et al., 2021; Pagliaccio et al., 2014). However, amygdala volumes were assessed among older children rather than infants, and cortisol was assessed in relation to non-caregiver-related stressors rather than in relation to aspects of maternal care.

To our knowledge, the only study in human infancy to assess relations between infant cortisol output and amygdala volumes was by Khoury et al. (2023a), among 57 mother-infant dyads stratified for mother's childhood history of maltreatment. Khoury et al. (2023a) found that increased infant cortisol output at 4 months during a mild caregiver-related stress paradigm (Still-Face Paradigm) was related to enlarged infant amygdala and hippocampal volumes assessed during the first two years of life (Fig. 4a,b). Elevated infant cortisol at 4 months was further related to concurrent disoriented maternal interaction with the infant in the Still-Face Paradigm (Fig. 5). Finally, mediational models supported a significant mediated relation from disoriented maternal behavior to enlarged infant amygdala and hippocampal volumes through elevated infant cortisol output.

It is notable that the dimension of maternal behavior associated with infant cortisol output was the dimension of disorientation, which indexes disconnected (odd or false) affect/behavior that blocks effective affective communication between mother and infant. Although the substantial differences between human and rodent caregiving make comparisons difficult, disoriented maternal behavior may be consistent with rodent models of low maternal nurturance/maternal unpredictability, where the rodent mother is either disinclined or anxious and distracted from nurturing her infant pups (Drury et al., 2016; Turecki and Meaney, 2016).

Also importantly, in light of rodent data on a hyporesponsive period to maternal aversive behavior, maternal harsh and intrusive components of interaction exhibited no relation to elevated infant cortisol levels. Maternal negative, hostile, or intrusive behavior has been the most widely studied aspect of problematic parenting, with negative effects spanning across development (e.g., Lyons-Ruth et al., 1999; Pinquart, 2017; Smith and Farrington, 2004). In infancy, negative-intrusive maternal behavior has been specifically associated both with a maternal history of abuse and with infant negative affect at four months of age (Khoury et al., 2022; Khoury et al., 2023). Thus, we might expect that maternal negative-intrusive behavior would be similarly associated with infant cortisol levels, but this was not the case.

Certain aspects of these early findings from human infants parallel the findings from the rodent literature, both in specifying a key role for cortisol levels in mediating effects of maternal behavior on enlarged amygdala volumes and in pointing to unresponsive but not actively threatening components of caregiving behavior as having particular relevance to the infant stress system. While these findings are only suggestive and need further exploration and replication, they suggest the importance of assessing infant cortisol in future work linking caregiver-related adversity to infant neurobiological development.

While less directly addressing the infant's own experience of care, further work in this sample is indicating that *the mother's* childhood history of neglect, but not abuse, was also related to increased infant cortisol output, and mother's history of neglect was indirectly related to her infant's enlarged amygdala and hippocampal volumes through the mediation of infant cortisol levels (Khoury et al., 2024). In contrast, the mother's history of childhood abuse was not related to early infant cortisol levels (Khoury et al., 2024).

Further, using the larger MIND sample (N = 181) from which the MRI subsample was recruited, the mother's childhood neglect was related to her current disoriented interaction with her infant. In addition, maternal childhood neglect and maternal disoriented interaction interacted to elevate infant cortisol output (Chasson et al., under review). Thus, the data are describing a pathway in which the mother's childhood experiences of neglect, in the context of her subsequent disoriented interaction with her infant, are related to increased infant cortisol output. As already described, cortisol output was further related to enlarged amygdala and hippocampal volumes.

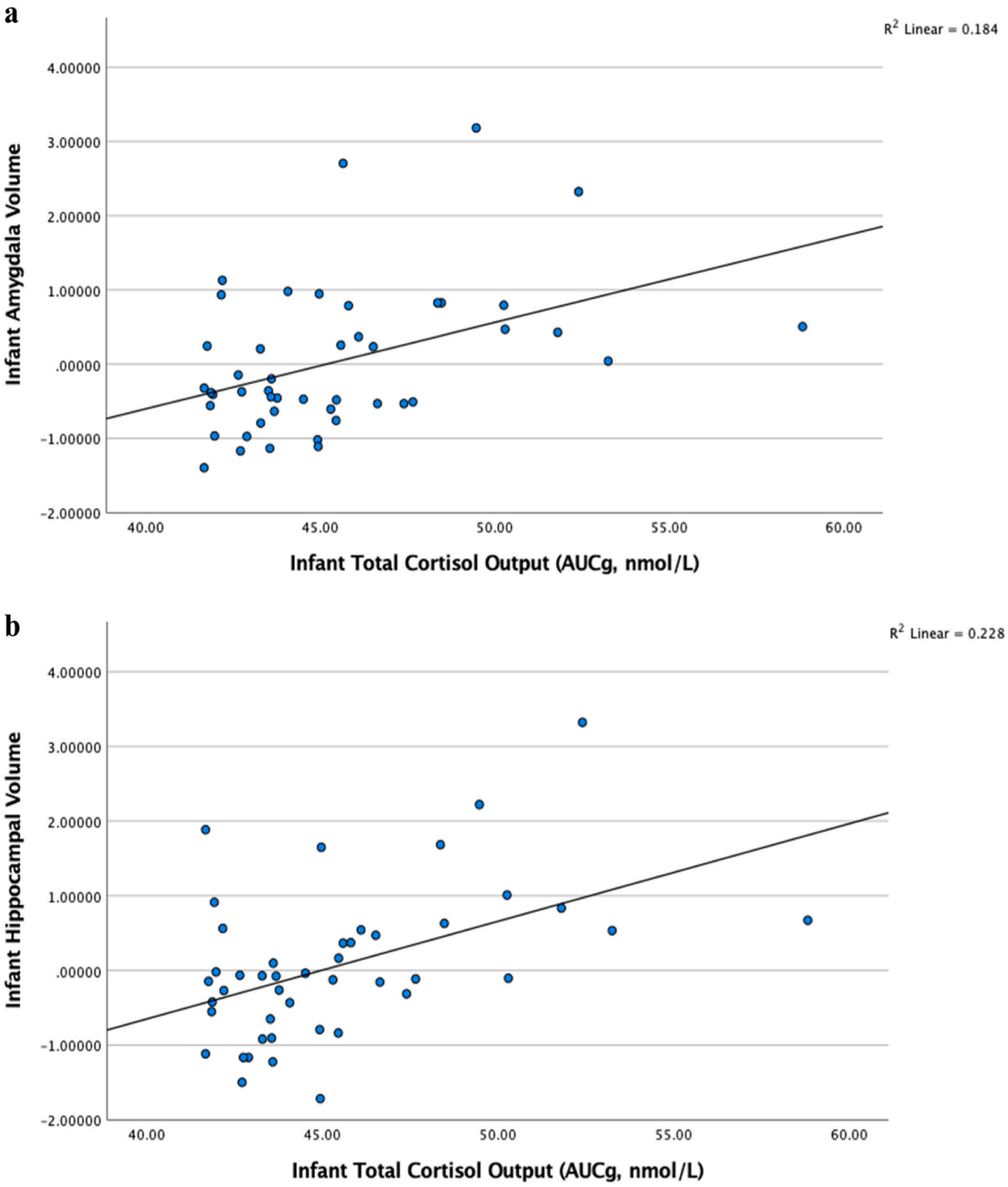

Fig. 4. a,b. Distribution of infant amygdala and hippocampal volumes as a function of infant cortisol output (AUCg), adjusted for effects of age at MRI, sex, and GMV. Note. Plots show standardized residuals. Limbic volume metric is mm3. Regression data presented without estimation of missing data, with age, sex, and GMV controlled; Plotted data reflect missing data on infant cortisol at one or more of the three time points contributing to AUCg for 10 infants and removal of one outlier for amygdala volume and two outliers for hippocampal volume, amygdala N = 46, hippocampus N = 45. AUCg was log-transformed and winsorized. Final regression analyses were conducted using FIML (N = 57). Reprinted from Khoury et al., (2023a), Psychoneuroendocrinology.

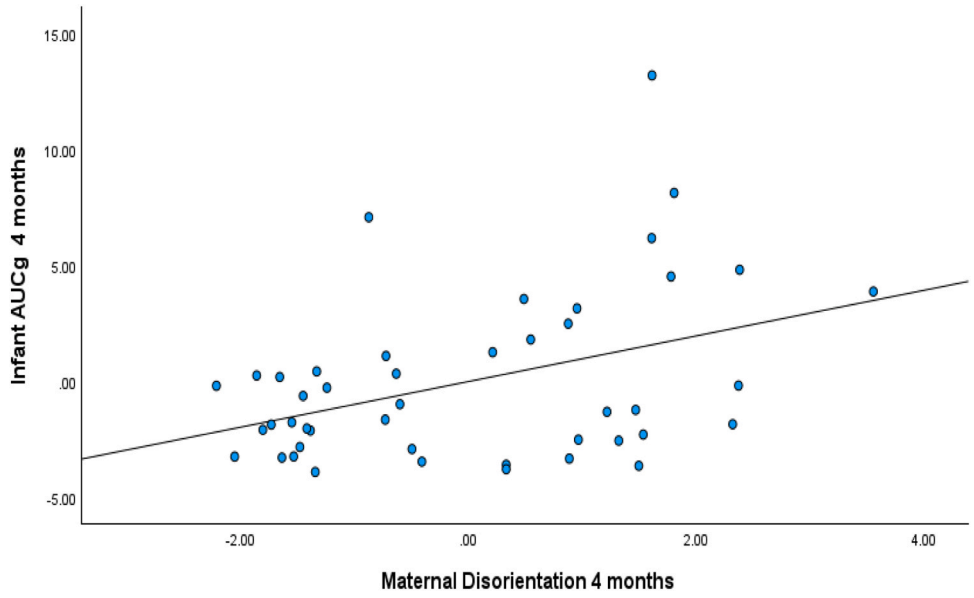

Fig. 5. Distribution of infant cortisol levels (AUCg) at four months as a function of maternal disorientation, adjusted for time of cortisol collection. Note. Plots show standardized residuals. AUCg was log-transformed and winsorized. AUCg metric is nmol/L. Regression data presented without estimation of missing data, with cortisol collection time controlled; Plotted data reflect N = 45, with missing data on maternal interaction for one mother and missing data on one or more of the three time points needed for computing AUCg for 10 infants. Final regression analyses presented in text were conducted using FIML (N=57). Reprinted from Khoury et al., (2023a), *Psychoneuroendocrinology*.

In contrast to these findings suggesting a pathway from the mother's childhood neglect to her infant's enlarged amygdala volume, the mother's childhood abuse was related to her infant's *reduced* amygdala volume, and this finding was specific to the right hemisphere (Fig. 6; Lyons-Ruth et al., 2023). This finding gains enhanced salience in light of the repeated finding among older children and adults that experiences of abuse are differentially associated with reduced amygdala volume, specifically in the right hemisphere (McLaughlin et al., 2019; Teicher et al., 2016). However, this relation to reduced right amygdala volume only became significant after 18 months of age. This later onset of an intergenerational effect on reduced infant amygdala volume after 18 months of age may also be consistent with Sullivan and colleagues' finding that abuse-related cues do not become salient to the HPA axis until after the consolidation of the primary attachment relationship (Sullivan et al., 2000). Because this finding indexes the mother's, rather than the infant's, experience of abuse, caution is needed in interpreting the finding without further evidence that the infant is also experiencing harsh and aversive treatment. However, this result points to an important direction for future work. Specifically, more studies are needed to map out what forms of caregiving adversity affect the HPA axis and limbic volumes, in what directions, and at what points in infant development.

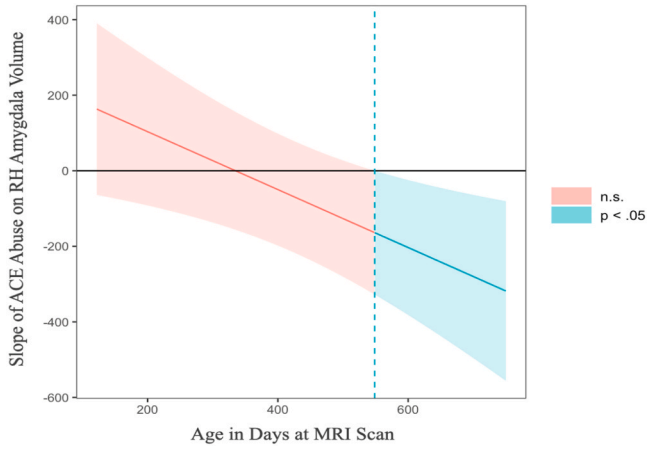

Fig. 6. Region of significance of the interaction between severity of maternal childhood abuse and infant age at MRI on infant right hemisphere amygdala volume. Note. Region of significance plotted using the Johnson-Neyman method (Johnson and Neyman, 1936). ACE = Adverse Childhood Experiences questionnaire. Graph derived using linear regression with MLR estimation, without FIML. N = 56 (one outlier removed). When infant age is outside the interval [-102.35, 548.65 days], or 18 months, the slope is significant, p <.05. Reprinted from Lyons-Ruth et al., *Research in Child and Adolescent Psychopathology,* 2023.

These results from human infants are preliminary given the modest sample size and the absence of a larger literature assessing caregiving adversity and cortisol levels in relation to amygdala volumes among human infants. However, the parallels that emerge with the large and well-controlled body of work with animal models and with the threat/deprivation literature among human children and adults underscore the need to clearly formulate and explore the questions that these literatures pose for studies of human infancy.

4. Toward a Developmental Salience Model of Threat in Human Infancy

One model with the potential to integrate animal and human literatures on sources of early threat is a developmental salience model of threat (Fig. 7). This model retains the crucial distinction between threat and deprivation advanced in human developmental neuroscience. However, it also integrates evidence from the rodent literature that threat of loss of care and threat of attack or injury may be temporally sequenced in relative salience to the amygdala across early development. If cues signaling lack of care are privileged by the threat detection system in early infancy, while threat of attack or injury becomes more salient during later development, this would call for an expanded model of threat, in which both threat of lack of care and threat of attack are separately modeled.

In early infancy, there is a survival imperative to engage the caregiver. Sustained attentiveness of the caregiver is essential to infant survival, both in humans and other altricial species where the infant requires extended care. Thus, offspring of most mammalian species are

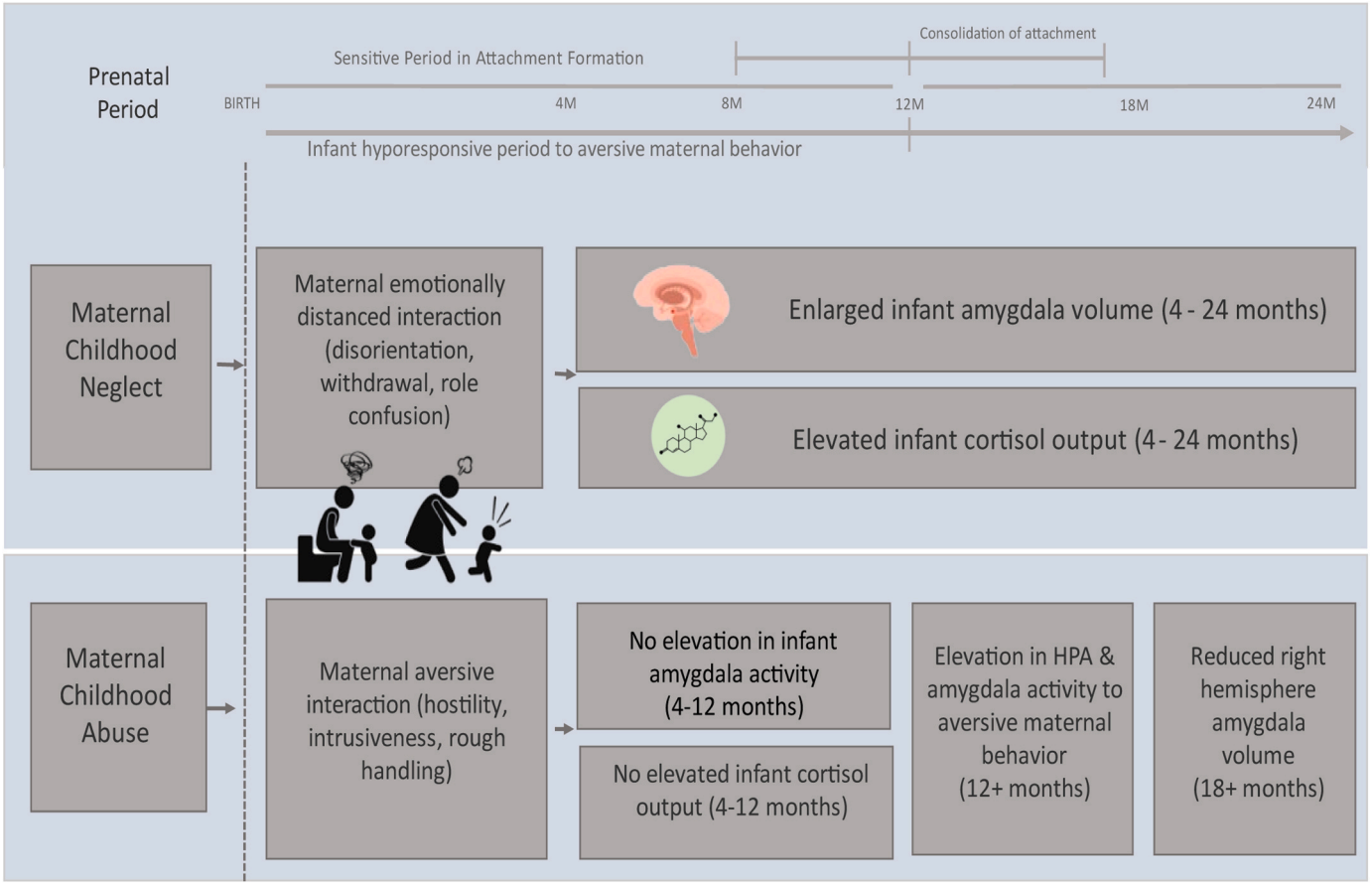

Fig. 7. Proposed Developmental Salience Model of Threat. Note. Model for human infancy showing low maternal nurturance/unpredictability activating the stress response circuit early in infancy, with a concurrent hyporesponsive period to aversive maternal behavior in the same time period. The hyporesponsive period is posited to wane after the period of peak attachment behavior established by attachment studies (12–18 months). In addition, emerging findings among human infants point to a potential intergenerational pathway from the mother's childhood experiences of neglect to early low nurturance of the infant.

highly attuned to the presence of maternal care and will engage in increased calling and contact-seeking when care is not adequate (Drury et al., 2016; McCormack et al., 2022; Turecki and Meaney, 2016). Thus, during the early period of extreme dependence on the caregiver for survival, the infant must attempt to elicit adequate responses from the caregiver, regardless of whether aspects of care are problematic or even harmful.

A developmental salience model would posit that in human infancy the most salient threat to the infant stress response system, including both HPA axis and amygdala, is the threat associated with low maternal nurturance/unpredictability. Only later in development, as the young child becomes less dependent on the caregiver, does threat of attack or injury become increasingly salient. This hypothesized timing draws from Sullivan and colleagues' thinking (Moriceau et al., 2010; Sullivan and Holman, 2010) that one function of the stress hyporesponsive period to maternal aversive cues may be to protect the formation of a selective attachment bond between caregiver and infant. Among human infants, clear behavioral evidence of selective attachment to familiar caregivers emerges around 12 months of age and is at its height between 12 and 18 months, with a gradual decline in the display of attachment behaviors after that point (e.g. Ainsworth et al., 1978; Matas et al., 1978).

A developmental salience model also calls for revisions in the widely accepted account of adaptive responses to threat, because threat of lack of care and threat of attack require very different defensive/adaptive responses (Lyons-Ruth et al., 2016). In most theorizing, threat is modelled as threat of attack or injury and this threat is viewed as mobilizing the defensive responses of fight, flight, or freeze (Barlow, 2002; Cannon, 1927). However, in the early years, low maternal nurturance/unpredictability may be the most developmentally salient form of threat, which can expose the infant to starvation and freezing, as well as predation. In the context of low maternal care or threat of abandonment, the defensive responses of fight, flight, or freeze would be highly maladaptive. Instead, across species, in response to threat of lack of care, infants signal for increased care by calling and contact-seeking to restore proximity to the caregiver, (e.g., (Ainsworth et al., 1978; Sanchez et al., 2015; Turecki and Meaney, 2016). Thus, across species, infants mount a stress response to low maternal care but respond to that threat with different adaptive behaviors than those elicited by threat of attack.

A developmental salience model also expands on the allostatic load model in specific ways. As articulated by McEwen and colleagues (McEwen, 1998, 2001), allostatic load refers to the physiologic cost to the individual of prolonged stress. While acute stress is initially associated with increased cortisol production and enlarged amygdala volume in rodent models, the prolonged cortisol elevation associated with continued stress has the potential to lead to a number of adverse effects, including hippocampal cell death, thus precipitating downregulation of the HPA axis and a blunted cortisol response to stressors to avert cell damage. However, the allostatic load model does not posit that deprivation/neglect may be the most salient form of threat in the first few years of life (McEwen, 2008). Relatedly, the allostatic load model has not explicitly incorporated the possibility of an early hypo-responsive period to aversive cues associated with the caregiver. A developmental salience model would posit that allostatic load on the stress response system would first begin with stress associated with threat of lack of care experienced during infancy, with any further stress associated with

threat of attack (including aversive or abusive caregiver behavior) adding to allostatic load at a later point in development, after the attachment relationship has been consolidated.

The developmental salience model outlined here is also compatible with the growing literature suggesting that one effect of early adversity may be an accelerated pace of development (Callaghan and Tottenham, 2016; Colich et al., 2020). Accelerated development is theoretically viewed as an adaptation to riskier environments to foster an earlier age at reproduction (Belsky et al., 1991; Del Guidice et al., 2011). A review by Colich et al. (2020) has shown that accelerated maturation is primarily associated with experiences of threat rather than deprivation, when assessed among older children and adults. The major implication of a developmental salience model of threat for this literature would be that during the first two years of life, the most salient threat may indeed be experiences of deprivation, a salience that may wane over the preschool years. Consistent with this model, Gee et al. (2013) and Herzberg et al. (2021) have presented evidence that institutional rearing in infancy was associated with more mature patterns of amygdala-ventromedial prefrontal cortex (vmPFC) connectivity (greater positive connectivity) among older children and early adolescents (see Callaghan et al., 2014, for review of this index of accelerated maturation). Thus, these studies suggest that early deprivation in infancy may also contribute to accelerated brain maturation. Also consistent with this possibility, though from an intergenerational transmission perspective, Hendrix et al. (2021) have shown that maternal childhood emotional neglect, but presumably not maternal childhood abuse (not reported on), was associated with increased amygdala-mPFC connectivity among neonates.

5. Future directions

Among the many questions raised by the proposed developmental salience model, three future directions of study seem particularly pressing. Below we briefly discuss each question and the potential directions for future work that each question raises.

First, is low maternal nurturance/unpredictability indeed a reliable stressor in early human infancy, with effects on both the HPA axis and limbic brain regions? This question is part of a broader question regarding what deviations in early care the human infant system can accommodate without elevated HPA-axis output and enlarged limbic volumes, that is, what deviations in early care fall outside the species experience-expectant range of care? To address this question, future work needs to differentiate low maternal availability (deprivation) from aversive/painful maternal behavior (threat). This differentiation has not been made consistently in behavioral studies of caregiving to date, with even fewer studies linking such variations in care to infant neurobiological development.

Less optimal caregiving in human infancy has been studied primarily in terms of the extent of caregiving disruption that impedes the caregiver's role as a buffer against external stressors, such as routine inoculations or brief separations (see Hostinar et al., 2014, for review). However, the work reviewed above clearly indicates that deviations in care also directly impact infant HPA axis and limbic responses to *the caregiver's behavior itself*, that is, to the threat to survival inherent in the quality of care. This view is consistent with an experience-expectant model of infant development, in which the infant needs certain types of nurturing care for the adequate maturation of infant brain circuits underlying emotional regulatory systems. The absence or reduced quality of these regulatory caregiving inputs would then stimulate increased infant arousal and more actively signaling to reinstate adequate caregiving. The novel aspect of this model is that it posits, congruent with extensive animal modelling, that deprivation of adequate care in very early life is salient to the infant stress response network and elicits elevated cortisol levels which, in turn, have a causal effect on enlarging amygdala volumes (Vyas et al., 2002; 2004; 2006). Thus, exploring the aspects of disrupted care that have salience to the infant stress response system at different points in early development is an important priority for future work.

A related question is whether there is a hyporesponsive period in human development to aversive maternal cues. While such a period has been shown in rodent models, it remains unclear whether an early hyporesponsive period to caregiver-related aversive cues exists among human infants.[3] More studies are needed to assess whether there is a relative lack of HPA response to

aversive components of maternal care in early infancy, compared to low nurturing/unpredictable components of care (Khoury et al., 2023a; Lyons-Ruth et al., 2023).

If such a period exists, we also need studies to define when such a period might wane. Sullivan's data on rodent pups have tied this transition roughly to the weaning period when the attachment relationship is no longer central to the pups' survival (Sullivan and Perry, 2015). Neurobiologically focused longitudinal studies beginning in infancy would need to extend well beyond the consolidation of the human attachment relationship between 12 and 18 months of age and into the preschool period to explore when a potential hyporesponsive period might wane.

Consistent with Sullivan's finding of a hyporesponsive period to aversive behavior, one attachment-focused longitudinal study of socially-at-risk infants from 12 to 18 months of age found that infants of more hostile mothers did not display disorganized attachment behavior toward their mothers at 12 months of age, as had been predicted, but did display disorganized attachment by 18 months, suggesting an increased sensitivity to aversive maternal behavior over this period (Lyons-Ruth et al., 1991). Maternal hostile-intrusive behavior was also more prevalent among mothers with current severe psychosocial problems (depression, child maltreatment, psychiatric hospitalization). Therefore, it was particularly unexpected that disorganized attachment behaviors were not shown by their infants until 18 months of age. However, maternal low involvement at 12 months *was associated* with infant disorganized attachment behavior at 12 months, again consistent with the hypothesis that low involvement may be more salient during early infancy. Doom et al. (2022) also reported results consistent with the view that early lack of care may be more salient than early aversive caregiver behavior to the infant threat response system, in that maternal disengagement at one year infant age was predictive of long-term blunting of cortisol output at age 15 years, while early aversive maternal behavior was not. More longitudinal work is clearly needed that separately assesses aversive and depriving aspects of early care.

A final important question that emerges from a developmental salience model of threat is how early experiences of low maternal nurturance/unpredictability may interact with concurrent or later experiences of threat of attack or injury? If deprivation indeed is prioritized by the infant stress response network, then the infant stress response network would be affected first by the degree of caregiving

[3] Note that Hostinar et al. (2014) propose a different model of the stress hyporesponsive period in humans than that demonstrated by Sullivan in rodents (Sullivan and Holman, 2010; Sullivan and Opendak, 2020). Hostinar et al. (2014) view stress hyporesponsiveness in early human development as emerging from effective maternal buffering of the infant stress response to stressors outside the caregiving system itself. This buffering function is associated with secure infant attachment to the caregiver, and, in the Hostinar et al. (2014) model, is viewed as lasting until adolescence. In contrast, among rodents, the stress hyporesponsive period demonstrated by Sullivan and colleagues (Sullivan and Holman, 2010; Sullivan and Opendak, 2020) constitutes an early developmental period immediately after birth, when the HPA axis and limbic system do not respond to aversive cues associated with the caregiver herself, including painful shock associated with the maternal odor. Thus, the caregiver as buffer model focusses on the sensitive caregiver emerging as a buffer for the infant in relation to stressors outside the caregiving relationship, while the model considered here focusses on an early hyporesponsive period to aversive caregiver behavior itself.

nurturance available. Subsequent threat experiences would then interact with this earlier substrate of HPA-axis arousal and enlarged limbic brain volumes. Based on this model, infants experiencing early neglect and associated HPA axis and amygdala response might be those most likely to show later allostatic overload in the context of subsequent stressors, with long-term blunting of the stress response. In addition, if early enlarged amygdala volume is one index of stress-related accelerated maturation (Callaghan and Tottenham, 2016; Vannucci et al., 2023), early neglect may also be associated with earlier plateauing of amygdala growth and less extended plasticity in brain development, consistent with the van Tiegham et al. (2021) findings.

Notably, the large volume of research on infant attachment behavior conducted since the early 1970's has not directly addressed these questions. Research on infant attachment behavior has explored the qualities of care differentiating secure, insecure, and disorganized infant attachment behavior, assessed in the context of brief separations from the mother (De Wolff and van IJzendoorn, 1997; Lyons-Ruth et al., 1999; Lyons-Ruth and Jacobvitz, 2016). A few studies have also linked infant disorganized attachment to elevated cortisol after a caregiver-related stressor at 12–18 months of age (Nofech-Mozes et al., 2020; Spangler and Grossmann, 1993). However, it is not yet clear whether the aspects of disrupted care related to activation of the stress response network during the first year of life will map onto the aspects of disrupted care related to insecure and disorganized attachment behavior, which first become apparent at 12 months of age.

This gap has occurred for two reasons. A large body of work has shown that a general measure of sensitivity/insensitivity of caregiving is associated with infant attachment security (meta-analysis: De Wolff and van IJzendoorn, 1997), as well as more positive HPA-axis regulation (review, Atkinson et al., 2016). However, few studies have differentiated among different types of insensitivity. Therefore, the attachment literature has not yet specifically addressed how more depriving versus more threatening aspects of 'insensitive' care may differentially affect early neurobiological development.

Secondly, most attachment studies have focused on the period *beginning* at 12 months of age, when infant attachment behaviors become reliably observable. Thus, few attachment studies have assessed the specific aspects of caregiver-related adversity that may be most salient to the HPA axis and amygdala development during the first year of life. Longitudinal studies of the developing infant HPA axis in relation to developing subcortical stress response regions, starting at birth, are needed to further specify the qualities of early care associated with elevated HPA- axis responses and enlarged amygdala volumes in early development, as well as with the disorganized attachment behaviors that begin to emerge from 12 to 24 months.

Another influential area of research that does not directly address the issues raised in this paper but will be important to consider in future work is the body of work on fetal programming of the infant stress response system. Rapid brain growth during the intrauterine period has led to the hypothesis that gestation may be a sensitive period during which maternal stress hormones influence fetal brain development. Relevant to the current paper, Buss et al. (2012) have shown that maternal stress hormone levels in human pregnancy are associated with subsequent child amygdala volume and child affect at age 7 years. While this paper did not assess potential postnatal influences, intrauterine effects of maternal stress hormones are likely to be another important contributor to modifications in infant brain development. A review of these effects is beyond the scope of the current paper. However, more comprehensive models of early neurobiological development will need to integrate prenatal hormonal influences (Buss et al., 2017; Khoury et al., 2023b; Moog et al., 2022), genetic loading (Pagliaccio et al., 2014), and epigenetic influences (Scorza et al., 2020) as important additional sources of variation in stress-system development, in addition to the post-natal influences on infant stress considered here.

6. Conclusions

Controlled animal studies have shown that the quality of care itself is salient to the infant stress response system in the early months of life, with low maternal nurturance/deprivation of care particularly salient in early infancy, while aversive or abusive caregiving becomes more salient after the early period of attachment formation. However, there is a dearth of research exploring the potentially developmentally sequenced effects of deprivation/low care versus threat/aversive care on the human infant's developing stress response system. New findings in human infancy suggest the relevance of rodent findings for the salience of low nurturance to the infant HPA axis and amygdala, with important implications for a revised developmental model of threat. More work is needed in human infancy to assess the reliability and implications of these emerging findings. The literatures reviewed here underscore the importance of designing future work that can continue to specify our models of threat as they apply to the rapidly developing infant brain.

Ethical approval statement

Study findings discussed in this review were approved by the Partners Healthcare Institutional Review Board [IRB Protocol #: 2014P002522] and parents provided written informed consent.

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Declaration of Competing interest

The authors declare that they have no competing financial or other interests that could appear to influence the current work.

Data availability

Data will be made available on request.

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None

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