Maternal Stress Effects Across Non-Primate and Primate Models

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Introduction

The Developmental Origins of Health and Disease (DOHaD) is an evolutionary approach for asking questions about how early life experiences can program predictive adaptive responses of the fetus in response to a variety of environmental cues (Wadhwa et al., 2009). DOHaD has been used to explain how the fetus can become nutritionally "thrifty" by decreasing its growth and by initiating hormonal/metabolic changes (Barker, 1992). This has important implications for a developing fetus depending on whether the offspring's future environment indeed matches the environment of the mother or does not. In other words, consider a mother who is undernourished during her pregnancy; she may produce an infant whose glucose-insulin metabolism is insensitive to insulin – a condition known as non-insulin dependent diabetes mellitus - if her offspring later is exposed to good postnatal nutrition. However, if her infant is also exposed to the same undernourishment in the postnatal environment, the infant may not exhibit any signs of diabetes (Barker, 1992). In this manner, the fetus is programmed based on the internal state of the mother during development, and the environment matching the conditions of the mother leads to the fetus being adaptively programmed to stressful environments. DOHaD discusses how environmental influences during early development can alter the developmental plasticity of the offspring in order to influence the risk of the offspring succumbing to non-communicable disease (Hanson and Gluckman, 2014). It has been expanded to a whole field of study which examines the potentially adaptive ways in which in utero programming can have for children. DOHaD reflects both the importance of a mother's signaling to her child about the environment and the fetus's developmental plasticity in response to those signals to be either adaptive or maladaptive for the offspring later on in life.

A mother's environment has the remarkable potential to influence the traits of their offspring in anticipation of environments they are likely to encounter. The phenotype of offspring are thus not only determined by the genotype and postnatal environment of the offspring but also by the genotype and environment of their mother; these effects are termed 'maternal effects' (Maestripieri and Mateo, 2009). Understanding maternal effects has the potential to greatly influence our understanding of the genetic basis of traits, since maternal effects represent a form of non-genetic transmission of phenotypic traits.

One of the best studied examples of maternal effects is the role that the maternal stress response plays in influencing offspring phenotype due to epigenetic effects during gestation that are associated with fetal exposure to maternal glucocorticoids (Berghanel, 2016). The effects of prenatal maternal stress can be persistent or fleeting, and it remains unclear whether maternal stress responses lead to adaptive or maladaptive outcomes for the offspring. In many species of mammals, larger mothers in good body condition can produce larger offspring because they can transfer a greater amount of nutrients to them during pregnancy and lactation (Maestripieri and Mateo, 2009). For instance, among a group of rhesus macaques (*Macaca mulatta)*, the reproductive status and rank of natal males was associated with their mother's but not their father's ranks (Smith and Smith, 1988). This is significant because it means that the sons of high-ranking females enjoyed greater reproductive status and were also high-ranking themselves which would increase their chances of mating, thereby conferring an advantage to them as the direct result of their mothers obtaining increased access to resources because of their high rank (Smith and Smith, 1988).

Although many researchers have assumed that maternal effects "prepare" the offspring for their future environment, as yet, we do not know whether maternal effects on offspring

phenotype are adaptive or not. In other words, has there been selection for maternal effects as a communication system between mother and offspring, or are maternal effects merely the inevitable result of constraints imposed by the mother's condition? Thus, two hypotheses have been proposed to explain maternal effects: the Developmental Constraints Hypothesis and the Predictive Adaptive Response (PAR) Hypothesis.

The Developmental Constraints Hypothesis is the idea that offspring development is constrained by energetic limitations imposed by the mother. Under this hypothesis, we expect that offspring born in high-quality environments will have higher investment in growth and development leading to higher fitness, effects that extend into adulthood regardless of the adult environment to which they are exposed (Lea et al., 2015). The logic behind the Developmental Constraints Hypothesis is that early life adversity serves as a predictive signal to the offspring about future life expectancy. Moreover, developmental constraints during gestation and infancy can result in adverse physiological consequences that alter adult phenotypes and lower life expectancy. For example, under the Developmental Constraints Hypothesis a high-ranking mother with greater access to resources and less psychosocial stress will have offspring that grow faster (Bernstein and Hinde, 2016; Alberts and Altmann, 2005; Alberts and Altmann, 1995), have fewer health complications, and have lower baseline glucocorticoid levels ("stress hormones") to help them handle stress better later on in life (Onyango et al., 2008). By contrast, a low-ranking mother with decreased access to resources that is exposed to more psychosocial stress will have offspring that grow slower (Bernstein and Hinde, 2016), experience more health complications, and have higher baseline glucocorticoid levels making them more prone to certain behavioral and physical detriments (Herrington et al., 2016; Murray et al., 2015).

By contrast, the Predictive Adaptive Response Hypothesis is the idea that cues offspring receive in early life from the maternal environment influence the development of the offspring's phenotype in a way that allows the offspring to phenotypically adapt to adverse conditions (Gluckman and Hanson, 2004). To use the same example as above, a low-ranking mother with decreased access to resources that is exposed to more psychosocial stress throughout her pregnancy will produce offspring that are well-adapted to this adverse environment and can therefore accelerate their own growth to grow faster (Berghanel et al., 2016; Hauser et al., 2007), avoid health complications, and have higher baseline glucocorticoid levels and/or develop a healthy stress response due to increased HPA axis (Hypothalamic Pituitary Adrenal) sensitivity (Murray et al., 2016; Clarke and Wittwer et al., 1994). In particularly poor maternal environments, this outcome can be thought of as offspring being able to make the most of a bad job.

An important feature of the Predictive Adaptive Response Hypothesis that distinguishes it from the Developmental Constraints Hypothesis is that it relies on predictability in the environment across time. If there is a mismatch between the conditions during gestation and the postnatal or adult environment, adverse consequences may arise for the offspring compared to conditions in which the early and late life environments are matched (Barker and Hales, 1992). For insistence, a prenatally-stressed mother may "program" her fetus to have increased HPA sensitivity and, under stressful life conditions, this can be adaptive to help fight off the stressor. However, under periods of stable life conditions, this increased HPA sensitivity can cause the offspring to remain anxious, unwilling to explore novel environments, and cause other psychological or physiological issues in several primate species, such as macaques (*Macaca mulatta*) (Clarke, 1996; Bardi and Huffman, 2005). Furthermore, the main outcome differing

between these two hypotheses is in the response of the offspring's growth to the environmental conditions; while a poorly nourished or prenatally stressed mother's offspring will exhibit stunted or delayed growth under the Developmental Constraints Hypothesis, the same offspring would experience accelerated growth for the Predictive Adaptive Response Hypothesis (Bernstein and Hinde, 2016; de Vries et al., 2007).

The Thrifty-Phenotype Hypothesis is similar to the Predictive Adaptive Response Hypothesis and evidence in support of the Thrifty Phenotype Hypothesis has also been cited as evidence for the Predictive Adaptive Response Hypothesis. Specifically, the Thrifty-Phenotype Hypothesis states that exposure to poor prenatal nutritional conditions can cause the offspring's phenotype to develop in a manner that allows them to survive in an environment where resources are scarce (Barker and Hales, 1992). Therefore, the offspring adaptively prepares itself for adverse environmental conditions by compensating in another part of their phenotype. The Thrifty-Phenotype Hypothesis has been used mainly to explain the prevalence of Type II Diabetes within offspring based on maternal nutrition and how that matches or does not match the environment of the offspring (Barker and Hales, 1992).

Importantly, maternal effects can occur at three different stages of offspring development: the prezygotic stage (prior to conception), the prenatal stage (gestation), and the postnatal stage (after birth) (Wade, 1998). One example of pre-zygotic maternal effects is when the maternal phenotype, influenced by divergent access to resources, affects the size and quality of her gametes. One example of a pre-zygotic maternal effect would be when a high-ranking mother has greater access to resources and therefore can invest more energy into the growth of her offspring during gestation and/or lactation (Bernstein and Hinde, 2016; Alberts and Altmann, 2005; Alberts and Altmann, 1995). Most of the prenatal maternal effects described in the

literature are the result of varying stress levels that arise during the mother's gestational period. For instance, researchers often analyze the offspring born to a primate that had been exposed to certain stressors during her pregnancy to see how the stress response of the offspring develop (Herrington et al., 2016; de Vries et al., 2007; Coe et al., 2003; Schneider et al., 1999). Postnatal maternal effects involve maternal care for the subsequent offspring that go on to shape that offspring's development and later health outcomes. Examples of postnatal maternal effects involve differences in the maternal care that may then go on to influence the phenotype and fitness of the offspring (Champagne and Meaney, 2006; Bardi and Huffman, 2005).

Despite its importance for understanding how early adverse conditions can have long-term effects on health, the study of maternal effects has been extremely limited across the primate taxa. Yet, research in rodents has provided some interesting avenues for further inquiry. For example, empirical evidence from rat studies (*Rattus sp.)* suggests that variation in maternal behavior of licking and grooming bouts mediates the behavioral and endocrine stress response in rodents. Evidence from rodent studies support the fact that maternal behavior of licking and grooming can foster stress resistance within pups by increasing the expression of glucocorticoid receptors within the hippocampus (Lee and Williams, 1974; Meaney, 2001). This leads to an attenuated stress response within pups who experienced intermittent separations from their mothers because the mothers increase licking and grooming upon reunion as well as throughout their development (Lee and Williams, 1974). It has also been shown to lead to increased stress resistance within pups who were not separated from their mothers but who naturally experienced higher levels of maternal care during development (Liu et al., 1997). These studies have repeatedly shown the importance of the role that maternal care plays in mediating subsequent stress resistance within the offspring.

Furthermore, the underlying molecular mechanisms responsible for the intergenerational transmission of maternal care have been elucidated in many rodents (Francis and Meaney, 1999; Champagne et al., 2003; Francis et al., 1999; Meaney et al., 2001). Since primate mothers devote a lot of resources towards the investment of their offspring and there is a greater degree of dependency of the offspring on the mothers, studies conducted within non-human primates can prove to be very beneficial since there is a greater potential for maternal influence to act on the offspring. Understanding how maternal effects act within non-human primates can allow us to extrapolate findings and apply them to better understand the role of maternal effects within human populations. Though examples of maternal stress effects within humans exist, it is unclear whether these effects impose constraints or confer adaptive benefits to the offspring and with additional research, perhaps the solutions to these questions can someday begin to be answered.

The Stress Response

I.   **HPA Activation and the Stress Response**

One of the primary areas of study on maternal effects has been through the effects that maternal stress has on her offspring either during or after pregnancy. To understand maternal stress, it is first important to understand the basics behind the stress response. Though commonly used today, the term "stress" in human physiology and health embodies a rather nebulous idea that is difficult to define. "Stress" was first defined in the context of physics as the external force, while the deformation on an object (the internal result) was called "strain," (Beehner and Bergman, 2017). However, once physiology adopted this terminology for the effects on the body of an adverse environment, the singular term "stress" was used to define the external force and the internal effect. One solution that helps correct the misuse of these terminologies is to use the

term "stressor" to define the external force (defined by any unpredictable or uncontrollable stimulus), and to use the term "stress response" to define the internal effect (defined as the physiological response due to the stressor (Beehner and Bergman, 2017)).

Short-term stress can play an adaptive role by facilitating the release of catecholamines, such as epinephrine and norepinephrine, from the sympatho-adrenomedulary system which can help to mobilize energy stores, increase attention, and increase cardiovascular function to help combat the stressful event (Francis and Meaney, 1999; Meaney, 2001). The acute stress response is activated when sensory information from a "stressor" arrives in the amygdala and causes the activation of the hypothalamic-pituitary-adrenal (HPA) axis (Beehner and Bergman, 2017). The HPA axis triggers enhanced secretion of catecholamines from the sympathetic nervous system (Beehner and Bergman, 2017). Eventually, the hypothalamic release of corticotropin- releasing hormone (CRH) and enhanced secretion of pituitary adrenocorticotropic hormone (ACTH) enter the blood's circulation (Saplosky et al., 2000). ACTH then travels to the adrenal cortex to cause the synthesis and secretion of adrenal hormones, including glucocorticoids, which are comprised of cortisol and corticosterone, and these hormones travel to their respective receptors in target tissues throughout the body (Beehner and Bergman, 2017). This response is very rapid, occurring within a few seconds which is beneficial for the organism because it leads to increased cerebral blood flow and cerebral glucose utilization, immune activation, and energy mobilization which are all useful for an organism to help fight off a short-term stressor (Saplosky et al., 2000). The HPA response controls the secretion of glucocorticoids through a negative feedback loop; glucocorticoids can inhibit the release of CRH from the hypothalamus or the release of ACTH from the pituitary in order to dampen the release of glucocorticoids from the adrenal cortex (Beehner and Bergman, 2017). A well-functioning HPA response is one in which there is a low

glucocorticoid baseline, fast glucocorticoid release, and a rapid stimulation of negative feedback (Breuner et al., 2008). The maintenance of a healthy HPA response is important because it allows the animal to form protective, adaptive responses to combat short-term stressors.

However, long-term exposure to stressors can cause the HPA response to decrease an organism's overall well-being and longevity (Juster et al., 2010). For instance, prolonged exposure to stress can have deleterious consequences for learning and health, which include hypertension, reduced immune function, insulin resistance, hypercholesterolemia, and increased anxiety (Francis and Meaney, 1999; Meaney, 2001). Chronic stress responses can lead to adverse consequences by failing to exhibit one or more of the qualities of a healthy HPA response described above (Beehner and Bergman, 2017).

II.   Stress Effects on the Brain

Stress effects refer to the long-term activation of the stress response that typically results in reductions in health. Though the mechanisms that govern maternal effects seem to be less clear, there is a great deal of evidence to support the idea that exposure to stress during pregnancy leads to an alteration of the stress response in the offspring as well. Though ACTH has a greater difficulty in crossing the placenta, it has been shown that maternal cortisol can more easily cross the placental boundary (Herrington et al., 2016). Furthermore, the deleterious effects of transferring higher loads of maternal cortisol seems to be sufficiently high that there are placental enzymes dedicated to metabolizing cortisol into less active forms, such as cortisone, in an effort to possibly "protect" the fetus (Seckl, 1997). Experiments studying long-term stress effects within animals tend to collect samples of cortisol, mostly from fecal matter.

It is well known that the effects of chronic stress in adult animals can have structural effects on the brain. The hippocampus is involved in the regulation of the HPA axis later on in life, and this structure in particular appears to undergo a drastic reorganization under chronic stress. For example, rats, exposure to prolonged glucocorticoids can cause neural degeneration in the amygdala, the prefrontal cortex, and the hippocampus. However, in the hippocampus in particular, it has been shown that stress can accelerate neuronal cell death and the aging process (Uno et al., 1989). A retrospective, neuropathological study conducted on eight deceased vervet monkeys (*Chlorocebus aethiops*) that had spontaneously passed away, were found to have multiple gastric ulcers (presumably due to a high incidence of bite wounds, inflicted on them due to subordination) and showed concomitant hippocampal degeneration (Uno et al., 1989). Furthermore, these animals also had hyperplastic adrenal cortices, consistent of sustained glucocorticoid release (Uno et al., 1989).

III.   Possible Sources of Stress in Wild Primates and Maternal Effects on Offspring

There are many external factors that can cause a stress response in wild primates. For a pregnant female in a group, some of these stressors can include the arrival of a new male due to a takeover, being low-ranking, having low resource availability, and being separated from her offspring (Herrington et al., 2016; Onyango et al., 2009; Altmann and Alberts, 2005; Schneider et al., 2004). Of all these factors, maternal rank appears to have the most significant effects on her own fitness as well as on her offspring's development. Primates are relatively social animals that very often form dominance hierarchies. An individual's dominance rank has important implications for the health of these primates and their offspring. Dominance rank may constitute an example of a pre-zygotic maternal stress effect because a female's dominance rank can

greatly affect her access to resources and can consequently impact the health of her offspring as well. Additionally, a female's dominance rank can predict the types of psychosocial stressors that she is exposed to. For instance, in yellow baboons (*Papio cynocephalus*), low-ranking females received more direct aggression than high-ranking females, and they also had less access to important food resources (Onyango et al., 2008). During periods of social instability, such as that which is incurred when a female belongs to a low-rank, glucocorticoid concentrations increase for the low-ranking females more than for high-ranking females (Cavigelli and Caruso, 2015). Therefore low dominance rank can be associated with higher metabolic costs in female primates. This higher metabolic cost can then influence the offspring in two ways. First, the mother can help alter the stress response within the fetus in either an adaptive or maladaptive manner. Second, the mother's rank largely determines her supply of energy that she has to invest in the production of her offspring. However, there is some debate about exactly *when* exposure to stress in the mother might have the greatest impact on the development of the offspring. Most researchers agree that a stressful maternal environment has the most impact at the pre-zygotic stage and the prenatal stage. For example, high-ranking mothers give birth to offspring who are better equipped to survive versus low-ranking mothers. Additionally, prenatal stress has a significant impact on altering subsequent stress response of the offspring in an adaptive or maladaptive way (Lea et al., 2015; Converse et al., 2013; Coe et al., 2003; Coe et al., 2007; Onyango et al., 2008; Alberts and Altmann, 1995). Most mammalian mothers are bound by their physiology to invest heavily in the reproduction and lactation of their offspring, which is an energetically costly process (Gomendio, 1991). Therefore, the mother's fitness will be maximized if her efforts are translated into the production of healthy, viable offspring, and this can be further helped through the exertion of maternal effects to help better prepare the offspring

for their environment. However, there are others who argue that maternal effects exert the most influence at the post-natal stage. For example, the period of dependency for some primate offspring on their mothers is high for juveniles, such as in wild chimpanzees (*Pan troglodytes schweinfurthii*), therefore allowing for a greater potential of maternal effects to exert its influence post-natally (Londsorf, 2005). The remainder of this review will focus on prenatal effects and whether they offer more support for the Developmental Constraints Hypothesis or the Predictive Adaptive Response Hypotheses. I will examine this question in rodents, primates, and finally within humans as well.

<u>Support for Developmental Constraints Hypothesis</u>

I.   Rodent Studies

   Data from rodent studies suggests that maternal behavior has important effects on shaping offspring responsiveness to stress. The effects of gestational stress can have unfavorable outcomes for the pups. For example, in the rat maternal care model, it was discovered that oxytocin receptors (OTR) were directly related to the degree of maternal care that they received as offspring. High licking and grooming (LG) mothers were known to have increased OTR in the medial preoptic area of the hypothalamus (MPOA) as compared to low LG mothers with decreased OTR expression (Champagne and Meaney, 2006). Researchers wanted to examine whether the cause behind this higher number of OTRs was due to maternal stress affecting her own degree of licking/grooming and then whether such effects would involve changes in offspring OTR. When high LG mothers received a stressor during the last week of gestation, this led to reduced OTR levels in their offspring as compared to offspring of mothers that did not receive this stressor. When these high LG offspring of stressed mothers became adults, they also

exhibited behavioral measures of high anxiety and maternal behavior similar to low LG offspring. These results indicate that stress during pregnancy has the ability of altering both OTR and the subsequent maternal care of the next generation (Champagne and Meaney, 2006). Furthermore, rats exposed to regimens of stress during pregnancy had male offspring that were unable to masculinize (Ward and Weisz, 1984; Ward and Weisz, 1980).

A majority of the studies examining development of the stress response within rodents comes from research that examines handling of rat mothers with separation from her pups (Francis and Meaney, 1999). In these set-ups, handling involves daily separation of the mother from the pup for a duration lasting between 3-15 minutes and responses to the stress response of the offspring are also recorded (Francis and Meaney, 1999). In one such study, it was found that rats subjected to maternal separation had increased hypothalamic corticotropin-releasing factor (CRF) mRNA levels compared to non-handled and handled rats that had lower CRF mRNA levels (Plotsky and Meaney, 1993). In a similar study, researchers injected carbenoxolone (CBX) into pregnant rat mothers to study subsequent HPA activity and regulation; CBX blocks 11beta-hydroxysteroid dehydrogenase whose role within many placental and fetal tissues is to rapidly inactivate glucocorticoids (Welberg et al., 2000). Results also showed that the offspring born to CBX mothers had decreased birth weights and increased corticotropin-releasing hormone (CRH) and reduced glucocorticoid receptor (GR) mRNA in the hypothalamic paraventricular nucleus (Welberg et al., 2000). This is significant because with the assumption that these increased mRNA levels will continue to activate the rest of the HPA axis as proteins to cause increased glucocorticoid secretion, this finding violates one of the factors that determines a healthy HPA response, which is lower glucocorticoids at baseline. All of these results demonstrate how gestational stress imposed constraints in the development of the subsequent offspring by altering

birth weight, causing HPA dysregulation, or inducing physiological and behavioral problems (Welberg et al., 2000; Plotsky and Meaney, 1993; Ward and Weisz, 1984; Ward and Weisz, 1980).

II.   Non-Human Primate Studies

It is easy to understand why individuals born in low-quality environments might be exposed to life-long disadvantages relative to individuals born in high-quality early environments, and there is a plethora of evidence within primates that lends credibility to this argument set forth by the Developmental Constraints Model. This model predicts that healthier mothers will have healthier offspring, with health being defined as low stress hormones and more access to resources. Researchers studied the fertility of wild female yellow baboons born during low-quality (drought) versus high-quality conditions to differentiate between the Predictive Adaptive Response or the Developmental Constraints Hypothesis (Lea et al., 2015). Females that were born in low-quality environments showed greater decreases in fertility during drought years than females born in high-quality environments. These results were found despite the fact that drought years matched the early conditions of females born into low-quality environments. Thus, this shows support for the Developmental Constraints Hypothesis rather than the Predictive Adaptive Response Hypothesis because the adverse early environment of drought did not adaptively prepare animals for similar challenges in adulthood. However, most of the evidence available from studies conducted on primates suggests that exposure to a stressor during pregnancy results in adverse outcomes for offspring. For instance, in a study examining maternal peripartum stress among captive rhesus macaques, researchers found that high peripartum cortisol levels and low maternal responsiveness caused greater infant anxiety (Bardi and Huffman, 2005). This finding

is supported by the fact that in yellow baboons, juveniles whose mothers showed greater stress-related behavior also exhibited more anxiety during a stress test (Bardi et al., 2005). A stressful environment during pregnancy can lead to lower birth-weight and greater risk of loss of offspring, and the effects of stress can exacerbate the adverse effects of alcohol rhesus monkey macaque infants (Schneider et al., 1997).

Exposure to stress during pregnancy also leads to physiologic changes that can be seen in the brain. In a group of rhesus macaques, a stressor inflicted during gestation led to increases in striatal midbrain dopamine transporter (DAT) availability within adult offspring. DAT availability was specifically studied because of the importance of the dopamine system in regulating mood, affect, motivation and reward responses, and initiation and control of motor behaviors (Converse et al., 2013). Prenatally-stressed offspring showed reduced habituation during behavioral tests (Converse et al., 2013). This is significant because it has been suggested from other studies that fronto-striatal DA dysfunction has been correlated with cognitive and behavioral impairments reported in children from prenatally-stressed pregnancies, such as attention deficit hyperactive disorder (ADHD) (Converse et al., 2013). Similar results have been found in studies with prenatally-stressed rats and studies that have been conducted in pregnant rhesus macaques exposed to stress (Son et al., 2007; Roberts et al., 2004). For instance, prenatal stress, both early and late in pregnancy, resulted in a 10-12% reduction in hippocampal volume and an inhibition of neurogenesis in the dentate gyrus within rhesus macaques.

Researchers have delved further into studying stress effects during pregnancy and have tried to tease out the exact point during pregnancy that such stressors can impact the subsequent offspring. The results of Coe et al. (2003) suggest that exposure to a stressor during a specific trimester within pregnancy is not as important as exposure to stress during any part of the

pregnancy; exposing pregnant rhesus macaques to noise stress during early and late gestation had similar effects with offspring of exposed mothers exhibiting less exploratory behavior and elevated baseline plasma cortisol levels as compared to control mothers. However, there are some studies that try to tease out when during pregnancy is exposure to stress the most detrimental for the well-being of the infant. One study found that captive female macaque mothers that experienced a male takeover during gestation across different trimesters had infants with elevated stress responses (Herrington et al., 2016). Infants born to captive mothers exposed to a matrilineal takeover in the first trimester of pregnancy exhibited elevated postnatal emotional responsiveness, while exposure to a matrilineal takeover in the second trimester resulted in elevated glucocorticoid output following maternal separation and lower hematocrit levels compared to control groups (Herrington et al., 2016). This study demonstrates how the prenatal experience affects postnatal phenotypic expression in offspring differentially depending on which trimester was the most stress inducing.

Additional studies conducted reinforce the importance of stress exposure during earlier rather than later parts of gestation. For instance, Coe et al. (2007) studied the effects that maternal stress during early versus late gestation would have on affecting iron deficiency (ID) as well as innate immunity of subsequent infant rhesus macaque offspring. Results showed that exposure to stress during early gestation had a higher impact in increasing the prevalence and magnitude of iron deficiency than did later in gestation though both did have significant effects in impacting iron deficiency. Furthermore, iron deficiency led to the decreased effect of natural killer cell activity thereby lowering innate immunity of offspring with ID. A different study conducted on pregnant rhesus female macaque monkeys exposed them to mild psychological stress during early, mid, or late gestation to examine the effects it would have on the offspring

(Schneider et al., 1999). Infants born to the early-stress gestation condition weighed less than did the mid- or late-gestation stress condition, and early gestation stress also caused greater neuromotor impairments than did late gestation stress, therefore arguing that exposure to stress during early gestation has the most deleterious and adverse consequences for the offspring. In another experiment also conducted on pregnant rhesus macaques, females were exposed to a 2-week ACTH treatment during mid-gestation and gave birth to infants that showed impairments in early motor coordination, muscle tonicity, and shorter attention spans as compared to controls (Schneider et al., 1992). At older ages, the rhesus monkeys from stressed pregnancies exhibited increased emotional reactivity and behavioral inhibition during stressful conditions. Exposure to stress during early pregnancy can have behavioral effects on an offspring's temperament even two years after birth, and stress related to the pregnancy can be more deleterious than generalized maternal anxiety (Bardi and Huffman, 2005). Coe and Lubach (1992) found that compared to infants born to mothers in the saline control group, two-week old infant macaques of mothers injected with ACTH during mid-pregnancy exhibited diminished motor coordination and shorter attention span. However, a lot of the differences in neuromotor development between the saline and ACTH treatment group infants disappeared around 4 weeks of age, which can be attributed to a potential ceiling effect in infants or the mitigation of this impairment by their own nervous systems. It is also important to realize that ACTH cannot cross the primate placenta in significant levels, which heightens the need to revisit studies examining the experimental effects that ACTH exposure has on pregnancy (Simmer et al., 1974). Stress is known to contribute towards fetal hypoxia, and since the hippocampus and cerebellum are two structures which are especially sensitive towards hypoxia, this can be a potential mechanism used to explain how stress leads to neuromotor impairments found in several of the studies above (Schneider et al., 1997).

Nevertheless, ACTH's secondary effects on causing the release of cortisol can be implicated as the physiological mediator of changes occurring in the fetus. These studies elucidate a recurring theme with maternal stress effects during pregnancy, specifically mid-gestation, which is that exposure to stress during gestation can have an adverse effect on the physical and emotional development of rhesus infant macaques, and these effect can have long-lasting consequences. However, much debate still remains over whether maternal stress exposure during early pregnancy has greater adverse outcomes for infants than exposure during late pregnancy. In summary, though we know that stress during pregnancy can lead to detrimental deficits within offspring development, there is a growing body of evidence that suggests that the timing of the stressor during pregnancy can have variable impacts on the offspring's well-being and development as well and more research needs to be conducted in order to elucidate the exact timing of when it has the greatest impact.

Another line of support for the Developmental Constraints Model comes from evidence that high-ranking mothers tend to give birth to healthier offspring. Dominance rank constitutes an example of a pre-zygotic maternal stress effect because a female's dominance rank can greatly affect her access to resources and can consequently impact the health of her offspring as well. Additionally, a female's dominance rank can predict the types of psychosocial stressors that she will be exposed to. Low-ranking females receive more direct aggression than high-ranking females and they also have less access to nutritional resources (Onyango et al., 2008). These factors can contribute towards affecting the pathology of subsequent offspring. Mid-ranking mothers produced milk with higher epidermal growth factor (EGF) than low-ranking mothers, and it was also found that Milk-EGF and EGF-R were positively correlated with infant body mass and growth rate for infant rhesus macaques (Bernstein and Hinde, 2016). Offspring of

female yellow baboons exposed to the food-enhanced foraging condition experience faster sexual maturity than completely wild-foraging groups, and high-ranking females and mulitparous females had large-for-age juveniles, which experienced earlier sexual maturity (Alberts and Altmann, 2005). Testicular enlargement also occurs earlier in male yellow baboons born to high-ranking mothers, which is a sign for the onset of puberty (Alberts and Altmann, 1995). Furthermore, it was found that males with high-ranking mothers also attained their dominance rank faster than did males born to low-ranking mothers. This finding has important implications for sexual reproduction, since the attainment of dominance rank was found to have preceded consortships with other females (Alberts and Altmann, 1995). Therefore, the age at which a male baboon can begin to sexually reproduce is largely influenced by maternal characteristics of dominance. This is surprising in baboons since maternal rank does not greatly influence the dominance rank of males nearly as much as it does in macaques. However, maternal rank does play a long-term and impactful role in influencing the reproductive maturity of male baboons. An additional study on wild yellow baboons found that fecal glucocorticoid concentrations (fGC) could be predicted by the mother's dominance rank at the time of conception; sons of high ranking mothers had lower fGC compared to sons of low-ranking mothers (Onyango et al., 2008). These effects were also long-lasting; the male baboons from which fGC samples were collected were subadult baboons who were 4-6 years past the period of infancy dependence on their mothers. The fact that there were long-lasting impacts of maternal rank on fGC demonstrates the pervasive ability of maternal effects to impact long-lasting change within offspring and opens up the possibility of maternal reprogramming of the HPA axis within their sons. Within a population of wild chimpanzees, it was discovered that low-ranking mothers had significantly higher fecal glucocorticoid metabolite (FGM) concentrations than did high-

ranking mothers during pregnancy and this subsequently caused them to have male offspring who also experienced higher FGM concentrations (Murray et al., 2016). The significance of this particular study is that it demonstrates the interplay between rank and stress levels, since low-ranking mothers carried their higher inclinations towards stress onto their pregnancies as well which reflected in the subsequent offspring born. Nonetheless, the aforementioned evidence collected from baboon and chimpanzees proposes that dominance rank, in addition to stress, can influence the mother's reproductive physiology to impact the health of subsequent offspring.

Support for Predictive Adaptive Response (PAR) Hypothesis

I.   Evidence from non-primates for PAR

The Predicative Adaptive Response (PAR) Hypothesis is an alternative to the Developmental Constraints Hypothesis. Rather than placing constraints on offspring development, this hypothesis proposes that any adverse effects from the maternal environment instead serve to better prepare the offspring for the environment they (the offspring) are about to encounter (Grafen, 1988). Although this hypothesis is meant to apply to many potential maternal effects, the majority of research on this hypothesis has been conducted on maternal stress. According to the PAR Hypothesis, offspring born to mothers exposed to stressful conditions will have increased HPA sensitivity (Liu et al., 1997; Clarke and Wittwer et al., 1994), higher baseline cortisol levels (Murray et al., 2016), and accelerated growth and life history (Vries et al., 2007). The idea behind the PAR is that a pregnant animal exposed to stressful environments, such as areas with high predation, is able to transmit a signal to the developing fetus to allow the fetus to alter its own HPA sensitivity to increase its chances of survival after birth (Matthews, 2002). Maternal stress effects have been studied mainly at the gestational level, since it is known

that pregnancy in mammals results in activation of the HPA axis, causing increases in GC concentrations in fetal-maternal circulation and that these increases are essential for promoting normal growth and development, aiding in parturition, and assisting the process of lactation (Pepe and Albrecht, 1995).

Overall, there is some evidence to suggest that maternal stress can alter the stress physiology of the offspring in adaptive ways (Vries et al., 2007; Berghanel et al., 2016). For example, captive female Asian elephants (*Elephas maximus*) born in high stress months, categorized by higher glucocorticoid metabolites due to a heavier workload season, exhibited faster reproductive senescence in adulthood and had significantly reduced lifetime reproductive success (Mumby et al., 2015). Additionally, in guinea pigs (*Cava aparea*) body weight was significantly larger for females born to prenatally stressed mothers compared to control female guinea pigs whose mothers were not exposed to prenatal stress (Schöpper et al., 2012). Additionally, in perhaps one of the best examples from a wild population of mammals, among a higher population density of red squirrels (*Tamiasciurus hudsonicus*), natural selection favors rapidly growing offspring (Dantzer et al., 2013). Maternal effects have the capability of inducing faster growth since territorial vocalizations emitted by the squirrels is a good indicator of the current population density. Experimenters found that the offspring born to squirrel mothers that experienced experimentally-heightened density (using audio playbacks to simulate vocalizations of many conspecifics in the area), had growth rates that were significantly faster than those produced by control females. Additionally, mother squirrels that experienced increased perceived density through the playback experiment also had concentrations of FCM that were 30% higher than control females (Dantzer et al., 2013). This is significant because based on analysis from a 23-year study, females that produced faster-growing offspring had more offspring survive their

first winter. This suggests that it is advantageous for the offspring's growth and survival to receive maternal feedback about the environment. Therefore, maternal stress effects have been shown to cause faster growth rates in non-primate models.

II.   Evidence from Rodent Studies for PAR

Evidence from rodent studies support the idea that maternal behavior of licking and grooming can foster stress resistance within pups by increasing the expression of glucocorticoid receptors within the hippocampus (Lee and Williams, 1974; Meaney, 2001). This leads to an attenuated stress response within pups that experienced intermittent separations from their mothers because the mothers increase licking and grooming upon reunion as well as throughout their development (Lee and Williams, 1974). It has also been shown to lead to increased stress resistance within pups that were not separated from their mothers but that naturally experienced higher levels of maternal care during development (Liu et al., 1997). These studies have repeatedly shown the importance of the role that maternal care plays in mediating subsequent stress resistance within the offspring.

Rodent models have proven most useful for studying how maternal stress effects can lead to adaptation and programming within offspring. The HPA axis of rats exposed to different maternal behavior exhibit large differences. Arched back nursing within mother rats is a good predictor of licking and grooming bouts displayed by the mother towards the offspring; Liu et al. (1997) found that 90% of the instances of licking and grooming occurred when the mother had assumed an arched-back posture. Rat offspring of high LG and arched-back nursing mothers show reduced plasma ACTH and corticosterone responses to restraint stress, increased hippocampal glucocorticoid receptor mRNA expression, and increased glucocorticoid negative

feedback sensitivity (Liu et al., 1997). Furthermore, the behavioral responsiveness of these offspring to different situations is altered amongst high and low licking and grooming (LG) and arched back nursing offspring (ABN). Low LG-ABN mothers showed less exploratory behavior and increased startle responses than did high LG-ABN (Liu et al., 1997). Furthermore, post-weaning isolation reduced exploratory behavior, maternal LG, and OTRs in offspring of high LG mothers, whereas social enrichment enhanced exploration, LG behavior, and OTR binding of low LG offspring (Champagne and Meaney, 2007). These findings are thought to reflect an adaptation for the offspring; under certain stressful environmental conditions, it should be beneficial for individuals to have a heightened behavioral and endocrine response to stress (Caldji et al., 2001). Therefore, licking and grooming bouts elicited by the mother play a significant role in altering HPA development for offspring.

These differences in maternal style have the capability of being transmitted intergenerationally. Female offspring of high LG-ABN mothers show significantly more LG-ABN than female offspring of low LG-ABN mothers (Liu et al., 1997). Additional studies have also focused on determining the time period during pregnancy when stress exposure causes the greatest impact on an offspring's body weight. Stress experienced late in pregnancy significantly increased offspring birth weights in wild type mice compared to unstressed controls. By contrast, stress experienced mid- to late-pregnancy led to male offspring being, on average, 15% heavier as adults (Mueller et al., 2006). Therefore, the timing of exposure to maternal stress also appears to play a role in determining the stress physiology of the offspring.

III.   Evidence from Non-Human Primates

Although the research is much more limited compared to that from rodents, there is some evidence to suggest that adaptive programming occurs within primates as well. In one particular study, researchers wanted to explore the relationship between maternal dominance and maternal FGM during pregnancy and lactation within wild chimpanzees (*Pan troglodytes*). Chimpanzees are a good model to study because the period of dependency on mothers is considerably lengthy which allows for a greater potential for maternal influence to act on the offspring (Murray et al., 2016). Results showed that low-ranking females experienced significantly higher FGM concentrations during pregnancy than high-ranking females and had male offspring that also exhibited higher baseline FGM levels (Murray et al., 2016). Thus, maternal rank and prenatal glucocorticoid levels differentially impact the stress physiology of the offspring, which may be adaptive. It may be advantageous for low-ranking mothers to have offspring with higher baseline FGM concentrations because it helps them to combat stressors in their life. It may even reflect postnatal differences in access to lower dietary quality, since offspring likely have access to the same quality of food and other resources as their mothers.

Additional experiments have been performed to support the adaptive effects of maternal stress exposure during the gestational period. Nyugen et al. (2008) examined a group of wild yellow baboon mothers to determine whether increases in GCs during pre or post-parturition alter maternal responsiveness to infant distress cries in an adaptive manner. Results showed that increases in GCs during late pregnancy facilitates increased attentiveness towards infant distress cries immediately after birth whereas increases in GCs during post-parturition leads to increased awareness for ongoing infant cries (Nyugen et al., 2008). This is a significant finding because it suggests that GC secretion can mobilize energy reserves and activate existing maternal neural

circuitry needed to cope and respond to anticipated challenges with offspring care (Nyugen et al., 2008). In a different experiment, six pregnant rhesus macaques were repeatedly removed from their home cages and exposed to unpredictable noise during mid- to late-gestation while six undisturbed pregnant mothers served as controls. Offspring of stressed mothers showed higher ACTH and cortisol levels than control offspring, which further reinforces the idea that offspring of primate mothers stressed during pregnancy show enhanced HPA axis responsivity to stressors later in life (Clarke and Wittwer et al., 1994).

There are several other studies in which stress within the mother is induced via administration of synthetic drugs in order to observe the effects of stress programming within the subsequent offspring. For instance, researchers administered differing levels of the synthetic glucocorticoid, dexamethasone (DEX), to pregnant African vervet (*Chlorocebus aethiops*) mothers in order to examine the effect that this would have on the offspring. The highest dose of DEX increased activation of the offspring HPA axis in vervets in response to mild stress exposure (Vries et al., 2007). The effects of DEX were studied within pregnant common marmosets (*Macaca assamensis*) as well. Pregnant marmosets (*Callithrix jacchus*) were exposed to daily repeated DEX treatments either during early or late pregnancy, and results of the experiment showed that early DEX treatment resulted in increased infant body weight (Hauser et al., 2007).

Though these results support that maternal stress effects can accelerate growth and improve HPA sensitivity, there are also tradeoffs to this metabolic shift. For instance, Berghanel et al. 2016 investigated whether prenatal maternal food availability and maternal glucocorticoids lead to developmental constraints or adaptive programming within Assamese macaques (*Macaca assamensis)*. Since the Assamese macaques live in unpredictable environments, it would be

advantageous for them to program their physiology based on the internal somatic state of the mother rather than alter their physiology in response to the environment they are surrounded by. Results showed that higher prenatally stressed mothers had infants that accelerated their growth but that also experienced lower immune functioning and decelerated motor skill acquisition (Berghanel et al., 2016). In conclusion, while stress can program the offspring to accelerate their life history as observed by increased growth it can also lead to lead to adverse outcomes, such as lower immunity, therefore imposing trade-offs.

Evidence from Human Populations

There are examples of both developmental constraints as well as predictive adaptive response programing within studies conducted on humans. Numerous studies conducted on human populations have supported the fact that maternal effects can exhibit adverse long-term effects on the health of their offspring, thereby supporting the developmental constraints hypothesis. These maternal effects also occur largely at the prenatal level. For instance, the Dutch Winter Hunger famine of 1944-1945 impacted many families living in the German-occupied Netherlands and caused long-lasting impacts in the health of offspring born to undernourished pregnant women (Roseboom et al., 2001). Even though infant birth weights did not appear to be lower than average, there were still numerous health implications that were displayed in these babies later on in life (Roseboom et al., 2001). These included greater risk of congenital heart defects, reduced glucose tolerance, and increased incidence of obstructive airways disease (Roseboom et al., 2001). These data support the idea that maternal effects can have long lasting impacts on the health and phenotype of offspring among humans. Severe stress

during the first trimester of pregnancy caused an increased risk of congenital abnormalities in offspring born with cleft palates and/or cleft lips (Hansen et al., 2000).

The most significant result of prenatal stress observed within humans is linked to an increased risk of preterm delivery, which also has important health implications for the child (Gitau et al., 2001). Hedegaard et al. (1993) surveyed over 8500 women and found that there was a significant association between psychological distress measured at 30 weeks of pregnancy and risk of preterm delivery; the risk of preterm delivery was almost two-fold for high distress than it was for low distress. Copper et al. (1996) also found that perceived stress was a risk factor for spontaneous preterm birth and lower birth weight (characterized as less than 2500g). These results are significant because lower birth weight and pre-term delivery are both linked to later health problems for the child (Barker, 1995). Lower birthweight may also be linked to mental health problems later on in life; Hultman et al. (1999) showed that boys who were underweight at gestational birth had a three-fold increased risk for schizophrenia.

Though there is a lot of evidence within humans to suggest that maternal stress can have deleterious consequences on the health of the child, there is also evidence to support that antenatal stress or anxiety can alter the behavioral development of the child as well. Mothers who exhibited elevated pregnancy-specific anxiety (PSA) during early gestation have children who exhibit more negative temperaments at the age of two, even after controlling for other potentially confounding socioeconomic factors (Blair et al., 2011). There also have been numerous reports that link maternal stress to the appearance of emotional problems, hyperactivity and attention deficit disorders within children (Weinstock, 2005).

However, there are examples of how adaptation and programming can occur within human offspring as the result of maternal stress effects and nutrition. For example, it has been

shown that maternal stress beginning in infancy predisposes children to increased HPA function during a period of concurrent stress which is significant because early exposure to stress sensitizes later HPA and behavioral responsivity (Essex et al., 2002). Yet, as mentioned earlier in the introduction, the two most well-known examples of adaptive programming within humans are the Barker Hypothesis, also known as the Thrifty Phenotype Hypothesis and the Fetal Origins of Adult Disease Hypothesis, and the Developmental Origins of Health and Disease (DOHaD). The Barker Hypothesis argues that the fetus adapts to a limited supply of nutrients by altering its physiology and metabolism and that these changes can increase the risk of disease later on in life (Barker, 1992; Roseboom et al., 2001). The Barker Hypothesis was instrumental in establishing the relationship between maternal in utero conditions and lifelong outcomes of health and disease for the offspring. It was significant because it set the groundwork for DOHaD to further study developmental plasticity during gestation in response to nutrition and stressors. DOHaD proposes that offspring have a developmental and adaptive response to security and scarcity in the maternal environment, and goes beyond the Barker Hypothesis to study the epigenetic mechanisms underlying predictive adaptive responses of the infant. It states that the fetus can become nutritionally "thrifty" by decreasing its growth and by initiating hormonal/metabolic changes, and it has been expanded into a whole new field of study today (Barker, 1992).

A major hurdle involved in studying human maternal stress effects involves ethical considerations regarding stress manipulations (Kaiser and Sachser, 2009). Manipulating hormone levels or exposing pregnant mothers to stress can have significant health implications for individuals, since there is still a great amount of unpredictability surrounding the consequences of such actions. Therefore, experiments studying maternal stress effects stem from

non-human animal models. However, researchers can take advantage of natural experiments in which mothers experienced elevated stressors because of their environment, and such opportunities must be seized in order to further elucidate mechanisms of maternal stress effect manifestation within humans.

Importance of Stress During Pregnancy & Transmittance of Maternal Effects

The timing of development and maturation of the HPA axis is highly dependent on the species, with animals giving birth to precocious young as experiencing a maximum proportion of neuroendocrine maturation in utero as compared to animals giving birth to altricial young where a majority of the neuroendocrine development occurs in the postnatal period (Matthews, 2002). This is significant because it can help to explain the importance of exposure of maternal stress during gestation within primates which seems to have an extremely significant impact on subsequent offspring as compared to during prezygotic and postnatal stress periods (Table 1). In contrast, the results seen from rat studies, which are an example of an altricial species, stress the importance of maternal care in altering HPA and GC receptor sensitivity (Liu et al., 1997).

Similar to rodents, mechanisms of transmission of maternal effects that are not related to stress can be caused by epigenetic mechanisms within primate populations (Aagaard-Tillery, 2008). There is evidence within primate literature to suggest that this is indeed the case for wild primates. For instance, Aagaard-Tillery (2008) examined whether maternal nutrition during pregnancy can lead to epigenetic modifications of fetal chromatin structure within Japanese macaques (*Macaca fuscata*). Results from their experiment showed that chronic consumption of a maternal high fat diet resulted in fetal chromatin restructuring, such as the covalent modification of histones, therefore increasing the likelihood of obesity within the subsequent

offspring. The mechanisms by which these maternal influences can be transmitted to the

offspring include maternal messenger RNAs stored into unfertilized eggs and ovules or through

maternal traits such as nutrition (Wolf and Wade, 2009).

However, more often, it appears that maternal effects re transmitted to the offspring by

maternal hormone transfer to the fetus (Kaiser and Sachser, 2009). Though the placenta serves as

a barrier to many maternal stress factors such as ACTH, Beta endorphins, glucocorticoids, and

catecholamines, several can still cross the placenta (Matthews, 2002). However, mechanisms are

set in place to help mediate stress within the placenta, most notably through the enzyme 11-Beta-

hydroxysteroid dehydrogenase (11β-HSD), which interconverts cortisol and corticosterone to

inactive products (Welberg et al., 2000; Matthews, 2002).

Table 1: Maternal Effects and Outcomes for Primate Models

Stage of Maternal Effect	Species	Author	Maternal Effect	Outcome	Hypothesis Supported
Pre-zygotic	*Maccaca mulatta*	Smith and Smith, 1988	Maternal Dominance Rank	Increased reproductive success of sons born to higher ranking females	Developmental Constraints
	Maccaca mulatta	Bernstein and Hinde, 2016	Maternal Dominance Rank	Mid-ranking mothers produced milk with higher epidermal growth factor (EGF) than low-ranking mothers (milk-EGF and EGF-R are positively correlated with infant body mass and growth rate)	Developmental Constraints
	Papio cynocephalus	Onyango et al., 2008	Maternal Dominance Rank	Low ranking females received more direct aggression and less access to quality resources	Developmental Constraints
	Papio cynocephalus	Alberts and Altmann, 2005	Maternal Dominance Rank	Offspring of female yellow baboons exposed to the	Developmental Constraints

			and Maternal Nutrition	food-enhanced foraging condition experience faster sexual maturity than completely wild-foraging groups, and high-ranking females had large-for-age juveniles, which experienced earlier sexual maturity	
	Papio cynocephalus	Alberts and Altmann, 1995.	Maternal Dominance Rank	Testicular enlargement also occurs earlier in male yellow baboons born to high-ranking mothers	Developmental Constraints
	Papio cynocephalus	Onyango et al., 2008	Maternal Dominance Rank	sons of high ranking mothers had lower fGC compared to sons of low-ranking mothers and effects were also long-lasting (4-6 years past dependency on mother by infant)	Developmental Constraints
	Pan troglodytes	Murray et al., 2016	Maternal Dominance Rank	low-ranking mothers had significantly higher fecal glucocorticoid metabolite (FGM) concentrations than did high-ranking mothers during pregnancy and this subsequently caused them to have male offspring who also experienced higher FGM concentrations	Predictive Adaptive Response Hypothesis
Prenatal	*Maccaca mulatta*	Bardi and Huffman, 2005	Gestational stress	high peripartum cortisol levels and low maternal responsiveness caused greater infant anxiety	Developmental Constraints
	Maccaca mulatta	Schneider et al., 1997	Gestational stress	Gestational stress can lead to lower birth-weight and greater risk of loss of offspring	Developmental Constraints
	Maccaca mulatta	Converse et al., 2013	Gestational stress	Increases in striatal midbrain dopamine transporter (DAT) availability within adult offspring (associated with cognitive and behavioral impairments)	Developmental Constraints
	Maccaca mulatta	Coe et al., 2003	Gestational stress	offspring of mothers exposed to noise stress during early or late pregnancy exhibited less exploratory behavior and elevated baseline plasma cortisol levels as compared to control mothers	Developmental Constraints
	Maccaca mulatta	Herrington et al., 2016	Gestational stress	elevated stress responses in offspring for mothers who exhibited takeovers during first trimester whereas exposure in the second trimester resulted in	Developmental Constraints

				elevated glucocorticoid output following maternal separation and lower hematocrit levels compared to control groups	
	Maccaca mulatta	Coe et al., 2007	Gestational stress	exposure to stress during early gestation had a higher impact in increasing the prevalence and magnitude of iron deficiency than did later in gestation	Developmental Constraints
	Maccaca mulatta	Schneider et al., 1992	Gestational stress	Infants born to the early-stress gestation condition weighed less than did the mid- or late-gestation stress condition and caused greater neuromotor impairments	Developmental Constraints
	Maccaca mulatta	Coe and Lubach, 1992	Gestational stress	two-week old infant macaques of mothers injected with ACTH during mid-pregnancy exhibited diminished motor coordination and shorter attention span	Developmental Constraints
	Maccaca mulatta	Clarke and Wittwer et al., 1994	Gestational Stress	Offspring of stressed mothers showed higher ACTH and cortisol levels than control offspring	Predictive Adaptive Response Hypothesis
	Chlorocebus aethiops	Vries et al., 2007	Gestational Stress	highest dose of DEX increased activation of the offspring HPA axis in vervets in response to mild stress exposure	Predictive Adaptive Response Hypothesis
	Papio cynocephalus	Nyugen et al., 2008	Gestational Stress	increases in GCs during late pregnancy facilitates increased attentiveness towards infant distress cries immediately after birth whereas increases in GCs during post-parturition leads to increased awareness for ongoing infant cries	Predictive Adaptive Response Hypothesis
	Callithrix jacchus	Hauser et al., 2007	Gestational Stress	early DEX treatment resulted in increased infant body weight	Predictive Adaptive Response Hypothesis
	Macaca assamensis	Berghanel et al., 2016	Gestational Stress and Maternal Nutrition	higher prenatally stressed mothers had infants that accelerated their growth but that also experienced lower immune functioning and decelerated motor skill acquisition	Predictive Adaptive Response Hypothesis
Post-natal	*Papio cynocephalus*	Lea et al., 2015	Low quality maternal environment (i.e. born in drought)	Females born in low-quality environments showed greater decreases in fertility during drought years than	Developmental Constraints

				females born in high-quality environments	
	Callimico goeldii and Callithrix jacchus	Ross et al., 2010	Maternal Care	*C. goeldii* infants gained weight faster from 0-18 months than *C. jacchus* since their mothers spent more time carrying their infant and were able to delay weaning	Developmental Constraints

Discussion

Maternal care plays an imperative role in aiding the healthy development and growth of an infant. For instance, despite the findings that the nutritional value of milk and prenatal efforts of the fetuses were similar for two species of marmoset monkeys (*Callimico goeldii* and *Callithrix jacchus*), *C. goeldii* infants gained weight faster from 0-18 months than *C. jacchus* since their mothers spent more time carrying their infant and were able to delay weaning since they bore one offspring at a time compared to the multiple that *C. jacchus* mothers had (Ross et al., 2010) . This shows the vast extent that maternal attentiveness can have on offspring, which is what makes the study of maternal effects particularly important. It was once commonly believed that there are critical time periods during postpartum in which mothers and infants form strong and affectionate bonds. However, this view has since been revised to say that the period after pregnancy is a period of maternal sensitivity during which mothers are very sensitive towards forming such infant bonds (Maestripiri, 2001). Primates are an especially good model to study the effects of maternal care since primates have slow life histories and exhibit greater dependence on mothers compared to other animal models (Jones, 2001). Therefore, the potential of maternal effects to exert their influence over offspring is fairly high.

As reviewed here, the most well-studied maternal effect is through the mediation of offspring stress physiology through maternal stress. The two main hypotheses regarding maternal stress effects both make differing predictions as to how stress manifests within the offspring; the Developmental Constraints Hypothesis argues that stress effects play a maladaptive role leading to the manifestation of diseased pathologies within offspring whereas the Predictive Adaptive Response Hypothesis posits that stress effects can help prepare the body to fight future stressful events (Lea et al., 2015; Gluckman and Hanson, 2004). Most of the information that we have about maternal effects stems from experimental rodent studies. These studies have elucidated that maternal licking and grooming behavior has the potential to increase glucocorticoid receptor expression and HPA sensitivity, therefore suggesting that maternal effects are adaptive (Lee and Williams, 1974; Liu et al., 1997; Meaney, 2001). Furthermore, rodent studies have been able to determine the intergenerational mechanisms of maternal stress effects to elucidate how these effects exert long-term impacts on subsequent offspring (Liu et al., 1997).

There have been more advances made towards understanding maternal effects within primates as well, and evidence from literature support both hypotheses of maternal effects. Studies performed have shown that high-ranking mothers with greater access to resources and less psychosocial stress will have offspring that grow faster, fewer health complications, and have lower baseline glucocorticoid levels ("stress hormones") to help them handle stress better later on in life as compared to a low-ranking mother with decreased access to resources that is exposed to more psychosocial stress will have offspring that grow slower, experience more health complications, and have higher baseline glucocorticoid levels making them more prone to certain behavioral and physical detriments (Alberts and Altmann, 1995; Alberts and Altmann, 2005; Onyango et al., 2008; Murray et al., 2015; Bernstein and Hinde, 2016; Herrington et al.,

2016). These results lend credence to the Developmental Constraints Hypothesis since stress is leading to adverse outcomes for the offspring rather than adaptive.

One obstacle in studying maternal effects is ethical considerations involving stress manipulations. Another major obstacle in studying maternal stress effects is that this term, along with Developmental Constraints and Predictive Adaptive Response theory is not widely used in common literature. In fact, only a handful of authors actually used these terms within their research to describe their findings (Altmann and Alberts, 2004; Lea et al., 2015; Onyango et al., 2009; Berghanel et al., 2016). This requires the researchers studying maternal effects to analyze and interpret the data in order to assess whether the experiment tests for maternal effects, and if they do, to determine which of the two hypotheses is supported by them. However, this endeavor requires a lot of devotion on the researcher's part as often results can seem misleading in favor of one hypothesis or the other if the paper was not read in its entirety. For example, in one particular study conducted on squirrel monkeys (*Saimiri sciureus*), mothers and infants were exposed to a series of brief separations to study behavioral and physiological responses to the stressor of these separations. Results showed that separated infants showed a marked and progressive decrease in distress calling across time (Coe et al., 1983). A researcher studying maternal effects could easily categorize this as support for Predictive Adaptive Response since infants seemed less emotionally distressed and could believed to have undergone a physiological adaptation to the separation. However, researchers go on to explicitly say that this was not the case since these separated infants also showed increased agitated activity and adrenal activation (Coe et al., 1983). Therefore, this example elucidates the importance of thoroughly examining the research in order to accurately assess the role that the evidence plays in support for either or neither of the two hypotheses.

Another major caveat of studying maternal effects is that the environmental context needs to be studied in order to accurately assess whether the outcome supports Developmental Constraints or the Predictive Adaptive Response hypotheses. For example, studies of maternal effects within guinea pigs have shown that in general, exposure to prenatal maternal stress leads to masculinization of behavior, endocrine and brain development within females as well as demasculinzation and/or delays in development within male offspring (Kaiser and Sachser, 2009; Del Giudice, 2012). These outcomes are adaptive in the sense that guinea pigs live in high density populations where it might be beneficial for mothers to masculinize their daughters to make them more robust and/or more competitive so that they can defend important resources, such as food (Kaiser and Sachser, 2009). Similarly, for males it is beneficial to have demasculinzation since under high density populations, males should avoid aggressive encounters that can harm their health until they have reached sexual maturity later on in life (Kaiser and Sachser, 2009). Simply stating that masculinization or demasculinzation occurs provides no sort of context regarding the behavioral relevance of such physiological changes. Therefore, having additional information about how these outcomes manifest themselves under certain environmental condition is important in order to accurately determine the adaptive value or lack thereof of fetal exposure to maternal stress.

Researchers have made significant advances in understanding maternal stress effects from rodent studies. Nevertheless, additional work needs to be conducted in our closest living relatives as well as within humans to elucidate the importance of maternal influence across different species in a comparative context. With heightened attention on the part of the researcher to clarify their terminology as well as increased experimentation on primates, we may

one day be able to understand the complex and pervasive role that mothers play in shaping their offspring's health and well-being.

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