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REVIEW

Fetal programming by maternal stress: Insights from a conflict perspective

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Summary Maternal stress during pregnancy has pervasive effects on the offspring's physiology and behavior, including the development of anxious, reactive temperament and increased stress responsivity. These outcomes can be seen as the result of adaptive developmental plasticity: maternal stress hormones carry useful information about the state of the external world, which can be used by the developing fetus to match its phenotype to the predicted environment. This account, however, neglects the inherent conflict of interest between mother and fetus about the outcomes of fetal programming. The aim of this paper is to extend the adaptive model of prenatal stress by framing mother-fetus interactions in an evolutionary conflict perspective. In the paper, I show how a conflict perspective provides many new insights in the functions and mechanisms of fetal programming, with particular emphasis on human pregnancy. I then take advantage of those insights to make sense of some puzzling features of maternal and fetal physiology and generate novel empirical predictions.

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1. Introduction

From conception to delivery, mammalian fetuses are exposed to a continual stream of chemical signals carried by maternal blood. Among these signals, a prominent role is played by the hormones associated with the stress response. A growing amount of evidence from human and nonhuman studies shows that maternal stress during pregnancy exerts pervasive, long-lasting effects on the development of the fetal nervous system — and, ultimately, on the offspring's physiology and behavior. In psychology and medicine, the classic approach to maternal stress has been to treat it as a disruptive influence on fetal development and a net risk factor for future pathology (e.g., Van den Bergh et al., 2005; Weinstock, 2005; Mennes et al., 2006). In marked contrast with this view, the last decade has witnessed the emergence and consolidation of an alternative model, based on evolutionary biology, in which fetal programming by maternal stress is seen as an evolved adaptive process (e.g., Matthews, 2002; Kaiser and Sachser, 2005, 2009; Kapoor et al., 2006; Talge et al., 2007; Glover, 2011; Pluess and Belsky, 2011; Sandman et al., 2012).

At the core of the adaptive model is the idea that maternal stress hormones carry useful *information* about the state of the external world — for example its safety and predictability, the presence of threats, and so forth — that is otherwise inaccessible to the fetus. The developing fetus can use this information as a "forecast" of the environmental conditions it will eventually face after birth, and start adjusting its physiological and behavioral profile to match the requirements of the world it will probably encounter. In this perspective, fetal programming is an instance of adaptive developmental plasticity (West-Eberhard, 2003). More specifically, it can be considered a *predictive adaptive response*, as the fetus makes use of present cues to entrain the development of alternative phenotypes that will become adaptive in the future (Hinde, 1986; Belsky et al., 1991; Bateson et al., 2004; Gluckman and Hanson, 2004; Gluckman et al., 2005).

The adaptive model of prenatal stress is a powerful application of evolutionary theory to early development. By uncovering the ultimate logic of physiological processes, it helps make sense of a broad array of empirical findings. Nevertheless, a crucial piece is still missing from the puzzle: the inherent *conflict of interest* between mother and fetus about the outcomes of fetal programming. The aim of this paper is to extend the adaptive model by framing mother-fetus interactions in an evolutionary conflict perspective. In the remainder of this section I will briefly review the behavioral and neurobiological outcomes of prenatal stress, introduce the theory of parent-offspring conflict, and discuss some conflictual aspects of mother-fetus interactions. In Sections 2 and 3, I will show how a conflict perspective provides many new insights in the functions and mechanisms of fetal programming. I will then take advantage of those insights to make sense of some puzzling features of maternal and fetal physiology, and generate novel empirical predictions.

1.1. Behavioral outcomes of prenatal stress as adaptive responses

A general pattern, observed in rats and nonhuman primates alike, is that the offspring of prenatally stressed mothers tend to show increased anxiety-like behaviors and reduced attentional span. They also show higher basal activity of the hypothalamic-pituitary-adrenal (HPA) axis, as well as potentiated and prolonged HPA responses to stressors (reviewed in Van den Bergh et al., 2005; Talge et al., 2007; Cirulli et al., 2009; Flinn et al., 2011). While the behavioral effects of prenatal stress may vary across species and between males and females, the big picture shows a consistent tendency toward hyper-responsivity. As an example of a more complex pattern, the offspring of guinea pigs exposed to social stressors during pregnancy show female masculinization and male infantilization (i.e., display of behavioral patterns typical of very young males). These behavioral outcomes can be adaptive because of the different implications of social instability for the males and females of this species (Kaiser and Sachser, 2005, 2009).

These disparate findings can be usefully integrated within the framework of life history theory (e.g., Kaiser and Sachser, 2005). In this perspective, information about key parameters of the environment (safety, predictability, resource availability, social competition, and so forth) can be used to inform the organism's reproductive strategy, for example by altering the trade-off between reproduction and survival, current and future reproduction, quality and quantity of offspring, or mating and parenting effort (see Belsky

et al., 1991; Ellis et al., 2009). Life history concepts have been explicitly invoked to explain the effects of postnatal care (and the associated exposure to stress) on the development of stress responsivity, both in rats (Cameron et al., 2005, 2009) and in humans (Del Giudice et al., 2011; see also Cameron et al., 2005; Meaney, 2007). In tandem with patterns of postnatal care, prenatal stress may contribute to potentiate the organism's defensive responses to threat, and adjust its reproductive and mating tactics to function optimally in a dangerous environment. Of course, behavioral and physiological adaptations to danger can be expected to impose some costs on the organism; however, what it takes for a trait to be biologically adaptive is that (on average) its fitness benefits outweigh the costs. Indeed, massively costly traits can be favored by natural selection if *not* expressing them would be even more detrimental to fitness (see e.g., Frankenhuis and Del Giudice, 2012).

1.1.1. The complex relation between stress hormones and environmental states

A standard assumption in the fetal programming literature is that higher levels of stress hormones signal a more dangerous and/or unpredictable environment (e.g., Kapoor et al., 2006; Talge et al., 2007; Glover, 2011; Sandman et al., 2012). This assumption, however, may be only partly correct. Fetal exposure depends on the combined effect of two factors: the amount of stressors in the environment and the mother's responsivity to stressors. Studies of humans and rodents show that both dangerous environments *and* very safe ones tend to promote the development of high HPA and autonomic responsivity, giving rise to a U-shaped relation between environmental quality and stress responsivity (e.g., Ellis et al., 2005; Macrì et al., 2007, 2009; Gunnar et al., 2009; Del Giudice et al., 2012; for reviews see Ellis et al., 2006; Del Giudice et al., 2011). The likely adaptive function of high responsivity in "good" environments is to increase the organism's openness to opportunities and resources, for example by enhancing social learning and affiliation (see Del Giudice et al., 2011). As a consequence, mothers raised in safe and predictable environments should respond strongly to mild stressors, thus producing comparatively high amounts of stress hormones even in absence of significant danger or uncertainty. Further implications of a nonlinear relation between environmental states and stress responsivity will be discussed in Section 3.

While these findings challenge the standard assumptions of programming models, they do *not* imply that the signals reaching the fetus look exactly the same in safe and dangerous environments. Even in presence of a curvilinear relation between environmental quality and stress responsivity, responsive mothers in safe environments should experience infrequent and short-lived bouts of HPA/autonomic activation, whereas mothers in truly dangerous environments should experience (and transmit) a steadier and more chronic pattern of physiological activity (Del Giudice et al., 2011). Thus, the fetus may still be able to discriminate between the two scenarios by separating the long-term and short-term components of hormonal signals. Indeed, there is some evidence from rodent studies that the placental mechanisms responsible for filtering out maternal cortisol respond differently to acute versus repeated stressors (Welberg et al., 2005).

1.1.2. Prenatal stress in humans

In human children, the outcomes of prolonged, intense maternal stress during pregnancy include higher anxiety and fearfulness, temperamental difficulty, impulsivity, reduced executive functions, impaired attention, higher aggression and risk-taking, and increased basal activity and responsivity of the HPA axis (reviewed in Glover et al., 2009b; Glover, 2011; Pluess and Belsky, 2011). Vigilance, impulsivity, and competitive risk-taking can all improve fitness in a dangerous, unpredictable world (Talge et al., 2007; Glover, 2011; Pluess and Belsky, 2011); as noted above (Section 1.1.1), high stress responsivity can also be adaptive in particularly safe and protected environments (Boyce and Ellis, 2005; Ellis et al., 2006; Del Giudice et al., 2011). While most empirical studies in humans lack controls for shared genetic effects in mothers and children, a genetically informative study by Rice et al. (2010) confirmed that the association between maternal stress during pregnancy and children's anxiety and antisocial behavior is environmentally mediated.

Other studies have detected associations between severe stress and increased risk for autism, schizophrenia, attention-hyperactivity disorder, and impaired cognitive ability (e.g., Bergman et al., 2007; Khashan et al., 2008; Kinney et al., 2008). These outcomes are more difficult to interpret in an adaptive light, and may simply reflect the damaging side effects of early stress. Glover (2011) recently speculated that autism, cognitive impairment, and attention-hyperactivity disorder may bring adaptive benefits to social groups by increasing cognitive diversity; however, such group-selection scenarios are problematic from an evolutionary standpoint, and will need additional unpacking before they can be accepted as plausible (see West et al., 2007; Gardner and Grafen, 2009). Finally, any evolved mechanism can lose its adaptive function — or even become maladaptive — if the environment undergoes rapid changes; accordingly, some theorists have suggested that fetal programming by maternal stress may no longer be adaptive in modern environments (e.g., Kapoor et al., 2006; Talge et al., 2007; Cottrell and Seckl, 2009). This caveat does not contradict the view that the evolved function of fetal programming is to improve the fitness prospects of the fetus, by helping match its phenotype to the characteristics of the external environment (Sandman et al., 2012).

1.2. Conflict in fetal programming

The standard version of the adaptive model assumes, albeit implicitly, that the interests of the fetus are best served by letting maternal signals program its future behavior. The process of fetal programming is seen as a fully cooperative transfer of information in which the mother supplies the information (encoded by her physiology, including her stress hormones) and the fetus accepts it at face value. This straightforward scenario, overlooks the fact that the mother may use hormonal signals to manipulate fetal development, so as to promote her own biological interests at the expense of those of the fetus. In fact, evolutionary theory provides compelling reasons to predict that mother-fetus transactions will involve cooperation, but also conflict and reciprocal manipulation (Haig, 1993; Love and Williams, 2008; Schlomer et al., 2011). Note that, in evolutionary biology, terms such as "conflict," "cooperation," and "manipulation" are used to summarize the fitness

consequences of behavioral and physiological processes. As such, they do not imply conscious deliberation or the explicit representation of goals. Likewise, any organism (including those without a nervous system) can be usefully described *as if* it were following a certain "strategy" (or "tactic"), irrespective of the exact nature of the processes involved.

The evolutionary logic underlying the conflict of interest between parents and their offspring is explained by *parent-offspring conflict theory* (Trivers, 1974; Parker, 1985; Parker et al., 2002; Royle et al., 2004. See Schlomer et al., 2011, for a non-mathematical overview). The key message of parent-offspring conflict theory is that, in most organisms, the genetic interests of parents and offspring are only partially overlapping. Whenever a given trait or behavior results in a cost to the parent and a benefit to the offspring (or vice versa), parent and offspring are expected to "disagree" about the optimal level of expression of that trait. Stated otherwise, the level of a trait that maximizes the parent's fitness will differ from the level that maximizes the offspring's fitness, resulting in a biological conflict of interest about the trait/behavior in question.

The logic of parent-offspring conflict is easy to illustrate in the case of parental investment (e.g., food provision). A parent has the same degree of relatedness to all its offspring (i.e., a gene in the parent has a 50% chance of being transmitted to each offspring), and therefore — all else being equal — will maximize its fitness by investing equally in each of them. However, an offspring is more closely related to *itself* than to its siblings; a gene in an offspring has only a probability, usually 50% or less, of being present in the other offspring (present or future) that compete for parental resources. Thus, natural selection will favor those offspring who increase their share of resources above the parental optimum. In pregnancy, for example, there is an intrinsic conflict about fetal growth (see Schlomer et al., 2011): in order to maximize its own biological fitness, the fetus should try to extract more nutrients from the mother (and grow at a faster rate) than is optimal for her, while the mother should try to reduce the flow of nutrients to the fetus, keeping it below its optimal growth rate.

1.2.1. Prenatal conflicts

In a landmark article, Haig (1993) examined mother-fetus interactions in the light of parent-offspring conflict. By adopting this counterintuitive perspective, he was able to explain a number of puzzling facts about the regulation of maternal physiology during pregnancy. For example, the hormone insulin reduces the blood concentration of glucose. In human mothers, insulin levels rise dramatically during the third trimester, but at the same time mothers develop strong insulin resistance. Insulin resistance can have severe adverse effects for the mother, both during pregnancy and later in life. The paradoxical combination of insulin hyperproduction and insulin resistance does not make sense until one realizes that insulin resistance is actually induced *by the fetus*, through secretion of placental hormones, as a way to increase glucose concentration in the blood flow. The most plausible candidate hormones are placental lactogen (hPL, as suggested by Haig, 1993) and placental growth hormone (hPGH; see Haig, 2008). Increased insulin secretion, then, can be seen as a (costly) maternal countermeasure against fetal manipulation.

Another crucial conflict in pregnancy concerns the regulation of maternal blood pressure. Cardiac output rises dramatically early in pregnancy and remains elevated until the third trimester; at the same time, vasodilation occurs, lowering arterial resistance during the first and second trimester. The net effect is a drop in blood pressure in early and mid-pregnancy, with pressure typically rising again during the third trimester. Vasodilation appears to put an unnecessary strain on the mother's heart; an efficient system would increase blood supply to the placenta by increasing arterial resistance (vasoconstriction). In fact, maternal vasodilation can be explained as a defense of mothers against fetal release of factors that induce constriction of maternal vessels. Since placental arteries have extremely low resistance, increasing maternal blood pressure benefits the fetus by directly increasing placental flow. The side effects of this physiological tug-of-war include the occasional risk of fetal-induced maternal hypertension (see Haig, 1993, 2007).

The examples just reviewed aptly illustrate four key features of mother-fetus conflict. First of all, the fetus (or, more precisely, the fetoplacental unit) is an active player rather than a passive recipient of maternal "decisions." Second, the escalation of conflict often results in the evolution of convoluted, costly, and apparently wasteful physiological mechanisms. The function of such mechanisms cannot be properly understood outside of an explicit conflict perspective. The intensity of the coevolutionary "arms race" between mothers and fetuses is reflected in the amazingly rapid evolution of placental genes in rodents and primates (Haig, 2008; Hou et al., 2009; Chuong et al., 2010). Third, the interplay between maternal and fetal manipulation and countermeasures can mask the true intensity of the underlying conflict: despite the strong competition between mother and fetus in the regulation of glucose concentration, the actual concentration remains within relatively narrow limits most of the times. Finally, fetal attempts at manipulation of maternal physiology typically occur through production of placental hormones (Haig, 1996).

1.2.2. Prenatal stress as a conflict arena

Maternal stress during pregnancy increases anxiety, impulsivity, and HPA responsivity in the offspring, with cascading effects on a wide range of traits and behaviors including exploration, dispersal from the natal environment, intrasexual competition, and so forth (see Meaney, 2007; Del Giudice et al., 2011; Pluess and Belsky, 2011). If these traits/behaviors differentially affect the fitness of mother and offspring, the mother will benefit by distorting the signals she is sending to the fetus, so as to move its developmental trajectory closer to her own optimum. This is the crucial dilemma of prenatal stress: the fetus is going to receive a mixture of useful information and manipulative signals, and needs to strike the right balance between the benefit of information and the cost of manipulation. The general problem has been recognized for some time by evolutionary biologists studying maternal effects (e.g., Love and Williams, 2008; Uller and Pen, 2011).

To date, fetal programming by maternal stress has never been examined from the standpoint of parent-offspring conflict. Although Wells (2003, 2006) explicitly considered mother-fetus conflict in his critique of the predictive-adaptive response model, he restricted his analysis to *metabolic*

programming. Nepomnaschy and colleagues (2006; see also Flinn et al., 2011) applied a conflict perspective to the abortogenic effects of maternal stress in humans. Since stress increases the likelihood of miscarriage during the first weeks of pregnancy, the mother's stress response is potentially dangerous for the fetus. Nepomnaschy and colleagues suggested that, over time, a "defensive fetus" actively gains control of its own gestation by reducing the efficiency of maternal abortive mechanisms, so that after the first weeks of pregnancy even severe stressors are unable to induce miscarriage. Despite these promising leads in the literature, the conflicts of interest involved in the regulation of prenatal stress have remained virtually unexplored. The goal of the following sections is to make a first step in this direction.

2. Theoretical insights

2.1. What is the conflict about?

From a conflict perspective, the first question to ask about prenatal stress is, do maternal and fetal interests diverge? And if so, why? The outcomes of prenatal stress (Section 1.1) are so varied that parent-offspring conflict might potentially arise about any one of them. While many of these outcomes can be seen as manifestations of underlying reproductive strategies, too little is known about the effects of offspring's reproductive strategies on parental fitness to formulate plausible hypotheses in this respect. However, that of specific behavioral outcomes may not be the most productive level of analysis. Instead, prenatal stress can be expected to reliably elicit parent-offspring conflict because of its crucial role in the development of *postnatal plasticity*.

Postnatal plasticity is the extent to which the postnatal environment can shape or modify the offspring's phenotype. More formally, the developmental reaction norms of more plastic individuals have a steeper slope and cover a broader phenotypic range (see Via et al., 1995; West-Eberhard, 2003; Stamps and Groothuis, 2010). In human developmental psychology, postnatal plasticity has been characterized (with somewhat different theoretical implications) as *biological sensitivity to context* (Boyce and Ellis, 2005) and *susceptibility to environmental influences* (Belsky, 1997, 2005; Belsky et al., 2007; Ellis et al., 2011). In species with prolonged maternal care, the mother constitutes a fundamental part of the postnatal environment; and by definition, high postnatal plasticity implies increased susceptibility to the effects of maternal behavior (including feeding, caring, protection, teaching, and so forth). Therefore, the mother would benefit if she were able — by whatever means — to increase the offspring's susceptibility to her own behavior beyond the offspring's optimum, as this would give her increased leverage in subsequent instances of parent-offspring conflict. Conversely, and all other things being equal, the offspring should avoid becoming *too* plastic and susceptible to maternal influence. In recent years, abundant evidence has accumulated showing that stress responsivity and negative emotionality dramatically increase early plasticity in humans, and the same may plausibly apply to other mammals; as a consequence, early postnatal plasticity can be modulated by the level of stress experienced by the fetus (Belsky and Pluess, 2009; Pluess and Belsky, 2011), thus setting the stage for pervasive parent-offspring conflict about fetal programming.

In summary, if prenatal stress contributes to determine postnatal plasticity in the offspring, mother and fetus can be expected to have conflicting optima about the level of fetal exposure to stress hormones. Specifically, the mother should favor higher exposure than is optimal for the fetus. This statement should be interpreted carefully, as the predicted conflict is about *relative* exposure levels. For example, both mother and fetus may benefit from high fetal exposure in a dangerous environment (Section 1.1); however, the optimal exposure level of the fetus — while high in absolute terms — is expected to be somewhat *lower* than that of the mother, resulting in some degree of mother-fetus conflict.

2.1.1. Prenatal programming of postnatal plasticity

There is remarkable individual variation in infants' and children's susceptibility to environmental influences. Some children are barely affected by experiences in their first years of life, while others respond strongly to the conditions they encounter early on (e.g., by developing aggressive, antisocial behaviors in response to harsh and abusive parenting). In fact, highly plastic children show enhanced responses to both positive and negative features of the environment; for example, the same children who would become highly aggressive when raised in harsh families tend to become even *less* aggressive than other children when reared in positive, safe environments. The bidirectional nature of plasticity is well captured by the phrase "for better *and* for worse" (Belsky et al., 2007). While much remains to be learned, substantial progress has recently been made in our understanding of what makes infants and children more or less susceptible to environmental effects, including those of parental behavior. At the genotypic level, it has been possible to identify a number of alleles (in genes such as *DAT1*, *DRD2*, *DRD4*, *5HTT*, and *MAOA*) that contribute to increased plasticity. The combined effect of allelic variation in those genes on developmental reaction norms has turned out to be substantial (Belsky et al., 2009; Belsky and Beaver, 2010). At the phenotypic level, it has become apparent that highly plastic infants and children are characterized by negative emotionality, temperamental difficulty, and high responsivity of the HPA axis (e.g., Boyce et al., 1995, 2006; Kochanska et al., 2007; Obradovic et al., 2010; O'Neal et al., 2010; reviewed in Belsky, 2005; Belsky and Pluess, 2009; Ellis et al., 2011; Pluess and Belsky, 2011). Indeed, one of the main functions of the stress response system is to modulate the organism's openness to the environment, which — at least in the first years of life — includes susceptibility to the behavior of one's parents (Ellis et al., 2006; Del Giudice et al., 2011). It is probably no coincidence that plasticity-related genes tend to be involved in serotonergic and dopaminergic pathways, which in turn interact deeply and reciprocally with the stress response system (Porter et al., 2004; van Goozen et al., 2007; Gotlib et al., 2008; Alexander et al., 2011).

The phenotypic correlates of early developmental plasticity have not been systematically investigated in nonhuman animals. However, there are reasons to believe that emotional reactivity and HPA responsivity increase postnatal plasticity in many different organisms (Coppens et al., 2010). In macaques, anxious temperament has been shown to increase susceptibility to disrupted social relations during

rearing (Stevens et al., 2009). Temperamentally reactive mice also show larger stress-induced changes in behavior (Veenema et al., 2004). In a study of rats by Francis et al. (1999), the biological offspring of dams who engaged in reduced maternal care (i.e., dams with a fearful and reactive phenotype; see Cameron et al., 2005; Meaney, 2007) became more fearful than other rats when reared by low-caring mothers, but *less* fearful when reared by high-caring mothers. This suggests that the genetic and/or epigenetic factors passed down by anxious dams increase the plasticity of pups and their response to variation in rearing conditions. Consistent with this hypothesis, the offspring of low-caring mothers showed enhanced behavioral responses to an enriched environment compared with the offspring of high-caring mothers (Champagne and Meaney, 2007). Finally, the genes that regulate plasticity in primates (Stevens et al., 2009) and rodents (Sachser et al., 2011) are found in stress-related serotonergic and dopaminergic pathways, the same pathways that regulate plasticity in humans. For example, knockout mice lacking expression of the serotonin transporter gene (*5HTT*) are characterized by exaggerated HPA/sympathetic reactivity. As expected, they are also more developmentally plastic: they grow up more anxious following poor maternal care (Carola et al., 2008; see also Heiming et al., 2009, 2011), as well as in response to mild early life stress (Carroll et al., 2007).

In summary, stress responsivity and emotional reactivity are key predictors of early postnatal plasticity, in humans and (most likely) other mammals as well. More responsive offspring are more susceptible to the effects of a whole range of (generally adaptive) maternal behaviors, which contribute to shape their developmental trajectories. Since prenatal stress increases HPA responsivity and emotional reactivity, postnatal plasticity can be programmed by prenatal exposure to stress, especially in those offspring who carry an already susceptible genotype (Belsky and Pluess, 2009; Pluess and Belsky, 2011; Pluess et al., 2011). Therefore, the prediction can be made that mothers should try to amplify the physiological effects of prenatal stress, while fetuses should try to reduce them.

The resulting conflict should be especially intense in species with extended postnatal care, in which a mother can greatly benefit from enhancing her offspring's plasticity. This, of course, does not rule out the existence of other sources of conflict concerning specific offspring traits (e.g., competitive risk-taking, reproductive timing, or the risk for schizophrenia). However, in species with sufficiently long periods of postnatal care, a mother has ample opportunity to shape her offspring's behavior after birth; this should limit the comparative benefits of directly programming specific behavioral features during gestation, and increase the benefits of enhancing offspring plasticity across the board.

Even if parent-offspring conflict is an inescapable outcome of evolutionary dynamics, the *intensity* of conflict can be increased or reduced by variation in ecological conditions. Specifically, conflict is maximized when (a) genetic relatedness between siblings is low (i.e., there is a high probability that one's siblings are in fact half-siblings), and (b) the interdependence between the reproductive success of mothers and fathers is low (Trivers, 1974; Lessels and Parker, 1999; see Schlomer et al., 2011). These conditions are both met in mating systems characterized by promiscuity and unstable pair relationships. An intriguing implication is that the intensity of conflict about postnatal plasticity may vary depending on the level of stress experienced by the mother. If stressful, dangerous environments are also characterized by unstable pair-bonds and promiscuous mating (as in human societies; see Belsky et al., 1991; Gangestad and Simpson, 2000; Quinlan and Quinlan, 2007; Ellis et al., 2009), then fetuses should tend to put up a stronger resistance to maternal programming when they are exposed to chronically high levels of stress hormones. Conversely, when hormonal signals are consistent with a safe, protected environment, fetuses should accept maternal programming to a greater extent.

To conclude this section, it is important to stress that parent-offspring conflict stands on a background of extensive mother-offspring cooperation. I am *not* arguing that conflict dominates prenatal interactions, nor that the signals carried by stress hormones are entirely manipulative and devoid of useful information; in other words, the perspective presented here is an extension of the standard adaptive model, not an alternative to it. The mother benefits (up to a point) from providing the fetus with correct information about the state of the environment, and the fetus benefits (up to a point) from letting maternal signals shape its developmental trajectory. The intricacy of mother-fetus interactions stems from this delicate balance of cooperation and conflict (Haig, 1993).

2.2. Fetal tactics, maternal tactics, and conflict outcomes

Provided that mother and fetus have conflicting goals concerning fetal exposure to stress hormones, what tactics do they have at their disposal? From the perspective of the fetus, an obvious tactic is to filter out maternal hormones before they reach its brain. Of course, completely filtering out maternal signals would deprive the fetus of useful information, so the filtering must be only partial. A possible maternal countermeasure to this tactic is to produce larger quantities of stress hormones, even if this may carry considerable physiological costs (see McEwen, 1998; McEwen and Wingfield, 2003; Ganzel et al., 2010). Another possible countermeasure (and a less costly one) is to directly interfere with fetal filtering mechanisms. Filtering is a passive tactic, but the fetus can also engage in active forms of manipulation. For example, the fetus could try to reduce the mother's stress responsivity, so as to dampen the hormonal peaks that follow a stressful event. In turn, the mother could try to resist fetal manipulation, either by interfering with fetal signals (a cheaper option) or by enhancing the reactivity of her own stress response system (a costlier option).

All of the above tactics and countermeasures concern the *intensity* of maternal signals, but signal *accuracy* is another parameter that might be manipulated by the mother and/or the fetus. In principle, the mother might not just become more (or less) responsive to stress, but also more uniformly responsive to different types of stressful events. This, of course, would make the signal less informative about the actual state of the environment.

A recent mathematical model by Uller and Pen (2011) can be used to inform predictions about the tactics and outcomes of mother-fetus conflict. In the model, the mother detects

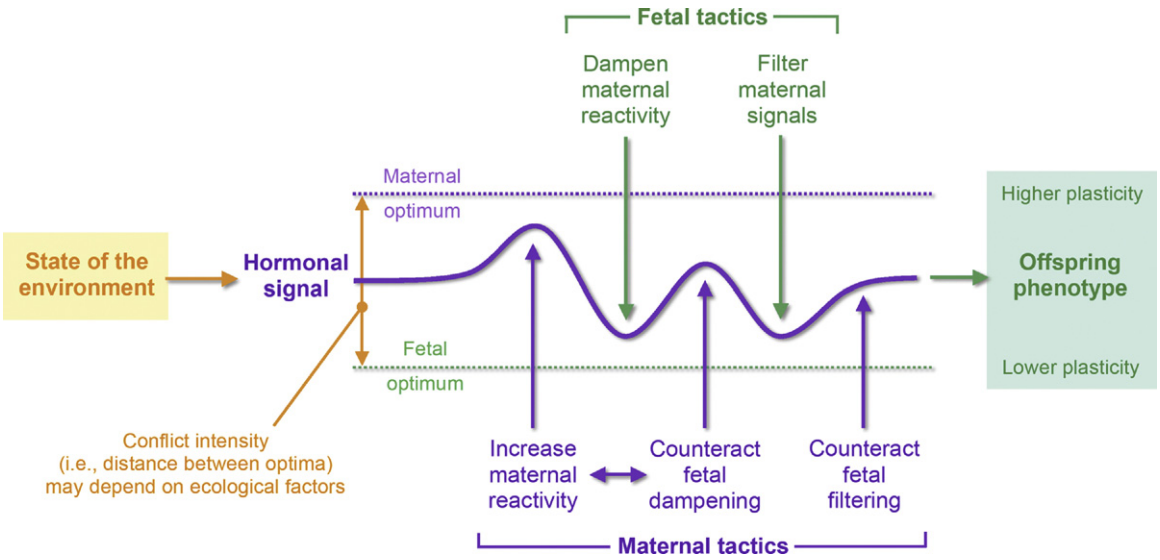

Figure 1 The logic of conflict in fetal programming.

the current state of the environment and uses this information to generate a signal; the offspring does the same, and the two signals jointly determine the offspring's phenotype. The resulting phenotype affects the fitness of both mother and offspring; however, the optimal phenotype in a given environment is not the same for the two actors, which sets the stage for parent-offspring conflict. The mother can use her signals to manipulate the offspring's phenotype, and the fetus can respond by filtering maternal signals (i.e., discounting them by some amount).

In brief, model results show that: (a) if signals are cost-free, and the offspring is constrained in its ability to filter maternal signals, the resulting phenotype will match the mother's optimum. (b) If signals are cost-free, and the filtering mechanism can evolve without constraints, the resulting phenotype will match the offspring's optimum, and a coevolutionary arms race will ensue between the genes expressed by the mother and the offspring; (c) this will happen even if the offspring has no independent information about the environment, because maternal signals still carry useful information. However, (d) if signals are costly, the outcome of the evolutionary process will often depart from both optima; and finally, (e) both parties benefit from an accurate assessment of the environment by the mother.

What do these results say about conflict in fetal programming? The relevant scenario is one in which stress hormones function as costly signals, and the fetus has no independent information about the external environment. First of all, the model suggests that fetuses will tend to evolve mechanisms that filter maternal hormones (and/or reduce their level by other means), because a fetus equipped with such mechanisms can dramatically shift the conflict outcome toward its own optimum. Over evolutionary time, the resulting arms race between maternal and fetal genes may lead to massive production of stress hormones by the mother coupled with nearly complete filtering of maternal hormones by the fetus (see Uller and Pen, 2011). Second, because of the physiological costs of stress hormones, the conflict outcome can be expected to depart in significant ways from both the maternal and the fetal optimum. In other words, conflicts about programming probably have no "winner" in a strict sense. Finally, tactics that reduce the accuracy of maternal signals (for example by making maternal physiology uniformly responsive to stressful and non-stressful events) can be ruled out, as they are ultimately detrimental to both mother and fetus. The range of plausible maternal and fetal tactics in fetal programming is summarized in Figure 1.

3. Physiological insights

Thanks to the insights gained in the previous section, the mechanisms of prenatal stress can be examined with an updated set of conceptual tools. While the focus of this section is on human pregnancy, the same principles can be applied to the physiology of other species. It should be noted that species differences involve not only the details of physiological functioning, but also the details of how parent-offspring conflict is played out — as, for example, in animals that give birth to litters instead of singletons (see for example Haig, 2008).

3.1. Maternal stress and fetal programming in humans

3.1.1. Pregnancy-related changes in stress physiology

During pregnancy, the mother's HPA axis undergoes remarkable functional changes. On the one hand, cortisol secretion increases steadily through gestation; on the other hand, the HPA axis becomes hyporeactive to stressors (reviewed in de Weerth and Buitelaar, 2005; Smirnaki and Magiakou, 2006; Russell et al., 2008; Brunton, 2010). Unsurprisingly, the fetus plays an active role in inducing maternal hypercortisolism: production of corticotropin releasing hormone (CRH) by the placenta starts around week 8–10, and is further stimulated by cortisol in a positive feedback cycle (Smirnaki and Magiakou, 2006). Since cortisol mobilizes metabolic resources and increases blood glucose, maternal hypercortisolism can be seen primarily as a way for the fetus to increase energy transfer from the mother. Interestingly, until week 33–34

most of the CRH produced by the placenta is inactivated by CRH-binding proteins (CRH-BP) in the mother's blood (Smirnaki and Magiakou, 2006), suggesting that placental CRH and maternal CRH-BP may be involved in a conflict about fetal nutrition. In the placenta, 50—90% of maternal cortisol is inactivated by the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) before it reaches fetal circulation (Section 3.2.1); as a result, cortisol concentration in fetal blood is much lower than in maternal blood (typically around 10—20% of maternal levels; see Murphy et al., 2006).

Pregnancy-related changes also occur in the sympathetic nervous system. The available data indicate that the epinephrine (E) response to stressors becomes blunted, whereas the norepinephrine (NE) response seems to remain intact (Russell et al., 2008). Accordingly, fetuses at different stages of gestation show real-time cardiac responses to induced maternal stress; interestingly, fetal responses appear to be even stronger in late pregnancy than at mid-pregnancy, despite the increasingly blunted response of the maternal sympathetic system (DiPietro et al., 2003).

Because of the combined effect of hypercortisolism and blunted HPA responsivity, cortisol levels in pregnancy can be expected to be only weakly correlated with the mother's subjective distress. Empirical findings are inconsistent (O'Donnell et al., 2009), with some studies finding a positive correlation between perceived stress and cortisol levels (e.g., Wadhwa et al., 2001; Diego et al., 2006; Rothenberger et al., 2011) and others finding no such correlation (Sarkar et al., 2006; Davis et al., 2010; Kaasen et al., 2011). None of these studies measured the relation between perceived stress and cortisol *responsivity*; however, cortisol peaks in response to stressors (and their pattern of occurrence over time) carry more information about the environment than the basal cortisol level, and can thus be expected to be more directly involved in fetal programming. The available data indicate that, despite physiological blunting, HPA responses can be elicited even in late pregnancy (de Weerth and Buitelaar, 2005; Nierop et al., 2006; de Weerth et al., 2007; Nierop et al., 2008). At a more fundamental level, the relation between environmental conditions and HPA responsivity is nonlinear (Section 1.1.1); testing for simple linear correlations between distress and indices of HPA functioning may provide incomplete or misleading answers.

3.1.2. Hormonal mediators of fetal programming

The information transfer between mother and fetus involves the action of multiple hormonal systems. One likely mediator of fetal programming is maternal cortisol, and extensive data from nonhuman animals support this prediction (Matthews, 2002). Cortisol secretion entails substantial physiological costs, and peaks in response to unpredictable and/or uncontrollable events. For these reasons, cortisol carries high-quality, reliable information about the severity of external stressors (see Del Giudice et al., 2011; Koolhaas et al., 2011), making it an ideal source of information for the fetus. Maternal cortisol levels have been shown to predict behavioral reactivity and HPA functioning in newborns and children (Gutteling et al., 2004, 2005; Davis et al., 2010). Further indirect support for a key role of cortisol comes from studies of licorice exposure in pregnancy. Glycyrrhizin (the main sweet-tasting compound in licorice roots) inhibits the enzyme 11β-HSD2, thus reducing the effectiveness of placental filtering and exposing the fetus to an increased influx of cortisol from maternal circulation. Predictably, the children of mothers who consumed high amounts of licorice during pregnancy show elevated diurnal cortisol and higher HPA responsivity to stressors (Räikkönen et al., 2010).

The role of cortisol in human fetal programming has been questioned by some authors. Davis et al. (2010) argued that cortisol is unlikely to mediate the effects of maternal stress, because of the weak and inconsistent association between self-reported distress and cortisol levels in pregnant women. However, the relation between environmental stress and HPA functioning may not be as straightforward as is often assumed; moreover, the physiological changes of pregnancy make correlations more difficult to detect (Section 3.1.1). Other researchers (Talge et al., 2007; Brunton, 2010) argued that the reduced HPA responsivity of the mother and the filtering action of 11β-HSD2 severely limit fetal exposure to cortisol peaks, thus making cortisol problematic as a mediator of fetal programming. This criticism can be addressed in two ways. First, as noted by Flinn et al. (2011), the difference in cortisol concentration between maternal and fetal circulation is so large that even small fluctuations in maternal cortisol can exert significant effects on fetal physiology. Second, and more important, in the following sections I will show that both cortisol filtering and HPA dampening can be understood as adaptive fetal tactics. Seen in this perspective, the problem evaporates: it is precisely *because* of the crucial role of cortisol in fetal programming that the fetus has evolved means to limit its own exposure to maternal cortisol peaks. In other words, I surmise that the mechanisms that limit the programming effectiveness of maternal cortisol are not "bugs" but adaptive, evolved features of fetal physiology.

In addition to cortisol, a number of stress-related hormones and neurotransmitters have been proposed as possible mediators of fetal programming. The main candidates are maternal and placental CRH (de Weerth and Buitelaar, 2005; Flinn et al., 2011); adrenocorticotropic hormone (ACTH; Kaiser and Sachser, 2005); the adrenal steroid dehydroepiandrosterone (DHEA; Kaiser and Sachser, 2005); serotonin (5-HT; Ponder et al., 2011); and norepinephrine (NE; Talge et al., 2007; Brunton, 2010). The available evidence suggests that NE is likely to play multiple roles in fetal programming. Like maternal cortisol, maternal NE is filtered by the placenta, specifically via uptake by norepinephrine transporter (NET; see Giannakoulopoulos et al., 1999). However, small amounts of maternal NE can reach the fetus and exert direct programming effects, especially if the expression of the NET gene *SLC6A2* is reduced (Ponder et al., 2011). In addition, NE indirectly contributes to programming by regulating fetal exposure to cortisol. In particular, NE inhibits expression of 11β-HSD2, thus increasing cortisol transfer from maternal to fetal blood (Sarkar et al., 2001; Murphy et al., 2006). Consistent with an indirect role of NE via cortisol regulation, a study by Glover et al. (2009a) found a large correlation between maternal and fetal cortisol in high-anxiety women, but no correlation in low-anxiety women (note that NE was not directly measured in this study). Also, O'Donnell et al. (2011) found that 11β-HSD2 expression in the placenta was inversely correlated to maternal trait anxiety before delivery. These findings suggest the intriguing, yet largely unexplored possibility that NE and cortisol may work

synergistically in fetal programming; if so, the interaction between the two hormones might prove more important and predictive than their individual effects.

3.2. Physiological conflicts in fetal programming

3.2.1. Placental filtering mechanisms

As outlined in Section 3.1, the placental dehydrogenase 11β-HSD2 inactivates 50–90% of maternal cortisol by converting it to cortisone. The expression of 11β-HSD2 in the placenta increases linearly during pregnancy, and is stimulated by cortisol (van Beek et al., 2004; Schoof et al., 2001). It is commonly assumed that 11β-HSD2 serves to protect the fetus from excessive cortisol exposure and the adverse effects of prenatal programming (e.g., Brunton and Russell, 2011). It is more difficult to explain why the decidua (i.e., the maternal tissue in direct contact with the placenta) does not express 11β-HSD2, but rather high amounts of the enzyme 11β-HSD1 (11β-hydroxysteroid dehydrogenase type 1). In live tissue, 11β-HSD1 functions mainly as a reductase: it converts cortisone to cortisol, thus counteracting the effects of 11β-HSD2 (Krozowski et al., 1999; Seckl, 2006). In other words, fetal tissue inactivates cortisol to cortisone, while maternal tissue converts cortisone back to cortisol at the interface with the placenta. This apparently paradoxical mechanism makes perfect sense from the vantage point of parent-offspring conflict, showing the interplay between a fetal tactic (i.e., cortisol filtering) and a maternal countermeasure (i.e., interference with placental filtering; see Figure 2). In addition to 11β-HSD2, the placenta expresses several other enzymes that metabolize cortisol and cortisone, including 3α/3β-HSD, 5β-reductase, and 20β-HSD (Pasqualini, 2005).

Placental filtering of catecholamines (NE in particular) can also be seen as a fetal defense from maternal manipulation. Indeed, the expression levels of the NET gene (*SLC6A2*) and the 11β-HSD2 gene (*HSD11B2*) are positively correlated (Ponder et al., 2011). By mediating NE uptake, NET substantially decreases NE concentration in fetal circulation (Ponder et al., 2011). Accordingly, we can predict the existence of maternal mechanisms that counteract the effects of NET, resulting in increased NE levels in fetal blood.

3.2.2. Fetal manipulation of maternal physiology

During pregnancy, the fetoplacental unit engages in active manipulation of maternal physiology, including the mother's HPA axis (Figure 2). As noted in Section 3.1, placental CRH contributes to elevate the basal level of maternal cortisol. However, conflict about programming should also lead the fetus to reduce the mother's responsivity to stressors. Indeed, during pregnancy the maternal HPA axis becomes hyporesponsive, largely as a result of fetal manipulation. The main physiological agents of fetal manipulation are progesterone (P4), its neuroactive metabolites pregnenolone (PREG) and allopregnanolone (ALLO), and human placental lactogen (hPL), a hormone with high affinity for prolactin receptors.

At the beginning of gestation, P4 is produced by the corpus luteum from maternal LDL cholesterol, following stimulation by placental gonadotropin (hCG). Direct placental production of P4 starts at about 8 weeks; over the course of pregnancy, P4 serum levels increase by about twenty times (Luisi et al., 2000; Smirnaki and Magiakou, 2006). In the classic view, maternal LDL cholesterol is the main substrate for placental P4 production (e.g., Tuckey, 2005); however, recent discoveries point to an additional metabolic pathway

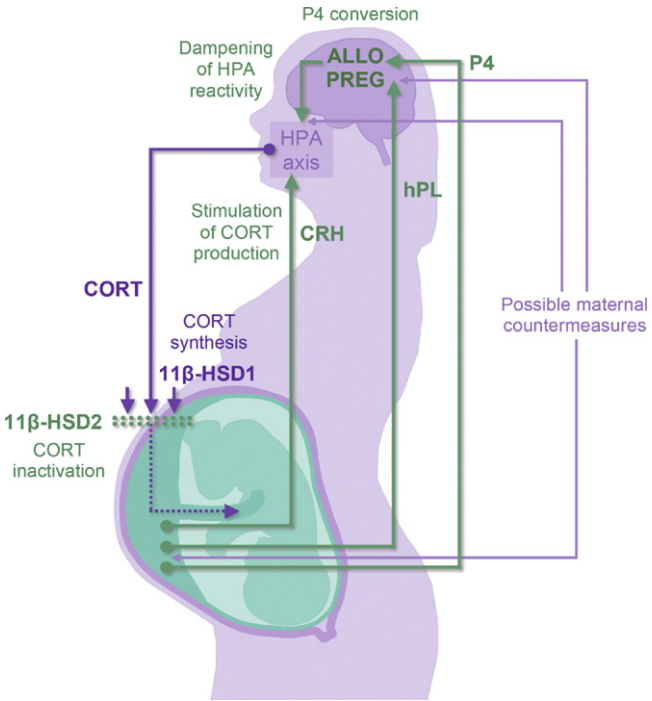

Figure 2 Schematic representation of the main physiological mechanisms that regulate fetal exposure to cortisol. Similar processes may be involved in the regulation of catecholamines (see text).

for P4 production, one that is independent from maternal substrates. Placental CRH stimulates secretion of sulfated steroids by the fetal zone of the fetal adrenal gland; adrenal steroids are converted to P4 in the placenta, and P4 is then released into maternal circulation (Hill et al., 2010a,b). This pathway effectively decouples placental P4 production from the availability of maternal substrates. In a conflict perspective, this allows the fetus to produce high amounts of P4 while curtailing opportunities for maternal countermeasures (e.g., the mother might down-regulate cholesterol production in order to limit P4 concentration). It is interesting to note that P4 reduces the activity of 11β-HSD2 (Murphy et al., 2006), and might thus interfere with cortisol filtering; however, placental tissue is able to degrade P4 via the action of 17β-hydroxysteroid dehydrogenases type 5 and 7 (17β-HSD5 and 17β-HSD7; see Hill et al., 2010b).

In the brain, P4 is converted to PREG and ALLO. These powerful neuroactive steroids exert anxiolytic effects via modulation of the $GABA_A$ receptor (especially at high doses), with an efficacy similar to that of benzodiazepines. Furthermore, they directly down-regulate the HPA response by inhibiting transcription of CRH and vasopressin (AVP), a process mediated by opioid signaling (reviewed in Diaz Brinton et al., 2008; Brunton and Russell, 2011; Wirth, 2011). While P4 may have minor anxiolytic effects via intracellular progesterone receptors (Wirth, 2011), it has to be converted to ALLO and PREG in order to exert maximal influence on the mother's HPA axis. Intriguingly, the brain's ability to convert P4 to neuroactive steroids such as ALLO is markedly increased in pregnancy because of enhanced 5α-reductase activity; the likely sources of increased 5α-reductase activity are prolactin and its placental analogue hPL (Brunton, 2010). Besides stimulating P4 conversion to ALLO, hPL can suppress the HPA response by binding to prolactin receptors in the hypothalamus (Numan and Woodside, 2010). In summary, the placental hormones P4 and hPL appear to act synergistically in the maternal brain, resulting in lowered anxiety and dampened reactivity of the HPA axis.

In a conflict perspective, fetal manipulation by P4 and hPL raises the question of maternal countermeasures. We can predict the existence of physiological mechanisms counteracting the action of P4, ALLO, PREG, and hPL in the mother's brain. Possible countermeasures might involve down-regulation of the prolactin receptor (PRL-R) and of the $GABA_A$ receptor, as well as enhanced metabolism of neuroactive steroids. The opioid system is another plausible target for maternal tactics.

Given the extensive evidence for fetal manipulation of the mother's HPA axis, it is reasonable to hypothesize that the fetus may also attempt to regulate maternal secretion of catecholamines. On the one hand, GABA-mediated inhibition (stimulated by ALLO and PREG) dampens not only the HPA axis but also the sympathetic system (e.g., Ulrich-Lai and Herman, 2009). On the other hand, the fetus may also be able to specifically target the mother's sympathetic physiology. As noted in Section 3.1.1, sympathetic suppression during pregnancy appears to be selective, with a blunted E response but intact NE reactivity. This finding may reflect a complex interplay between maternal and fetal tactics, with the mother ultimately having the "upper hand" in NE signaling (for example because suppressing the NE response would be too dangerous for the mother, the fetus, or both).

3.3. A role for imprinted genes?

Nested within the biological conflict between mother and fetus, a different kind of conflict takes place between the maternal and paternal halves of the fetal genome. This form of intragenomic conflict is played out by imprinted genes. A gene is labeled as imprinted if its expression is conditional on the parent of origin, i.e., on whether it was contained in an ovum or a sperm. For example, the *IGF2* gene (see below) is paternally expressed in humans, and its homologues are paternally expressed in various mammals including rats, mice and sheep (see Haig, 2004). This means that although every individual inherits two copies of the gene, only the paternally derived copy is actually expressed, while the maternally derived one is silenced (usually by DNA methylation and histone modification) and has no effect on the organism's development. Imprinted genes are found in mammals and angiosperm plants; complex imprinting patterns can be observed as, for example, some genes show parent-specific expression only in specific tissues or only during certain phases of development (see Bartolomei and Tilghman, 1997; Wilkins, 2008).

The *kinship theory* of genomic imprinting (Haig, 1997, 2004; Wilkins and Haig, 2003) predicts that, in most species, paternally expressed genes should "side" with the offspring in the regulation of maternal investment, and evolve so as to increase the transfer of maternal resources to the offspring (for example, by increasing fetal growth rate). Maternally expressed genes are expected to evolve in the opposite direction, thus inhibiting the transfer of maternal resources to the offspring. The conflict between maternally and paternally derived genes stems from asymmetric relatedness: whenever there is some degree of multiple paternity, the genetic similarity between siblings born from the same mother is lower from the perspective of paternal genes than from that of maternal genes. If a given maternal allele is present in one of the siblings, there is a 50% chance (assuming Mendelian inheritance) that the same allele will be present in any other sibling; whereas, owing to multiple paternity, the chance that a paternally derived allele will be present in another sibling is less than 50%. As a result, paternal genes are expected to value the fitness of one's siblings less than maternal genes. The resulting tug-of-war between maternally and paternally imprinted genes is expected to lead to costly manifestations of conflict at the physiological and/or behavioral level.

Unsurprisingly, several imprinted genes are involved in the physiology of prenatal conflicts. For example, the insulin-like growth factor II gene (*IGF2*) is paternally expressed in humans and promotes fetal growth; *IGF2* over-expression results in overgrowth symptoms and is associated with the Beckwith-Wiedemann syndrome, a condition involving prenatal overgrowth and enlarged placenta. Another gene, *H19*, is maternally expressed and has opposite growth-inhibitory effects. *H19* produces a noncoding RNA that apparently acts by suppressing *IGF2* expression, thus providing an example of direct antagonism between a paternally and a maternally expressed gene. In mice (but not in humans), the IGF-II receptor gene (*Igf2r*) is maternally expressed and behaves in a similarly antagonistic way: the IGF-II receptor promotes the degradation of paternally expressed IGF-II. Another growth-related gene in humans (and mice) is the maternally

expressed *IPL*, which is highly expressed in the placenta and, if inactivated, results in placental overgrowth. Many other imprinted genes are expressed during fetal development, although their function and their relevance to the kinship theory are presently less clear (reviewed in Haig, 2004).

3.3.1. Imprinted genes and fetal programming

Given the involvement of imprinted genes in both fetal conflict and fetal programming (e.g., Heijmans et al., 2008), it is natural to ask whether they may be implicated in the physiology of fetal programming by maternal stress, and (if so) what specific roles they might play in the mechanisms reviewed above. Unfortunately, the amount of relevant evidence is extremely limited. Some findings suggest that the gene coding for the β-subunit of hCG may be imprinted and paternally expressed (Goshen et al., 1994), and that the hCG receptor on the maternal side may be imprinted too (Allen et al., 2003). This is intriguing, since hCG stimulates P4 production in early pregnancy. However, hCG is simultaneously involved in a number of other physiological processes related to prenatal conflict (e.g., prevention of spontaneous abortion, induction of pregnancy sickness; see Del Giudice, 2007); thus, parent-specific expression of hCG may have more to do with the regulation of parental investment than with stress-related programming. The same interpretive problem would apply to imprinted genes in the hPL pathway, since hPL may also be involved in the regulation of fetal nutrition (Section 1.1).

While there is a dearth of relevant empirical data, it is possible to make a preliminary theoretical point. If the theory advanced in this paper is correct, the likelihood that imprinted genes are involved in fetal programming should *decrease* to the extent that both parents benefit from enhanced postnatal plasticity. When the mother is the only beneficiary of offspring plasticity (as in the standard mammalian pattern of exclusive maternal care), paternally expressed genes can be expected to reduce plasticity, thus favoring the offspring's genetic interest at the expense of the mother. This makes it more likely — though by no means certain — that placental genes involved in fetal programming (e.g., *HSD11B2*) will evolve a pattern of paternally biased expression. In the human species, however, both parents (and their kin) potentially interact with the infant/child, and both can benefit from the opportunity to shape his/her behavior according to their own interest. This may dramatically reduce interparental conflict about prenatal exposure to stress hormones, and render the evolution of imprinted expression patterns considerably less likely.

In summary, to the extent that imprinted genes are involved in prenatal stress physiology, there are grounds to expect adaptive species-specific patterns of imprinting. The evolution of imprinting effects should depend at least in part on the relative amount of care by fathers (and/or paternal kin) and mothers (and/or maternal kin), as well as on the specific effects of the offspring's reproductive strategy on maternal and paternal fitness (Sections 1.1 and 2.1; see also Del Giudice et al., 2010; Úbeda, 2008). The expression pattern of 11β-HSD2 is an interesting case in point. In humans, the *HSD11B2* gene is located on chromosome 16. Its promoter region comprises four CpG islands (there is only one in the rat homologue); these CpG islands are potential targets for methylation, which represses *HSD11B2* transcription both in vivo and in vitro (Alikhani-Koopaei et al., 2004; Marsit et al., 2012). This raises the possibility that *HSD11B2* may show a pattern of parent-specific expression. However, a study by McTernan et al. (2001) found biallelic transcription of *HSD11B2* in three out of three genetically informative placentas. Thus, the available evidence suggests that *HSD11B2* is not imprinted in the placenta, which is consistent with the hypothesis that parental conflict about plasticity is weak or absent in our species. Still, much additional research will be needed before firm conclusions can be drawn. The regulation of 11β-HSD2 expression depends on a host of other genes; for example, the p38 mitogen-activated protein kinase (MAPK) critically up-regulates 11β-HSD2 expression in the placenta by altering mRNA stability (Sharma et al., 2009). The genes involved in the regulation of 11β-HSD2 expression may eventually show imprinting effects, even if *HSD11B2* itself does not. Hopefully, the role of imprinted genes in fetal programming will become clearer as empirical findings accumulate.

4. Conclusions

4.1. Summary of the paper

In this paper, I have shown how a conflict perspective generates novel insights in the logic and physiology of fetal programming by maternal stress. In the adaptive model of programming, maternal stress hormones provide useful information to the fetus, and the fetus makes use of that information to adaptively adjust its developmental trajectory. A conflict perspective extends this model by highlighting the ways in which maternal and fetal interests diverge, and provides a framework for making sense of the many apparent paradoxes generated by conflictual dynamics.

On a theoretical level, the key hypothesis developed in this paper is that, in species with extensive postnatal care, the regulation of postnatal plasticity is an important source of conflict between mother and fetus. Maternal stress hormones do not only carry information about the features of the external environment, but also make the fetus more open to later behavioral influences from the mother (and other caregivers). For this reason, the mother benefits by increasing fetal exposure to stress hormones beyond the fetal optimum, while the fetus benefits by reducing it below the maternal optimum. The fetus can accomplish this by filtering out maternal hormones and/or dampening the mother's response to stressors; these fetal tactics, and the corresponding maternal countermeasures, can be identified in human prenatal physiology (Figure 1). The puzzling opposition between fetal 11β-HSD2 and maternal 11β-HSD1 can be explained by the interplay between a placental filtering mechanism and a maternal attempt to interfere with that mechanism. Similarly, the combined effect of progesterone (P4) and placental lactogen (hPL) on the maternal brain can be understood as a fetal attempt to manipulate the mother's HPA axis so as to lower its responsivity to stressors (Figure 2).

A deeper and more integrated understanding of known facts about prenatal physiology is desirable, but new theories should also generate novel empirical predictions. In this paper, I advanced four such predictions: (a) the existence of maternal mechanisms that interfere with placental filtering of norepinephrine (NE); (b) the existence of maternal

countermeasures against the action of P4 and/or hPL; (c) the existence of a system of fetal manipulation specifically targeted at sympathetic catecholamine signaling, and of the corresponding maternal countermeasures; (d) the prediction that higher levels of biparental care (and/or care by both maternal and paternal kin) should decrease the involvement of imprinted genes in the physiology of prenatal stress.

4.2. Further implications

While the consequences of mother-fetus conflict are usually constrained by the reciprocal interaction between opposing physiological mechanisms, there may be occasions in which conflict imposes severe costs on one or both parties. For various reasons (including high genotypic susceptibility of the fetus), the physiological arms race between mother and fetus may sometimes escalate beyond control, resulting in a net fitness cost for the mother, the fetus, or both. For example, prenatal conflicts in the regulation blood glucose (Section 1.2.1) sometimes end up causing gestational diabetes, a dangerous condition that increases the risk for later health problems, both in the mother and the fetus (e.g., Haig, 1993; Boney et al., 2005; Feig et al., 2008). This suggests the intriguing possibility that the severe, fitness-reducing pathologies associated with prenatal stress — including autism and schizophrenia — may actually represent the side effects of escalated conflict. In other words, the increased risk for severe psychopathology following maternal stress might not be a "design feature" of prenatal programming (as suggested by Glover, 2011), but rather an occasional maladaptive consequence of the conflictual interplay between adaptive mechanisms in the mother and fetus. This seems a worthy topic of future research: a better understanding of the side effects of prenatal conflict would greatly help in drawing the line between adaptive and maladaptive outcomes of fetal programming (Section 1.1.2), and may eventually lead to devise effective prevention strategies.

On a more general level, the conflict perspective developed here has far-reaching implications for theories of developmental plasticity. Belsky (1997, 2005; see also Ellis et al., 2011) proposed that differential susceptibility to rearing (i.e., differential plasticity) is adaptive for both parents and children, because less susceptible children are also less likely to suffer from fitness-detrimental parental influences. While parents attempt to shape their offspring's phenotype so as to match future environmental conditions, their predictions inevitably contain some error, and sometimes turn out to be mistaken. For example, a mother may estimate that the environment will remain safe and resource-rich in the foreseeable future, and shape the behavior of her offspring accordingly (e.g., by making them less vigilant and aggressive). If the prediction turns out to be wrong, however, those offspring who resisted parental influence will enjoy higher fitness than those who let themselves be shaped by the parent. A conflict perspective adds a layer of complexity to this view, because it suggests that — all else being equal — reduced plasticity should benefit the offspring more than the parent. Thus, as long as they can benefit from a plastic phenotype in their offspring, parents should engage in behavioral and physiological strategies that increase the offspring's plasticity. Of course, all else may *not* be equal; in particular, the intensity of conflict may be reduced in safe, predictable contexts (Section 2.1), thus shifting the offspring optimum toward higher levels of plasticity and favoring increased acceptance of parental influences. Still, an unknown proportion of between-individual variance in postnatal plasticity may ultimately be explained by the interplay of conflict-related mechanisms in prenatal development.

Finally, when postnatal plasticity benefits one parent more than the other, interparental conflict may result, with one parent (usually the mother) promoting plasticity and the other (usually the father) promoting the development of a more fixed phenotype. Of course, the biological interests of an absent father may be furthered by paternal kin, as well as by paternally expressed genes in the offspring's genome (Section 3.3).

The discovery that parent-offspring interactions are intrinsically driven by conflict as well as altruism (Trivers, 1974) has been a major propulsive force in evolutionary biology. After a long delay, this perspective is starting to make way in psychology (Schlomer et al., 2011). In the field of prenatal development, however, the logic of parent-offspring conflict is still not widely appreciated, despite its remarkable explanatory and heuristic potential. That between the mother and the developing fetus is one of the most vital, intimate, and complex relationships between two living beings. In order to fully understand it, we need to appreciate how conflict and cooperation can go hand in hand, and learn to look for their traces in the dazzling intricacy of physiological mechanisms.

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