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Stacy S. Drury, *Tulane University School of Medicine*  
[Maria Sanchez](#), *Emory University*  
Andrea Gonzalez, *McMaster University*

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## When mothering goes awry: Challenges and opportunities for utilizing evidence across rodent, nonhuman primate and human studies to better define the biological consequences of negative early caregiving\*

Stacy S. Drury<sup>a</sup>, Mar M. Sánchez<sup>b,c</sup>, and Andrea Gonzalez<sup>d</sup>

Stacy S. Drury: sdrury@tulane.edu; Andrea Gonzalez: gonzal74@gmail.com

<sup>a</sup>Tulane University School of Medicine, Department of Psychiatry and Behavioral Sciences, 1430 Tulane Ave, #8055, New Orleans, LA 70112, United States

<sup>b</sup>Department of Psychiatry & Behavioral Science, School of Medicine, Emory University, Atlanta, GA 20322, United States

<sup>c</sup>Yerkes National Primate Research Center, Emory University, Atlanta, GA 20329, United States

<sup>d</sup>Offord Centre for Child Studies, McMaster University, Department of Psychiatry and Behavioural Neurosciences, 1280 Main Street West, Hamilton, ON, L8S 4K1, Canada

### Abstract

Across mammalian species, mothers shape socio-emotional development and serve as essential external regulators of infant physiology, brain development, behavior patterns, and emotional regulation. Caregiving quality, consistency and predictability shape the infant's underlying neurobiological processes. Although the requirements for “optimal” caregiving differ across species, the negative long-term consequences of the absence of needed caregiving (e.g. neglect) or the presence of harmful/aversive caregiving (e.g. physical abuse), are translatable across species. Recognizing the significant potential of cross species comparisons in terms of defining underlying mechanisms, effective translation requires consideration of the evolutionary, ecological, and fundamental biological and developmental differences between and among species. This review provides both an overview of several success stories of cross-species translations in relation to negative caregiving and a template for future studies seeking to most effectively define the underlying biological processes and advance research dedicated to mitigating the lasting negative health consequences of child maltreatment.

### Keywords

Maltreatment; Cross-species; Development; HPA axis; Epigenetics; Neurobiology

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Correspondence to: Stacy S. Drury, sdrury@tulane.edu.

## Introduction

Across mammalian species, mothers shape socio-emotional development, serving as essential external regulators of infant physiology, neurodevelopment, behavior, and emotion regulation. This theory, initially proposed by Myron Hofer, has since been substantiated by a multitude of studies across a range of different mammalian species (e.g. (Hofer, 1984; Howell and Sanchez, 2011; Kuhn et al., 1991; Raineki et al., 2014; Rincon-Cortes and Sullivan, 2014). Extending from this foundational theory, variations in caregiving quality and consistency, particularly extreme deviations from the unique species typical pattern of caregiving early in life, further shape an infant's underlying neurobiological processes, leading to life-long alterations. Despite the wide variability of what comprises “optimal” or typical caregiving, even within closely related species such as the Great Apes, negative caregiving, defined in this review as the absence of needed caregiving (e.g. neglect, beyond separation consistent with species typical experiences) or the presence of harmful/aversive caregiving (e.g. physical abuse beyond species typical exposures), is consistently linked to lasting negative neurobiological effects.

Animal models, both rodent and nonhuman primate (NHP), have been critical in delineating the persistent effects and biological mechanisms underlying early negative caregiving induced developmental psychopathology in humans. Further advances in maltreatment research now require an enhanced trans-disciplinary perspective that acknowledges both the similarities in maternal regulation of infant developmental processes across species as well as the species-specific methodological, ethological, and developmental limitations. By keeping these in mind, studies can better integrate innovative research designs that more accurately reflect negative and positive caregiving experiences in a species-specific manner. Utilization of this approach is expected to result in greater clarification of the underlying molecular pathways and neurobiological mechanisms.

In this review, we first outline potential challenges facing cross-species comparisons. Next, we showcase examples of “success” stories of translational research related to several distinct biological systems: (1) stress neuroendocrine systems, focusing predominantly on the Hypothalamic-Pituitary-Adrenal Axis (HPA), (2) neurodevelopment, focusing on the prefrontal-limbic system, and (3) epigenetic modifications, focusing on methylation. These systems were selected given the preponderance of existing data across species, established links to negative caregiving and associated developmental psychopathology, and burgeoning data suggesting interactive pathways between them. Examples are provided in an effort to be representative, but not exhaustive. In the near future greater integration of cross-species data related to other systems, particularly the immune and autonomic nervous systems, will likely provide novel additional insight into the lasting impact of early negative caregiving beyond the systems presented here. Given the significant variation in the characterization of early life adversity across species, we further limit this review to data obtained from studies focused on physical abuse or neglect paradigms. Despite this restrictive approach, it is notable that these paradigms range from total maternal separation found in rodent models, peer reared nonhuman primate models, and human early institutional rearing, to models of both naturally occurring and environmentally induced physical abuse in rodent and nonhuman primates. Although the downstream impacts of negative caregiving may differ as

a result of abuse compared to neglect, there remains substantial value to synthesizing data from various models.

We conclude by outlining critical considerations for future cross-species studies and presenting immediately addressable design challenges while highlighting the value of existing studies. Abusive caregiving, or absence of adequate caregiving (neglect), are substantial adverse infant experiences with enduring effects across biological systems and species. Translational studies across species, while methodologically complex, are needed to both identify novel targets for intervention and provide a neurobiologically informed platform upon which to drive public health and policy change focused on mitigating the lasting impact of child maltreatment.

## Conceptual and definitional challenges for cross-species comparisons

Exposure of children to neglect, physical, and emotional abuse remains a persistent and cross-cultural experience. In the United States rates of documented child maltreatment range between 8 and 11%, although determination of baseline prevalence rates remains difficult (Fallon et al., 2010). The first years of life represents a time-period of increased risk of exposure to maltreatment. This is particularly concerning given this period also represents a time when a vast array of neurodevelopment is occurring. Overall boys and girls are exposed equally to maltreatment, with the exception of sexual abuse where girls are at greater risk. Child maltreatment cuts across racial, ethnic and socioeconomic lines. Even within NHP, maltreatment is evident across all social hierarchy strata (from higher ranking animals — socially dominant, to the lowest social ranks — subordinate animals). In addition, maltreatment appears to span generations, with increased familial risk and family clustering that is replicated in rodent and NHP cross-fostering studies (Francis et al., 1999; Roth et al., 2009; Sanchez et al., 2010b). While hinting at underlying molecular and epigenetic pathways, these findings also suggest that failure to effectively intervene in the current generation may have consequences for subsequent generations. Beyond elevated risk for psychological disorders, increased risk of other biological and negative health outcomes are reported in children exposed to maltreatment, implying that multiple biological pathways are impacted (Hemmingsson et al., 2014; Nikulina and Widom, 2014; Rich-Edwards et al., 2012; Teicher et al., 2003; Widom et al., 2012). To date the molecular and neurobiological pathways leading to these negative effects, and the efficacy of interventions at alleviating biological risk, not just psychological symptom reduction, remains limited. Bridging this mechanistic gap requires effective integration of data from naturalist human studies with controlled preclinical data from animal models.

## Overall definitional challenges

As a first step toward more informative cross-species comparisons, challenges, some modifiable and others that will remain important caveats, need to be recognized. One primary consideration centers on the clarification of the type of negative caregiving experienced (e.g. abuse compared to neglect; emotional compared to physical; exposure to multiple types of abuse) and utilization of animal model systems that most effectively mirror the “human” experience. The root of this conceptual challenge arises from within the human literature. The terms childhood adversity, child maltreatment, early life stress, and toxic

stress are used interchangeably, referring to a broad range of experiences that include chronic stress, traumatic experiences, extreme poverty, neglect, and physical and emotional maltreatment. Much of the current literature conceptualizes maltreatment from a chronic stress or allostatic load perspective (Cohen et al., 2013), often combining maltreatment exposures and failing to address other relevant confounders such as poverty, sex, race, and nutrition. This conceptualization of adversity, while an unfortunately accurate reflection of the human experience, limits the ability to translate findings across species as the majority of animal models focus on specific types of maltreatment, controlling the broader context in which maltreatment occurs such as nutrition, warmth, and housing. Although human studies have limited ability to control other contextual factors, analytic approaches, such as stratification of victims of physical abuse based on nutritional status, are feasible, albeit requiring larger sample sizes. An alternative approach would be to specifically create variation in these factors within animal models. For example creating a maternal separation paradigm that integrated specified variation in bedding and food. These integrative study designs are more consistent with human maltreatment and both approaches are likely to result in more translational and ecologically valid models.

### **Defining the type of negative caregiving**

In human research maltreatment exposure is often classified as categorical. For example, studies have defined maltreatment as physical, sexual, or emotional abuse, and/or physical/emotional neglect. In addition to these categories, a substantial body of literature has focused on the neurobiological impact of extreme psychosocial neglect as a result of early institutional care, which may be distinctly different from neglect in other settings (Sheridan et al., 2010). Natural variation, as well as inducible extremes of caregiving that potentially map onto these categories, exist in both rodent and NHP species. For example, natural variations in maternal behaviors such as pup licking and grooming in rodents suggest that dams in the extreme low end of the normal distribution exhibit caregiving reflective of physical neglect in humans. In addition to studies of natural variation in caregiving, a multitude of experimental manipulations of caregiving exist in different rodent species which range from maternal restraint, variable handling and separation paradigms, to other approaches of stressing mothers to produce aberrant caregiving (i.e. reduced bedding). At the extreme end of the experimental continuum, Fleming and colleagues utilized an artificial rearing paradigm, which involves complete removal of the pup from mother and littermates from postnatal day (PND) 3 until weaning (Gonzalez et al., 2001). This particular experimental approach may be most reflective of extreme neglect and care found in institutional settings (Brett et al., 2015). As an example of more “active” negative caregiving paradigms, Sullivan and colleagues developed a rodent model of aversive caregiving within an attachment-learning paradigm (see Perry & Sullivan, 2014; Rincon-Cortes and Sullivan, 2014 for reviews). This model involves limiting bedding/nesting to the dam (PND 1-7, 3-8, or 8-12) which results in rough handling of pups, trampling and decreased bouts of nursing, mimicking the inconsistent and unpredictable characteristics of abusive human mothers (Rainecki et al., 2012, 2010).

Although rodent models have significant utility for maltreatment research, NHP models may better address some questions given the closer evolutionary relation with humans and the

greater similarity in terms of expected caregiving experiences (e.g. single offspring) and developmental timing. Infant maltreatment has been documented in both wild and captive populations of NHP species (Brent and Koban, 2002; Johnson et al., 1996; Maestripieri, 1998; Maestripieri and Carroll, 1998). In macaques, often during the first three months postpartum, two behaviors resembling child maltreatment occur that result in overt signs of infant distress (screams, tantrums): (1) physical abuse, which involves violent behaviors toward the infant that cause pain and distress (e.g. dragging, crushing, throwing the infant) and (2) infant rejection, which consists of pushing the infant away when it solicits contact with the mother (Maestripieri, 1998; McCormack et al., 2006). In NHP, infant physical abuse, more commonly studied than rejection, is transmitted from generation to generation and appears to cluster within families suggesting both a experiential and a genetic and/or epigenetic contribution, similar to reports from rodent models (Maestripieri, 2005; Maestripieri and Carroll, 1998; Maestripieri et al., 2000). While the utility of these classifications of the type of negative caregiving (e.g. abuse compared to neglect) may be more amenable to cross-species comparisons than early life stress, caution is warranted.

When considering maternal separation paradigms as models of neglect, careful attention to the normative species-specific patterns of maternal caregiving is required. In some species normative caregiving involves the infant in continuous direct contact with the mother during infancy, while for other species, including humans, regular separations from the mother for sleeping, alternative caregiving etc., are normative. Different NHP species, and to some extent human cultures, also vary in the amount of maternal caregiving, compared to paternal or familial, that is typical or expected. For example, in Titi monkeys fathers carry the infants except for brief nursing by the mother through most of infancy. Alternatively in spider monkeys mothers almost exclusively provide all parental care (Allman et al., 1998). These inherent differences require that research integrate expected normative behaviors when designing and analyzing experiments as maternal separation in Titi monkeys may result in very different consequences than similar amounts of maternal separation in spider monkeys.

Another obstacle facing cross-species comparisons is the high rate of exposure in humans to multiple types of abuse. Current evidence suggests that there are differential neurobiological consequences as a result of the type of maltreatment; thus, disentangling these effects is necessary (Humphreys and Zeanah, 2014). To address the co-occurrence of adversity, studies have examined the association between outcomes and the number of maltreatment composite exposures (cumulative risk count) (Arata et al., 2007). An alternative approach is to differentiate maltreatment experiences as deprivation, (e.g. neglect or absence of caregiving) versus threat exposure (e.g. physical abuse/emotional or verbal abuse) (McLaughlin et al., 2014). The advantages of the later approach are that it permits exploration of both combined and interactive effects on neurodevelopment by separately measuring unique effects and that it is more amenable to comparison to animal models where exposure to a single type of negative caregiving is typical. Advancement of maltreatment research requires both definitional clarity and the implementation of novel research paradigms.

## The issue of timing

In addition to precision in defining the quantity and type of negative caregiving, two aspects related to developmental timing are important for translation across species. The first concerns the organism's developmental stage when the negative caregiving occurs. In rodent studies maternal separation paradigms are typically instituted right after birth, a time-period more consistent with the third trimester in human gestation, posing challenges to temporal comparisons (Workman et al., 2013). The second temporal consideration relates to the intrinsic biological differences in neurodevelopmental tempo and relative rate of growth across different brain regions. While there are substantial neurodevelopment similarities between NHP and humans, comparisons are still confounded by the differences in the relative rate of development between regions of the brain, particularly in motor and prefrontal cortex development (Brett et al., 2014; Sclafani et al., 2015). Thus, the difference in both the developmental stage at which rodents and primates are born, and in the relative rate of neurodevelopment across brain regions, adds additional, but addressable, complexity to cross-species comparisons (Molet et al., 2014).

We outline these issues in order to spark innovative conceptualization for future studies and novel analytic approaches for examination of existing data sets. Advances in maltreatment research is expected to be enhanced by focused research on modifiable factors in study design, such as precise characterization of the type of negative caregiving experienced, coupled with acknowledgement of factors, such as differential patterns of brain growth, that are not modifiable. To demonstrate the utility of this approach we provide examples of convergent findings spanning rodent, NHP and human research, focusing on cross-species data associated with negative caregiving that encompasses species atypical amounts of maternal separation/deprivation (neglect) and active aversive/aggressive maternal behaviors (abuse) toward offspring.

## Cross-species success stories

### Brain development: focus on prefrontal-limbic impact of negative mothering

Both genetic factors and environmental input regulate brain maturation. Early exposure to negative caregiving occurs during rapid developmental changes in the brain, creating “windows of vulnerability” in which adverse experiences are encoded (Andersen, 2003; Knudsen, 2004; Rice and Barone, 2000). As brain regions mature at different velocities and trajectories, with substantial inter-species variability (Avishai-Eliner et al., 2002; Workman et al., 2013), region-specific sensitive periods exist that, depending on the species, may last for several years (e.g. in primates) or have much shorter window of sensitivity, as a result of protracted or accelerated developmental trajectories (Andersen, 2003). Cortical maturation, here defined as postnatal gray matter loss, occurs in “low-order” regions (e.g. regions that process visual or somatosensory stimuli) prior to the association cortices that integrate this sensory input such as portions of the temporal and frontal cortices (Giedd and Rapoport, 2010; Gogtay et al., 2004). This step wise development follows the maxim “ontogeny recapitulates phylogeny” where phylogenetically older regions such as the entorhinal cortex mature before evolutionarily newer regions such as the prefrontal cortex (PFC) (Giedd, 2004; Giedd and Rapoport, 2010; Gogtay et al., 2004; Shaw et al., 2008). The protracted

developmental trajectory of these regions, including the PFC, association cortices, amygdala and hippocampus, likely heightens the vulnerability of these regions to the effects of negative caregiving. Indeed alterations in these structures are associated with deficits in emotion and stress regulation with substantial relevance in developmental psychopathology and established links to early life adversity. Further, clinical (Bick et al., 2015a, 2015b; De Bellis, 2005; De Bellis et al., 1999a, 1999b; Drevets, 2008; Teicher et al., 2003; Tottenham and Sheridan, 2009) and preclinical studies (Arabadzisz et al., 2010; Bale et al., 2010; Coplan et al., 2010; Coplan et al., 2001, 1998, 1996; Jackowski et al., 2011; Law et al., 2009a, 2009b; Mathew et al., 2003; O'Connor and Cameron, 2006; Pryce, 2008; Pryce et al., 2005; Sánchez et al., 2001) consistently report negative effects of early adverse caregiving on the structure and the function of the PFC, amygdala, hippocampus and the tracts connecting them. These same cortico-limbic circuits contribute to the regulation of the neuroendocrine (HPA) axis (Herman et al., 2003; Herman et al., 2005; Ulrich-Lai and Herman, 2009), providing a convergent developmental and neurobiological foundation for the cross-system effects of adverse caregiving on physiologic, behavioral, and emotional outcomes.

This evidence also applies to the specific definition of negative caregiving employed in this review. For example, recent NHP neuroimaging studies have demonstrated a positive correlation between abuse rates experienced during infancy and amygdala volume, as well as reduced white matter integrity in tracts important for behavioral and emotional regulation that were also associated with elevated levels of cortisol in abused infants (Howell et al., 2014, 2013). These findings parallel findings reported in maltreated humans and children exposed to extreme psychosocial deprivation as a consequence of institutional care. Collectively these studies have reported brain structural abnormalities, including differences in the amygdala, insula, orbitofrontal cortex, anterior cingulate gyrus, caudate and corpus callosum volumes (Dannowski et al., 2012; McCrory et al., 2012; Sheridan et al., 2012; Teicher et al., 2014) as well as alterations in white matter integrity that, in at least one case, were partially corrected with foster care placement (Bick et al., 2015a). Functional impairments are also evident in maltreated humans, with greater amygdala activation in response to emotional stimuli and hypo-activation of the medial PFC. (Dannowski et al., 2012; McCrory et al., 2013; van Harmelen et al., 2010).

Now, is there an evolutionary purpose for the elevated responsivity of these PFC-amygdala circuits to differences and disturbances of early maternal care? In general, if the early adverse environment persists throughout life, it could be adaptive to incorporate neurodevelopmental programming that encodes behavioral and physiological reactive strategies (high vigilance, stress reactivity, aggression) to increase the organism's survival in the expected, persistent, high-risk environments. This persistent hyper-vigilant state, while from one perspective “adaptive,” may result in later biological and negative health consequences-outcomes often seen in individuals with a history of early maltreatment (Felitti et al., 1998). The once held view of the infant brain as an immature version of the adult brain inadequately captures the dynamic and adaptive nature of the developing brain that appears uniquely designed for survival early in life.

In mammals, one unique feature of infant behavior, likely embedded in evolutionarily conserved neuroanatomical regions, is the intensity of the bond with the caregiver in spite of any potential negative consequences. Rodent models have been powerful in mapping some of the mechanisms through which particular maternal behaviors shape and regulate the plastic infant brain (Eghbal-Ahmadi et al., 1999; Howell and Sanchez, 2011; Korosi and Baram, 2009; Sánchez et al., 2001). Examples include the regulation of the pup's heart rate through maternal milk's actions on gastrointestinal receptors and the activation of the sensory pathways that modulate the development of limbic circuits, including the amygdala-PFC connections, by tactile stimulation associated with licking, grooming, and retrieving maternal behaviors. These maternally triggered somatosensory cues in the peripheral nervous system of the infant travel along the spinal cord to the central nucleus of the amygdala (CeA) via afferents from the pedunculo pontine and lateral dorsal tegmental nuclei. Maternal grooming behaviors, and even simply maternal presence within the nest environment, directly modulate infant cortical activity early in life, in part via a noradrenergic mechanism (Sarro et al., 2014). Maternal absence from the nest leads to increased cortical desynchrony, while her return results in increased cortical synchrony, providing powerful evidence of the influence of maternal behavior and presence on infant neural activity, cortical synchrony, and development.

Research efforts in mammalian models, particularly rodents, have also mapped the neurobiological systems that underlie the infant's development of a bond with a preferred caregiver (Moriceau and Sullivan, 2005; Sullivan and Lasley, 2010), regions predicted to be significantly influenced by abusive caregiving (Rincon-Cortes and Sullivan, 2014). Sullivan and colleagues' studies in rat pups have shown similarities with human and NHP in terms of the neurobiological circuitry involved in the formation and maintenance of the maternal-infant bond, although rat pups do so primarily through the olfactory system. Their initial studies suggested that the neonatal rat uses a different learning circuit than adults, which includes the locus coeruleus (LC) noradrenergic (NE) system. This LC-NE system is hyper-functional during the sensitive period for formation of attachment to the mother that coincides with PND 1–9, a time-period when the pups are confined to the nest. The release of high levels of NE during interactions with the mother at this age, consolidate a rapid and robust preference for her. In addition, the brain circuits responsible for fear and avoidance learning (i.e., amygdala) are turned “off” during this sensitive period for attachment formation. There is additional evidence that the HPA axis plays an important modulatory role in infants' fear learning by switching whether amygdala activation results in attraction or avoidance behaviors (Rincon-Cortes and Sullivan, 2014). These findings provide a neurobiologically informed explanation for why the maternal-infant bond is not broken to avoid pain when the caregiver is physically abusive, as has been shown in humans (Helfer et al., 1997), NHPs (Harlow and Harlow, 1965; Sanchez et al., 2010b) or even dogs (Fisher, 1955).

Sullivan's lab has further demonstrated that when rat pups start exploring outside the nest (after PND 10), the sensitive period of enhanced approach and attenuated aversion/fear learning ends, representing a developmental “switch point” that is critical for survival in altricial species. Thus, early on proximity to the mother provides the infant with nutrition, protection, comfort and physiological regulation. At the same time the suppression of the

fear system protects the bond and gives the infant the boldness to explore in the presence of the mother as she serves as an external regulator and secure base. However, as the infant ages, survival dictates activation of the fear circuitry when exploring. During a transitional period (PND 10–15), maternal presence maintains low corticosterone levels which suppresses amygdala activity resulting in preference learning and promotion of attachment to the mother. However, during this time period, removal of the mother results in increased corticosterone, amygdala activity, and avoidance learning (Rincon-Cortes and Sullivan, 2014). Between 7 and 9 months of age, when children are beginning to move independently, a similar developmental switch point occurs in humans. This expected behavioral change, called stranger anxiety, is characterized by increased fear behaviors such as freezing and gaze-aversion toward strangers and preferential attention to known caregivers (Sroufe and Waters, 1977). This matching behavioral switch across species occurs concurrently with the developmental switches in the amygdala's role in fear regulation and its connectivity with the PFC in humans (Gee et al., 2013) and NHP primates (Raper et al., 2014). Human studies indicate that in childhood, but not in adolescence, mothers modulate this amygdala-PFC connectivity, such that maternal presence suppresses amygdala reactivity, similar to the suppression observed in rodent models. The strength of the mother-child relationship is also associated with greater maternal influence on amygdala-prefrontal circuitry (Gee et al., 2013). Heightened sensitivity to negative caregiving likely exists during these critical developmental switch points, particularly as the strengthening of these connections is influenced by experience. Future studies that time exposure to maternal absence or aversive caregiving based on when these switch points occur in each species may provide unique data about underlying mechanisms.

In rodent and primate studies exposure to negative caregiving has been found to alter the timing of this transition. Alterations of maternal care induced through environmental manipulations (e.g. reduced bedding) lead to increased corticosterone secretion in rat pups and early emergence of fear learning combined with preemptive termination of the attachment sensitive period (Rincon-Cortes and Sullivan, 2014). In humans both the timing and tempo of this developmental switch are altered by maternal deprivation which seems to drive the earlier development of “adult” patterns of connectivity between the amygdala and PFC (Gee et al., 2013). Childhood maltreatment has also been associated with impaired amygdala-PFC connectivity (Fan et al., 2014; Herringa et al., 2013). Recent studies indicate that increased HPA axis activity, in particular elevated cortisol levels, mediate the association between early life adversity and alterations in development of amygdala-PFC connectivity (Burghy et al., 2012; Gee et al., 2014; Veer et al., 2012). In other words, evidence across species support the existence of a developmental switch point in amygdala-PFC connectivity that is driven, in part by the developmental changes in HPA axis activity. Importantly, cross-species data suggests that negative maternal caregiving shifts this developmental switch point earlier, potentially resulting in lasting perturbations in PFC-amygdala connectivity. Better understanding of both the impact of this developmental shift, as well as the underlying molecular pathways responsible, may provide novel targets for intervention and prevention efforts.

## The HPA axis

One vulnerable and well-studied stress-responsive biological system that undergoes marked development during the early postnatal period is the HPA axis. Physical or psychological stressors stimulate the HPA axis through specific neural pathways resulting in activation of parvocellular neurons of the paraventricular nucleus of the hypothalamus (PVN) and the release of corticotropin-releasing hormone (CRH). CRH then acts on the anterior pituitary to cause the release of adrenocortico-tropic hormone (ACTH) into the general circulation. ACTH activates cells in the adrenal cortex stimulating the release of glucocorticoids (cortisol in primates and corticosterone in rodents) (Sanchez, 2006). The regulation of the HPA axis reactivity occurs through negative feedback at multiple levels including the pituitary, PVN, hippocampus, amygdala and prefrontal cortex (Ulrich-Lai and Herman, 2009). In addition to this stress-reactive component, the HPA axis follows a circadian pattern of glucocorticoid (e.g. cortisol) release that is also modulated by maternal caregiving (Bublitz and Stroud, 2012; Gunnar and Donzella, 2002; Shirtcliff et al., 2012). Rodent pups, during the first two postnatal weeks, exhibit a diminished HPA axis response to mild and moderate stressors, termed the stress hypo-responsive period (SHRP) (Rosenfeld et al., 1992; Vasquez, 1998). However, the SHRP seems to be stressor specific with the HPA axis system particularly tuned and responsive to relevant stressors for the neonate, including cold exposure and saline injections (Walker et al., 1991; Yi and Baram, 1994). Although not as clear cut as in rodents, there is evidence to suggest that human infants exhibit a period of dampened stress reactivity within the first year of life that also is stressor specific (Gunnar et al., 2006; Jansen et al., 2010; Lupien et al., 2009). In NHPs there is no evidence in support of the SHRP (Sánchez et al., 2001), with neonates exhibiting a robust HPA response to stress early in development (Parker and Maestripieri, 2011) at least when exposed to challenges alone (Sanchez et al., 2015). However, when the mother is present during exposure to similar stressors, the infant's HPA axis is not activated. This dampened response suggests that infant NHP, similar to humans and rodents, exhibit a relatively quiescent HPA axis until weaning, although this is likely due to the inhibitory effect of the mother's presence on the infant's stress response rather than an overall dampening of the HPA axis (Hostinar et al., 2014; Sanchez et al., 2015).

Converging research across species demonstrates that both HPA axis reactivity and diurnal patterns are shaped by early negative caregiving. Caregiver presence is essential for buffering the infant's physiological response to stressors (Gunnar et al., 2015; Hostinar et al., 2014; Sanchez et al., 2015). Across species there is evidence that both the removal of the mother from the infant and variations in maternal behavior, either naturally occurring or stress-induced, alter infant HPA axis function. In rodents, maternal deprivation typically results in HPA hyperactivity, including response to acute stress (Avishai-Eliner et al., 1995; Ladd et al., 2004; Liu et al., 2000; Stanton et al., 1988). Both natural variations in maternal care (low licking/grooming) and paradigms modeling maternal abuse and neglect through altered environments (i.e., reduced bedding), or extreme deprivation (artificial rearing), result in similar HPA-axis dysregulation. These paradigms are associated with elevated basal corticosterone levels, hyper-reactivity in response to acute stressors, impaired negative feedback, dendritic atrophy, mossy fiber expansion, and molecular changes to the glucocorticoid (GR) and CRF-receptors, including decreased hippocampal GR mRNA

expression (Belay et al., 2011; Brunson et al., 2005; Ivy et al., 2008; Kaffman and Meaney, 2007; Meaney, 2001; Rice et al., 2008). Similar findings have been reported in some, but not all, NHP studies. In rhesus macaques, the quality of maternal care also has a strong effect on infant HPA axis response to stress (Sanchez, 2006), with evidence that maltreating mothers are less able to buffer their infants' cortisol stress responses (Sanchez et al., 2015). Early in development abused infants exhibit higher basal cortisol levels compared to controls, however there is apparent normalization of basal function at later ages (Howell et al., 2013; Koch et al., 2014; McCormack et al., 2003). Despite the normalization of basal HPA axis activity as the animal ages, abused individuals demonstrate persistent alteration in HPA reactivity, including increased cortisol and decreased ACTH in response to CRH challenge (McCormack et al., 2003; Sanchez et al., 2010a). The findings in NHP studies parallel some results in humans with a history of abuse where lasting changes in cortisol reactivity is seen in both youth and adults (Carpenter et al., 2007; Heim and Nemeroff, 2001). In humans, however, conflicting results have been reported with blunted cortisol levels reported in some studies (Carpenter et al., 2011) but HPA hyperreactivity reported in women with histories of physical and sexual abuse (Heim et al., 2002). These discrepant findings suggest that greater attention to the characterization of maltreatment type and the developmental timing of exposure is needed.

In addition to these changes in HPA axis reactivity, dysregulation of diurnal profiles are also evident. Repeated maternal separations, followed by mother-infant reunion, are one experimental manipulation with cross-species validity, however incorporation of species typical patterns of maternal-infant contact is warranted. Repeated maternal separation in NHPs is associated with a pattern of initial cortisol increase in the first year of life followed by a flattened day cortisol rhythm during the juvenile period (Dettling et al., 2002; Feng et al., 2011; Sanchez et al., 2005). These findings are consistent with diurnal cortisol profiles measured in human maltreatment studies (Bremner, 2003; Bremner et al., 2007; Power et al., 2012). Longitudinal studies have reported that maltreated children have higher initial cortisol levels but show cortisol suppression over time, suggestive of HPA blunting. However, in these studies, the specific type of maltreatment (e.g. abuse or neglect or both) was not specified (Doom et al., 2014; Trickett et al., 2010). These convergent results in both humans and NHP suggest a temporal switch from hypercortisolism to hypocortisolism. This switch could be the result of the down-regulation of CRH receptors in the pituitary, altered epigenetic mechanisms, and/or shifts in the tempo and trajectory of the HPA axis development, similar to the proposed mechanisms associated with the negative caregiving induced changes in amygdala-PFC connectivity (Parker and Maestripieri, 2011; Sanchez, 2006). Future research into the mechanistic control of these developmental changes and the moderating role of the quality of maternal care on the timing of these shifts in the HPA response may lead to novel insight into the lasting negative effects of negative caregiving.

A unique extension of the findings of altered HPA axis regulation as a consequence of aberrant maternal care is whether these physiological alterations can be mitigated by subsequent caregiving quality. Across species, both quality and quantity of maternal caregiving are important for normal physiologic development (Molet et al., 2014). In rodents, maternal tactile stimulation (i.e., licking) not only moderates HPA axis activity (Champagne et al., 2003), but also reverses the negative effects of separation on the HPA

axis and other biological systems (Burton et al., 2007). Rodent models of ‘enhanced’ maternal care demonstrate improved response to later stress and resilience to psychopathology (Fenoglio et al., 2005; Korosi and Baram, 2009). Similar to what is seen in the rodent model, following mother-infant separation in NHP, the strength of mother-infant contact during the reunion appears to buffer the infant's reactivity to the separation and moderates later appropriate HPA axis function (Sanchez et al., 2005). These findings suggest reversibility of HPA axis dysfunction through psychosocial interventions promoting increased attachment and caregiving sensitivity, a hypothesis with increasing support from human research (Slopen et al., 2014). Differences in maternal responsiveness and sensitivity is associated with the infant's cortisol recovery in response to a stressor (Atkinson et al., 2012). Therapeutic interventions for at-risk children focused on the maternal-child dyad and the attachment relationship have been found to normalize HPA axis reactivity (McLaughlin et al., 2015) and diurnal cortisol levels in both short and long-term studies (Bernard et al., 2014; Bernard et al., 2015; Dozier et al., 2008; Fisher et al., 2007; Fisher et al., 2011; Laurent et al., 2014). These changes in HPA axis function co-occurred with improved behavioral functioning (Dozier et al., 2008; Fisher et al., 2007). Collectively these studies indicate that the HPA-axis is partially mutable across early development, influenced by both negative and positive caregiving, and that the alterations triggered by negative early caregiving may be mitigated by improvement in later caregiving quality. Given the evidence that altered HPA axis function is associated with increased risk of both mental and physical health problems across the life course, these findings underscore the importance of the early implementation of dyadic-based interventions for at-risk infants and children.

## Epigenetics

The established association between early negative caregiving and elevated health and psychological risk throughout the life course suggests that these early experiences are embedded across multiple biological systems. Epigenetic marks, such as methylation, histone modification, non-coding RNAs and telomeres, are likely part of molecular memory of negative early caregiving and key pathways through which the environment “gets under the skin” (Shonkoff et al., 2012). The epigenome is primarily responsible for the regulation of gene transcription and DNA structure, acting as primary sensors of changing environmental conditions and subsequently influencing the adaptability and responsiveness of biological systems. Initially considered immutable, epigenetic marks are now recognized as dynamic and interactive processes influenced by a range of factors including stress, trauma, sleep, nutrition, pharmacologic agents, and normative development (Anderson et al., 2012; Massart et al., 2014a; Numata et al., 2012). While some epigenetic marks appear to be correlated across tissues and therefore measurable in peripheral tissues (Smith et al., 2015), the most accurate reflection of downstream effects of epigenetic marks necessitates examination within target organs. For this reason demonstration of consistent effects of negative early caregiving across species, in both the target organ (e.g. the brain) and peripheral samples (e.g. peripheral blood, saliva, or buccal epithelial cells) provides the greatest scientific rigor. Similar to the previous sections we provide illustrative examples of cross-species epigenetic convergent findings, with particular emphasis on genetic pathways relevant to the HPA axis and neurodevelopment.

## Methylation and maltreatment

DNA methylation refers to the covalent modification of cytosine residues located predominantly at CpG dinucleotide sequences, although methylation also occurs on histones and other chromosomal structures (Lister et al., 2009). Initially thought to only silence gene expression, methylation is actually a developmentally sensitive dynamic process regulating gene expression as well as overall genomic integrity and structure (Guo et al., 2011; Numata et al., 2012). Methodological considerations in methylation, as with most epigenetic studies, include the selection of the biological source for DNA (e.g. central, or peripheral), correlation across tissues, cross study and cross-species alignment of methylation sites, and selection of assay (e.g. CpG microarrays, bisulfite sequencing methods, methylation specific PCR, methylated DNA precipitation (MeDIP), methylated DNA binding sequencing (MBD-seq), and pyrosequencing) (Eads et al., 2000; Harris et al., 2010). Sensitive periods for epigenetic remodeling likely exist, particularly prenatally and during infancy (Schwarz et al., 2010).

### Specific gene findings, NR3C1 as prototype

Methylation of the glucocorticoid receptor gene (*NR3C1* or *GR*) is one of the most widely examined epigenetic marks in the early life stress literature. The GR receptor is widely expressed throughout the brain and body with abundant expression in the hippocampus and the PFC, two neuroanatomical regions in which evidence of the impact of early negative caregiving and maltreatment is well documented. The exploration of methylation changes in this gene represents an obvious target for maltreatment research, particularly as altered GR function is one hypothesized mechanism predicted to alter the regulation of both the HPA axis and PFC-amygdala connectivity. The association between *NR3C1* methylation and more broadly defined measures of early life stress is comprehensively reviewed elsewhere (Turecki and Meaney, in press) as such in this review we specifically focus on results associated with negative caregiving.

The initial studies documenting the epigenetic embedding of variation in maternal caregiving were reported in rodent cross-fostering experiments. In these studies an association between naturally occurring variations in maternal care and both *NR3C1* methylation and mRNA expression in the hippocampus were observed (Weaver et al., 2004). Additional rodent studies have explored alterations in methylation at this loci as a function of a range of different maternal care paradigms, both naturally occurring and experimentally induced, while studies in humans have explored retrospective reports of maltreatment and psychopathology. To date, while multiple studies in rodents and humans have linked child maltreatment and negative early caregiving to increased methylation in the *NR3C1* gene, no studies in NHP have reported an association.

In the first human study, McGowan and colleagues reported increased *NR3C1* methylation and decreased mRNA in the hippocampus of suicide victims with a history of child abuse compared to both control individuals with no abuse or psychiatric history as well as suicide victims without a history of child maltreatment but matched for psychiatric diagnoses (McGowan et al., 2009). A series of additional studies in humans followed, relying predominantly upon retrospective reports of maltreatment, with few studies including

children. In a cohort of patients with bipolar disorder patients and retrospectively reported childhood maltreatment there was a stepwise relationship between methylation at multiple CpG sites in *NR3C1* and traumatic exposures; however, a study of patients with Bulimia Nervosa found no association between child abuse and methylation (Perroud et al., 2014; Steiger et al., 2013). Using whole blood from adults, Tykra et al. reported increased *NRC3I* methylation associated with a cumulative adversity index but maltreatment was not independently examined (Tykra et al., 2012). In this study, increased methylation was also associated with a blunted cortisol response, providing support for a mechanistic link between these pathways and also consistent with the predicted functional significance of methylation differences in *NR3C1*. In a small study, children with documented physical abuse had significantly higher methylation, in DNA extracted from whole blood, in exon 1f (*NR3C1*) compared demographically similar children without any documented abuse (Romens et al., 2014). A second study, using salivary DNA, demonstrated that children exposed to maltreatment, validated using a multi-informant method, had significantly higher *NR3C1* methylation compared to controls (Weder et al., 2014).

Several rodent studies have examined the association between variations in maternal care and methylation at the homologous locus; however, only four studies have specifically examined paradigms putatively consistent with child maltreatment, specifically maternal separation, three in mouse models and one in rats. Two studies failed to find methylation differences between typically reared and maternally separated rodents at postnatal day 21 and 25, while two other studies found increased methylation in the hippocampus in adult animals who had been maternally separated earlier in life (Daniels et al., 2009; Desarnaud et al., 2008; Kember et al., 2012; Kundakovic et al., 2013). While these studies suggest the cross-species validation of increased *nr3c1* methylation in association with early negative caregiving, the inconsistent findings within the rodent literature suggests that the developmental timing of maternal separation, as well as the age when methylation is examined, are critical covariates. Rodent studies of different maltreatment paradigms, including altered pup retrieval and abusive behaviors, that concurrently test methylation in peripheral blood and the brain, are promising future complements to the existing literature.

Two other genes that are linked to neurodevelopment and the HPA axis, brain derived neurotrophic factor (*BDNF*) and the serotonin transporter (*SLC6A4*), also have cross-species evidence of negative caregiving induced methylation changes (Beach et al., 2010). One powerful advantage of the rodent model is the ability to manipulate the mechanisms controlling methylation and demonstrate causation. Roth et al. demonstrated that maternal abusive behavior resulted in increased DNA methylation of the *bdnf* gene and associated decreased *bdnf* mRNA in the PFC (Roth et al., 2009). Critically, not only was this finding transmitted across generations, but treatment with a DNA methylation inhibitor, blocked the effect on both methylation and gene expression. In a cross fostering study, Roth et al. subsequently demonstrated increased *bdnf* methylation in the hippocampus in female rats, and decreased methylation in the amygdala in male rats exposed to an abusive caregiver; indicating both regional and sex specific differences (Roth et al., 2014). In humans, Perroud et al. demonstrated overlapping alterations in *BDNF* methylation in peripheral blood in patients with a history of maltreatment and borderline personality disorder (Perroud et al.,

2013). Similar cross-species support has been reported for the serotonin transporter. Within the Bucharest Early Intervention Project, a randomized trial of institutional care compared to foster care, methylation in the *5HTTLPR* in buccal epithelial cells at age 12 was significantly correlated with the amount of time a child spent in institutional care across the life course (Non et al., under review). In humans and NHP models this relationship, as well as the impact on down-stream gene expression appears to be further influenced by the *5HTTLPR* genotype, a polymorphic variant not found in rodent species (Kinnally et al., 2010). In a study of 8 rhesus monkeys, 4 maternally reared and 4 surrogate peer reared animals, significant differences in PFC 5hmC hydroxymethylation were found for the serotonin transporter (*SLC6A4*), as well as several other genes (Massart et al., 2014b). Lower observed maternal care was associated not only with altered methylation in *SLC6A4*, but also with negative health outcomes. Together these findings suggest a mechanistic pathway through which early maternal care influences epigenetic marks, leading to altered health outcomes across the life course (Kinnally, 2014). Several differentially methylated loci have also been associated with prenatal maternal stress levels, suggesting that complex models of prenatal and post-natal exposure in animal models are needed (Cao-Lei et al., 2014; Devlin et al., 2010).

### Whole genome studies

Animal models and human studies have also explored the relation between negative caregiving and the methylome. Advantages of the hypothesis neutral, exploratory, aspect of whole genome studies should be balanced with a cautious interpretation of findings, and ideally independent replication, due to the substantial number of independent sites tested. That being said, cross-species replication of genome wide findings, in both peripheral and centrally obtained tissues, can provide powerful novel insight, particularly when one considers that multiple biological systems and pathways are likely impacted by negative caregiving.

Evidence in support of global changes in methylation are found in both animal and human studies. McGowan et al. demonstrated broad alterations in epigenetic patterns within the hippocampus when comparing pups born to high versus low licking mothers, suggesting that more global epigenetic alterations occurred as a consequence of variation in maternal care (McGowan et al., 2011). In NHPs, surrogate-peer rearing has been associated with global alterations in the methylome in the prefrontal cortex and T-cells (Provençal et al., 2012). In humans with a maltreatment history wide spread methylation differences, specifically in microRNA genes and the KEGG WNT signaling pathways, have been reported (Suderman et al., 2014). Interestingly, the authors note that the WNT pathway complex has also been associated with obesity and diabetes, health problems increased in individuals with abuse histories. In a racially diverse cohort of adults where specific genes were examined for differential methylation, European Americans with a history of child abuse demonstrated altered methylation, independent of a diagnosis of alcoholism, compared to adults without a history of child maltreatment (Zhang et al., 2013). In a comparative study of individuals with PTSD, with and without child maltreatment, significant differences in methylation patterns were observed suggesting that maltreatment effects were different than other traumatic exposures and independent of the development of downstream psychopathology,

highlighting the need for careful assessment of maltreatment type and other traumatic experiences (Mehta et al., 2013). Differences in genome wide methylation have also been demonstrated in youth. In a study of maltreated youth and matched controls differential methylation, both increased and decreased, was detected at a significant number of loci indicating the effect of child maltreatment on methylation is not universally unidirectional; a finding supported in the preclinical rodent and NHP studies (Yang et al., 2013). One of the first papers to concurrently report cross-species genome wide methylation changes found differential methylation of *MORIC*, a gene previously associated with depression, in peripheral and central tissues from humans, NHP and rodents (Nieratschker et al., 2014). The authors examined methylation in CD3+ cells from umbilical cord blood in both humans and NHP, CD3+ cells from adolescent NHP, and the prefrontal cortex in rodents. Although it is unclear why prenatal stress models were utilized in the human and rodent studies, whereas maternal deprivation was utilized for the NHP model, the consistency of methylation differences across species, and across peripheral and central tissue, offers support for future studies seeking to link alterations in the methylome across rodent, NHP and humans (Nieratschker et al., 2014). The convergent cross species findings of altered methylation in genes connected to the HPA axis and the connectivity between the PFC and amygdala suggests a mechanistic model whereby early negative caregiving shapes gene regulation, through epigenetic changes, resulting in differential neurobiological development and lasting phenotypic changes in stress reactivity and neural function.

## Conclusions

Exposure to negative early caregiving is a well-documented risk factor for developmental psychopathology. While there is no substitute for studying maltreatment directly in human populations, animal models offer unique opportunities, albeit with important caveats, to understand the basic neurobiological, cellular, and developmental mechanisms. Consistency across models relative to the specific type of maltreatment experience (e.g. physical abuse, emotional neglect/rejection) and both the onset and duration of maltreatment need to be integrated into study design. Animal studies characterizing epigenetic and gene expression changes concurrently, in both peripheral and central tissues, are critically needed to establish the utility and validity of peripheral measurements when inferring neurobiological effects of early negative care-giving. Study design should incorporate both a clear understanding of the normative parental care expected for each species as well as assurance that the laboratory setting does not so significantly deviate from expected experiences as to threaten validity. Greater definitional precision of early life stress, maltreatment, and adversity are also needed as even when adopting a targeted focus on negative caregiving, cross-species definitions remain complex. For example, while direct physical maltreatment of the infant has cross-species validity, (e.g. rough handling in rodents; dragging/throwing infant in NHP; physical abuse in humans), inadequate, insensitive or disorganized maternal caregiving is less clear. Although models of maternal responsiveness to infant cues may be translatable across species, as maternal behavioral responses to infant vocalization and distress can be categorized in all species, deficits in contingent, and dyadic interactions are likely more challenging to translate across species. Additionally baseline differences in the expected amount and quality of physical contact with the mother, involvement of other caregivers,

and influence of the broader social context, represent important considerations, particularly for studies examining reversibility or resilience to negative early caregiving.

Several additional factors that have received inadequate attention warrant mention. Consistent with the mandate from the National Institute of Health requiring examination of sex differences in animal models, this needs to be considered at the outset of any study, particularly as the limited existing data suggests that the sex of the child is an important moderator for long-term consequences (Zeanah et al., 2009). The increasing data describing the evolutionarily conserved neurobiological basis of the attachment relationship, its critical interface with approach/avoidance and threat response circuitry, and the established behavioral assessment paradigms suggest this is an important research direction. Lastly, an under studied area of research is related to the question of “why” mothering goes awry. Although most of the literature focuses on the study of infant developmental outcomes and maternal behaviors that predict them, greater attention to the core alteration in the maternal instinct that drives abuse and neglect is needed. Initial evidence suggests that it may be due to alterations in maternal sensitivity and responsivity (Bernard et al., 2012). Perhaps characterization of exposure based on the dyadic interactions or maternal caregiving behaviors, rather than maltreatment exposure per se, may provide novel insight into the neurobiological consequences of aberrant maternal caregiving that is less dependent on the more complex models attempting to address all levels of exposure type and duration (Bernard et al., 2012; Merrick et al., 2013).

A better understanding of the neurobiological mechanisms underlying increased risk for developmental psychopathology following exposure to negative early caregiving has resulted in targeted research and the development of effective early treatment and prevention strategies. An important, but often overlooked, requirement for this process is a strong understanding of the normative patterns of neurobehavioral development across species (Machado and Bachevalier, 2003), and the use of model systems with sufficient ethological validity to provide translation to the human condition. One research area that has, to date, yet to adequately explored is the integration of neurobiological outcomes, in addition to symptoms, into treatment studies for children exposed to negative early caregiving. While improvement in psychological symptoms represents an important goal, failure to ensure improvement in the underlying neurobiological pathways may leave these children with elevated future, and perhaps unrecognized, vulnerability. In summary this review highlights the powerful role that maternal care plays in regulating the developmental trajectory of the infant, identifies areas of research where significant cross-species validation has occurred, and outlines the challenges, and opportunities, of translational maltreatment research across species.

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