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Abstract

In many species of vertebrates, prenatal and early postnatal stress can have long-lasting consequences for neuroanatomical, neuroendocrine, or behavioral development. In primates including humans, prenatal psychosocial stress and postnatal psychosocial stress induced by the mother's behavior represent important sources of nongenetic maternal effects through which mothers can modify their offspring's phenotype. Prenatal and maternal psychosocial stress are probably mediated by similar physiological mechanisms and primarily including the HPA axis. The biomedical/clinical view, the stress-inoculation model, and the adaptive calibration model make different assumptions and predictions concerning the adaptive or maladaptive developmental consequences of prenatal and maternal psychosocial stress. Studies of experimentally induced prenatal psychosocial stress in primates indicate that fetal programming occurs with characteristics similar to those observed in laboratory rodents and in humans. Studies of naturally occurring maternal psychosocial stress in primates have focused on maternal abuse and rejection of offspring. Although the developmental consequences of exposure to maternal abuse or high rates of maternal rejection are unlikely to be adaptive, exposure to moderate levels of rejection appears to result in physiological and behavioral changes that enhance resilience later in life. It is possible that some aspects of normal parenting in nonhuman primates and humans are designed to be stress inducing to prepare offspring to deal with the psychosocial stress that is an inevitable part of life in complex and competitive social environments.

Chapter 3
Prenatal and Maternal Psychosocial Stress in Primates: Adaptive Plasticity or Vulnerability to Pathology?

Dario Maestripieri and Amanda Klimczuk

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3.1 Introduction

Maternal effects are influences a mother's phenotype has on her offspring's phenotype that occur independent of the offspring's genotype (Mousseau and Fox 1998; Maestripieri and Mateo 2009). Maternal phenotypic traits that influence the offspring's phenotype are subject to natural selection so long as they are both variable and heritable. Such traits are *genetic* maternal effects, and the genes underlying them are called *maternal effect genes*. In contrast, *environmental* maternal effects are nonheritable, because variation in these traits results from extrasomatic rather than genetic differences. A maternal phenotype that is maladapted to the environment—as manifested, for example, in pathological alterations in nutritional state, key physiological parameters, or behavior—negatively impacts the offspring's ability to survive or reproduce. However, environmental maternal effects can sometimes be adaptive for a mother or her offspring. On the one hand, maternal effects can help to maximize the mother's fitness by allowing her to adjust her level of parental investment in accordance with prevailing conditions (e.g., by reducing offspring size or growth rate when food is scarce). On the other hand, maternal effects can also benefit offspring by providing preemptive information about the environment they will likely be born into, thereby enhancing their abilities to survive and reproduce in such an environment. Because the time and energy a mother invests in her current offspring is unavailable for future reproductive effort, the mother and the offspring have different investment optima. Environmental maternal effects are one arena in which this mother–offspring conflict can be staged (see Uller and Pen 2011). (As discussed below, whether maternal effects primarily benefit mothers or their offspring has resulted in different adaptive interpretations of prenatal stress.)

Maternal effects are classified as prenatal or postnatal depending on whether parental modification of the offspring phenotype occurs before or after birth. Both types of effects have been documented in many vertebrate species. Prenatal maternal effects can be especially strong in birds because mothers can affect offspring development by depositing varying amounts of nutrients, hormones, and other biological substances in their eggs. In placental mammals, prenatal maternal effects are collectively referred to as *fetal programming*. Fetal programming can be very powerful because the mother's body serves as the fetus's environment for an extended period of gestation, opening many opportunities for maternal influence of fetal development through nutritional and other physiological mechanisms.

Postnatal maternal effects in vertebrates can be quite heterogeneous; they include food provisioning and other forms of parental care that alter offspring body condition, metabolism, and, later, behavior. Maternal effects can also occur in the social domain. For example, in cercopithecine monkeys, a female's dominance rank can affect her offspring's growth rate, age at first reproduction, and adult behavior (see Maestripieri 2009 for a review). In both birds and mammals, maternal effects may facilitate learning and imprinting of social, habitat, and food preferences that match early experiences (Mateo 2009). Other effects are more indirect: for example, parental nest site choice determines the offspring's social environment, which in

turn affects the production of hormones that may have long-term consequences for behavior (Price 1998).

The question of whether maternal effects are adaptive or maladaptive for the offspring is especially relevant for issues of prenatal or maternal psychosocial stress. Prenatal psychosocial stress refers to environmental psychosocial stress the mother experiences during pregnancy and *communicates* to the fetus via transfer of hormones and other physiological substances through the placenta. In utero, maternal hormones can directly affect the fetus's hormones, body, and brain. After birth, the mother's hormones are transferred only through breast milk; however, because she is still the most important aspect of the offspring's early postnatal environment, the mother herself can be a significant source of environmental stress. Therefore, we refer to the psychosocial postnatal stress induced in offspring by the mother's behavior as *maternal stress*. Maternal stress may be only a subset of all psychosocial stress experienced by a young individual, but it is clearly an important source of maternal effects (see the *maternal mediation hypothesis* of environmental stress; e.g., Macrí and Würbel 2006, 2007).

Prenatal and maternal psychosocial stress have been extensively studied in laboratory rodents and in humans. Less is known about these maternal effects in primates (but see Maestripieri 2009; Maestripieri and Groothuis 2012). Studies of nonhuman primates provide important links between the research literature in rodents and humans. If the findings of rodent studies are replicated in nonhuman primates, there is a greater probability that they also apply to humans. Conversely, if processes occurring in humans can also be demonstrated in nonhuman primates, it is likely that such processes have a biological basis and can be studied in other animal models as well.

The effects of prenatal and maternal psychosocial stress are likely mediated by common physiological mechanisms, the most important of which is the hypothalamic–pituitary–adrenal (HPA) axis. Many studies of prenatal stress in laboratory rodents and humans suggest that the most likely mediator of fetal programming is maternal cortisol (e.g., Welberg and Seckl 2001; Glover et al. 2010; Oitzl et al. 2010). Cortisol increases significantly and predictably in relation to a wide range of acute psychosocial stressors. In addition, the difference in concentration between maternal and fetal cortisol is so large that even small fluctuations in maternal cortisol can exert significant effects on fetal physiology (see Del Giudice et al., Chap. 1; Flinn et al. 2011; Del Giudice 2012). Maternal cortisol levels during gestation have been shown to predict behavioral reactivity and HPA functioning in infants and children (Glover et al. 2010; Del Giudice 2012). A number of additional stress-related hormones and neurotransmitters have also been proposed as possible mediators of fetal programming, including maternal and placental corticotrophin-releasing hormone (CRH), maternal adrenocorticotropic hormone (ACTH), adrenal steroid hormone dehydroepiandrosterone (DHEA), serotonin (5-HT), and norepinephrine (NE) (Talge et al. 2007; Glover et al. 2010).

Long-term HPA axis alterations (involving basal secretion of ACTH or cortisol, or hormonal secretion in response to stress or CRH/ACTH challenges or to dexamethasone-induced glucocorticoid negative feedback) induced by prenatal or

maternal psychosocial stress could underlie adaptive adjustments in reactivity to environment (e.g., emotional reactivity or metabolic responsiveness), or they could reflect chronic stress-related pathologies such as posttraumatic stress disorder (PTSD). Both phenomena have been well studied in humans and have their parallels in nonhuman primates. In this chapter, we will review and discuss the literature on the effects of prenatal and maternal psychosocial stress in nonhuman primates, addressing whenever possible both their potential adaptive significance and their underlying mechanisms. However, we will first address some conceptual issues regarding the interpretation of these forms of stress.

3.2 Prenatal Stress

3.2.1 Conceptual Interpretations of Prenatal Psychosocial Stress

A great deal of developmental research conducted by psychologists, psychiatrists, and biomedical scientists is based on a normative view of brain, neuroendocrine, behavioral, social, emotional, and cognitive development in which any significant deviations from the norm are construed as pathological and maladaptive for the developing organism. Such deviations may include alterations of basic physiological parameters outside their normal ranges for a particular age and gender, of the timing of particular events during development, or of developmental trajectories such as growth or maturation curves. From this biomedical/clinical perspective, all forms of stress have a negative connotation by definition, and prenatal psychosocial stress is considered a significant risk factor for abnormal fetal and childhood development and health. Studies informed by this perspective and conducted with humans and laboratory rodents have reported a host of adverse developmental consequences of prenatal psychosocial stress (e.g., Dodic et al. 1999; Kofman 2002; Maccari et al. 2003; Talge et al. 2007; Glover 2011; Morley-Fletcher et al., Chap. 7). [AU1]

In contrast to the biomedical/clinical view, an evolutionary perspective on development posits that since the environment in which organisms develop can be highly variable, developmental variation may represent adaptation to different environmental circumstances rather than pathology. Evolutionary scientists realize that psychosocial stress is an integral part of the lives of all social organisms and that these organisms possess a number of strategies to cope with such stress. Some of these strategies represent short-term responses to acute perturbations of the environment, while others represent long-term adjustments to chronic stressors and other stable features of the environment. Early life, especially in utero, is characterized by high plasticity in brain structure and physiological function and therefore is an ideal period in which to make long-term adjustments to stable characteristics of the environment.

Evolutionary interpretations of prenatal psychosocial stress recognize that the maternal body and the placenta acquire information about stressful features of the

mother's social environment and shape the neural and neuroendocrine development of the fetus to be well suited for that environment. One version of these evolutionary interpretations, the *adaptive tuning hypothesis*, suggests that prenatal environmental stress mediated by the mother's body acts as a developmental cue to offspring, predictively programming their future phenotypes to better survive in suboptimal environmental conditions (Gluckman and Hanson 2004; Horton 2005). The adaptive tuning hypothesis assumes that, with the exception of the extremely high levels of stress that tend to result in maladaptive outcomes, the stress an organism experiences prenatally will optimize its postnatal phenotype in an environment featuring that level of stress. However, pathologies can arise if the later environment does not match the early prenatal environment that induced tuning. An extended and more sophisticated version of the adaptive tuning hypothesis of prenatal stress, which also explains postnatal stress, is represented by the adaptive calibration model of stress responsivity (Del Giudice et al. 2011; see below).

A different evolutionary hypothesis proposed by Hayward and Wingfield (2004) maintains that maternally mediated prenatal stress programs the offspring so as to reduce the need for parental investment. In other words, if a mother is stressed and her ability to invest resources in her offspring is diminished, prenatal programming will produce a *thrifty* (smaller, slower growing, or less demanding) offspring to match her offspring's needs to her current provisioning ability. In this case, the maternal/fetal matching benefits the mother at the expense of the fetus. This hypothesis was tested in a series of studies conducted with birds in which both maternal ability and prenatal exposure to stress hormones were experimentally manipulated: mothers had their wing feathers clipped to reduce their foraging ability, and chicks were exposed to higher than average doses of corticosterone through injections into the eggs (Love and Williams 2008; see also Breuner 2008). Increased prenatal corticosterone exposure resulted in higher brood mortality and in the production of lighter offspring, thus matching offspring demand to maternal condition. The results of these studies are consistent with Hayward and Wingfield's hypothesis and showed stress-related increases in egg corticosterone to be an important mechanism underlying *selfish* maternal effects.

Taken together, these different evolutionary hypotheses suggest that developmental programming can be adaptive for offspring as well as mothers. Because maternal and fetal interests overlap significantly, we expect some level of cooperation in the extent to which the fetus is susceptible to the effects of prenatal stress. However, reducing investment in the offspring through brood or litter reduction or by producing smaller and less demanding offspring can provide additional benefits to mothers at a cost to an individual offspring. Insofar as the interests of mothers and offspring diverge, there should be conflict and competition over the extent of fetal programming. The idea that fetal programming could represent an important arena for mother–offspring conflict has been elaborated by Del Giudice (2012).

Del Giudice (2012) challenges the main assumption of the adaptive tuning hypothesis, which views the process of fetal programming as a fully cooperative enterprise in which the mother supplies environmental information via her stress hormone levels and the fetus passively accepts it. He argues instead that the mother

and the fetus should be in conflict over the extent of postnatal plasticity, the process through which the after-birth environment can shape or modify the offspring's phenotype (Ellis et al. 2011). By definition, high postnatal plasticity implies increased susceptibility to the effects of maternal behavior. Thus, the mother would benefit if she were able to increase the offspring's susceptibility to her own behavior beyond the offspring's optimum, as this would give her increased leverage in all subsequent instances of parent–offspring conflict. Conversely, the offspring should avoid becoming too plastic and too susceptible to maternal influence.

A growing body of research has shown that there is a great deal of individual variation in vulnerability to early environmental influences, and that this variation is in part genetic and in part environmental (Belsky and Pluess 2009; Ellis et al. 2011). Since prenatal stress increases HPA responsiveness and emotional reactivity, postnatal plasticity can be programmed by prenatal exposure to psychosocial stress, especially in those offspring who carry *plasticity* genes. Therefore, mothers may be selected to amplify the physiological effects of prenatal stress by releasing increasing amounts of stress hormones during pregnancy, while fetuses may be selected to reduce them by limiting the levels of maternal hormones that cross the placental barrier. One mechanism for such filtering is the conversion of 50–90% of maternal cortisol into its inactive form, cortisone, by the enzyme placental dehydrogenase 11β-HSD2, which normally serves to protect the fetus from excessive cortisol exposure. Additional mechanisms also exist for filtering other maternal hormones and neurotransmitters (Del Giudice 2012).

3.2.2 Prenatal Psychosocial Stress in Primates

There are only a handful of studies of the long-term effects of prenatal stress in nonhuman primates. Most of them have been conducted by the same group of researchers, utilizing one of two species (squirrel monkeys or rhesus macaques) and similar experimental procedures. Schneider and Coe (1993) investigated the effects of chronic prenatal stress in squirrel monkeys by removing pregnant females from their groups and rehousing them with other pregnant females. One group of subjects was rehoused only once; another group was relocated three times into groups with shifting social compositions. After birth, infants were subjected to a standardized battery of neuromotor tests. The offspring of chronically stressed mothers did not differ in body weight from non-stressed controls, but they showed a host of other abnormalities including delayed motor maturation, reduced activity, shortened attention spans, less visual orienting, and poorer balance.

A subsequent series of studies by Schneider, Coe, and collaborators investigated the effects of prenatal stress on offspring behavioral and neuroendocrine development in rhesus macaques (see Coe et al. 2010 for a review). In these experiments, pregnant females were removed from their home cages and exposed to loud, unpredictable noise bursts once per day, 5 days per week, for approximately 25% of pregnancy. The prenatally stressed infants were reared together with non-stressed

controls in a nursery to eliminate possible confounds from postnatal maternal behavior. Stressed infants tended to have lower birth weight than controls despite normal gestational length. Additionally, they performed more poorly on neurobehavioral outcomes than controls. Some of these effects appeared to vary based on the timing of prenatal stress: infants stressed early in gestation (days 45–90) performed more poorly on measures of attention (visual orienting) and motor maturity (head posture) than those stressed later in gestation (days 120–134).

The researchers also observed behavioral effects. Prenatally stressed individuals showed reduced exploratory behavior (less climbing and play), increased reactivity to novelty (e.g., higher emotionality and anxiety, more disturbance behavior, stereotypies, clinging and self-clasping, and freezing), and lower sociability (e.g., less time playing and grooming, and less time in proximity to cagemates) in various testing situations. Some of these effects persisted until 4 years of age. These behavioral modifications were accompanied by enhanced basal activity and stress responsivity of the HPA axis (mainly ACTH, not cortisol), as well as by alterations in brain monoamine neurotransmitters: higher cerebrospinal fluid (CSF) levels of MHPG and DOPAC under basal conditions and higher MHPG and NE levels in response to stress. Fetally stressed infants also demonstrated a prolonged HPA axis response to a pharmacological challenge, suggesting impairment in the glucocorticoid negative feedback system. Finally, at 4 years of age, fetally stressed infants showed decreased neurogenesis in the dentate gyrus and significant decreases in hippocampal volume and in the size of the corpus callosum, indicating long-term effects of prenatal stress on brain structure. Some of the effects of prenatal stress were replicated by administering ACTH for 14 days mid-gestation, confirming hormonal etiologies for the observed changes. Like their stressed counterparts, fetuses experimentally exposed to higher ACTH levels had delayed motor development, shorter attention spans, and increased anxiety and irritability after birth (Coe et al. 2010).

Further evidence that prenatal alterations in HPA axis function can result in long-term neuroanatomical and physiological consequences comes from studies in which pregnant female monkeys were treated with the synthetic glucocorticoid hormone dexamethasone (dex). An early study by Uno et al. (1990) reported that administering dex to pregnant rhesus monkeys as late as 72 h before delivery significantly reduced the density of the newborns' pyramidal neurons, as well as the thickness and circumference of their Ammon's horn and dentate gyrus in the hippocampus. Concordantly, infants whose mothers were treated for 30 days with dexamethasone had smaller hippocampi than controls, with a dose-related loss of neurons. More recently, DeVries et al. (2007) treated pregnant female vervet monkeys with three doses of dex and found that it reduced maternal cortisol in a dose-dependent manner at 22 weeks of pregnancy without affecting gestation length or birth weight. However, the dex treatment did delay postnatal growth. Furthermore, high-dose infants had comparatively heightened cortisol responses to the mild stress of blood sampling when tested at 8 months of age, and all dex-treated infants showed cardiovascular signs of hypertension such as increased heart rate and blood pressure. At 12–14 months of age, dex-treated infants were subjected to a dexamethasone suppression test, which normally suppresses cortisol levels in the evening before

they return to basal levels in the morning. The infants showed no difference in morning cortisol in relation to prenatal treatment relative to controls, suggesting no alterations in the glucocorticoid negative feedback mechanism.

Taken together, the findings of the limited research on the developmental effects of prenatal psychosocial stress in nonhuman primates demonstrate that fetal programming does indeed occur, and that it produces long-term alterations in emotional and behavioral reactivity, neuroendocrine function, and, in some cases, neuroanatomy, similar to those observed in studies of laboratory rodents and humans. Studies mimicking prenatal stress effects with administration of exogenous ACTH or synthetic cortisol have confirmed that maternal corticosteroids are functionally important for fetal programming. Unfortunately, all studies of prenatal psychosocial stress in primates to date have tested individuals housed in artificial experimental laboratory conditions (i.e., adults housed in single cages or small groups, or infants who were permanently separated from their mothers and reared with peers) and have utilized nonnaturalistic psychosocial stressors. Although neuroanatomical alterations induced by severe prenatal stress or the administration of large doses of hormones should probably be interpreted as pathological, no studies have been designed that explicitly test the possible adaptive value of behavioral and physiological changes induced by more moderate levels of stress. Lack of data concerning the social, mating, and reproductive success, or overall health and survivorship of prenatally stressed individuals makes even post hoc tests of these hypotheses impossible.

3.3 Maternal Stress

3.3.1 Conceptual Interpretations of Maternal Psychosocial Stress

The clinical/biomedical view of prenatal stress, which interprets all prenatal perturbations as potentially pathological, can be extended to encompass postnatal psychosocial stress as well. The idea is that it is best for the organism to develop in a safe and supportive environment in which all stressors are absent. This view assumes that stressors encountered in the early environment generate damage in a dose-dependent manner such that exposure to moderate stress results in a moderately negative developmental outcomes, while exposure to severe or intense stress results in serious negative developmental outcomes. That is to say, it proposes a linear relationship between the degree of early stress and the severity of its maladaptive consequences.

In contrast to the clinical/biomedical view, the *stress-inoculation* model suggests that there is a J-shaped relationship between early stress and unfavorable developmental outcomes (Parker et al. 2006; Parker and Maestripieri 2011; Seery 2011). Like the clinical/biomedical model, the inoculation hypothesis predicts that severe or intense early stress will result in serious maladaptation. However, it argues that

too little stress exposure in early life leaves the organism unprepared for future stressful situations, while moderate stress exposure results in adaptive physiological and behavioral adjustments that better prepare the individual to cope with future challenges. In other words, exposure to moderate stress *inoculates* the individual against subsequent exposure, just as exposure to moderate numbers of specific bacteria or viruses allows the body to build an immune response to them in preparation for future encounters.

While the inoculation model makes relatively simple predictions concerning the effects of low, moderate, and high stress on the organism's subsequent resilience and vulnerability to unfavorable circumstances, the *adaptive calibration model* (Del Giudice et al. 2011) makes more complex predictions about the phenotypic consequences of early stress exposure using *conditional adaptation* and life-history theory as its guiding principles. This model predicts that in relatively non-stressful environments, organisms are at low risk of mortality and are thus free to exhibit *slow* lifestyles characterized by unhurried physical and sexual maturation, low anxiety, increased time devoted to learning, less risk taking, and more delayed gratification. Exposure to moderate stress should result in increased resilience, including low anxiety and reactivity to challenges but high sensitivity to social feedback. Finally, exposure to high stress, which indicates that the external environment is dangerous or unpredictable, should produce phenotypes adapted for *fast* lifestyles with high vigilance and anxiety, riskier behavior, and less delayed gratification. Even physiological and psychological alterations induced by severe early stress, such as hyporeactivity of the HPA axis, hyperaggressiveness, and reduced empathy, could be adaptations to life in a dangerous environment.

The three models discussed above—clinical, stress inoculation, and adaptive calibration—apply to all forms of postnatal psychosocial stress, including psychosocial stress induced by the mother's behavior. Human empirical research, which is usually conducted from the biomedical/clinical perspective, has tended to interpret all deviations in maternal responsiveness and parenting style from what is considered the norm or the optimum as damaging for children. For example, the insecure–ambivalent, insecure–avoidant, and especially the insecure–disorganized–disoriented patterns of attachment are all conceived as pathologies that result from suboptimal parental responsiveness or even from abusive or neglectful parenting behavior. However, the adaptive calibration model acknowledges that all insecure attachment patterns might have adaptive value (Del Giudice et al. 2011). For example, ambivalently attached children display patterns of HPA axis, sympathetic, and behavioral reactivity that would be useful in a socially unpredictable environment, while the insecure–avoidant attachment pattern is associated with patterns of HPA axis, sympathetic, and behavioral reactivity that suggest adaptation to a harsh and unsupportive environment (Loman and Gunnar 2010). Even the disorganized–disoriented attachment pattern, with its reactive neuroendocrine profile characterized by extremely elevated and sustained cortisol responses to psychosocial stress (Loman and Gunnar 2010), could have functional value if it successfully prepares children to deal with hostile and dangerous relationships (Del Giudice et al. 2011).

3.3.2 *Maternal Psychosocial Stress in Primates*

A great deal of research on early psychosocial stress and development in primates has focused on stress experimentally induced by separating infants from their mothers and rearing them under conditions of social deprivation (see Parker and Maestripieri 2011 for a review). Much less attention has been devoted to psychosocial stress naturally induced through maternal behavior. Such studies have mainly been conducted with cercopithecine monkeys and have focused on two aspects of stress-inducing maternal behavior: abusive behavior and rejection.

3.3.2.1 Maternal Abuse

Among rhesus macaques and other cercopithecine monkeys living in large captive groups, 5–10% of all infants born in a given year are physically abused by their mothers (Maestripieri et al. 1997; Maestripieri and Carroll 1998a, b). In rhesus macaques, abusive mothers may drag their infants by their tail or leg, or throw them in the air. Abuse bouts last only a few seconds, and the rest of the time abusive mothers show competent patterns of maternal behavior. Abuse is most frequent in the first month of infant life and rare or nonexistent after the third month, when infants are more independent from their mothers (Maestripieri 1998). Rhesus mothers can give birth once a year, and abusive mothers generally maltreat all of their infants with similar rates and patterns of behavior (Maestripieri et al. 1999). The contributions of infant behavior to the occurrence of abuse are negligible, whereas abusive behavior appears to be a stable maternal trait that is transmitted across generations, from mothers to daughters. As a result, it is concentrated in particular families and absent in others (Maestripieri and Carroll 1998a). Cross-fostering experiments demonstrated that early experience plays an important role in the intergenerational transmission of infant abuse (Maestripieri 2005). Approximately half of cross-fostered and non-cross-fostered females abused early in life exhibit abusive parenting with their first-born offspring (Maestripieri 2005), and those who do so have lower CSF concentrations of the serotonin metabolite 5-HIAA than those who do not (Maestripieri et al. 2006a, 2007).

Maternal abuse is both physically and psychologically stressful for a monkey infant. Moreover, even if abuse is limited to the first months of infant life, continuous coexistence with the abusive mother and observation of abuse being repeated with younger siblings could contribute to reinforce and perpetuate the traumatic effects of abuse into adulthood. Observations of social and behavioral development have suggested that abused infants may be delayed in the acquisition of independence from their mothers and in the development of peer relations in the first year of life (Maestripieri and Carroll 1998b). In addition, the stressful experience of being abused early in life results in both acute and long-term alterations in HPA axis function.

In a preliminary study, 10 abused and 10 control infants were studied during their first 6 months of life (McCormack et al. 2009). Basal morning levels of cortisol

were measured at 1, 3, and 6 months of age, and ACTH and cortisol responses to stress were measured in month 6. In addition, infants were genotyped for the serotonin transporter (SERT) gene, and individuals carrying one or two copies of the short allele of this gene were compared to those carrying two copies of the long allele. During the first month, when physical abuse rates were the highest, abused infants had elevated basal morning cortisol levels compared to controls and showed greater distress responses to handling. In addition to a main effect of abuse on basal cortisol levels, there was also a significant interaction between early experience and SERT genotype: the effects of abuse on basal cortisol levels were especially strong in infants carrying the short SERT allele. After the first month, abused infants' basal HPA axis function recovered to levels similar to controls. Despite the normalization of basal activity, there were group by sex effects on the HPA axis stress response in month 6: abused males showed significantly higher ACTH stress responses than control males when exposed to novelty stress in the absence of the mother. The heightened ACTH stress responses were associated with higher levels of anxious behaviors at that age. Thus, abused infants—especially those with genetic vulnerabilities—exhibited both increased HPA axis activity and increased emotional reactivity not only during, but also a few months following, abuse.

In a larger follow-up study comparing 22 abused and 21 nonabused rhesus monkey infants over the first 3 years of life, plasma cortisol responses to psychosocial stress (a novel environment test) were assessed at 6-month intervals, and behavioral measures were assessed at 1-month intervals. Infants showed a significant increase in cortisol in response to stress test at all ages, and infants that were physically abused by their mothers showed a higher cortisol response than control infants at 1 year of age (Koch et al. 2011). Furthermore, abused infants showed significantly different responses to CRF challenges performed at 6-month intervals during their first 3 years of life when compared to nonabused infants (Sanchez et al. 2010). Specifically, the administration of exogenous CRF resulted in a greater increase in plasma cortisol concentrations in both male- and female-abused infants at 6, 12, 18, 24, 30, and 36 months of age. Abused infants also showed a blunted plasma ACTH response to CRF, but this difference was observed only at 6 months of age. This dampened ACTH response may be the result of negative feedback glucocorticoid inhibition, which normally inhibits the secretion of ACTH when there is a rapid increase in circulating cortisol, or of dysfunctional mechanisms that regulate the anterior pituitary's response to hypothalamic CRF. Altogether these results suggest that early maternal abuse results in greater adrenocortical (and possibly pituitary) responsiveness to challenges later in life.

All of the published research on the developmental effects of maternal abuse in macaques has been conducted with infants exposed to relatively low rates of abuse, whose life was not in jeopardy and who, in many cases, suffered only minor bruises and scratches that did not require external intervention. Since no data are available on the behavioral and neuroendocrine development of infants exposed to much more severe levels of abuse, the effects of variation in abuse intensity on the development of stress vulnerability vs. resilience are not well understood. The data reviewed above suggest that infants exposed to moderate levels of abuse exhibit

increased vulnerability to stress later in life. This effect, however, may be driven by the high rates of maternal rejection that typically accompany maternal abuse rather than to abuse itself. Further research is needed to examine the effects of different levels of abuse on development and to disentangle the effects of high maternal rejection and abuse when they co-occur.

3.3.2.2 Maternal Rejection

Maternal rejection describes behaviors a mother performs that prevent the infant from making contact with her body or gaining access to her nipples (such as holding the infant at a distance or blocking her chest with an arm), as well as behaviors that forcefully remove the infant from the nipple and interrupt physical contact (such as pushing the infant away). Mothers also reject their infants by administering painful hits or bites. Being denied bodily contact and access to the nipples, even in the absence of physical aggression, causes significant distress to infants, who respond with loud and persistent vocalizations (screams and geckers) and temper tantrums (lying on ground and acting as if they are having seizures) (Maestripieri 2002). Frequently rejected infants also show behavioral signs of depression. Maternal rejection is clearly a physically and psychologically stressful experience for primate infants.

Although maternal rejection rates change as a function of infant age and the mother's own age and experience, individual differences in rejection rates are generally consistent over time and across infants (Fairbanks 1996). In rhesus monkeys, infants are generally rejected in the third or fourth week of life at the rate of 1 episode every 2 h, or less (Maestripieri 1998). The rate of rejection gradually increases as infants grow older, peaking at 6 months of age when mothers resume their mating activities. However, some infants do not experience rejection at all, while others are rejected at the rate of 3–4 or more episodes per hour as early as in their first week of life (Maestripieri 1998).

Several studies of macaques and vervet monkeys have examined variation in infants' independence from their mothers and their tendency to explore the environment or respond to challenges, at various ages in relation to exposure to variable levels of maternal rejection in early infancy. An early study of rhesus monkeys reported that, following a 2-week separation from their mothers, infants whose mothers had been highly rejecting prior to the separation exhibited elevations in cortisol at reunion, while infants with non-rejecting mothers showed a marked decrease in cortisol levels (Gunnar et al. 1981). This finding may suggest that highly rejected infants are anxious about their relationships with their mothers and that they are not soothed by a reunion following separation because they may anticipate rejection. Consistent with the hypothesis that highly rejected infants are anxious, rhesus monkeys exposed to high levels of maternal rejection in the first few months of life tend to explore their environments less (Simpson 1985; see also Maestripieri et al. 2009). Other studies, however, found that infants reared by highly rejecting mothers generally develop independence (e.g., spend more time out of contact with

their mothers, explore the environment more, and play more with their peers) at an earlier age than infants reared by mothers with low rejection levels (Simpson et al. 1989; Simpson and Datta 1990; Bardi et al. 2005; Bardi and Huffman 2006). These seemingly conflicting results can be reconciled by the notion that maternal rejection has opposite short- and long-term effects on infant dependence; highly rejected infants initially respond with increased clinginess and reluctance to leave their mothers, but eventually resign themselves to independence (Maestripieri et al. 2009).

Long-term effects of maternal rejection on reactivity to the environment can be observed in adolescence and also in adulthood. In vervet monkeys, adolescent males reared by highly rejecting mothers were more willing to approach and challenge a strange adult male (Fairbanks et al. 1989). Similarly, in Japanese macaques, Schino et al. (2001) found that individuals that were rejected more by their mothers early in life were less likely to respond with submissive signals or with avoidance to an approach from another individual and exhibited lower rates of scratching in the 5-min period following the receipt of aggression. Finally, Maestripieri et al. (2006b) showed that rhesus macaques that were rejected more by their mothers in the first 6 months of life engaged more in solitary play and showed greater avoidance of other individuals at age 2. In this study, the association between maternal behavior and offspring behaviors later in life was also reported in infants that were cross-fostered at birth and reared by unrelated adult females, which rules out potential confounds of inherited temperamental similarities between mothers and offspring.

Developmental differences in reactivity to novel stimuli or responsiveness to other individuals are likely to be accompanied by differences in the neurochemical and neuroendocrine substrates that regulate emotional and social processes. Maestripieri et al. (2006a, b) reported that offspring reared by mothers with higher levels of maternal rejection exhibited lower CSF levels of the serotonin metabolite 5-HIAA, the norepinephrine metabolite MHPG, and the dopamine metabolite HVA in the first 3 years of life than offspring reared by mothers with lower levels of rejection. These differences were observed in both non-fostered and cross-fostered infants. Furthermore, CSF MHPG levels in the second year of life were negatively correlated with solitary play and avoidance of other individuals, while CSF 5-HIAA levels were negatively correlated with scratching rates, suggesting that individuals with low CSF 5-HIAA had higher anxiety. A significant association between exposure to high maternal rejection and low CSF levels of 5-HIAA in the offspring was also reported in another population of free-ranging rhesus monkeys (Maestripieri et al. 2009). In this study, rhesus mothers who rejected their infants at high rates exhibited higher cortisol responses to stress, suggesting that these may be individuals under chronic stress. Altogether, these studies suggest that exposure to maternal rejection early in life may affect the development of different neural circuits underlying emotion regulation, ranging from fear to anxiety to impulse control.

When the behavioral and physiological effects of maternal rejection are considered together, they are generally consistent with the predictions of the stress-inoculation model. In fact, the data reviewed above suggest that infants that experience little or no rejection become fearful and behaviorally inhibited later in life, whereas those exposed to extremely high rates of rejection become highly

anxious and impulsive. The behavior of infants exposed to moderate levels of rejection in the first few months of life suggests that they show adaptive responses to challenges and resilience to stress later on. An ongoing longitudinal study in our laboratory is investigating the development of the HPA axis and of the brain monoaminergic systems in three groups of rhesus monkey infants exposed to low, moderate, and high rates of maternal rejection early in life. Following the inoculation model, we predict that infants exposed to high and low levels of maternal rejection will exhibit stress-vulnerable neurobiological phenotypes (e.g., high basal cortisol levels, increased HPA axis responses to social and pharmacological challenges, dysregulation of peptide and monoamine systems involved in arousal and affective responses) compared to infants that received moderate levels of maternal rejection and exhibit resilient neurobiological phenotypes (e.g., comparatively lower basal cortisol levels; diminished HPA axis responses to social and pharmacological challenges; normative CSF levels of peptides and monoamine metabolites involved in arousal and affective responses). To assess whether these effects of early maternal rejection on offspring emotional and stress reactivity are adaptive and will help these individuals cope with psychosocial stressors later in life, we will analyze the different patterns of emotional and stress reactivity in relation to differences in dominance rank, aggression performed and received, mating success, heath, and ultimately longevity and reproductive success.

While the fitness consequences remain unproven, exposure to variable maternal rejection has definite phenotypic consequences for grown offspring for which adaptive hypotheses can be advanced. Two different studies so far have reported positive significant correlations between the rejection rates of rhesus mothers and those of their adult daughters (Berman 1990; Maestripieri et al. 2007), indicating that rejection rates are transmitted across generations. Maestripieri et al. (2007) found significant similarities in maternal rejection rates between mothers and daughters for both non-fostered and cross-fostered rhesus females, suggesting that the daughters' behavior was affected by exposure to their mothers' rejection in their first 6 months of life. Both non-fostered and cross-fostered rhesus females reared by mothers with high rates of maternal rejection had significantly lower CSF concentrations of the serotonin metabolite 5-HIAA in their first 3 years of life than females reared by mothers with lower (below the median) rates of maternal rejection, and low CSF 5-HIAA was associated with high rejection rates when the daughters produced and reared their first offspring (Maestripieri et al. 2006a, 2007). Therefore, the lower serotonergic function resulting from exposure to high maternal rejection rates in infancy contributes to the expression of high maternal rejection rates in adulthood in these females.

Different maternal rejection rates may represent adaptations to particular maternal characteristics (e.g., dominance rank, body condition, or age) or demographic and ecological circumstances (e.g., availability of food or social support from relatives) (Hauser and Fairbanks 1988; Fairbanks and McGuire 1995). For example, rejection rates are generally high in females of high dominance rank and good body condition who are under pressure to wean their infants quickly and produce an infant every year. Rejection rates, however, are also high in extremely old females

in poor body condition, or in females under severe nutritional or social stress, because these females must reduce investment in their offspring to concentrate on their own survival and future reproduction. In cercopithecine monkeys, mothers and daughters have very similar dominance ranks and share their environment as well. Both dominance ranks and patterns of rank-related psychosocial stress are extremely stable for rhesus females, not only during their life span but also across generations within their families. Therefore, insofar as a particular rate of maternal rejection represents an adaptation to a stressful social microenvironment, the transgenerational conservation of parenting style via stress effects and social learning represents a likely avenue for non-genomic transmission of behavioral adaptations.

3.4 Conclusions

Prenatal psychosocial stress, mediated by the mother's body and her hormones, and postnatal psychosocial stress induced by the mother's behavior can have similar programming effects on the infant's or child's social, emotional, and neuroendocrine development. These effects represent one particular type of evolutionary maternal effects, in which the mother's phenotype influences and shapes the offspring's phenotype, without direct transmission of genetic information or modification of the offspring's genotype. The physiological mechanisms underlying the prenatal and postnatal effects of psychosocial stress are probably similar, or the same, and involve the HPA axis and other neuroendocrine systems involved in emotion regulation and reactivity to the environment. Although stress-related maternal effects and their underlying mechanisms have been investigated to a lesser extent in nonhuman primates than in laboratory rodents or in humans, the available evidence suggests that these processes are largely similar across these different species of mammals.

Rodents and primates (including humans), however, differ in some key aspects of their life histories and social environments, and this has potentially important implications for the occurrence, characteristics, and possible adaptive significance of prenatal and postnatal stress-related maternal effects. First, many rodent species have a relatively short life span: they become reproductively active rapidly and reproduce quickly, and through the production of large litters, the processes of pregnancy and lactation are brief, and mothers have relatively few opportunities to shape the phenotype of the offspring, aside from the windows of time provided by pregnancy and the immediate postpartum period. Second, although it is relatively easy to experimentally induce psychosocial stress in pregnant or lactating laboratory rodent females, for example, by altering their housing conditions, it is not immediately clear what the naturalistic equivalents of these laboratory stressors may be and what are the most common forms of psychosocial stress encountered by pregnant or lactating females in the wild. Rodents do not live in complex societies similar to those of some primate species, in which psychosocial stress is an integral part of life; the extent to which prenatal or postnatal psychosocial stress is an important

source of maternal effects in wild population of rodents is unclear. Moreover, even though laboratory rodents exhibit naturally occurring differences in maternal care styles that have important consequences for offspring development (see Champagne and Curley 2009 for a review), it is not clear that these effects are mediated by stress-related mechanisms. For example, to our knowledge, rodent mothers do not spontaneously exhibit stress-inducing behaviors toward their offspring that are structurally or functionally similar to maternal rejection/neglect or abusive mothering in monkeys and humans.

In primates that live in complex and highly competitive societies such as humans, chimpanzees, and many cercopithecine monkeys, the mother–infant relationship is deeply embedded in the social environment so that, for example, other social relationships the mother has with her partner, or previous children, or other family members, friends, coworkers, and competitors can have a direct and profound influence on her psychological well-being, her neuroendocrine function, her health, and therefore also on the quantity and quality of her interactions with her fetus, infant, or child. The long periods of gestation and lactation and the correspondingly long and slow process of growth and maturation of the offspring provide many opportunities for prenatal and postnatal maternal effects to operate.

The question of whether prenatal and postnatal maternal psychosocial stress have adaptive or maladaptive consequences in primates remains open to empirical investigation and to debate. It is possible to hypothesize that, during the evolutionary history of humans and other primates, psychosocial stress was such an inevitable and significant feature of the pregnancy and lactation periods that the maternal body at some point became selected to use the mechanisms and effects of such stress to influence and shape the phenotype of the developing offspring in a manner that was adaptive to herself or the offspring or both. In other words, since psychosocial stress during pregnancy and lactation is inevitable and may also be a good predictor of stressors encountered later in life, mothers began to *prepare* their fetuses, infants, and children and endow them with physiological, behavioral, and emotional/cognitive adaptations that would allow them to cope with stress in an optimal way throughout their life. Exposure to moderate stress early in life can promote the acquisition and fine-tuning of these physiological, behavioral, and emotional/cognitive mechanisms to cope with stress similar to the process through which exposure to moderate amounts of pathogens early in life strengthens the immune system and inoculates the body against future exposure to the same or similar pathogens. Thus, it is possible that mothers are not simply vehicles for passively transferring information from a surrounding stressful environment to their offspring, but in some cases they actively generate a moderate amount of psychosocial stress through their behavior so as to give their offspring the opportunity to develop the tools to deal with it.

Nonhuman primates are ideal animal models with which to test this hypothesis and other similar hypotheses concerning the adaptive significance of prenatal and postnatal maternal psychosocial stress. Primate mothers encourage the nutritional and social independence of their infants through behaviors such as rejection, which have the long-term effects of reducing the amount and frequency with which infants

seek to be in contact and gain access to their mothers' nipples for suckling. We believe that the fact that maternal rejection generates significant psychosocial stress in the offspring is not an inevitable and inconsequential by-product of the weaning process. Rather, this stress is a phenomenon that needs an explanation. And this explanation may be that when mothers reject their infants, they simultaneously accomplish different goals: they encourage their infants to be nutritionally and socially independent, and they also give them the opportunity to develop the appropriate tools to deal with psychosocial stress and be inoculated against future exposures later in life.

The notion that parenting behavior can shape the physiological, behavioral, and emotional/cognitive mechanisms with which children react to stress is clearly applicable to humans. Authoritative parents often discipline their children in ways that generate a moderate amount of stress in the children. The traditional interpretation of parental discipline is that it is aimed at shaping the behavior of the child in way that conforms to the norms and expectations that society and parents have about child's behavior. The hypothesis that parentally induced psychosocial stress has the adaptive effect of enhancing the child's mechanisms for coping with stress is empirically testable and, if supported by data, would significantly increase our understanding of parent–child relationships, of the development of stress reactivity over the life span, and of the role of maternal effects in the process of adaptation to the environment.

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