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Authors

Hartman, Sarah
Belsky, Jay

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Prenatal Stress and Enhanced Developmental Plasticity

Sarah Hartman and Jay Belsky

Department of Human Development and Family Studies

University of California, Davis

Corresponding Author:
Sarah Hartman
One Shields Avenue, 3321 Hart Hall
Davis, CA 95616
slhartman@ucdavis.edu
(925) 848 -8978

ABSTRACT

Two separate lines of inquiry indicate (a) that prenatal stress is associated with heightened behavioral and physiological reactivity and (b) that these postnatal phenotypes are associated with increased susceptibility to both positive and negative developmental experiences and environmental exposuresinfluences. This research considered together raises the intriguing hypothesis first advanced by Pluess and Belsky (2011) that *prenatal stress fosters, promotes or “programs” postnatal developmental plasticity*. In this paper, we review further evidence consistent with this proposition, including a novel animal study which experimentally manipulated both prenatal stress and postnatal rearing. Directions for future work focused on mechanisms mediating the plasticity inducing effects of prenatal stress and the moderators of such effects ~~Future directions of research pertaining to potential mechanisms instantiating postnatal plasticity and moderators of such prenatal programming effects~~ are outlined.

Keywords: Prenatal stress; Prenatal programming; Differential susceptibility; Developmental plasticity; Prenatal stress mechanisms.

Prenatal Programming of Postnatal Plasticity

Prenatal stress has been of special interest to researchers and clinicians alike because of its association to adverse child functioning across a variety of domains, including increased risk for chronic health, behavioral, and cognitive problems (for a review see Van den Bergh, Mulder, Mennes & Glover, 2005; Glover, 2014; Entringer, Buss & Wadhwa, 2015; [Tarabulsy et al., 2014](#)). ~~Thus, in such work,~~ prenatal stress has been associated—in prospective studies—with preterm birth and low birth weight (for review, see Wadhwa et al., 2002), deficiencies in intellectual and language functioning (Laplante et al., 2004), ADHD symptoms (Grossman, Churchill, McKinney, Kodish, Otte & Greenough, 2003), externalizing and anxiety problems (Glover, 2011), and motor and mental developmental disorders (Kofman, 2002; [Tarabulsy et al., 2014](#)). Although such findings, from observational studies, ~~cast have characterized~~ prenatal stress ~~in as being~~ solely negative and detrimental ~~terms vis-à-vis to~~ child development, in what follows, we present evidence for a different view on how and why prenatal stress has been repeatedly associated with impaired functioning. Specifically, we argue that *prenatal stress programs postnatal developmental plasticity*, based on the hypothesis first advanced by Pluess and Belsky (2011). ~~Even though For the scope of this review, we will focus on this review on the plasticity-enhancing effects of prenatal stress, we do not mean to deny or ; but, it should be noted that this proposition does not preclude the existence of negative main effects of prenatal stress on offspring. Indeed, it seems eminently plausible It may be the case that under some conditions, possibly dependent of timing and intensity of stress, prenatal stress wouldmay have only adverse~~

consequences for exert solely negative effects on offspring whereas under outcomes while in other conditions prenatal stress induces plasticity.

We begin by outlining the theoretical framework of differential susceptibility which has been used to guide much recent research on individual differences in environmental sensitivity (Belsky, 1997, 2005; Belsky & Pluess, 2009, 2013; Belsky, Bakermans-Kranenburg & Van IJzendoorn, 2007; Ellis, Boyce, Belsky, Bakermans-Kranenburg & van IJzendoorn, 2011; Ellis, Shirtcliff, Boyce, Deardorff, & Essex, 2011). Within this first section, we highlight empirical evidence that infant negative emotionality and physiological reactivity—two well-documented sequelae of prenatal stress—are markers of increased susceptibility to both positive and negative developmental experiences and environmental exposures. In the paper’s second section we review a separate line of research that has consistently linked prenatal stress to these two susceptibility markers, heightened negative emotionality and physiological reactivity. This leads us to return to Pluess and Belsky’s (2011) hypothesis that prenatal stress programs postnatal plasticity and review, in which we share both observational and experimental evidence consistent with this claimproposition. In a final section wWe conclude by outlining future directions for research, focusing on biological mechanisms that could instantiate enhanced plasticity and potential moderators of prenatal programming effects.

Differential Susceptibility

By applying an evolutionary analysis to human development, Belsky (1997, 2005; Belsky & Pluess, 2009, 2013) proposed that individuals should vary in their susceptibility (i.e., developmental plasticity) to environmental influences and especially those of the rearing environment (see also Boyce & Ellis, 2005). This proposition was based on appreciation that the future is—and always has been—inherently uncertain. Thus, to maximize the likelihood of genetic material being passed from one generation to the next (i.e., reproductive fitness), natural selection should have crafted offspring to vary in their susceptibility.

The reasoning for this claim becomes apparent when we consider the case of an environmental mismatch between the rearing environment and the future context in which the developing individual finds him/herself. If, for instance, an environmental mismatch occurred whereby the adult environment seriously deviated from the rearing environment ~~did not match the adult environment~~, it would prove more costly for the individual whose development was heavily influenced by his or her early environment than, perhaps, the individual who was not—and might better fit that future environment. In an effort to mitigate this ever-present risk of a potentially changing environment, Belsky (1997, 2005) theorized that natural selection should have crafted selected for humans to vary in their susceptibility to parental as well as other environmental influences. This way, not every individual would end up developmentally mismatched to his/her future environment when the rearing environment and the future environment turned out to be rather different (i.e., mismatched).

On the basis of this theoretical analysis, it follows that individuals should vary in their susceptibility to environmental influences. One can think, typologically, then, of two developmental strategies: “plastic—or conditional—strategists” are those whose development is heavily shaped by their developmental experiences, whereas “fixed—or alternative—strategists” are those whose development is relatively unaffected by their early environment and whose development is more rather than less canalized (Belsky, 2000). It should be appreciated that the kind of variation in developmental plasticity just illustrated may be best conceptualized in dimensional rather than typological terms, with some being more and some less susceptible to environmental factors and forces rather than some being highly susceptible and others not at all susceptible. This, ultimately, is an empirical question.

Having delineated the theoretical logic underlying differential-susceptibility thinking, attention is now turned to organismic factors associated with greater developmental plasticity.

We consider first negative emotionality and, thereafter, physiological reactivity.

Negative Emotionality as a Phenotypic Indicator of Plasticity

Some of the earliest evidence documenting differential susceptibility to environmental influences emerged from research on temperament-X-parenting interaction (Belsky, 1997, 2005; Belsky et al., 2007), a long-standing focus of developmental inquiry (Rothbart & Bates, 2006; Slagt, Dubas, Deković, & van Aken, 2016). In reviewing relevant evidence, Belsky (2005) observed that the effect of rearing experience on a variety of psychological and behavioral ~~phenotypes~~ ~~outcomes~~ was consistently greater for a subgroup of infants and toddlers who could be characterized as highly negatively emotional (e.g., irritable~~le~~ity, fearful~~ness~~, inhibit~~ed~~ion) or as having a difficult temperament. Notably, even if such temperamental styles conferred developmental risk under aversive contextual conditions (e.g., maternal depression, harsh parenting), as long appreciated, they also predisposed children to benefit more than others from benign or especially supportive developmental circumstances (e.g., sensitive parenting, high-quality child care). Such enhanced susceptibility to effects of both positive and negative contextual conditions has been referred as increased likelihood of being affected “for better and for worse” (Belsky et al., 2007).

In their reviews of the differential-susceptibility-related literature, Belsky and Pluess (2009, 2013) highlighted a range of evidence indicating that negative emotionality functioned as a plasticity marker. This included work documenting the heightened environmental sensitivity —“for better and for worse”—of children with high levels of negative emotionality in studies linking maternal empathy (Pitzer, Jennen-Steinmetz, Esser, Schmidt, & Laucht, 2011) and anger (Poehlmann et al., 2012) with externalizing problems; mutual responsiveness observed in the mother–child dyad with effortful control (Kim & Kochanska, 2012); intrusive maternal behavior

(Conway & Stifter, 2012) and poverty (Raver, Blair, & Willoughby, 2012) with executive functioning; sensitive parenting with social, emotional, and cognitive–academic development (Roisman et al., 2012); teacher–child conflict with change in [psychiatric](#) symptomology during the primary-school years (Essex, Armstrong, Burk, Goldsmith, & Boyce, 2011); mother’s depressive symptoms with child [behavioral](#) adjustment (Dix & Yan, 2013); maternal responsiveness with adolescent allostatic load (Dich, Doan, & Evans, 2015); and of coercive parenting with adolescent alcohol use (Rioux et al., 2016). Perhaps qualifying some of these findings are the results of a recent meta-analysis of research on parenting-X-temperament interaction. ~~I, as it~~ revealed that the for-better-and-for-worse, differential-susceptibility-related effect was restricted to investigations that assessed negative emotionality in infancy, not later in life; in fact, when, meta-analytically, negativity was examined as a moderator of parenting effects at older ages, results proved consistent with diathesis-stress thinking (Slagt et al., 2016). [Such a perspective stipulates that organismic “vulnerability” factors—like difficult temperament—result in problematic or poor functioning under conditions of contextual risk \(e.g., poverty, maternal depression\), but exert no influence under benign or supportive ones.](#)

It is well appreciated that rearing effects chronicled in observational studies like those just cited may actually be the result of third variables (e.g., genetics) and not capture true causal influence. This makes experimental research particularly important (Bakermans-Kranenburg & van IJzendoorn, 2015). Especially notable, then, are findings from a recent randomized control trial evaluating the effects of an intervention designed to enhance children’s language development (van den Berg & Bus, 2014). In line with differential-susceptibility thinking, highly-reactive children whose parents received the intervention showed the greatest increase in language development skills—and the poorest performance when randomized to the control group—with the intervention proving entirely ineffective for children who were not highly

reactive. Thus, findings from both observational and experimental studies prove consistent with the proposition that negative emotionality is a behavioral indicator of enhanced developmental plasticity—for better and for worse. No longer, then, should negativity be regarded solely as a development risk factor. It would seem to be just as much an “opportunity” factor.

Physiological Reactivity as an Endophenotypic Indicator of Plasticity

Boyce and Ellis’ (2005) also advanced an evolutionary-inspired differential-susceptibility model of environmental influences, referred to as the biological-sensitivity-to-context (BSC) framework. In contrast to Belsky’s (2005; Belsky & Pluess, 2009, 2013; Belsky et al., 2007) theorizing, the BSC model was based on a biological mechanism instantiating differential susceptibility to environmental influence, namely, physiological reactivity. Children with heightened physiological reactivity, Boyce and Ellis (2005) theorized, would be more affected by their environment—in a for-better-and-for-worse manner—than those not as physiologically reactive. Notably, this theorizing was post-hoc and emerged in attempt to explain unanticipated findings emanating from work carried out a decade earlier by Boyce and associates (1995). In this way it differed from Belsky’s (1997, 2005) theorizing from first principles, independent of any evidence of differential susceptibility.

Empirical support for BSC thinking emerged in the years since the theory was promulgated. Indeed, evidence consistent with the claim that more physiologically reactive children would prove more susceptible—for better and for worse—to environmental effects—for better and for worse—than other children has emerged been detected in research evaluating effects of actual marital conflict (Obradović, Bush, & Boyce, 2011) and simulated interparental aggression (Davies, Sturge-Apple, & Cicchetti, 2011) on externalizing problems; of family adversity on school achievement (Obradović, Bush, Stamperdahl, Adler, & Boyce, 2010); of attachment security, presumed to itself reflect rearing experience, on problem behavior (Conradt, Measelle, & Ablow, 2013); of changes in paternal depressive symptoms on child internalizing

behavior (Laurent et al., 2013); of family aggression on post-traumatic-stress symptoms/antisocial behavior (Saxbe et al., 2012); of the family environment on pubertal development (Ellis et al., 2011); of teacher-child conflict on change in psychiatric symptom severity (Essex et al., 2011); of harsh discipline on externalizing problems (Chen et al., 2015); and of family income on early executive function (Obradović, Portilla, & Ballard, 2016). Despite numerous studies documenting such effects, it should be appreciated ~~considered~~ that, unlike negative emotionality, there has not been a meta-analysis documenting physiological reactivity as a marker of susceptibility. Thus, although the cited ~~such~~ research indicates heightened physiological reactivity as a marker of increased susceptibility, more studies are needed to determine if this is indeed the case.

Given concerns already raised about the limits of observational research when it comes to inferring causation, it is also notable that there also is some experimental evidence documenting the plasticity-enhancing role of elevated physiological reactivity. Specifically, highly reactive children notably benefited from a psychotherapeutic intervention designed to reduce problem behavior, whereas the same was not so for other children (van de Wiel, van Goozen, Matthys, Snoek, & Engeland, 2004). Heightened physiological reactivity would also seem to function, then, as both a risk and opportunity factor.

Prenatal Stress and Emotional/Physiological Reactivity

Evidence just summarized indicating that highly negatively emotional and physiologically reactive infants, toddlers and perhaps children as well evince greater developmental plasticity than do others becomes especially intriguing when juxtaposed to independent evidence linking prenatal stress with eachboth of these plasticity markers. It is well documented that prenatal stress, measured in a variety of ways (e.g., maternal anxiety, cortisol), predicts greater behavioral and physiological dysregulation in infancy and childhood. With regard to behavioral dysregulation, exposure to prenatal stress, measured in a variety of ways and

(e.g., ~~maternal psychological distress, maternal cortisol~~) at different gestational times, is associated with increased displays of sadness, frustration, and fear, as well as a stable disposition of heightened (negative) emotional reactivity (Van den Bergh, et al., 2005; Huizink, De Medina, Mulder, Visser, & Buitelaar, 2002).

Research also documents associations linking maternal psychological stress during late pregnancy with the increased behavioral reactivity of four-month olds (Davis et al., 2004) [and of toddlers \(Lin et al., 2017\)](#) and ~~the same exposure maternal psychological distress,~~ during early pregnancy ~~with,~~ to irregular sleeping and eating patterns of six-month olds and heightened inhibition and negative emotionality of five-year olds (Martin, Noyes, Wisenbaker & Huttenen, 1999). [Additionally, pregnant mothers with greater pregnancy-specific anxiety across mid- to late-pregnancy reported their babies to be more negatively emotional at six months of age \(Nolvi et al., 2016\).](#) Relatedly, higher levels of maternal cortisol in late pregnancy forecast fussier infant behavior, including more negative facial expressions and increased frequency of crying at seven weeks of age (de Weerth, van Hees & Buitelaar, 2003). Especially noteworthy is research showing that elevated levels of both maternal cortisol in late pregnancy and psychosocial problems (i.e., anxiety and depression) in mid- and late pregnancy predict greater infant negativity at two months of age *even when controlling for maternal postnatal psychological state* (Davis et al., 2007).

Just as notable, perhaps even more so, is a recent prospective study exploring effects of prenatal stress, indexed via amniotic cortisol during the second trimester of pregnancy, on ~~child's~~ birth weight and ~~three-month t~~temperament ~~at three months of age~~ (Baibazarova et al., 2013).

Results revealed that higher levels of amniotic cortisol predicted more negative temperament via reduced birth weight (i.e., cortisol $\square$ birth weight $\square$ temperament). In addition, low birth weight, which has been consistently linked to prenatal stress, even in genetically informed work (Rice et

al., 2010), is associated with negative emotionality (Pluess & Belsky, 2011). Notable, too, is work showing that pregnant women exposed to a natural disaster (i.e., the 1998 Canadian ice storm) who experienced greater subjective distress or illness/infection at various time points in their pregnancy, had infants with more difficult temperaments; and these relations, too, remained significant after controlling for postpartum depression and major life events (Laplante, Brunet, & King, 2015).

~~Despite Although the just-cited, we would be remiss if we did not call attention to such research is compelling, the~~ results of a meta-analysis examining the association between maternal cortisol levels during pregnancy and child development, as it yielded ~~outcomes found mixed results when predicting child temperament~~ (Zijlmans, Riksen-Walraven, & de Weerth, 2015). ~~Although some studies found , including ones just described, found that greater maternal cortisol during pregnancy was associated with more difficult temperament, other work revealed found no such association between the two~~ (Zijlmans et al., 2015). ~~Clearly more research Thus, more work is needed to illuminate the conditions under which elevated more conclusively determine whether maternal cortisol during pregnancy is and is not associated with child temperament. Some insight into what such additional research might show comes from~~ ~~However,~~ another recent review which included prenatal stressors such as maternal psychological distress, exposure to major life events, and experiencing natural disasters. ~~It found found that~~ greater prenatal stress ~~to be~~ was associated with more negative affectivity and difficult temperament (Van den Bergh et al., 2017). ~~It may well be the case, then, that it is the psychological experience of stress rather than cortisol levels per se that are predictive of heightened Thus, there is evidence that prenatal stress is predictive of greater child negative emotionality early in life, but some measures of prenatal stress may be more strongly associated.~~

Turning to prenatal stress effects on physiological functioning, research reveals that prenatal-stress exposure is associated with dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis in infants and children. More specifically, as reflected in greater maternal depression in mid- pregnancy has been found to forecast predicting elevated basal cortisol concentrations in newborns (Field et al., 2004), while and higher maternal cortisol in mid- and late- pregnancy has been found to predict increased ing greater cortisol response to a heel-prick 24 hours after birth (Davis, Glynn, Waffarn, & Sandman, 2011). These latter effects appear to be at least partially mediated via epigenetic changes in the glucocorticoid receptor gene (*NR3C1*) which encodes for glucocorticoid receptor (GR)—a major component of the stress response (Oberlander et al., 2008). Such effects on children’s cortisol levels—as a function of expectant-mothers’ heightened pregnancy-specific fears and cortisol levels measured at multiple times throughout pregnancy—extend to even the first day of school (Gutteling, de Weerth & Buitelaar, 2005). The results of a natural experiment in humans positioned near the World Trade Center on 9/11 also documents prenatal-stress effects on infant stress physiology; pregnant mothers present or near the 9/11 terrorist attacks who subsequently developed post-traumatic stress disorder (PTSD) had infants with dysregulated diurnal cortisol rhythms at one year of age relative to infants of other mothers (Yehuda et al., 2005). Such findings ~~These results~~ are consistent with experimentally documented prenatal-stress effects ~~findings~~ in rodents, including work studies indicating that prenatal-stress induced by physical restraint ~~stress~~-or social conditions ~~stress~~-is associated with higher baseline and reactive-corticosterone levels in offspring (Maccari, Krugers, Morley-Fletcher, Szyf & Brunton, 2014).

What about meta-analytic studies? Evidence from ~~Furthermore, results of two meta-~~
analyses provide strong support for prenatal stress programming child physiological reactivity.
The first meta-analysis documented support for the association between greater maternal cortisol

levels during pregnancy and greater child cortisol levels (Zijlmans et al., 2015); ~~while the~~ second indicated meta-analysis found that a variety number of prenatal various stressors experienced prenatally (e.g., substance use, maternal psychological stress) forecast predicted changes in both child baseline and reactive cortisol levels (Pearson, Tarabulsky, & Bussières, 2015). In summary, then, diverse approaches to measuring prenatal stress, ranging from maternal psychological distress to maternal cortisol levels, highlight its effects on both children's emotional and physiological dysregulation in children postnatally.

Prenatal Programming of Postnatal Plasticity

Consideration of both sets of evidence summarized through this point—one indicating that prenatal stress is associated with elevated behavioral and physiological dysregulation and the other that such phenotypic functioning is associated with heightened susceptibility to positive and negative environmental influences—raises the intriguing hypothesis first advanced by Pluess and Belsky (2011) that *prenatal stress fosters, promotes or “programs” postnatal developmental plasticity*. If true, this hypothesis might could account for many of the adverse, later developing phenotypes long associated with prenatal-stress exposure, including behavioral problems and academic difficulties: Perhaps the reason that prenatal stress is associated with problematic functioning in childhood and adolescence in observational research is because the very forces that engendered stress in pregnancy (e.g., poverty, unemployment, marital conflict, maternal depression) continue postnatally for many children whose prenatal experience fostered heightened developmental plasticity. Thus, when these children are exposed, postnatally, to conditions of adversity that persist beyond pregnancy, they prove especially susceptible to their undermining influence.

Notably, the same prenatal-programming process could also account for why beneficial effects of prenatal stress have sometimes been detected—in studies of well-resourced families.

Consider in this regard DiPietro and colleagues' (2006) work showing that prenatal stress,

measured via maternal psychological distress during mid-pregnancy, predicted better infant mental scores in a well-educated, mostly white and married sample (DiPietro, Novak, Costigan, Atella, & Reusing, 2006). Quite conceivably, the prenatally-stressed infants who postnatally encountered supportive rearing environments proved especially sensitive and responsive to the psychological and behavioral “nutrients” available to them and thus disproportionately flourished due to their prenatally induced and enhanced developmental plasticity. In summary, would-be prenatal-stress effects may not so much be directly the result of the prenatal experience but rather reflect the enhanced influence of the postnatal environment on children especially susceptible to both supportive and unsupportive developmental experiences and environmental exposures.

When Pluess and Belsky (2011) first postulated their prenatal-programming-of-postnatal-plasticity hypothesis, based on the two independent literatures highlighted in the opening paragraphs of this paper, they provided accompanying empirical evidence to support their claims. One relevant investigation relied on data from the NICHD Study of Early Child Care (Early Child Care Research Network, 2005) and linked prenatal stress—indexed via low birth weight—to infant negative emotionality which, in turn, was associated with infants being more susceptible—in a to-for-better-and-for-worse manner—to parenting effects on behavioral and cognitive functioning (Pluess & Belsky, 2011). More recently, longitudinal work by Sharp and associates (2015) revealed that maternal prenatal anxiety, measured during late pregnancy, increased children’s developmental responsiveness to postnatal maternal stroking during the first few weeks of life with regard to later anxious/depressive symptoms. In this case, children exposed to high levels of prenatal anxiety evinced greater anxious/depressive symptoms when they experienced limited maternal stroking postnatally, yet very little symptomology when exposed to a great deal of maternal stroking—an effect found to be especially pronounced in femalesgirls. The same was not true of children whose mothers experienced little anxiety during

pregnancy. Although these results are consistent with indicate prenatal programming of postnatal plasticity, it should be noted that the sample size was small (N =243) for detecting such an interactive effect and is thus in need of further replication. ~~In fact~~ Despite this, in both cited works, regression slopes linking the environmental-exposure predictor with the measured outcome revealed that those exposed to high levels of prenatal stress, manifest both the highest and lowest levels of all study members on the outcomes measured.

Further evidence of prenatal programming of postnatal plasticity comes from research comparing pre-term and full-term babies. There is a substantial body of work indicating that showing psychosocial stress is to be an etiological risk factor for pre-term birth (Shapiro, Fraser, Frasch, & Seguin, 2013)—even when controlling for other well-known risk factors (e.g., twin pregnancy, tobacco use, infection, premature contractions; Lilliecreutz, Laren, Sydsjo, & Josefsson, 2016). Thus, pre-term birth can be considered a marker of prenatal stress. Pertinent to the issue of prenatal programming of postnatal plasticity, then, is an investigation which examined the differential effects of the caregiving environment on infant cognitive and social functioning in pre-term and full-term infants (Gueron-Sela, Atzaba-Poria, Meiri, & Marks, 2015). Results revealed that pre-term infants were more developmentally responsive to their caregiving environment, evincing the greatest social and cognitive functioning when exposed to a high-quality caregiving environment yet ~~but~~ the lowest social and cognitive functioning when they experienced a low-quality caregiving environment. Notably, caregiving quality did not predict social and cognitive development in the case of full-term infants. These findings are in line with those of earlier work which chronicled stronger associations between maternal responsiveness and cognitive growth in the case of preterm infants than full-term ones (Landry, Smith, Swank, Assel, & Vellet, 2001). In fact, an intervention designed to promote maternal responsiveness proved successful in doing so, but when it came to effects on children's

development, the benefits of being in the experimental ~~group~~ rather than the control group proved greater ~~for in the case of~~ children born preterm rather than full-term (Landry, Smith, & Swank, 2006).

Beyond Observational Evidence of Prenatal Programming of Postnatal Plasticity

Even if all the findings reviewed through this point appear consistent with the claim that prenatal stress promotes enhanced susceptibility to postnatal experiences—via heightened negative emotionality and physiological reactivity (or preterm birth/low birth weight)—the work cited is not without limits. As already noted, observational studies, in particular, do not provide a basis for strong causal inference. After all, a mother could carry certain genes which increase her chances of becoming anxious or depressed during pregnancy, genes which she could pass on to her child which, in turn, could make him or her more susceptible to postnatal environmental influences. Were that the case, we would have misinterpreted much of the evidence reviewed in discussing the ~~hypothesisclaim~~ that prenatal stress programs postnatal plasticity.

Notable, then, However, there is work using genetically-controlled designs in humans that documents prenatal--stress effects independent of genetic inheritance. Consider in this regard work by Specifically, Rice et al. (2009, 2010) who studied children who prenatal effects on child development by examining mothers who were either biologically related or unrelated to their motherchild as a resultproduct of in-vitro fertilization. Evidence indicated Results showed that prenatal stress predicted child antisocial behavior and anxiety in both related and unrelated mother-child pairs, thus indicating strong influence of the prenatal environment independent of genetic inheritance (Rice et al., 2010). Similarly, another unique design using the consumption of licorice during pregnancy has also been able to disentangled prenatal stress from genetic effects. Licorice contains a compound, glycyrrhizin, which inhibits placental 11 β -hydroxysteroid dehydrogenase type 2, an enzyme responsible for breaking down maternal cortisol thereby greatly reducing fetal exposure. ThusConsequently, pregnant women who consume higher

amounts of licorice may inadvertently increase fetal exposure to maternal cortisol ~~which we have already seen can affect have effects on the child's HPA system. As it turns out, Indeed, a series of studies find that have shown the~~ greater licorice consumption during pregnancy predicts greater HPA reactivity in children (Räikkönen et al. 2010), increased risk of externalizing behaviors (Räikkönen et al., 2009), and greater risk for ADHD problems (Räikkönen et al., 2017). ~~Such results indicated This is further support that prenatal stress effects are not only nearly the product of genes shared by genetics between mother and child.~~ One obvious scientific solution to this empirical conundrum would involve experimentally increasing the stress of pregnant women in order to determine if this affects infant emotional and/or physiological reactivity. But even if this proved to be the case—were such unethical research undertaken—there would still be the issue of differential susceptibility to postnatal environmental influences.

In ~~addition to these unique research designs just highlighted, experiments, another way to evaluate proceed~~ circumstances such as this, one way to proceed to further the empirical ~~evaluation of a hypothesis of interest—in this case the prenatal-programming hypothesis in a manner that would afford strong causal inference would be —is~~ to conduct an animal experiment. And this is ~~exactly~~ what we proceeded to do, using prairie voles (*Microtus ochrogaster*) as our experimental subjects (Hartman, Freeman, Bales, & Belsky, 2018). We chose prairie voles ~~as study animals~~ because they display key characteristics of social monogamy and selective social behavior, including preference for a familiar partner, an emotional attachment to the pair-mate, and male care of offspring. Social attachments are a key aspect of the early environment for humans and many other mammalian species (Mason & Mendoza, 1998). Other common rodent models, like rats and mice, do not form selective social attachments (except filial attachment) as adults, whereas prairie voles, like humans, do so. Furthermore,

prairie voles naturally vary—in trait-like fashion across multiple litters—in the amount of care they display toward their pups (Perkeybile, Griffin, & Bales, 2013). Whereas some engage in high levels of licking and grooming their newborn pups, others engage in very little. Thus, prairie voles are an optimal animal to use in cross-fostering paradigms—that afford the contrasting effect of more and less “supportive”-parenting—when testing hypotheses based on findings from human studies.

Our study design involved, in its first stage, assigning pregnant voles on a random basis to a social-stress or no-stress condition during the last week of pregnancy. Those assigned to the experimental group were exposed to an unfamiliar and lactating—hence, aggressive—female vole for 10 min/day for 5 consecutive days, using a plexiglass divider to keep the animals separate (and physically unharmed). This paradigm is known to increase stress reactivity in offspring, both behaviorally and physiologically (Brunton & Russell, 2010). Those in the control condition were left undisturbed.

The second stage of our investigation occurred postnatally when the offspring born to both experimental and control mothers were cross fostered, again on a random basis, to either high- or low-quality rearing by (unrelated adults)-rearing parents. We felt confident in characterizing the two groups of parents this way because we utilized a previously established method of quantification that has been shown to be effective in distinguishing high- and low-quality parents in prairie voles (Perkeybile et al., 2013). Specifically, we recorded parenting behaviors (e.g., nursing, contact, licking and grooming) before the start of the experiment to quantify each pair’s natural level of parenting (Perkeybile et al., 2013). These parenting scores were summed and the top-ranked quartile became the high-quality parental group and, the bottom quartile the low-quality parental group in the cross-fostering phase of our experiment.

In sum, the research we undertook used a 2 (Prenatal Stress: Yes vs. No) X 2 (Postnatal Rearing: High vs. Low quality) research design. Based on everything stipulated through this point, we predicted that large differences would emerge in the development of the prenatally-stressed voles reared under high- and low-quality conditions—due to their heightened susceptibility to rearing effects—but that the same would not be true of those voles not exposed to stress prenatally. Moreover, we hypothesized that group differences would take the for-better-and-for-worse, differential-susceptibility-related form: The prenatally-stressed voles would score highest and lowest of all four groups of voles on the outcome variables measured (see next paragraph), with the scores of the unstressed voles falling in between.

For the most part, results ~~of our experiment~~ proved consistent with the prenatal-programming-of-postnatal-plasticity hypothesis. That is, prenatally-stressed voles were more developmentally responsive to the rearing environment than voles not prenatally stressed. Specifically, voles cross-fostered to high-quality rearing environments displayed, as adults, the least behavioral and physiological reactivity when subjected to a stressor (i.e., forced swim), but the most if they were exposed ~~to~~ low-quality rearing environments. In fact, in the case of voles in the control condition that were not prenatally stressed, postnatal rearing ~~environmental~~-quality exerted no effect whatsoever on later reactivity. Notably, in attempt to illuminate brain processes that might mediate the effects of prenatal stress on postnatal plasticity, we discovered that voles prenatally stressed and cross-fostered to high-quality rearing environments had the most vasopressin 1a receptor density in the amygdala. We chose this potential mediating factor to study because it was previously shown to be related to anxiety behavior and social functioning (Carter, Grippo, Pournajafi-Nazarloo, Ruscio, & Porges, 2008).

Future Research Directions

The fact that our experimental animal study generated results strikingly consistent with what has been found in human research provides strong evidence that prenatal stress programs

postnatal plasticity, at least in voles. Even so, research to date documenting the potential beneficial effects of prenatal stress—when matched with a supportive postnatal environment—remains limited. This dearth of relevant work ~~research~~ is likely due to the almost exclusive focus on the *adverse* effects of prenatal stress with little consideration of postnatal experiences; and this itself is due to the fact that even when the interaction of prenatal and postnatal environments is considered, it is usually examined in terms of the “risk and resilience” or diathesis-stress framework (Zuckerman, 1999). This results in an exclusive focus on pathological outcomes (e.g., anxiety, depression, cognitive disorders, poor health), which leaves little opportunity to illuminate the (postnatal) conditions under which prenatal stress may actually promote more rather than less competent development. Clearly, future inquiry ~~further research~~ should consider the interaction between the quality prenatal environment and postnatal environment on outcomes which can range from positive (i.e., high functioning) to negative (i.e., low functioning).

Having said that, there are many other ways that future ~~investigation~~ inquiry could seek to illuminate the prenatal programming of postnatal plasticity. In what follows, we consider first a variety of study designs with humans that could further illuminate ~~be used to determine the~~ effects of prenatal stress on susceptibility to postnatal environmental influences. Thereafter we turn attention to potential mechanisms instantiating postnatal plasticity via prenatal stress, as these too merit future attention. Finally, we entertain the prospect that some individuals may be more susceptible than others to prenatal-stress effects in hopes of encouraging future work on moderators of the enhanced-plasticity programming process under consideration.

Human Research Designs

As described previously, a major limitation of prenatal-stress research is genetic similarity of mother and fetus which confounds prenatal-stress effects with genotypic effects. Fortunately, one may address this limitation using different study designs, some of which ~~are~~

described previously, include gestational cross-fostering and licorice consumption. In addition to those designs, adoption, interventions, and natural experiments are also potentially fruitful avenues of research, as we make clear which are discussed in more detail below.~~include adoption, gestational cross-fostering, interventions, and natural experiments.~~

Utilizing adoption studies is a potentially fruitful avenue of research considering that the prenatal environment would be unrelated to the postnatal one, much akin to cross-fostering experiments in animals (presuming adoptive and biological mother are themselves unrelated). Such research would, of course, necessitate gathering measurements of the stress the biological mother experienced during pregnancy which may present formidable challenges. Nevertheless, ~~by using~~ adoption studies, ~~one~~ could effectively disassociate ~~the~~ prenatal effects from ~~the~~ postnatal ones while controlling for genetic influence. This empirical direction would seem to be especially worth pursuing because pregnant mothers who place children for adoption may be under a greater amount of distress than the average population, potentially leading their infants to being especially developmentally plastic. However, another potential challenge that may be encountered with such adoption research is that children often experience several caregiving settings (e.g., multiple foster homes; institutional care) prior to a stable placement (Rubin, O'Reilly, Luan, & Localio, 2007). Hence, these children may not only be exposed to several rearing ~~environments~~ ~~conditions~~ that ~~could~~ ~~may~~ vary in quality but also experience these contexts at different time periods which may, in turn, be more or less influential in programming their development (i.e., timing effects). Therefore, investigators pursuing this line of ~~inquiry~~ ~~research~~ should explore how both ~~variation in the differing~~ quality and timing of exposure to these various settings may influence children's developmental trajectories.

Another desiderata of future research should be to determine whether effective treatments for prenatal anxiety and depression—essentially experiments which down-regulate prenatal

stress—reduce infant’s susceptibility to postnatal environmental influences. It is quite conceivable that any random control trials (RCTs) seeking to reduce prenatal stress may already provide experimental evidence as to whether the postnatal rearing environments of women randomized to control/no-treatment conditions actually exert more influence—or at least predictive power—than those of women successfully treated for their anxiety and depression prenatally. We hypothesize that the association between postnatal experiences (e.g., parenting quality) and child development would be weaker for experimental mothers who received (and responded positively to) stress-reducing treatment during pregnancy and stronger for the control group whose stress was not down-regulated. It should be noted, however, that interventions aimed at reducing stress during pregnancy may also affect the postnatal environment. For example, an intervention designed to reduce anxiety during pregnancy by providing the mother with enhanced coping skills and/or emotion-regulation strategies may very well influence mother-child interactions postnatally. Thus, one would need to account for any intervention effects on measurements of postnatal environmental quality when interpreting the effects of prenatal stress interventions on child susceptibility.

Natural experiments, including exposure to natural disasters, might also afford insight into prenatal-stress effects on postnatal plasticity due to their random nature. Specifically, one benefit of utilizing these types of investigations is that the stressor is an objective hardship, in which duration and intensity can be measured, that is randomly distributed in the population. Hence, experiencing a natural disaster is independent of the mother’s personality, behavior, and genetic predisposition, unlike other forms of stressors such as interpersonal conflict (e.g., Jaffee & Price, 2007). Admittedly, the very same exposures can be differentially stressful to different individuals (e.g., high vs. low neuroticism). Nevertheless, the This type of work in question could, potentially, further illuminate prenatal-stress effects by reducing even if not entirely

~~eliminating the amount of~~ maternal confounding factors. ~~Having said this, investigators would be wise to entertain the possibility that some mothers may be more sensitive to the adverse experience of a natural disaster than others (i.e., differential susceptibility).~~

Proposed Mechanisms of Plasticity

In turning to consider candidate biological mechanisms potentially instantiating developmental plasticity resulting from prenatal stress, we draw heavily, even if not exclusively, on ideas advanced by Boyce and Ellis (2005) and, more recently and extensively, Moore and Depue (2016). Given the ubiquitous effects of prenatal stress and thus numerous possible mechanisms, ~~we should make clear that~~ we will be limited in our focus. While acknowledging that prenatal stress has significant effects on infant microbiota (e.g., Zijlmans et al., 2015), epigenetic machinery (e.g., non-coding RNAs, DNA [methyltransferases](#); Cruceanu, Matosin, & Binder, 2017), integrity of the placenta (O'donnell, O'Connor, & Glover, 2009) and inflammatory processes (e.g., Coussons-Read et al., [2007](#)), all of which could ~~be potentially~~ instantiate enhanced developmental plasticity resulting from prenatal stress, biological mechanisms, these will not be considered in detail in this report, as they are considered in such detail elsewhere (although see Hartman & Belsky, (in press) for a further discussion.

Physiological reactivity. As described previously, heightened reactivity of the HPA system is the key mechanism proposed by Boyce and Ellis (2005) responsible for enhanced environmental sensitivity. Recall, also, that increased physiological reactivity has consistently been linked to prenatal-stress exposure. Thus, it would follow that prenatal stress would foster greater physiological reactivity and, thereby, increased developmental plasticity (i.e., prenatal stress $\rightarrow$ greater physiological reactivity $\rightarrow$ increased plasticity). Although portions of this process have been studied in isolation, the entirety of this potential mechanistic pathway has yet to be evaluated empirically. In addition, by examining this candidate pathway, we are likely to identify

additional biological processes that contribute to the instantiation of environmental sensitivity (e.g., epigenetics, neural connectivity).

Consider in this regard the growing interest in the mediating role of epigenetics with respect to effects of prenatal stress on physiological reactivity. Most epigenetic studies have focused on the programming effects of early *postnatal* life with the seminal study by McGowan and associates (2011) showing that, in rats, early postnatal stress influences hippocampal DNA methylation in the promoter region of *NR3C1*, the gene coding the glucocorticoid receptor (GR), which regulates the stress response. Notably, research in both humans and animals suggests that prenatal stress may induce the same epigenetic modifications in homologous promoter regions of *NR3C1*. For example, Mueller and Bale (2008) found that, in mice, prenatal stress increased stress reactivity and hypothalamic methylation in the promoter region of *NR3C1*. Several human studies using neonatal cord blood ~~indicate have found~~ that prenatal anxiety (Hompes et al., 2013), maternal exposure to interpartner violence (Radtke et al., 2011), and depressive symptoms (Conradt, Lester, Appleton, Armstrong, & Marsit, 2013; Oberlander et al., 2008), all indisputable markers of prenatal stress, are associated with differential methylation patterns in the promoter region of *NR3C1*. In fact, one recent investigation examining pregnant mothers exposed to chronic stress in Democratic Republic of Congo showed that infants had differential methylation patterns across several genes (i.e., *CRH*, *CRHBP*, *NR3C1*, and *FKBP5*) shown to regulate the HPA axis (Kertes et al., 2016). ~~Intriguingly~~Notably, these methylation patterns were associated with infant birth weight, a well-documented proxy for prenatal stress.

Even if most epigenetic work has focused primarily on methylation of the candidate gene *NR3C1*, prenatal-stress effects on stress reactivity undoubtedly involve a cascade of multiple genetic, endocrine, and epigenetic factors. Thus, even if less well-studied than the HPA system, it should be appreciated that the sympatho-adrenomedullary (SAM) system is another crucial

component of the stress response, one involved in the release of catecholamines such as norepinephrine (NE) and epinephrine (E). Even if most catecholamines are metabolized by enzymes in the placenta, results of several studies suggest that reduced amounts are still transferred from mother to fetus; moreover, fetuses can produce their own catecholamines in response to maternal stress (for a review see Merlot, Couret, & Otten, 2008). Although the effect of prenatal stress on fetal exposure to catecholamines and later postnatal development remains unclear, one investigation did find that greater (???) maternal E and NE levels during pregnancy predicted reduced (???) infant soothability—and thus heightened (????) negative emotionality—thereby raising the possibility that maternal activation of the SAM system may be linked to postnatal plasticity (Wroble-Biglan, Dietz, & Pienkosky, 2008). BE SURE TO CLARIFY THE THREE POINTS MADE, EITHER ACCEPTING OR MODIFYING THEM. NOT ENOUGH TO SAY THAT THINGS ARE RELATED; NEED TO SAY HOW.

However limited the research thus far, NE was highlighted by Moore and Depue (2016) as a key regulator of environmental reactivity. These scholars hypothesized that high levels of NE would modulate environmental effects—for better or for worse. Specifically, high levels of NE under stressful conditions would produce hypervigilance and impaired cognition whereas higher levels of NE under supportive circumstances could yield ideal levels of attention to facilitate exploration and ability to take advantage of opportunities in the environment.

Therefore, NE could have an important role in regulating developmental plasticity.

In sum, prenatal stress appears to affect have significant effect on programming the HPA system, via epigenetic mechanisms and, potentially, the SAM system. Relatedly, prenatal stress is known to affect brain areas such as the prefrontal cortex, hippocampus, and amygdala that also regulate the HPA axis (Lupien, McEwen, Gunnar, & Heim, 2009). In the following section, we will highlight the amygdala as an additional potential mechanism although future research should

consider multiple brain areas known to be affected by prenatal stress. YOU SAY IN THE PRECEDING SENTENCE THAT THE NEXT SECTION IS AMYGDALA, BUT IT IS PLACENTAL MODULATION, SO YOU NEED TO MODIFY PRECEDING SENTENCE, ORBY THE WAY, MARCO HAS A BIG PAPER ON THE PLACENTA (GOOGLE IT) AND SO PERHAPS WE SHOULD CITE IT EARLY IN THIS SECTION, EVEN REFER THE READER TO IT DEPENDING ON ITS FOCUS. HE MAY BE TOO MODEST TO SAY, LIKE BELSKY (□), “CITE ME”.

Role of the placentaPlacental modulation. Recent investigations of prenatal programming have begun to explore the role of the placenta as a key mediator of prenatal-stress effects on fetal development. The placenta is an organ that serves as the interface between mother and fetus and can quickly adapt to changes in ~~from~~ the maternal environment (e.g., prenatal stress). The role of the placenta is well-known in actively modulating vital functions of the fetus, such as nutrient and oxygen exchange (Jansson & Powell, 2007), but also plays a pivotal role in the production and modulation of glucocorticoids and amines.

In particular, the placenta affects HPA axis regulation in both the mother and fetus. Specifically, exposure to maternal cortisol stimulates the placenta to produce placental CRH (pCRH) in response to maternal cortisol which is released into both maternal and fetal circulation (Gitau et al., 2004, Mastorakos & Ilias, 2003). For the fetus, pCRH is able to pass the fetal blood-brain barrier causing greater fetal adrenal cortisol production which, in turn, leads to more pCRH production (Mesiano, 2014). Because of its responsiveness to both maternal and fetal cortisol, some have argued that pCRH levels may be a more accurate indicator of fetal exposure to prenatal stress ~~rather~~ than maternal cortisol only (Howland, Sandman, Glynn, Crippen, & Davis, 2016). One study by Howland et al. (2016) found that pCRH but not maternal cortisol

was associated with greater child internalizing problems. This may be the reason why the previously described meta-analysis of maternal cortisol levels during pregnancy predicting child temperament yielded found mixed results (Zijlmans et al., 2015). Of special significance to this paper is that another investigation found that greater pCRH levels during mid-gestation predicted greater infant fear and distress (Davis et al., 2005). Thus, it appears one way the placenta may regulate maternal signals of stress during pregnancy is through the production of pCRH.

Another ~~additional~~ mechanism by which the placenta may regulate fetal exposure to stress is through the placental barrier enzyme 11 β -hydroxysteroid dehydrogenase Type II (11 β -HSD2). Specifically, the placenta serves as plays a protective factor against maternal cortisol by inactivating it using 11 β -HSD2---which results in only 10-20% of the cortisol from maternal circulation reaching the fetus. Intriguingly, prenatal stress not only increases maternal cortisol but also is linked to a reduction in the expression and activity of the placental 11 β -HSD2 (Pena, Monk, & Champagne, 2012; O'Donnell et al., 2012). In turn, these epigenetic changes in placental 11 β -HSD2 are themselves related to DNA methylation in the fetal brain as well as increases in fetal corticosterone levels (Pena, Monk, & Champagne, 2012). Furthermore, the reduction in placental 11 β -HSD2 activity is associated with early development, including fetal growth restriction (Börzsönyi et al., 2012), prematurity (Demendi et al., 2012) and low birth weight (Green et al., 2015).

Thus, it appears that prenatal stress may alter the transplacental barrier via epigenetic changes in 11 β -HSD2, thereby resulting in increased fetal exposure to maternal cortisol and phenotypic development outcomes. Similarly, prenatal stress may increase placental permeability; and thus fetal exposure; to other hormones. In humans, prenatal stress ~~is has been~~ associated with increased levels of serotonin and NE transporters as well as ~~thea~~ down regulation of monoamine

oxidase in placental cells which would lead to increased intrauterine availability of these hormones (Blakeley, Capron, Jensen, O'Donnell, & Glover, 2013; Ponder et al., 2011). Thus, a major mechanism by which prenatal stress may affect the fetus is through alterations to the placental barrier which increase fetal exposure to select hormones (Aye & Keelan, 2013; Seckl & Holmes, 2007; Beiheers, Buitelaar, & de Weerth, 2014). Of special significance to this paper is the fact that these changes in the placenta have been tied to aspects of infant temperament, with higher levels of placental mRNA in serotonin and glucocorticoids being associated with greater behavioral dysregulations in infants (Räikkönen et al., 2015). Taken together, it appears that the placenta plays a critical role in modulating fetal exposure to stress via production of pCRH and 11 β -HSD2. Thus, future work should consider how these endocrine activities in the placenta may influence how maternal exposure to stress is transmitted to the fetus, with consequences for susceptibility to postnatal environmental exposures and developmental experiences. -

Amygdala. A wealth of evidence indicates has demonstrated that the brain is highly sensitive to prenatal programming (Charil, Laplante, Vaillancourt, & King, 2010). Indeed, research shows there is work showing that prenatal stress affects the structure and functionality of many different brain regions, including the corpus callosum, hippocampus, amygdala, and hypothalamus (Charil et al., 2010). Although prenatal stress is known to impact these various regions, the following discussion is restricted to for the purpose of this paper, our focus will be on the amygdala as a plausible biological mechanism for developmental plasticity because of its consistent links to prenatal stress and behavioral/physiological reactivity.

The amygdala is part of the limbic system and plays a critical role in memory and emotions (Seymour & Dolan, 2008). In particular, the amygdala is regarded has been highlighted in the literature as a key mechanism and regulator of physiological and behavioral responses

during fear and anxiety in both rodents and humans (Davis & Whalen, 2001). On a mechanistic level, ~~research has shown that~~ the amygdala is a central regulator of the HPA axis (Herman & Cullinan, 1997). Specifically, the amygdala contains glucocorticoid (GR) and mineralocorticoid (MR) receptors that, when activated, have positive feedback loops on the hypothalamus and thus regulate the stress response (Charil et al., 2010). Furthermore, the amygdala is essential ~~to in~~ modulating the perception of emotionally salient events which determines whether the HPA axis initially becomes activated (Das et al., 2005).

In considering individual differences in behavioral and physiological reactivity, the amygdala ~~is regarded as has been suggested to be~~ a major neural substrate of inhibited and anxious temperament (Kagan & Snidman, 2004). Specifically, in non-human primates, hyperactivity in the amygdala predicts greater HPA reactivity and more anxious behaviors (e.g., freezing; Shackman, Fox, Oler, Shelton, Davidson, & Kalin, 2013). In human imaging studies, anxious/inhibited temperament ~~has been shown to predicts~~ greater amygdala reactivity to novel and familiar faces. ~~(Blackford et al., 2003).~~ For example, Blackford and colleagues (2009) examined a group of young adults who did or did not have a childhood history of behavioral inhibition. ~~Those individuals~~ who were inhibited ~~early in life as children~~ had greater amygdala activation to both novel and familiar faces compared to individuals who were not inhibited as children. Taken together, increased amygdala activity appears to be associated with both higher physiological and behavioral reactivity which ~~speaks to indicates~~ its potential involvement in heightened plasticity.

In addition to these findings, prenatal stress has repeatedly been shown to predict differences in amygdala structure and function. For example, in rodents, administration of synthetic glucocorticoid dexamethasone during pregnancy increases CRH mRNA levels in the

central amygdala and increases GR and MR in the basolateral nucleus of the amygdala (Makino, Gold, & Schulkin, 1994; Walberg & Seckl, 2001). In addition, offspring of rats exposed to prenatal stress via handling, novel exposure, and saline injection have a decreased number of neurons and glial cells in the amygdala as well as ~~overall~~ smaller overall volumes (Kraszpulski et al., 2006).

Consistent with this rodent work, human studies also provide evidence of a link between prenatal stress and altered amygdala function. Specifically, in the first weeks of life, infants ~~who were~~ exposed to ~~prenatal~~ maternal depression prenatally showed lower fractional anisotropy, a measure of microstructural maturation, in the right amygdala compared to infants with no such exposure (Rifkin-Graboi et al., 2013). ~~A~~In addition, another study found that 6-month-old infants displayed altered functional connectivity of the amygdala to other brain regions if they were exposed to prenatal maternal depression even when controlling for postnatal maternal depressive symptoms (Qui et al., 2015). Importantly, these investigations chronicle~~show~~ differences in amygdala function early in life in contrast as opposed to the majority of studies which examine amygdala function in adulthood and often as an outcome of early-postnatal stress (e.g., ???REF HERE??). ~~That~~ Because such differences in the amygdala exist early in life and are related to measures of physiological and behavioral reactivity suggests that ~~that~~ altered amygdala function may be a mechanism for plasticity rather than just an early response to -postnatal stress ~~outcome~~.

Indeed, there is other evidence to suggest that the amygdala may be a target brain region to investigate~~study~~ with regards to developmental plasticity. Recall, for example, the study in prairie voles by Hartman et al. (2018) which found differences in V1aR in the amygdala. Specifically, voles exposed to prenatal stress were more sensitive to the positive environment as indicated by greater V1aR density in the amygdala if reared by high-quality parents. In addition,

greater activity in the amygdala has been linked to other known markers of heightened susceptibility such as the short allele of 5-HTTLPR (Hariri et al., 2002; see below for a more detailed discussion on serotonin). Although such research indicates the heightened amygdala activity may be related to increased developmental plasticity, it will be important for future ~~inquiryresearch~~ to determine whether the amygdala is hyperactive to both negative and positive stimuli since most studies, thus far, have ~~regarded focused on the~~ hyperactivity in the amygdala as pathological and ~~resulting from a function of~~ environmental stress. To do so, future research should employ a longitudinal ~~designstudy~~ examining exposure to prenatal stress, amygdala reactivity at an early age to both positive and negative stimuli, and subsequent development ~~phenotypesal outcomes~~ that ~~reflect both positive and negative capture a full range of~~ functioning.

Serotonin. Although prenatal stress involves a cascade of complex and diverse endocrine actions, serotonin may be of particular importance when considering programming effects. Serotonin, a neurotransmitter that is widely distributed throughout the brain, is crucial for neuronal development early in life, operating in two major ways: (1) as a growth factor regulating development of neural systems (Whitaker-Azmitia, Druse, Walker, & Lauder, 1996) and (2) as a trophic factor regulating synaptogenesis and dendritic pruning (Gaspar, Cases, & Maroteaux, 2003). It seems likely, therefore, that if prenatal stress affected these processes during fetal development, then the developing child could be ~~affected influenced~~ in lasting ways. After all, serotonin activity is known to play a role in regulating, perhaps most notably, stress reactivity later in life (Canli & Lesch, 2007).

As it turns out, there is ample evidence in animal studies that prenatal stress produces lasting alterations in the serotonin system (Van den Hove et al., 2006; Mueller & Bale, 2008; Miyagawa et al., 2011). For example, prenatally-stressed mice evince lower serotonin transporter

levels and a depressive-like phenotype (Mueller & Bale, 2008). In humans, increased maternal depressive mood during the 2nd trimester of pregnancy is associated with reduced methylation in the promoter region of maternal and infant *SLC6A4*, the locus of the serotonin gene which codes for the serotonin transporter (Devlin, Brain, Austin, & Oberlander, 2010). Thus, it appears that prenatal stress exerts programming effects on the serotonin system; ~~this which~~ is not surprising given ~~the~~ evidence that the HPA and serotonin systems are cross-regulated (see St-Pierre et al., 2016 for review).

In addition to prenatal-stress effects, the serotonin system has been ~~associated with~~ ~~linked~~ ~~to~~ variation in developmental plasticity. In fact, the serotonin transporter linked polymorphic region (5-HTTLPR) of *SLC6A4*, is one of the most well-studied genetic polymorphisms found to be associated with individual differences in susceptibility to environmental influences. Consider in this regard that individuals carrying one or more short alleles evince “for-better-or-for-worse” plasticity when the rearing predictor and child outcome are, respectively, maternal responsiveness and moral internalization (Kochanska, Kim, Barry, & Philibert, 2011); child maltreatment and antisocial behavior (Cicchetti, Rogosch, & Thibodeau, 2012); stressful life events and preschool-onset depression (Bogdan, Agrawal, Gaffrey, Tillman, & Luby, 2014); and supportive parenting and positive affect (Hankin et al., 2011). Somewhat qualifying these findings is a meta-analysis of gene-X-environment studies focusing on 5-HTTLPR. -Itwhich found that 5-HTTLPR moderated positive and negative environments on child phenotypes outcomes in a manner consistent with differential susceptibility, but only among Caucasian samples (van IJzendoorn, Belsky, & Bakermans-Kranenburg, 2012). Just as significantly In addition, 5-HTTLPR short alleles have been linked to greater negative emotionality and physiological reactivity, ~~phenotypes outcomes~~ associated with prenatal stress as previously

reviewed, in both humans and non-human primates (e.g., Lakatos et al., 2003, Champoux et al., 2002).

Given evidence that prenatal stress produces alterations in the serotonin system and that the serotonin system appears to be systematically related to variation in developmental plasticity, it stands to reason that serotonin should be a key mechanism for instantiating prenatal-programming effects. Investigators examining use of selective serotonin reuptake inhibitors (SSRIs) on women during pregnancy may thus want to consider effects on offspring susceptibility to environmental influences.

Oxytocin and vasopressin. Oxytocin (OT) and arginine vasopressin (AVP) are two closely-related nonapeptides thought to influence, among other things, the regulation of social behavior (e.g., attachment, affiliation, social dysfunction; Carter, Grippo, Pournajafi-Nazarloo, Ruscio, & Porges, 2008; Carter, 2014). Additionally, OT and AVP play a critical role in regulating the HPA axis. Specifically, OT can attenuate the stress response by down regulating the sympathetic nervous system (Carter, 2014), while AVP mRNA expression plays a critical role in regulating anxious and depressive behaviors (Wigger et al., 2004).

OT, though not AVP, was highlighted by Moore and Depue (2016) as a mechanism for instantiating environmental responsivity. Indeed, some evidence indicates that single nucleotide polymorphisms (SNPs) in the OT receptor gene (*OTR*) moderate environmental effects in a differential-susceptibility-like fashion. Specifically, SNPs in *OTR* moderate effects of perceived threat on charitable behavior (Poulin, Holman, & Buffone, 2012); socioeconomic status on obesity risk (Bush et al., 2016); alcohol use on aggressive behavior in men (Johansson et al., 2012); supportive parenting on adolescent social anxiety (Olofsdotter et al., 2017); and harsh parenting on young-adult allostatic load (Brody, Miller, Yu, Beach, & Chen, 2016). [Even with such evidence, it is important to note that gene-environment studies examining *OTR* are limited](#)

in number and suffer from small sample sizes; thus, whether -OTR as a genetic marker of differential susceptibility is remains uncertain still tentative at this point in time.

Even though variations in OT have been primarily studied with respect to effects of maternal care and other early postnatal experiences and exposures, there is some evidence to suggest that it may also be subject to prenatal programming. A study by Unternaehrer and associates (2016) found that maternal cortisol during the second trimester predicted greater oxytocin-receptor methylation in neonatal cord blood. In rats, the negative effects of prenatal stress on social behavior were ~~found to be~~ reversed by oxytocin administration (Lee, Brady, Shapiro, Dorsa, & Koenig, 2007). However, given its critical role in quality of early maternal care, it will be imperative for future inquiryresearch to distinguish ~~the~~ effects of the prenatal ~~and vs.~~ postnatal environment on differences in OT.

As compared to OT, AVP has received far less empirical attention with respect to either early-life effects or variation in susceptibility to environmental influences. Nevertheless, there is reason to believe that AVP has a central—and perhaps even greater—role than OT when it comes to prenatal-programming effects. Consider in this regard the aforementioned vole study by Hartman et al. (2018); it found that vasopressin 1a receptor density in the amygdala helped account for the effect of high-quality rearing in the case of prenatally stressed animals. Although oxytocin-receptor binding was also examined as a possible mediator of such prenatal-stress effects, no evidence for such a role emerged.

Further evidence of the special significance of vasopressin relative to oxytocin is research indicating (a) that effects of prenatal stress on social memory in rats is mediated by vasopressin 1a receptor mRNA expression but not oxytocin receptors (Grundwald, Benítez, & Brunton, 2016) and (b) that prenatal exposure to AVP or caffeine, but not OT, alters learning in female rats (Swenson, Beckwith, Lamberty, Krebs, & Tinius, 1990). Also of significance is that whereas OT is first detected a few days following birth, AVP can be detected in the prenatal and perinatal

periods in the fetal brain, and **WHAT?/UNCLEAR: OT OR AVP?** is thought to play a significant role in central nervous system maturation (Bloch et al., 1990; Tribollet, Goumaz, Raggenbass, Dubois-Dauphin, & Dreifuss, 1991). Thus, alterations in AVP may be a prime target of inquiry in investigations of mechanisms instantiating prenatal programming of postnatal plasticity.

With respect to susceptibility to environmental effects, there is extremely limited work investigating whether variations in AVP ~~isare~~ associated with differences in susceptibility: in consequence, -any and all and thus, conclusions drawn regarding this subject should be considered tentative. However, data do underscore ~~have indicated~~ the relevance of the *AVPR1A* polymorphism, the gene coding for vasopressin 1a receptor, on human behavior, with studies documenting main effects of *AVPR1A* variants on autism (Kim et al., 2002), age of first sexual intercourse (Prichard, Mackinnon, Jorm, & Easteal, 2007), and pair-bonding behavior in men (Walum et al., 2008). Furthermore, there is some evidence to suggest that variation in the *AVPR1A* is related to differences in environmental sensitivity. At a neurological level, *AVPR1A* variants differentially predict amygdala reactivity to faces (Meyer-Lindenberg et al., 2009). In addition, a study by Poulin and colleagues (2012) found that the *AVPR1A* polymorphism interacted with perceived threat to predict commitment to civic duty in a for-better-and-for-worse, differential-susceptibility-related manner. Specifically, individuals who carried the short/long genotype had the highest commitment to civic duty under low-perceived-threat but the lowest commitment under high-perceived-threat conditions. For other genotypes, there was no association between perceived threat and civic commitment. Likewise, research by Tabak and colleagues (2015) showed that administration of intranasal AVP, but not OT, increased empathic concern but only if individuals were exposed to high levels of childhood paternal warmth. There was no association between intranasal AVP and empathetic concern under conditions of low

paternal warmth; thus, this study documented variation in sensitivity to the positive environment only, a phenomenon referred to as vantage sensitivity (Pluess & Belsky, 2013). In sum, research indicates that the AVP system is sensitive to prenatal effects and appears to be linked to human social behavior and environmental sensitivity. Future work should consider **variations-in** AVP as a candidate mechanism by which prenatal stress may instantiate postnatal plasticity.

Also worth considering is that prenatal stress effects on AVP may be mediated through increases in fetal androgen exposure. The vasopressin system is sexually dimorphic and highly steroid responsive. For example, in rats, castration results in a significant decrease of vasopressin expression while testosterone replacement ameliorates such effects (Devries, Buijs, Van Leeuwen, Caffé & Swaab, 1985). In humans, prenatal stress is tied to higher fetal cortisol and, unlike **adults OR RATS?**, fetal cortisol and testosterone are positively correlated **IN WHOM? CHILDREN? SENTENCE INCOMPLETE/UNCLEAR** (Gitau, Adams, Fisk & Glover, 2005). Likewise, multiple studies document effects of prenatal stress on masculinization of brain and behavior, especially in females (e.g., Anderson, Rhees & Fleming, 1985). Findings such as these led Del Giudice and associates (2018) to hypothesize -that fetal androgen exposure may increase developmental plasticity, a proposition that also seems worthy of empirical attention.

Potential Moderators of Plasticity

Having highlighted candidate mechanisms which may link prenatal stress and heightened developmental plasticity, attention is now turned to potential moderators that may enhance or reduce the effect of prenatal stress on susceptibility to postnatal environmental influences. After all, if differential-susceptibility theory stipulates that children should vary in their susceptibility to environmental influences, there is no reason this thinking should not be extended to effects of prenatal stress. Thus, could some children be more susceptible to prenatal programming of postnatal plasticity? Here we address this possibility after considering timing and type of

prenatal stress. We end this section on moderational factors by considering maternal-fetal genetic conflict.

Timing and type of prenatal stress. It is clear from the work reviewed herein that many different types of stressors can influence child development, including maternal anxiety and depression (O'Connor et al. 2003; Van den Bergh et al. 2008), pregnancy-specific anxiety (Huizink et al. 2002), and exposure to acute disasters such as a Canadian ice storm (Laplante et al. 2008) and the 9/11 terrorist attacks (Yehuda et al. 2005). This diversity of stressors also extends to animal work, some of which include repeated restraint (e.g., Henry et al., 1994), electric shock (e.g., Takahashi & Kalin, 1991), chronic-unpredictable stress (e.g., Mueller & Bale, 2008), and social stress (e.g., Brunton & Russell, 2010). These different types of stressors are likely to vary in intensity, duration, and predictability, all of which may result in divergent effects on the mother and fetus.

In particular, evidence indicates that the intensity of prenatal stress may matter with respect to its postnatal consequences. In the previously mentioned work of DiPietro and colleagues (2006), mild prenatal stress was found to positively affect infant motor development and cognitive ability, at least in the advantaged sample they were studying. Such results led the authors to propose a curvilinear response to prenatal stress with the greatest negative effects emerging under intense and chronically stressful conditions and the most positive effects resulting from conditions of mild to moderate stress. Of note is that this hypothesis was empirically confirmed using data on pregnant women who experienced the aforementioned Canadian ice storm (Laplante et al., 2008). Hence, the cited theorizing and research make clear that the intensity of a stressor should be considered when seeking to understand its effects on the child.

Future work should also seek to determine whether the distinctive effects of varying intensity of stress applies equally to different types of stressors (e.g., depression vs. anxiety vs. daily hassles vs. bereavement) and why that might be the case. Perhaps, different stressors ~~are~~^{may be} linked to unique physiological profiles in mothers and therefore exert varying effects on their fetus. Important to note, though, is that multiple stressors frequently co-occur, thus making this research proposition somewhat difficult to address. However, other work, examining the unique influence of particular components ~~of in~~ⁱⁿ a stressful environment, has shown that specific experiences, even if related, may be more or less ~~influential~~^{salient} in ~~regulating~~^{directing} child development (Hartman, Sung, Schlomer, Simpson, & Belsky, 2017).

Relatedly, the timing of prenatal stress may also be important to consider. For example, it has been suggested that perturbations early in pregnancy are likely to produce more severe neurological insults than later stressors, perhaps via effects on placental functions and neural organization (Watson & Cross, 2005). Notable, then, is evidence that exposure to stress in the first trimester rather than later in gestation heightens the risk of schizophrenia (Khashan et al., 2008). Also, work by Davis and Sandman (2010) shows that the effects of maternal cortisol on infant cognitive development is dependent on timing of exposure. In fact, whereas higher maternal cortisol levels early in gestation predicted lower mental development scores in offspring, the very same physiological condition predicted better mental development when it occurred late in gestation! PERHAPS IF THEIR'S WAS A LOW-RISK SAMPLE, THIS SHOULD BE NOTED. Intriguingly, the opposite seems true when it comes to prenatal-stress effects on emotional and behavioral problems during childhood (O'Connor, Heron, Golding, Beveridge, & Glover, 2002). Clearly, it should not be assumed that when it comes to the timing of prenatal stress that effects will be most pronounced when stress occurs early in pregnancy.

Genetic moderation of prenatal stress effects. As previously noted, there is evidence, in humans, that prenatal stress appears to increase postnatal plasticity. Notably, some gene-X-environment interaction work calls attention to the possible genetic moderation of such prenatal programming. As previously noted, the serotonin transporter linked polymorphic region (5-*HTTLPR*) is a genetic variant which has been consistently identified as a genetic marker of plasticity with ~~the~~ short allele carriers showing greater variation in response to postnatal environmental exposures (Belsky & Pluess, 2009, 2013; Van IJzendoorn et al., 2012). Pluess et al. (2011) tested the hypothesis that it would be fetuses carrying the 5-*HTTLPR* short allele who, if exposed to elevated levels of maternal anxiety prenatally ~~—in (measured via self-reported anxiety mid-pregnancy—)~~, would be most likely to develop negatively emotional temperaments; results proved consistent with this proposition.

A study by Babineau and colleagues (2014) extended this work upon examining the interaction of prenatal depression and 5-*HTTLPR* in predicting infant and early childhood behavioral dysregulation. These investigators observed that greater prenatal depression measured mid- or late-pregnancy predicted more infant and early childhood dysregulation from 3 to 36 months of age but, like Pluess et al. (2011), only for short-allele carriers of 5-*HTTLPR* ~~(Babineau et al., 2014)~~. Notably, the detected genetic moderation took the form of differential susceptibility—because when children with short alleles were exposed prenatally to high levels of maternal depression, they had the highest levels of dysregulation, but when exposed to lower or little prenatal depression, they had the lowest levels. Finally, a recent inquiry by Green et al. (2017) revealed that prenatal depression measured mid- to late-pregnancy interacted with a polygenic profile score that was, in part, based on 5-*HTTLPR* in predicting infant negative temperament. After compositing a number of “susceptibility” alleles (i.e., genetic variants shown to make individuals more environmentally responsive) from 5-*HTTLPR* and the dopamine-receptor D4

(*DRD4*) gene, results indicated that prenatal depression only predicted greater infant negative emotionality for those carrying more susceptibility genotypes.

Given this work documenting genetic moderation of prenatal-stress effects on infant temperament, we would encourage future investigators not only to expand their genetic focus beyond the two candidate genes just highlighted—and thus polygenic scores—, but also consider maternal genotype. After all, genetic make-up of the fetus may not only moderate prenatal-stress effects on the infant, but maternal genotype might affect whether mothers differ in their stress-related responses to potentially stress-inducing experiences and exposures. It is possible, after all, that mothers with more susceptible genotypes experience greater subjective stress than do others even when exposed to the same would-be stressor. Because the fetus and mother are biologically related, it will be important to disentangle maternal-genotypic effects from fetal-genotypic effects, possibly through adoption studies or, in the case of animal studies, cross-fostering designs. It is certainly conceivable that fetal and maternal genotype could interact when it comes to prenatal stress influencing the postnatal plasticity of offspring.

Maternal-fetal conflict. Another potential dynamic that could moderate the effects of prenatal stress on offspring plasticity stems from the evolutionary perspective on parent-offspring conflict (Trivers, 1974). : From what we have argued thus far, prenatal stress is thought to program enhanced developmental greater plasticity in the offspring. However If this is true, then there may be an inherent conflict of interest between the mother and the fetus in the optimal results of fetal programming (Del Giudice, 2012). As described in parent-offspring conflict theory (Trivers, 1974; Parker, 1985; Parker et al., 2002; Royle et al., 2004), most parent-offspring pairs only have partial overlap in their genetic interests. As a result, and thus the degree to which a trait (e.g., plasticity) is optimal for the parent may differ from the offspring.

Take, for example, conflict between mother and fetus over fetal growth during pregnancy. It may be advantageous for a fetus to maximize nutrient input from the mother, thereby increasing its robustness, own growth and physical quality but it may be better for the mother to limit-lower her nutrient flow to the fetus, thereby preserving-saving resources for her own health and/or future offspring (THIS IS A BAD CITE; I THINK THE MARCO PREGNANCY CITE I REFERRED TO EARLIER WOULD BE MUCH BETTER. Schlomer et al., 2011). Thus, the optimal levels of nutrient input may conflict between mother and fetus may well “disagree” when it comes to how much nutritional resources should be devoted to the fetus. .

In terms of variations in plasticity, Del Giudice (2012) argued that increased plasticity in the offspring that are exposed to prolonged maternal care may prove be more beneficialbeneficial to the mother than the fetus because she would be more readily able to influence the offspring's development and behavior. This Having a child who is highly plastic to maternal care would afford then-give her the mother the advantage in subsequent instances of parent-child conflict. However, it may be in the best interest of the child to have decreased plasticity to avoid being overly influenced by maternal behavior. But the situation may be even more complicated than this. Consider the possibility, for example, that harsh parenting under conditions of contextual adversity may a way for the mother to, unconsciously, send the message to the (highly plastic?) child to disregard her; that she has limited assistance and insight to offer the child vis-à-vis his/her future well-being; and thus that she or he is better taking guidance from others, including peers.

Whatever the case, appreciation of the inherent conflict between mother and child should inform investigators thinking about This evolutionary perspectiveargument can help

~~us researchers better understand the dynamic between~~ maternal signals of stress during pregnancy and the fetus' reaction to them. It may be the case that some fetuses are able to be easily programmed by prenatal stress to be highly responsive to postnatal care but that others are more "resistant" to it. ~~have greater developmental plasticity while others are not.~~ The placenta may also ~~play have~~ a critical role in this intrauterine dynamic because, as previously described, it acts as ~~the an~~ interface between mother and fetus. Consider in this regard ~~One such example comes from~~ a review describing the role of pCRH in ~~maternal-fetal other-fetus~~ conflict over glucose production (Gangestad, Hooper, & Eaton, 2012). Placental production of CRH is largely released into the mother's bloodstream and stimulates greater maternal glucose production. Thus, higher levels of pCRH are beneficial to the fetus because it increases the flow of nutrients and thus growth rate. However, optimal levels of pCRH for the mother are likely lower than that of the fetus. Consequently, as a possible counter response, mothers can develop a pituitary insensitivity to CRH, ~~making them -and are therefore-~~ less responsive to it.

~~This could Perhaps, this may also be why~~ pCRH may be a more accurate predictor of child development than ~~outcomes as compared to~~ maternal cortisol during pregnancy. It is conceivable that although maternal cortisol may be at comparable levels across pregnancies, some placentas may be more effective in breaking down maternal cortisol ~~whereas~~ while others are not. Thus, the endocrine actions of the placenta may be subject to maternal-fetal conflict. By the same token, it may be the case that a fetus may enact measures, possibly through the placenta, ~~to which could~~ counteract maternal stress signals and therefore reduce plasticity-inducing effects. ~~This raises the issue of whether it is conflict or war that is occurring between mother and fetus!~~

Timing and type of prenatal stress. It is clear from the work reviewed herein that many different types of stressors can influence child development, including maternal anxiety and

depression (O'Connor et al. 2003; Van den Bergh et al. 2008), pregnancy-specific anxiety (Huizink et al. 2002), and exposure to acute disasters such as a Canadian ice storm (Laplante et al. 2008) and 9/11 terrorist attacks (Yehuda et al. 2005). This diversity of stressors also extends to animal work, some of which include repeated restraint (e.g., Henry et al., 1994), electric shock (e.g., Takahashi & Kalin, 1991), chronic-unpredictable stress (e.g., Mueller & Bale, 2008), and social stress (e.g., Brunton & Russell, 2010). These different types of stressors are likely to vary in intensity, duration, and predictability, all of which may result in divergent effects on the mother and fetus.-

In particular, evidence indicates that the intensity of prenatal stress may matter with respect to its postnatal consequences. In the previously mentioned work of DiPietro and colleagues (2006), mild prenatal stress was found to positively affect infant motor development and cognitive ability, at least in the advantaged sample they were studying. Such results led the authors to propose a curvilinear response to prenatal stress with the greatest negative effects emerging under intense and chronically stressful conditions and the most positive effects resulting from conditions of mild to moderate stress. Of note is that this hypothesis was empirically confirmed using data on pregnant women who experienced the aforementioned Canadian ice storm (Laplante et al., 2008). Hence, the cited theorizing and research make clear that the intensity of a stressor should be considered when seeking to understand its effects on the child. Future work should also seek to determine whether the distinctive effects of varying intensity of stress applies equally to different types of stressors (e.g., depression vs. anxiety vs. daily hassles vs. bereavement) and why that might be the case. Perhaps, different stressors may be linked to unique physiological profiles in mothers and therefore exert varying effects on their fetus. Important to note, though, is that multiple stressors frequently co-occur, thus making this

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Relatedly, the timing of prenatal stress may also be important to consider. For example, it has been suggested that perturbations early in pregnancy are likely to produce more severe neurological insults than later stressors, perhaps via effects on placental functions and neural organization (Watson & Cross, 2005). Notable, then, is evidence that exposure to stress in the first trimester rather than later in gestation heightens the risk of schizophrenia (Khashan et al., 2008). Also, work by Davis and Sandman (2010) shows that the effects of maternal cortisol on infant cognitive development is dependent on timing of exposure. In fact, whereas higher maternal cortisol levels early in gestation predicted lower mental development scores in offspring, the very same physiological condition predicted better mental development when it occurred late in gestation! Intriguingly, the opposite seems true when it comes to prenatal-stress effects on emotional and behavioral problems during childhood (O'Connor, Heron, Golding, Beveridge, & Glover, 2002). Clearly, it should not be assumed that when it comes to the timing of prenatal stress that effects will be most pronounced when stress occurs early in pregnancy.

Conclusion

In this paper, we have ~~considered evidence indicating highlighted evidence showing~~ that heightened behavioral and physiological reactivity are markers of increased developmental plasticity and that these markers are associated with prenatal stress. Subsequently, we described and provided evidence, in both human and animal studies, consistent with the hypothesis that prenatal stress programs postnatal plasticity. This led us to ~~posit~~suggest plausible biological

mechanisms, including various neuroendocrine actions ~~and as well as~~ heightened activity in the amygdala, ~~as well as and~~ potential moderators of the prenatal programming of postnatal plasticity. ~~hypothesized pathway~~. Taken together, the work presented in this review certainly suggests that prenatal stress effects on child development should be considered in relation to the postnatal environment, including its aspects supporting and undermining well-being, broadly conceived, full range of the postnatal environment from positive to negative. This effort could fundamentally change how policy-makers and clinicians view and treat prenatal stress. Rather than regarding it as an inherent ill, as most thinking does, it is time to consider it as a process which promotes postnatal plasticity—for better and for worse, depending on the nature of the postnatal environment. Needless to say, enhanced understanding ~~Furthermore, a greater knowledge of events and experiences the factors~~ affecting an organism's responsiveness to the environment has far-reaching implications for early-life intervention, perhaps especially in the case of our understanding, for instance, of remediation strategy for early childhood trauma or abuse (Bateson et al., 2004; Hertzman & Power, 2004).

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