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## Social Buffering of Stress Responses in Nonhuman Primates: Maternal Regulation of the Development of Emotional Regulatory Brain Circuits

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### Abstract

Social buffering, the phenomenon by which the presence of a familiar individual reduces or even eliminates stress- and fear-induced responses exists in different animal species, and has been examined in the context of the mother-infant relationship in addition to adults. Although it is a well-known effect, the biological mechanisms, which underlie it, as well as its developmental impact are not well understood. Here we provide a review of evidence of social and maternal buffering of stress reactivity in nonhuman primates, and some data from our group suggesting that when the mother-infant relationship is disrupted maternal buffering is impaired. This evidence underscores the critical role that maternal care plays for proper regulation and development of emotional and stress responses of primate infants. Disruptions of the parent-infant bond constitute early adverse experiences associated with increased risk for psychopathology. We will focus on infant maltreatment, a devastating experience not only for humans, but for nonhuman primates as well. Taking advantage of this naturalistic animal model of adverse maternal caregiving we have shown that competent maternal care is critical for the development of healthy attachment, social behavior and emotional and stress regulation, as well as of neural circuits underlying these functions.

### Keywords

social buffering; nonhuman primates; stress reactivity; HPA axis

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## Stress, the Hypothalamic-Pituitary-Adrenal (HPA) Axis and Early Experiences

Animal models of early adverse experience, primarily involving disruption of the mother-infant relationship, have played a critical role in understanding how early social experiences “get under the skin” and change developmental trajectories through the identification of biological mechanisms by which the mother regulates brain, behavioral, and physiological development of the infant. Recently identified biological mechanisms go beyond the effects of stress hormones and stress-induced inflammation, and include alterations in the gut microbiome that lead to neurotransmitter changes in the infant’s brain (Borre et al., 2014; Cryan & Dinan, 2012), as well as epigenetic modifications that translate experiences into molecular changes in DNA that can be transmitted from one generation to another (Champagne, 2008; Roth et al., 2009; Weaver et al., 2004). In this paper we will focus on an additional regulatory mechanism of maternal care on infant development: maternal buffering of stress and fear responses. We will first describe the HPA stress response and its development, as well as the control of the stress and fear response by the central nervous system. From there we will review our current understanding of social buffering, both peer and maternal, in nonhuman primates. We will conclude with a review of the impact that disruptions of the mother-infant relationship have on neurodevelopment of the stress and fear response.

The presence of a sensitive and responsive caregiver serves as a potent external regulator of the infant’s physiology, buffering its fear and stress responses early in life through sensory, nutritional, motor and thermal pathways (Hofer, 1984; Howell & Sanchez, 2011; Kuhn et al., 1991; Rainekei, Lucion, & Weinberg, 2014; Rincón-Cortés & Sullivan, 2014). Thus, maternal behaviors could potentially control the maturational rates of emotion and stress self-regulatory strategies and the underlying brain circuits in the offspring. This ability of early experience and the environment to modulate development may have evolutionary roots in which early experiences and environments program physiological and brain development to support behaviors, cognitive, and biological processes that help the offspring (and future generations) adapt to that particular environment. However, the early critical or sensitive periods of increased neuroplasticity that serve as windows of opportunity for adaptation to the environment may also serve as windows of vulnerability.

Much of the literature examining the biological mechanisms linking early adversity (including mother-infant relationship disruption) and developmental psychopathology has focused on the HPA axis because it is activated in response to early stressful experiences (Heim, Ehlert, & Hellhammer, 2000; Sánchez et al., 2005) and can cause long-term neurobiological changes via genomic mechanisms (Barr et al., 2003; Kinnally et al., 2011). Stressful stimuli activate stressor-specific pathways that converge onto and activate neurons in the hypothalamic paraventricular nucleus (PVN) triggering the release of corticotropin-releasing factor (CRF) into the anterior pituitary that in turn releases adrenocorticotrophic hormone (ACTH) into the systemic blood circulation. ACTH provokes the synthesis and release of glucocorticoids (GCs: cortisol in primates), which are highly catabolic steroid hormones. Limbic regions such as the amygdala and hippocampus, as well as the

ventromedial prefrontal cortex (vmPFC), regulate HPA axis activity through indirect projections to the PVN, and they also express glucocorticoid receptors (GR), mediating GC negative feedback (Herman et al., 2003; Herman, Ostrander, Mueller, & Figueiredo, 2005; Ulrich-Lai & Herman, 2009). Stressors, including mother-infant relationship disruption, activate the HPA axis and associated brain areas, including the cortico-limbic structures mentioned above (vmPFC, amygdala, hippocampus). Other neurobiological systems, such as the sympathetic nervous system, are also activated during threatening situations. Chronic stress or traumatic experiences early in life can impact the way these stress-response systems mature, leading to extreme emotional and stress reactivity and other psychopathologies. Much of the evidence supporting a role for variations in maternal care in stress response function comes from studies in rodent and nonhuman primate animal models, making it essential to understand how the stress response matures in these species across development.

A stress hyporesponsive period (SHRP) has been reported in rodent pups during which the HPA axis is less responsive to stress, with an inability to mount a corticosterone (GC produced by the adrenal cortex in rodents) response to stressors that can effectively activate the axis at later ages (Gunnar & Vazquez, 2006; Sanchez, Ladd, & Plotsky, 2001). Given the wide effects of GCs on homeostasis and gene expression, the role of the SHRP is thought to be to keep GC levels low to avoid massive effects on normative brain growth and development (Sapolsky & Meaney, 1986). Although the SHRP involves an immature HPA axis, there is also strong evidence that the dam's presence plays a major role in maintaining low GC levels during the SHRP, and that she also regulates the development of the pup HPA axis and fear systems during the transition out of the SHRP (Moriceau & Sullivan, 2006; Stanton, Wallstrom, & Levine, 1987; Stanton, Gutierrez, & Levine, 1988). In humans and nonhuman primates, although there is also some evidence of an early period of relative stress hyporesponsivity, it is (1) primarily dependent on the buffering effect of maternal (or paternal) presence and not on the immaturity of the HPA axis (unlike the rodent SHRP), (2) highly dependent on quality of parental care and (3) may extend through childhood (Gunnar & Fisher, 2006; Hostinar, Sullivan, & Gunnar, 2014; McCormack, Newman, Higley, Maestripieri, & Sanchez, 2009). Although the underlying mechanisms of this period of stress hyporesponsivity are different for rodents and primates, the evidence from both models supports the hypothesis that GC levels need to be tightly regulated during brain development to facilitate typical maturation.

The development of the HPA axis in nonhuman primates follows a similar pattern as that observed in humans, making them ideal model organisms when attempting to investigate complex sequelae related to stress physiology. The presence of a basal HPA diurnal rhythm has been reported in infant rhesus monkeys, but it still appears to be immature at 5 months of age (comparable to 18–24 months in humans (Raper, Bachevalier, Wallen, & Sanchez, 2013). By the juvenile stage (starting around 12 months, comparable to 4 years in humans) rhesus monkeys show an adult-like diurnal pattern of cortisol secretion (Barrett et al., 2009; Raper et al., 2014; Sánchez et al., 2005). Although there is no solid evidence of a true SHRP in rhesus monkeys, socially familiar cues, specifically the presence of a nurturing mother, do buffer the HPA axis stress responses in infant rhesus macaques (McCormack et al., 2009; Sanchez, 2006). Thus, as described for humans above, nonhuman primate mothers also function as external regulators of infant HPA axis activity, serving as strong social buffers

that prevent stress-induced activations to potential threats. This highlights the importance of early social experiences, in particular the role of nurturing caregiving, on the development of the HPA axis across different mammalian species, as well as the utility of animal models to study the role of adverse caregiving on the etiology of early life stress-induced developmental psychopathology.

Multiple neural pathways transmit information about specific types of threat to the mammalian PVN (Herman et al., 2003; Herman et al., 2005; Ulrich-Lai & Herman, 2009). Psychological and emotional stressors are evaluated and transmitted by brain regions including cortico-limbic structures such as the vmPFC, amygdala, and hippocampus, as described above. These regions change drastically, and over relatively long periods of time, during both pre- and postnatal development in mammals, which is thought to make them particularly sensitive and vulnerable to early social experiences (Andersen, 2003). Recent research has elucidated a critical role of the development of vmPFC-amygdala circuits for proper development of the HPA axis and emotional regulation. Lesion studies represent a successful approach when attempting to describe the complex relationships that exist between these highly interconnected structures during development. Recent studies by our group have shown that when the amygdala is lesioned around 2 weeks of age both HPA axis reactivity and basal function are altered. Lesions of the amygdala during this neonatal period are associated with heightened –not blunted- basal and stress-induced HPA axis reactivity during infancy and the juvenile period (Raper et al., 2013; Raper et al., 2013; Raper, Wilson, Sanchez, Machado, & Bachevalier, 2013; Raper et al., 2014), despite a well established role of the amygdala in stimulating the HPA axis in adult animals, supported by adult lesions of the amygdala resulting in blunted HPA axis reactivity (Kalin, Shelton, & Davidson, 2004; Machado & Bachevalier, 2008), without effects on basal HPA axis activity (Kalin et al., 2004; Machado & Bachevalier, 2008; Norman & Spies, 1981; Sapolsky, Zola-Morgan, & Squire, 1991). These findings suggest that the influence of the amygdala on the HPA axis may change across development, and may have seemingly paradoxical roles, inhibiting HPA axis activity in primates early in development, and then switching later into a stimulatory role on cortisol release. Interestingly, adult and neonatal lesions of these limbic circuits result in similar alterations in emotional reactivity, (Kalin et al., 2004; Machado & Bachevalier, 2008; Machado et al., 2008; Machado, Kazama, & Bachevalier, 2009; Raper et al., 2013; Raper, Wilson et al., 2013), which combined with the differential effects of lesion timing on the HPA axis described above highlights the need for further experiments to determine the underlying brain-behavior relationships.

## **Social Buffering of Stress Responses in Nonhuman Primate Species**

As defined above, social buffering is the phenomenon in which the presence of another animal, or group of animals, can reduce or even eliminate the HPA activation of another individual when exposed to stressful stimuli (Levine, Johnson, & Gonzalez, 1985). This phenomenon has been observed in several species, including humans and non-human animals, and has been reported during development in the context of the mother-infant relationship, as well as in familiar adults.

The first descriptions of social buffering in nonhuman primates were reported in studies examining mother-reared and surrogate-reared infants. Hill, McCormack, & Mason (1973) examined the HPA axis response of surrogate-reared rhesus monkeys when exposed to novelty, and reported that the HPA response was significantly lower when the infant was in the presence of their surrogate mother compared to when alone. Mendoza, Smotherman, Miner, Kaplan, & Levine (1978) also examined the HPA responses of mother-reared and surrogate-reared squirrel monkey infants in response to separation and reunion with the mother/surrogate. All infants demonstrated heightened levels of plasma cortisol in response to the separation from the mother, and all infants demonstrated a return to baseline cortisol levels when reunited with their mothers/surrogates. These findings indicate that infants not only developed an attachment to their mother-figure, but that both mothers and surrogate mothers helped dampen the infant stress response at reunion.

Following the comparison studies on the bonds between monkey infants and their mothers/surrogates, research began to focus specifically on the HPA axis response of squirrel monkey (a New World primate species) infants under a variety of stressful situations, and the ability of the mother to buffer the stress response. Many of these landmark studies were conducted by Seymour Levine. In one of the first studies, Coe, Mendoza, Smotherman, & Levine, (1978) examined the plasma cortisol levels of infant squirrel monkeys under 4 conditions: 1) baseline, 2) 30 minutes after a brief separation and reunion from the mother, 3) 30 minutes after the infant was removed from the social group and housed alone in a cage, and 4) 30 minutes after the mother was removed from the group, while the infant remained in the group. Infants did not demonstrate an elevation in cortisol levels after the brief separation and reunion from the mother, suggesting that the resumption of contact with the mother eliminated an HPA axis reaction to the brief separation. Compared to baseline cortisol values, infants showed a significant increase in cortisol levels when they were separated from the group, as well as when the mother was separated from the group (and the infant was left in the social group). However, infant cortisol levels were not as high following maternal separation when they remained in the group, suggesting that the social group may have buffered the stress response of the infant while the mother was removed. Additional support for a social buffering effect on infant HPA reactivity was later reported (Coe, Wiener, & Levine, 1983; Wiener, Johnson, & Levine, 1987), such that squirrel monkey infants showed a lower HPA axis response to maternal separation when the infant remained in the social group compared to being removed from the social group. In another study, Levine, Wiener, & Coe (1993) demonstrated that not only physical contact, but even olfactory and auditory cues from the mother were able to reduce the HPA axis response of a separated squirrel monkey infant compared to complete isolation from the mother. Altogether these studies suggest that squirrel monkey infants can use social companions to buffer their HPA stress response in response to challenges (e.g. the face of novelty stress), with direct contact with mother having the strongest ability to buffering effect on the HPA axis stress activations (Levine, 2000).

Additional studies conducted on the rhesus monkey mother-infant relationship confirmed findings reported in squirrel monkeys. Gonzalez, Gunnar, & Levine (1981) examined both mother and infant HPA axis responses to several separation conditions, including being removed from the social group but housed together, and being removed and housed

separately. The cortisol levels of the infants when separated with the mother were moderately low compared to when housed during complete separation. In addition, the infants also appeared to dampen the stress response of the mothers, suggesting that social buffering can be bi-directional between mothers and infants during stressful situations. Additional studies in rhesus macaques further validated the finding that in the presence of the mother, rhesus infants showed small to no elevations in cortisol when exposed to novelty (Gunnar, Gonzalez, & Levine, 1980; Levine et al., 1985).

Several studies further manipulated the degree of maternal presence when exposing rhesus infants to novelty to determine what specific maternal cues were necessary to elicit social buffering. Levine et al. (1985) reported that infant cortisol was buffered when the infant was removed from the social group while in contact with the mother, even if they were just in visual contact. Interestingly, the behavioral profile was very different, in that the infants were more likely to vocalize toward the mother when she was only accessible visually. Bayart, Hayashi, Faull, Barchas, & Levine (1990) also reported that infants who had visual and auditory access to their mother during a separation from their social group showed lower cortisol responses compared to those that were in complete isolation, although the behavioral profiles were more reactive than during the alone condition. They also reported increased 3-methoxy-4-hydroxyphenylglycol (MHPG), a norepinephrine metabolite, levels in the complete isolation condition compared to separation in the presence of the mother. Levine et al. (1985) suggested that the inverse relationship that is observed between behavioral reactivity and physiological reactivity when rhesus infants are isolated in the presence of the mother may be explained as a coping mechanism. Specifically, the vocalizations may serve as a coping strategy to the stressful situation, allowing for reduction of physiological arousal in the infant, in addition to serving as solicitations for aid.

Finally, several studies have examined the extent to which the social group can help buffer infants' HPA axis response in the face of a stressor. Coe, Wiener, Rosenberg, & Levine, (1985) examined the response of rhesus infants during two forms of separation: infant removal from the mother and the social group, or mother removal from the social group while the infant remained in the group. They found that when the infants remained in the social group while their mother was removed, their cortisol reactivity was blunted in comparison to when they themselves were removed from the group, suggesting that the social group acted as a social buffer by helping reduce the infant stress response to the mother being removed from the group. It is also possible that the first form of separation (maternal and group) combined with exposure to novelty more strongly activated the HPA response than just removing the mother from the social group (i.e. no exposure to a novel environment). Further experiments that systematically address the effect of each condition would need to be conducted to clarify this point.

More recently Winslow, Noble, Lyons, Sterk, & Insel (2003) examined the effect that social partners have on buffering the stress response of 3 year old rhesus macaques who were either mother-reared or peer-reared during the first year of life. Social partners were able to buffer the stress response of the mother-reared animals, but the same degree of buffering was not observed in the nursery-reared animals, suggesting long-term impact of the mother-infant relationship on the ability of primates to benefit from social buffering effects.



Taken together, these results suggest that, during normative development, separation from the social group does not strongly activate the HPA axis of monkey infants when the infants are left in contact with the mother. When the infant is exposed to the stress of group separation, and allowed visual, auditory, or olfactory access to the mother, behavioral reactivity increases, yet cortisol levels are maintained at approximately baseline levels. Finally, when the mother is removed from the infant, but the infant remains in the social group, its HPA axis is not activated as strongly as when the infant is removed from the group alone, suggesting that familiar conspecifics may also act as social buffers. These results collectively suggest that the mother, and in some cases other animals, play an important role in reducing arousal in infants (Gunnar et al., 1980). It appears that physical contact with the mother helps reduce both the physiological and the behavioral responses to stressful stimuli in infants (Gunnar et al., 1980). According to Levine (2000) the mother is the primary source of security for an infant, and by being able to maintain proximity to her in the face of uncertainty, the infant is able to use her to control its arousal level.

Social buffering has also been examined in adult animals. The first studies were conducted in squirrel monkeys, and found that the presence of several group members had the strongest effect at reducing the stress response in the face of a stressor. When adult male squirrel monkeys were placed in a novel environment with visual access to a snake, they showed increased levels of cortisol when tested alone or with a partner; however, when tested with their group, they did not show cortisol elevations (Coe, Franklin, Smith, & Levine, 1982; Vogt, Coe, & Levine, 1981). Likewise when adult male squirrel monkeys were exposed to fear conditioning (light-shock pairing), their cortisol levels were elevated when tested alone, while cortisol elevations were attenuated when tested with a social partner, and returned to baseline when several social partners were present (Stanton, Patterson, & Levine, 1985). These results suggest that the presence of several social partners is most effective for reducing the HPA axis activation of adult squirrel monkeys when exposed to a stressor.

Social buffering has also been reported in marmosets, another New World primate species. Smith, McGreer-Whitworth, & French (1998) found that marmosets placed in a novel environment exhibited lower levels of urinary cortisol when exposed with their heterosexual pair mate compared to when tested alone. Rukstalis & French (2005) examined whether or not the vocalizations of a pair mate would have an effect on an isolated adult marmoset's HPA response. Adult marmosets who were separated from their group, and who heard the vocalizations of their pair mate throughout the separation, had significantly lower levels of urinary cortisol compared to when tested alone or when tested with the sounds of an unfamiliar animal. This demonstrated the effect referred to as "vocal buffering".

Social buffering has also been reported in adult macaques. Gust, Gordon, Brodie, & McClure (1994) examined the cortisol and immunological response of adult female rhesus monkeys exposed to a 96 hour separation from their social group. Compared to baseline values, the immunological response to the separation was significantly reduced when the separated animals had a social companion with them, compared to being alone. However, the presence of another animal did not buffer the cortisol responses of the separated animals. In a more naturalistic design, Young, Majolo, Heistermann, Schulke, & Ostner (2014) examined the role that social support had on the stress response of wild male Barbary

macaques. The researchers evaluated levels of fecal cortisol in these animals during 2 stressful events: when exposed to low temperatures, and when exposed to group aggression. They found that the animals who had stronger social ties had lower levels of fecal cortisol compared to those with weaker social bonds. This suggests that even when faced with naturalistic stressors, social buffering is a powerful phenomenon that influences HPA axis responses.

Taken together, these findings suggest that the presence of social partners can also attenuate the stress response of adult nonhuman primates when exposed to different stressor types. However, it appears that there are species-specific differences in whether or not one animal can have such an effect, or whether it takes several known social partners. Galvao-Coelho, Silva, & De Sousa (2012) further suggested that there are sex differences in the effect that one or more social members have to buffer the stress response of adult animals.

### **Social Buffering Following Disruption of the Mother-Infant Relationship**

For primates the mother-infant relationship is arguably the most salient early experience. This has been demonstrated by the strong link between disruption of this relationship and poor behavioral and physiological outcomes in the infant. The effects of this form of early adversity are thought to be due in part to a disruption in the mother's ability to buffer her infant's stress response, as described previously. This could thus lead to exposure to elevated levels of cortisol and alterations in HPA function. This is supported by studies in several nonhuman primate species and models of mother-infant relationship disruption, discussed below.

Disruption of the mother-infant relationship results in alterations in HPA axis function, including the ability of familiar conspecifics to buffer the stress response, i.e. social buffering. One very potent, albeit severe, method of disrupting the mother-infant relationship is to prevent the formation of that bond/relationship as in the case of nursery-rearing infant monkeys. This manipulation causes a broad range of behavioral and HPA axis alterations, including altered circadian cortisol rhythms (Boyce, Champoux, Suomi, & Gunnar, 1995), increased basal HPA function (Higley, Suomi, & Linnoila, 1992), and decreased basal HPA function (Clarke, 1993) (for review, see Sanchez et al., 2001). In contrast to mother-reared infant rhesus monkeys, who are able to use familiar conspecifics to buffer their responses to stress (Coe et al., 1978; Levine, 2000; Mendoza et al., 1978; Wiener et al., 1987), nursery-reared animals do not show this effect and show alterations in salient social behaviors including excessive allogrooming and intermale mounting (Winslow et al., 2003). As mentioned above, Harry Harlow's group also investigated the cortisol responses of surrogate- and mother-reared infants to a stressor during separation from the attachment figure (i.e. the surrogate or the mother). They demonstrated that mother-reared infants showed similar pretest cortisol levels and cortisol reactivity prior to a separation period as compared to the surrogate-reared group while the surrogate was present; however after separation, while neither the surrogate- or mother-reared animals showed differences in cortisol increases between pretest and posttest measures, mother-reared animals showed increased pretest –baseline– cortisol levels (Meyer, Novak, Bowman, & Harlow, 1975). The authors further explained that this effect was driven by an order-effect in the mother-reared



infants in which the second infant to be tested each day had elevated pretest cortisol levels (Meyer et al., 1975). The results of this study suggest alterations in the surrogate-reared animals' ability to use social information to modulate their stress physiology. All of this evidence combined suggests that the species typical mother-infant relationship plays a unique role in modulating the infant's ability to use other conspecifics to buffer their stress response, and that replacing the mother with a cloth surrogate, although this has been shown to represent an attachment relationship, is not enough to normalize this aspect of HPA axis function. Further evidence of this effect comes from a recent study that reported elevated levels of cortisol accumulated in hair (a measure of chronic GC exposure) that were related to anxious behavior in animals raised in a nursery with access to same age peers, suggesting that peers are not able to buffer stress and emotional reactivity like mothers do (Dettmer, Novak, Suomi, & Meyer, 2012).

Maternal separation is another experimental manipulation of the mother-infant relationship that has been used to investigate the role of the mother in modulating the developing HPA axis. As described above, both New and Old World nonhuman primates, including rhesus monkeys, squirrel monkeys (*Samiri sciureus*), and common marmosets (*Callithrix jacchus*) have been studied using variations of this paradigm. In rhesus monkeys, short maternal separations result in infants' increased activity, frequency of vocalizations, and HPA axis activations (Bayart et al., 1990; Harlow, Harlow, & Suomi, 1971). Repeated maternal separation in infancy leads to increased cortisol reactivity and flattened diurnal rhythms in females later in life, during the juvenile period (Sánchez et al., 2005). These effects, though, are dependent on the timing of the separation as demonstrated by elegant work by Lyons and colleagues. There is an interesting body of literature supporting "stress inoculation" effects, the concept that certain types of stress at specific times during development actually increase resilience when the individual faces challenges later in life. Most of the evidence for this phenomenon in nonhuman primates comes from studies of squirrel monkeys exposed to mild intermittent stress consisting of separation from the mother and social group at developmentally distinct times during developmental (i.e. weaning, when they are no longer dependent on their mothers). This stress exposure appears to be protective, allowing the animal to better adapt to environmental challenges later in life (Lyons & Parker, 2007; Lyons, Parker, & Schatzberg, 2010; Parker, Buckmaster, Schatzberg, & Lyons, 2004). In these animals there is also evidence that the HPA stress response is better calibrated to handle challenges, as demonstrated by reduced basal levels of stress hormones while mounting comparable neuroendocrine responses to moderate stressors as compared to unexposed animals (Parker, Buckmaster, Lindley, Schatzberg, & Lyons, 2012). In this model, the distribution of the glucocorticoid receptor (GR) in the brain was also changed as a result of stress exposure (Patel, Katz, Karssen, & Lyons, 2008). The GR has also been implicated in models of care disruption using marmosets (a biparental primate species) separated from their parents daily between days 2 and 28 of life. These repeated separations resulted in reductions in GR mRNA in the hippocampus in adolescent marmosets (Dettling, Feldon, & Pryce, 2002a; Dettling, Feldon, & Pryce, 2002b). Altogether, these GR effects suggest that maternal (or parental) presence at certain points in development can lead to specific cellular changes that may be partly responsible for the ability of the mother to modulate the HPA stress response.

The variable foraging demand (VFD) model contrasts with the models described above in that it is an ethologically valid model of early life adversity that exploits the species typical behavior of foraging for food. Leonard Rosenblum and colleagues first developed this model in bonnet macaques (*Macaca radiata*), which consists of variable and unpredictable food availability (e.g. periods of intense foraging alternated with periods of free access to food) (Rosenblum & Pauly, 1984). This manipulation results in disruption of the early mother-infant relationship by altering maternal behavior (i.e. reducing the amount of time spent responding to infant solicitations for care) (Rosenblum & Pauly, 1984). Infants exposed to the high foraging demand condition showed physiological hyper-responsiveness to stressful stimuli, as well as elevated levels of CRF in cerebrospinal fluid (CSF), but reduced levels of cortisol as compared to those raised under low foraging demand (Coplan et al., 2001; Coplan et al., 1996). Just as the models described above that involved more invasive manipulations of maternal care, the more ecologically and ethologically valid VFD model points to similar alterations in the HPA stress response associated with changes in mother-infant interactions that may be related to the mechanisms involved in social buffering of the stress response.

Another ethologically valid model of mother-infant relationship disruption is naturally occurring infant maltreatment in nonhuman primates. Infant maltreatment is not a uniquely human phenomenon, but has also been reported in both wild and captive populations of nonhuman primate species, including macaques, baboons, and marmosets (Brent, Koban, & Ramirez, 2002; Johnson, Kamilaris, Calogero, Gold, & Chrousos, 1996; Maestripieri & Carroll, 1998; Troisi, D'Amato, Fuccillo, & Scucchi, 1982). Our group has studied this phenomenon in rhesus monkeys and defines maltreatment as an adverse early experience that includes two comorbid types of maternal behavior that both result in overt signs of infant distress (vocalizations, tantrums, etc.): (1) physical abuse consisting of aberrant violent behaviors exhibited toward the infant causing pain and distress (drags, crushes, sits on, or roughly grooms the infant), typically occurring during the first 2–3 months of life, and (2) high rates of infant rejection beginning early in life, consisting of pushing the infant away when it solicits maternal contact (Maestripieri & Carroll, 1998; McCormack, Sanchez, Bardi, & Maestripieri, 2006). Several alterations in the HPA axis have been associated with this disruption in species typical mother-infant behavior, including increases in both basal and stress levels of cortisol, and blunted ACTH responses to a CRF pharmacological challenge, reflecting down regulation of CRF receptors in the pituitary as a consequence of chronic CRF overactivity by the hypothalamic PVN, which further supports stress-induced activation of central components of the HPA axis –i.e. the “H”ypothalamus and the “P”ituitary- (Koch, McCormack, Sanchez, & Maestripieri, 2014; Sanchez, 2006; Sanchez et al., 2010). Altogether these findings suggest that maltreatment is a stressful experience that results in elevated activity of the HPA axis, likely including overproduction of hypothalamic CRF which leads to pituitary down regulation of CRF receptors.

This early infant maltreatment experience is more complicated than just being stressful for the infants. Additional findings from our lab suggest that the ability of the mother to buffer the infant's stress reactivity is also impaired in maltreating mothers, which deepens the developmental impact of this poor caregiving experience. Figure 1 shows an impaired ability

of the mother's presence to buffer stress-induced cortisol increases in maltreated infants ( $t(18)=-1.936$ ,  $p=0.034$ , one-tailed). In that study, mother-infant pairs (10 control, 10 maltreated) were exposed together to a novel stress test when the infant was 2 months old (see (McCormack et al., 2006) for a description of the selection of subjects and characterization of early maternal care). A baseline blood sample was collected from both mother and infant, and another blood sample was collected 30 min following exposure to the novel cage and room (post-stress, 30 min) for measures of plasma cortisol concentrations by radioimmunoassay (RIA; Diagnostic Systems Lab commercial kit, Webster, TX). Infants' plasma cortisol concentrations (in  $\mu\text{g/dl}$ ) are plotted in reference to the average stress-induced cortisol levels reached when infants are exposed to a novel stress test alone (without the mother) at similar ages. Thus, while the presence of a sensitive/responsive caregiver (control/competent, mother) prevents stress-induced cortisol elevations in the infant, the presence of maltreating mothers did not buffer the stress responses in their offspring. Of course, one possibility is that this is due to maltreating mothers exhibiting negative behaviors towards the infants during testing. However, analysis of mother-infant interactions from the video-recorded sessions did not show any significant differences in the behaviors exchanged during the test in comparison to control mother-infant pairs. We also examined whether higher stress responses in the maltreating mothers could account for the elevated cortisol responses of their infants, but did not find significant differences between control and maltreating mothers (both groups showed significant cortisol elevations in response to the novelty test:  $t(18)=-1.58$ , n.s.). No correlations were found between the stress-induced cortisol increases in moms and infants, either ( $r(18)=0.26$ , n.s.).

## Long-term Impact of Maternal Care on Development of Emotional and Stress Regulation Brain Circuits

Although some of the adverse caregiving experiences and stress activations described above are limited to the infant period, their long-term impact can be significant. For example, in the infant maltreatment model recent neuroimaging studies have begun to map the long-term consequences for structural brain development. Among other ongoing studies, our group has reported associations between elevated basal cortisol levels in maltreated infant macaques at 1 month of age, when abuse rates were highest, and reduced white matter integrity in tracts important for behavioral and emotional regulation, visual processing, somatosensory, and motor integration during adolescence (Howell et al., 2013). But this is just one example, and we will review below evidence of long-term impact of maternal care on the development of neurocircuits involved in stress and emotion regulation.

Adverse caregiving experiences such as those reviewed above happen at a time of rapid neurodevelopmental changes, creating windows of high plasticity in which early experiences are encoded (Andersen, 2003; Knudsen, 2004; Rice & Barone, 2000). The developmental trajectories and sensitive periods are regionally dependent, with cortical maturation happening first in low order sensory cortices (such as visual and somatosensory processing areas), followed by the association cortices that integrate those sensory inputs (e.g. temporal and prefrontal areas) (Giedd, 2004; Giedd & Rapoport, 2010; Gogtay et al., 2004; Shaw et al., 2008). This literature suggests that brain regions with extended development (PFC,

association cortices, amygdala, hippocampus) are particularly sensitive and vulnerable to early experiences, especially maternal care. Studies in humans (Bremner et al., 1997; De Bellis et al., 1999; De Bellis, Keshavan et al., 1999; De Bellis, 2005; Drevets, 2008; Teicher et al., 2003; Tottenham & Sheridan, 2010) and animal models (Arabadzisz et al., 2010; Bale et al., 2010; Coplan et al., 1998; Coplan et al., 2001; Coplan et al., 2010; Coplan et al., 1996; Howell et al., 2014; Jackowski et al., 2011; Law et al., 2009; Law, Pei, Feldon, Pryce, & Harrison, 2009; Mathew et al., 2003; O'Connor & Cameron, 2006; Pryce et al., 2005; Sanchez et al., 2001; Spinelli et al., 2009) have provided compelling evidence that the link between adverse caregiving and problems with emotional and stress regulation is, indeed, greatly due to alterations in the typical development of these cortico-limbic circuits. As an example, recent neuroimaging studies by our group in the nonhuman primate model of infant maltreatment demonstrated an association between abuse rates received by infant rhesus monkeys and bigger amygdala volumes and emotional reactivity during adolescence (Howell et al., 2014). These findings parallel some long-term effects in maltreated humans, including structural differences in amygdala, orbitofrontal cortex, anterior cingulate cortex among other regions (Dannowski et al., 2012; McCrory, De Brito, & Viding, 2012; Teicher, Anderson, Ohashi, & Polcari, 2014).

The plasticity of PFC-amygdala circuits in infants and their sensitivity to early maternal care may have an adaptive role. A main goal of the infant brain is to bond to the caregiver at any cost. Elegant rodent studies (reviewed in another paper in this issue by Regina Sullivan and colleagues), have mapped some of the neurobiological mechanisms underlying the regulation of maternal behaviors on the pup's brain development (Eghbal-Ahmadi, Avishai-Eliner, Hatalski, & Baram, 1999; Howell & Sanchez, 2011; Korosi & Baram, 2009; Sanchez et al., 2001). Examples of these mechanisms include the regulation of the pup's physiology through effects of milk on the gastrointestinal tract, stimulation of sensory pathways by the mother that regulate the development of PFC-amygdala circuits and recent work demonstrating that the presence of the mother increases cortical synchronization in pups (Sarro, Wilson, & Sullivan, 2014). Seminal work by Sullivan and colleagues has also characterized the neurobiological systems that allow rat pups to attach to the dam (Moriceau & Sullivan, 2005; Sullivan & Lasley, 2010) and that are particularly vulnerable to poor maternal care (Rincón-Cortés & Sullivan, 2014). These studies have shown that the mammalian infant brain is wired to form and maintain strong bonds with the mother, though may use different sensory systems in different species (e.g. olfactory, in rats). Their initial studies showed that pups use a different learning circuit (brainstem noradrenergic) than adults, which helps them quickly learn a robust preference for their mother, while at the same time fear/avoidance brain circuits are "off". These results explain why the strong bond with the mother is preserved even when she is physically abusive, as shown in humans (Helfer, Kempe, & Krugman, 1999), nonhuman primates (Harlow & Harlow, 1965; Sanchez et al., 2010), and even dogs (Fisher, 1955). Once the pups start exploring the environment, that fear/avoidance learning system is turned "on" to keep them away from danger and the attachment/approach automatic system becomes less automatic and more regulated (Rincón-Cortés & Sullivan, 2014). Similar behavioral switches towards increased fear are present in primates when they start exploring the environment (e.g. around 7–9 months in humans when we start walking; (Sroufe, 1977)). The parallel developmental switches in approach/

avoidance strategies across rodent and primate species seem supported by developmental switches reported in the amygdala's role regulating fear and stress responses, as well as in its connectivity with the PFC both in humans (Gee et al., 2013) and nonhuman primates (Raper et al., 2014). Although the emerging evidence is compelling, we need to better understand the tempo and role of these normative developmental switches before we can map the impact of poor caregiving.

## Conclusions and Future Directions

The evidence for social buffering of primate stress and emotional responses, particularly from the presence of a responsive mother, is quite compelling. We are just beginning to understand the underlying neurobiology of this phenomenon. Using nonhuman primate models, we have identified critical brain circuits (i.e. prefrontal-limbic circuits) and developmental periods during which the formation of strong mother-infant bonds seems to be particularly important for proper development of stress and emotional regulation. Prefrontal-limbic circuits are sensitive to adversity early in life (Howell et al., 2013; Howell et al., 2014; Jackowski et al., 2011) and have been implicated in poor health outcomes associated with adverse early experience (Howell et al., 2014). Recent investigations into the impact of early life adversity in human children have been guided by and are consistent with these findings from animal models, reporting alterations in both PFC and limbic brain regions (Ansell et al., 2012; Dannlowski et al., 2012; Frodl et al., 2012; Pechtel & Pizzagalli 2011; Wang et al., 2014). Given the worldwide prevalence (Kessler et al., 2010) and negative social and economic impact of early adversity (Saul et al., 2014), particularly of parent-infant relationship disruption, it is critical to further elucidate its neurobiological underpinnings, and the biological processes that translate the mother's presence into infant's physiological and behavioral regulatory responses so that tractable targets for prevention and intervention can be identified. Further nonhuman primate work is needed to dissect the critical biological pathways of maternal communication (olfactory, visual, tactile, auditory signals) and how they provoke neural, behavioral, and physiological changes in their infants. This will explain the relationships suggested by human work. We will also need to consider other developmental periods such as adolescence. By utilizing nonhuman primate models we have the opportunity to parse out the neurobiological and physiological mechanisms of social buffering during development, which would help provide the basis for efficacious treatments and preventative strategies in humans.

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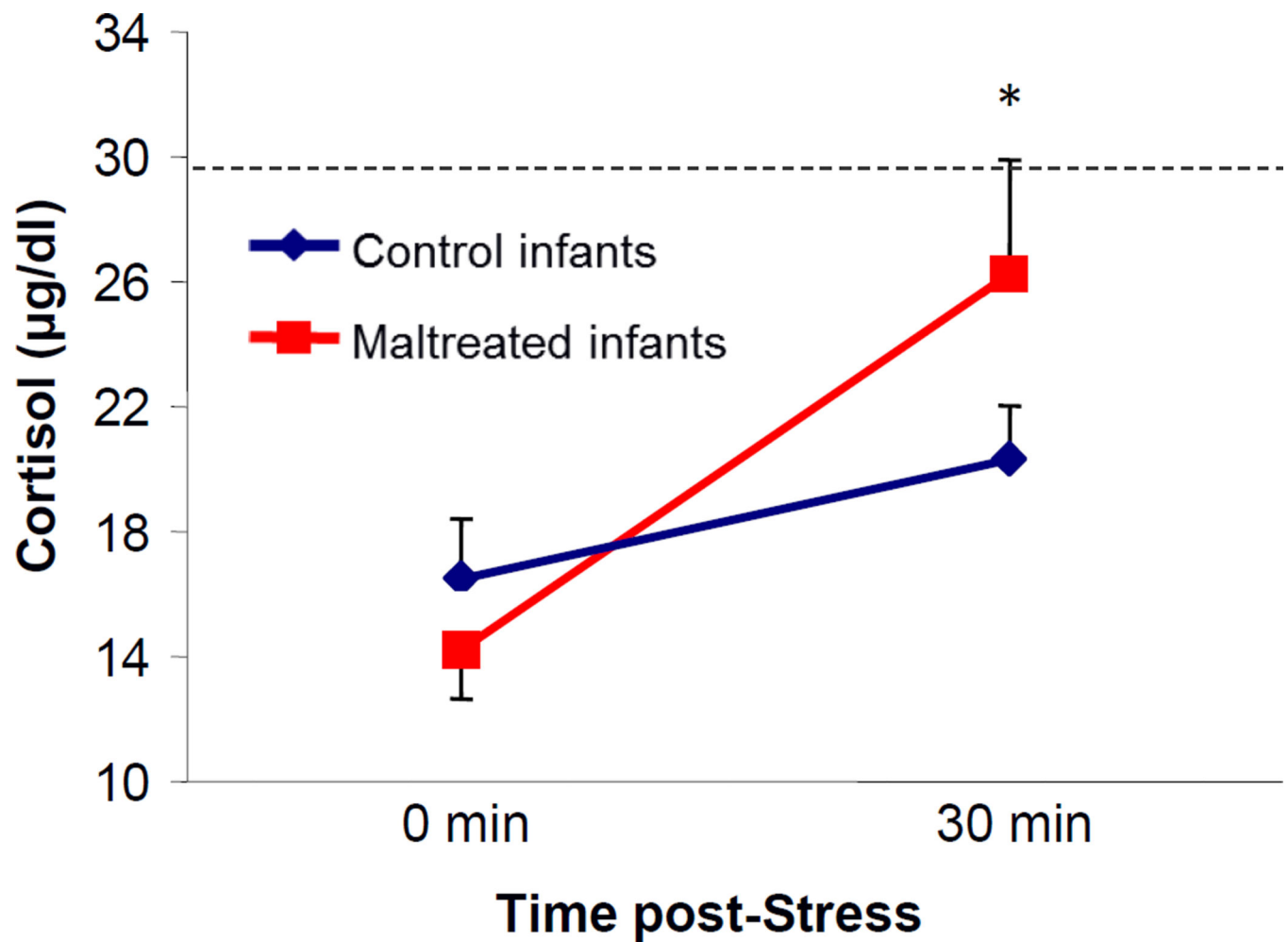
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**Figure 1.**

Impaired ability of the mother's presence to buffer stress-induced cortisol increases in maltreated infants. Mother-infant pairs were exposed together to a novel stress test when the infant was 2 months old. A baseline (0 min) blood sample was collected from both mother and infant, and another blood sample was collected 30 min following exposure to the novel cage and room (post-test, 30 min). Infants' plasma cortisol concentrations (µg/dl) are plotted in comparison to the average stress-induced cortisol levels reached when the infants were exposed to a novel stress test alone (without the mother). \* Significant difference between the stress-induced increase in cortisol (delta: stress-baseline) of control and maltreated infants ( $t(18)=-1.936$ ,  $p=0.034$ , one-tailed).