Title
Prenatal programming of postnatal plasticity revisited—And extended

Journal
Development and Psychopathology, 30(3)

ISSN
0954-5794

Authors
Hartman, Sarah
Belsky, Jay

Publication Date
2018-08-01

DOI
10.1017/s0954579418000548

Peer reviewed

Development and Psychopathology **30** (2018), 825–842

doi:10.1017/S0954579418000548

Prenatal programming of postnatal plasticity revisited—And extended

SARAH HARTMAN AND JAY BELSKY
University of California, Davis

Abstract

Two sets of evidence reviewed herein, one indicating that prenatal stress is associated with elevated behavioral and physiological dysregulation and the other that such phenotypic functioning is itself associated with heightened susceptibility to positive and negative environmental influences postnatally, raises the intriguing hypothesis first advanced by Pluess and Belsky (2011) that *prenatal stress fosters, promotes, or "programs" postnatal developmental plasticity*. Here we review further evidence consistent with this proposition, including new experimental research systematically manipulating both prenatal stress and postnatal rearing. Collectively this work would seem to explain why prenatal stress has so consistently been linked to problematic development: stresses encountered prenatally are likely to continue postnatally, thereby adversely affecting the development of children programmed (by prenatal stress) to be especially susceptible to environmental effects. Less investigated are the potential benefits prenatal stress may promote, due to increased plasticity, when the postnatal environment proves to be favorable. Future directions of research pertaining to potential mechanisms instantiating postnatal plasticity and moderators of such prenatal-programming effects are outlined.

Extensive evidence suggests that prenatal stress is a risk factor, undermining child well-being, as reflected in chronic health, behavioral, and cognitive problems (for a review, see Entringer, Buss, & Wadhwa, 2015; Glover, 2014; van den Bergh, Mulder, Mennes, & Glover, 2005). For example, prenatal stress is 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), attention-deficit/hyperactivity disorder symptoms (Grossman et al., 2003), externalizing and anxiety problems (Glover, 2011), and motor and mental developmental disorders (Kofman, 2002). Although such findings are routinely interpreted in the human literature as evidence that prenatal stress disrupts "optimal" development, herein we review evidence for a radically different interpretation of how and why prenatal stress is associated in observational studies with the negative developmental phenotypes to which it has been repeatedly related. We build the case that *prenatal stress programs postnatal developmental plasticity*, further developing an argument first advanced by Pluess and Belsky (2011).

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, Bakermans-Kranenburg, & van IJzendoorn, 2007; Belsky & Pluess, 2009, 2013; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011; Ellis, Shirtcliff, Boyce, Deardorff, & Essex, 2011). Within this first major 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 major 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, sharing recent evidence consistent with this proposition, including new *experimental* research in which prenatal stress is manipulated, as is postnatal rearing. In so doing, we will highlight the many different ways in which prenatal stress has been operationalized in the developmental literature. After reviewing this work, we outline future directions for research, focusing on mechanisms that could instantiate enhanced plasticity and potential moderators of prenatal programming affects. After considering, then, how prenatal stress may promote postnatal plasticity and for whom this may be more and less likely, we conclude by considering the ultimate, evolutionary issue, namely, why such prenatal programming in response to prenatal stress may have evolved.

Differential Susceptibility

By applying an evolutionary analysis to human development, Belsky (1997, 2005; Belsky & Pluess, 2009, 2013) proposed

Address correspondence and reprint requests to: Sarah Hartman, One Shields Avenue, 3321 Hart Hall, Davis, CA 95616; E-mail: slhartman@ucdavis.edu.

that individuals should vary in their susceptibility (i.e., developmental plasticity) to environmental influences and especially those of the rearing environment (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 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 nature should have 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.

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 × 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). Appreciation of the role that temperament might play in making some children more susceptible to environmental influences than others was not the result of any theoretical analysis or expectation but rather emerged as an empirical observation once evidence consistent with differential-susceptibility theorizing was sought. In reviewing relevant evidence, Belsky (2005) observed that the effect of rearing experience on a variety of psychological and behavioral outcomes was consistently greater for a subgroup of infants and toddlers who could be characterized as highly negatively emotional (e.g., irritability, fearfulness, and inhibition) or as having a difficult temperament. Even if such temperamental styles conferred developmental risk under aversive contextual conditions (e.g., maternal depression and 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 and 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 factor. 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 symptomology during the primary-school years (Essex, Armstrong, Burk, Goldsmith, & Boyce, 2011); mother's depressive symptoms with child adjustment (Dix & Yan, 2014); 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 × Temperament interaction, 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. 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).

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's (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 et al., 2007; Belsky & Pluess, 2009, 2013) 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. Of note, this theorizing was post hoc and emerged in attempt to explain unanticipated findings emanating from work carried out a decade earlier by Boyce et al. (1995).

Empirical support for BSC thinking emerged in the years since the theory was promulgated. Evidence consistent with the claim that more physiologically reactive children would prove more susceptible to environmental effects, "for better and for worse," than other children has 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 posttraumatic stress symptoms/antisocial behavior (Saxbe, Margolin, Spies Shapiro, & Baucom, 2012); of the family environment on pubertal development (Ellis, Boyce, et al., 2011); of teacher–child conflict on change in symptom severity (Essex et al., 2011); of harsh discipline on externalizing problems (Chen, Raine, et al., 2015); and of family income on early executive function (Obradović, Portilla, & Ballard, 2016).

Given concerns already raised about the limits of observational research when it comes to inferring causation, it is also notable that there is some experimental evidence documenting the plasticity-enhancing role of elevated physiological reactivity. Specifically, highly reactive children 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 an 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 both of these plasticity markers. It is well documented that prenatal stress, measured in a variety of ways (e.g., maternal anxiety and 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 (e.g., maternal psychological distress and 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 (Huizink, De Medina, Mulder, Visser, & Buitelaar, 2002; van den Bergh et al., 2005). Research also documents associations linking maternal psychological stress during late pregnancy with the increased behavioral reactivity of 4-month-olds (Davis et al., 2004) and maternal psychological distress, during early pregnancy, to irregular sleeping and eating patterns of 6-month-olds and heightened inhibition and negative emotionality of 5-year-olds (Martin, Noyes, Wisenbaker, & Huttenen, 1999). Relatedly, higher levels of maternal cortisol in late pregnancy forecast fussier infant behavior, including more negative facial expressions and increased frequency of crying at 7 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 middle and late pregnancy predict greater infant negativity at 2 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 temperament at 3 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 → birth weight → 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).

Turning to physiological functioning, research reveals that prenatal-stress exposure is associated with dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis in infants and children, as reflected in greater maternal depression in middle pregnancy predicting elevated basal cortisol concentrations in newborns (Field et al., 2004) and higher maternal cortisol in middle and late pregnancy predicting greater cortisol response to a heel-prick 24 hr after birth (Davis, Glynn, Waffarn, & Sandman, 2011). These latter effects appear to be at least partly mediated via epigenetic changes in the glucocorticoid receptor gene (*NR3C1*), which encodes for glucocorticoid receptor, 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 posttraumatic stress disorder had infants with dysregulated diurnal cortisol rhythms at 1 year of age relative to infants of other mothers (Yehuda et al., 2005). These results are consistent with experimentally documented findings in rodent studies indicating that prenatal stress induced by restraint stress or social stress is associated with higher baseline and reactive-corticosterone levels in offspring (Maccari, Krugers, Morley-Fletcher, Szyf, & Brunton, 2014). In summary, then, diverse approaches to measuring prenatal stress, ranging from maternal psychological distress to maternal cortisol levels, highlight its effects on children's emotional and physiological dysregulation 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 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, and 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 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, Novak, Costigan, Atella, and Reusing's (2006) work showing that prenatal stress, measured via maternal psychological distress during middle pregnancy, predicted better infant mental scores in a well-educated, mostly white and married sample. 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 (NICHD 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 to "for better and for worse" parenting effects on behavioral and cognitive functioning (Pluess & Belsky, 2011). More recently, longitudinal work by Sharp, Hill, Hellier, and Pickles (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 girls. The same was not true of children whose mothers experienced little anxiety during pregnancy. 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 of the outcomes measured.

Further evidence of prenatal programming of postnatal plasticity comes from research comparing preterm and full-term babies. There is a substantial body of work showing psychosocial stress to be an etiological risk factor for preterm birth (Shapiro, Fraser, Frasch, & Seguin, 2013), even when controlling for other well-known risk factors (e.g., twin pregnancy, tobacco use, infection, and premature contractions; Lilliecreutz, Laren, Sydsjo, & Josefsson, 2016). Thus, preterm birth can be considered a marker of prenatal stress. Pertinent to the issue of prenatal programming of postnatal plasticity, then, is an investigation that examined the differential effects of the caregiving environment on infant cognitive and social functioning in preterm and full-term infants (Gueron-Sela, Atzaba-Poria, Meiri, & Marks, 2015). Results revealed that preterm infants were more developmentally responsive to their caregiving environment, evincing the greatest social and cognitive functioning when exposed to a high-quality caregiving environment but the lowest social and cognitive functioning when they experienced a low-quality caregiving environment. Caregiving quality did not, however, predict social and cognitive development in the case of full-term infants. These findings are in line with those of earlier work that 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). 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 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 that increase her chances of becoming anxious or depressed during pregnancy, genes that 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 claim that prenatal stress programs postnatal plasticity. 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. However, 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 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, is to conduct an animal experiment. This is 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, such as 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 traitlike fashion across multiple litters, in the amount of care they display toward their pups (Perkeybile, Griffin, & Bales, 2013). Thus, prairie voles are an optimal animal to use in cross-fostering paradigms, which 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 a 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 (unrelated) 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)$\times$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 by low-quality rearing environments. In the case of voles in the control condition that were not prenatally stressed, rearing environmental quality exerted no effect whatsoever on later reactivity. In an 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 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, and 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, further research should consider the interaction between the quality prenatal environment and postnatal environment on outcomes that can range from positive (i.e., high functioning) to negative (i.e., low functioning).

Having said that, there are many other ways that future 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 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 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 and institutional care) prior to a stable placement (Rubin, O'Reilly, Luan, & Localio, 2007). Hence, these children may not only be exposed to several rearing conditions that 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 research should explore how both the differing quality and the timing of exposure to these various settings may influence children's developmental trajectories.

Similar to adoption studies, a gestational cross-fostering research design innovated and employed by Rice et al. (2009) may also help disentangle the effects of genetics and the prenatal environment. Specifically, Rice et al. (2009) studied prenatal effects on child development by examining mothers who were either biologically related or unrelated to their child as a product of in vitro fertilization. By comparing these pairs, Rice et al. (2009) were able to determine the influence of the prenatal environment independent of genetic continuity. Future work may also utilize this novel design

in order to distinguish prenatal stress effects from genetic ones.

Another desiderata of future research should be to determine whether effective treatments for prenatal anxiety and depression (essentially experiments that downregulate prenatal stress) reduce infant's susceptibility to postnatal environmental influences. It is quite conceivable that any random control trials 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 downregulated. 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 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). This type of work could, potentially, further illuminate prenatal-stress effects by reducing 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 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 neural activation and connectivity (e.g., Buss, Davis, Muftuler, Head, & Sandman, 2010), epigenetic machinery (e.g., noncoding RNAs and DNA methyltransferases; Cruceanu, Matosin, & Binder, 2017), and inflammation processes (e.g., Coussons-Read, Okun, & Nettles 2007), all of which could be potential biological mechanisms, these will not be considered in detail in this report.

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 → greater physiological reactivity → 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 and 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 et al. (2011) showing that, in rats, early postnatal stress influences hippocampal DNA methylation in the promoter region of *NR3C1*, the gene coding the glucocorticoid receptor, which regulates the stress response. 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 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*. 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). These methylation patterns were associated with infant birth weight.

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 sympathoadrenomedullary (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 maternal E and NE levels during pregnancy predicted infant soothability, and thus negative emotionality, thereby raising the possibility that maternal activation of the SAM system may be linked to postnatal plasticity (Wroble-Biglan, Dietz, & Pienkosky, 2009).

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 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). While outside the scope of this review, it is likely that the functioning and connectivity of these regions has a major role in developmental plasticity (Moore & Depue, 2016). Therefore, their relation to prenatal stress should be explored further.

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: as a growth factor regulating development of neural systems (Whitaker-Azmitia, Druse, Walker, & Lauder, 1996) and 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 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 (Miyagawa et al., 2011; Mueller & Bale, 2008; van den Hove et al., 2006). 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 second trimester of pregnancy is associated with reduced methylation in the promoter region of maternal and infant *SLC6A4*, the locus of the serotonin gene that codes for the serotonin transporter (Devlin, Brain, Austin, & Oberlander, 2010). Thus, it appears that prenatal stress exerts programming effects on the serotonin system, which is not surprising given the evidence that the HPA and serotonin systems are cross-regulated (see St.-Pierre, Laurent, King, & Vaillancourt, 2016, for review).

In addition to prenatal-stress effects, the serotonin system has been linked to variation in developmental plasticity. 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). Just as significantly, *5-HTTLPR* short alleles have been linked to greater negative emotionality and physiological reactivity, outcomes associated with prenatal stress as previously reviewed, in both humans and nonhuman primates (e.g., Champoux et al., 2002; Lakatos et al., 2003).

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 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, 2014; Carter et al., 2008). In addition, OT and AVP play a critical role in regulating the HPA axis. Specifically, OT can attenuate the stress response by downregulating 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. Some evidence indicates that single nucleotide polymorphisms in the OT receptor gene (*OTR*) moderate environmental effects in a differential-susceptibility-like fashion. Specifically, single nucleotide polymorphisms

in *OTR* moderate effects of perceived threat on charitable behavior (Poulin, Holman, & Buffone, 2012); socioeconomic status on obesity risk (Bush et al., 2017); alcohol use on aggressive behavior in men (Johansson et al., 2012); supportive parenting on adolescent social anxiety (Olofsdotter, Åslund, Furmark, Comasco, & Nilsson, 2017); and harsh parenting on young adult allostatic load (Brody, Miller, Yu, Beach, & Chen, 2016).

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 et al. (2016) found that maternal cortisol during the second trimester predicted greater OT-receptor methylation in neonatal cord blood. In rats, the negative effects of prenatal stress on social behavior were found to be reversed by OT administration (Lee, Brady, Shapiro, Dorsa, & Koenig, 2007). However, given its critical role in quality of early maternal care, it will be imperative for future research to distinguish the effects of the prenatal versus 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 OT-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 OT is research indicating (a) that effects of prenatal stress on social memory in rats is mediated by vasopressin 1a receptor mRNA expression but not OT 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). Of significance also 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 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 are associated with differences in susceptibility. However, data 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 et al. (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 et al. (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.

Worth considering as well 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, Caffe, & Swaab, 1985). In humans, prenatal stress is tied to higher fetal cortisol, and unlike adults, fetal cortisol and testosterone are positively correlated (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 et al. (2018) to hypothesize that fetal androgen exposure may increase developmental plasticity, a proposition that also seems worthy of empirical attention.

Role of the placenta. 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 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, the placenta produces corticotropin-releasing hormone in response to cortisol, which modulates the maternal HPA axis in a positive loop. In addition, the placenta plays a protective role against maternal cortisol by inactivating it using the placental barrier enzyme 11β-hydroxysteroid dehydrogenase Type II (11β-HSD2). This results in only 10%–20% of the cortisol from maternal circulation reaching the fetus (Gitau, Cameron, Fisk, & Glover, 1998). In rats, prenatal stress induced by restraint stress not only increased maternal cortisol but also was linked to a reduction in the expression and activity of the placental 11β-HSD2 (Peña, Monk, & Champagne, 2012). In turn, these epigenetic changes in placental 11β-HSD2 were themselves related to DNA methylation in the fetal brain as well as increases in fetal corticosterone levels (Peña et al., 2012). Furthermore, in humans, greater maternal anxiety measured 1 day prior to birth predicted lower gene expression of placental 11β-HSD2 (O'Donnell et al., 2012) and decreased activity of placental 11β-HSD2 is associated with early development, including fetal growth restriction (Börzsönyi et al., 2012), prematurity (Demendi et al., 2012), and low birthweight (Green et al., 2017).

Considered together, it appears that prenatal stress may alter the transplacental barrier via epigenetic changes in 11β-HSD2, thereby resulting in increased fetal exposure to maternal cortisol, with consequences for phenotypic outcomes. Evidence to such an effect comes from a study by Glover, Bergman, Sarkar, and O'Connor (2009), which examined women at various stages of their pregnancy ranging from early to late. They found that the correlation between maternal and amniotic fluid cortisol levels was greater in women with elevated anxiety compared to less anxious women (Glover et al., 2009). Similarly, prenatal stress may increase placental permeability, and thus fetal exposure, to other hormones. In humans, prenatal stress indexed by maternal psychological distress during late pregnancy has been associated with increased levels of serotonin and NE transporters as well as a downregulation 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). Of special significance to this paper, 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).

Overall, then, the work cited suggests that prenatal stress may increase fetal sensitivity to maternal influences via greater placental permeability. Consequently, one might begin to consider whether all placentas are equally reactive to fluctuations in maternal physiology or whether there might be differences in how sensitive the placenta is, thereby moderating maternal effects on the fetus. One might imagine that some placentas may be very sensitive to changes in maternal physiology, such as greater stress, thus rapidly adjusting accordingly, whereas other placentas may be more resilient and need stronger or more consistent maternal signals to respond. This would have consequences for the fetus with some being more protected than others from the placental changes induced by prenatal stress.

As it turns out, placentas do appear to differ in their sensitivity to maternal signals. One recent study of rats revealed that the placental response of 11β-HSD2 to prenatal stress in the form of social and restraint stress administered daily throughout pregnancy depends on the genetic makeup of the mother (Lucassen et al., 2009). Specifically, rats selectively bred for high anxiety and exposed to prenatal stress showed a greater reduction in placental 11β-HSD2 compared to their low-anxiety counterparts. Furthermore, there is variation in the placental response to stress based on the sex of the fetus. For instance, in response to prenatal stress, placentas of male fetuses tend to become insensitive to glucocorticoid levels, with females remaining sensitive (reviewed in St.-Pierre et al., 2016). This observation suggests that males and females have opposing adaptions to prenatal stress, with males increasing growth at the risk of decreased survival while females experience reduced growth to promote survival (St.-Pierre et al., 2016).

Given this emerging research, future studies should investigate the role of the placenta in prenatal programming of postnatal plasticity. It is clear that the placenta plays a major role in transmitting maternal signals, including stress, to the fetus. It may be the case, as already suggested, that some placentas are more responsive to maternal stress than others, which may either attenuate or amplify the effects of prenatal stress.

Intestinal microbiota. An additional way that prenatal stress may affect a child's susceptibility to environmental influence is through the colonization of intestinal microbiota. It has become increasingly clear that intestinal microbiota influence brain development and behavior via the microbiome–gut–brain axis. For example, alterations in the microbiome have been linked to psychological disorders including depression and anxiety (see Sherwin, Rea, Dinan, & Cryan, 2016, for a review). Specifically, animal studies have shown that germ-free and antibiotic-treated mice exhibit anxiety-like and depressive-like behavior as well as alterations in the serotonergic, neurotrophic, and HPA systems (Bercik et al., 2011). If treated with probiotics, mice showed a reduction in anxiety-like and depressive-like behavior (Bravo et al., 2011), an effect that has been replicated in humans (Messaoudi et al., 2011).

Particularly relevant to this report, microbiome patterns have been linked to temperament and stress physiology, two established markers of developmental plasticity. A number of animal studies indicate that the microbiome regulates activation of the HPA axis with germ-free mice and rats showing elevated stress responses (see Sherwin et al., 2016, for a review). In human infants, microbiota patterns have been

linked to negative temperament with lower diversity and stability of microbiota during the first weeks of life predicting greater crying, fussiness, and colic (de Weerth, Fuentes, Puylaert, & de Vos, 2013; Pärtty, Kalliomäki, Endo, Salminen, & Isolauri, 2012). Moreover, a study by Christian et al. (2015) found that patterns of bacterial diversity were related to sociability and activity levels during early childhood.

A separate line of work has established prenatal stress as a predictor of infant intestinal microbiota. Take, for example, research by Bailey, Lubach, and Coe (2004) indicating that in rhesus monkeys, prenatal stress adversely affected the intestinal microbiota of offspring. Another investigation, using mice, revealed that prenatal stress predicted offspring intestinal microbiota as well as anxiety-like behavior in adults (Gur et al., 2017). These findings extend to humans with both subjective reports of stress and cortisol exposure during pregnancy predicting differences in infant microbiota diversity, which, in turn, are linked to infant health (Zijlmans, Kopela, Riksen-Walraven, de Vos, & de Weerth, 2015).

Taken together, this literature calls attention to another potential mechanistic pathway instantiating enhanced developmental plasticity: prenatal stress affects infant intestinal microbiota, which, in turn, influences environmental susceptibility, perhaps through temperamental negativity. This suggests that there may be utility in evaluating whether intake of probiotics during infancy and early childhood is linked to reduced plasticity via easier temperament.

One important consideration to this proposition, however, is the growing literature that breastfeeding influences infant intestinal microbiota (Penders et al., 2006). Specifically, breastfed infants at 1 month of age show a different intestinal microbiota profile than formula-fed infants even when accounting for other various factors known to affect infant intestinal microbiota (e.g., method of delivery; Penders et al., 2006). In addition, there is evidence that prenatal maternal depression may affect whether and how long mothers chose to breastfeed and also that engaging in breastfeeding may reduce postpartum depression (Figueiredo, Canário, & Field, 2014). Thus, future research aimed at identifying whether changes in infant intestinal microbiota is a mechanism by which prenatal stress influences postnatal plasticity should also consider the maternal influence of breastfeeding on infant microbiota composition and the quality of the postnatal environment.

Potential moderators of plasticity

Having highlighted candidate mechanisms that may link prenatal stress and enhanced 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.

Genetic moderation of prenatal stress effects. As previously noted, there is evidence, in humans, that prenatal stress appears to increase postnatal plasticity. Some Gene × 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 that 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, Belsky, & Bakermans-Kranenburg, 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 (measured via self-reported anxiety during middle pregnancy), would be most likely to develop negatively emotional temperaments; results proved consistent with this proposition. A study by Babineau et al. (2015) 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 during middle 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., 2015). Of note, the detected genetic moderation took the form of differential susceptibility, because when children with short alleles were exposed prenatally to 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 during middle 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 but also to consider maternal genotype. After all, genetic makeup 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, gestational cross-fostering (Rice et al., 2009), or in the case of animal studies, cross-fostering. It is certainly conceivable that fetal and maternal genotype could interact when it comes to prenatal stress influencing the postnatal plasticity of offspring.

Sex differences. Sex differences in response to prenatal stress are often of specific interest especially in animal studies. In rats, some commonly investigated outcomes of prenatal stress, such as anxiety-like behavior and hippocampal neuroplasticity, have been found to be sex dependent such that females display greater anxiety-like behavior while males show decreased hippocampal neuroplasticity as a result of prenatal stress (Zuena et al., 2008). Other prenatal stress outcomes, including depression-like behavior, appear to be not sex dependent (van Waes et al., 2011). In human research, it is even less clear whether and how sex interacts with prenatal stress. One inquiry, using data from pregnant mothers who were exposed to flooding, revealed that higher levels of hardship during pregnancy predicted greater infant irritability, but only for boys (Simcock et al., 2017). Other research finds girls to be more sensitive to prenatal-programming effects (e.g., Sharp et al., 2015). These mixed findings may partly be due to sex-dependent differences in the outcome of interest. For example, boys present more frequently with intellectual impairment and childhood behavioral disorders related to prenatal stress whereas girls may develop subtler, later-onset anxiety and affective disorders (Davis & Pfaff, 2014). Thus, whether one discerns prenatal-stress effects for only males or only females may depend on whether one is investigating, respectively, male- or female-biased phenotypes.

It seems quite possible that there may be different biological mechanisms in males and females that are activated by prenatal stress. As stated previously, the response of the placenta due to prenatal stress appears to differ for male and female. In addition, work with rodents indicates that prenatal stress increases hedonic preferences in males but such preferences are reduced in females due to lower estrogen levels (Reynaert et al., 2016). Taken together, this work suggests that sex may have a significant role in moderating prenatal stress effects; however, more research is needed to determine whether there are consistent sex differences in response to prenatal stress and, specific to this paper, whether, should that be the case, this translates into sex-based differences in postnatal plasticity resulting from prenatal stress.

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, Heron, Golding, & Glover, 2003; van den Bergh, van Calster, Smits, van Huffel, & Lagae, 2008), pregnancy-specific anxiety (Huizink et al., 2002), and exposure to acute disasters such as a Canadian ice storm (Laplante, Brunet, Schmitz, Ciampi, & King, 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, Kabbaj, Simon, Moal, & Maccari, 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 et al. (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 research proposition somewhat difficult to address. However, other work, examining the unique influence of particular components in a stressful environment, has shown that specific experiences, even if related, may be more or less salient in 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). In addition, work by Davis and Sandman (2010) shows that the effects of maternal cortisol on infant cognitive development is dependent on timing of exposure. 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. Yet 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, effects will be most pronounced when stress occurs early in pregnancy.

Conclusion

Having cited evidence, including new experimental research, consistent with the proposal that prenatal stress programs

postnatal plasticity and considered in some detail how such programming might be biologically instantiated and which children might be most susceptible to such programming effects, in concluding this report, we turn attention to the ultimate question central to evolutionary analysis: why should prenatal stress influence postnatal plasticity? Before addressing this issue we should make clear that what we offer is a post hoc argument. Unlike the notion of differential susceptibility to environmental influences, which was based on theoretical first principles rather than existing evidence (Belsky, 1997, 2005; Belsky & Pluess, 2009), the basis of Pluess and Belsky's (2009), the hypothesis that prenatal stress programs postnatal plasticity was derived from consideration of two independent sets of evidence, as made clear in the opening paragraphs of this paper.

Prenatal-stress research is often framed in terms of the fetal-programming hypothesis, which stipulates that the fetus adapts its phenotype to the anticipated postnatal environment based on maternal cues regarding the quality of the extrauterine ecology (Barker, 1998; Bateson et al., 2004; Gluckman, Hanson, Spencer, & Bateson, 2005). The evolutionary biologic here is that such a "predictive adaptive response" (PAR) would increase the likelihood of the developing individual fitting, both biologically and behaviorally, the specific environment in which he or she will live postnatally, thereby increasing reproductive fitness (see Belsky, 2012; Belsky, Steinberg, & Draper, 1991, for related theorizing and evidence about PAR). According to the original formulation of the prenatal-programming hypothesis, a fetus exposed to prenatal stress should develop a "thrifty" phenotype (i.e., small body size) because it would be advantageous in a food-limited and harsh environment. After all, a larger body would require greater nutritional resources than a smaller one to remain healthy.

Although this PAR-related view seems to make intuitive sense, it would seem to disregard the fact that the future is inherently uncertain and thus the prenatal environment may not accurately map on to future postnatal conditions. Were that so, a developmental mismatch would occur, as previously noted. Hence, it may not always be beneficial to canalize development according to the intrauterine environment. Given this, we still need to address the question of why, from an evolutionary perspective, prenatal stress would foster greater responsiveness to the postnatal environment.

Insight into this issue would seem to come from considering the mother herself. One possibility, suggested by M.B. Hennessy (personal communication, November 8, 2015) is that if a woman is stressed during pregnancy, she is not fitting her environment very well. Should that be the case, it would seem advantageous for the fetus to adopt a wait-and-see approach, being especially sensitive to the postnatal environment before committing to a developmental trajectory (see Frankenhuis & Del Giudice, 2012). After all, the fetus might not necessarily "know" whether the stress experienced by the mother is state or trait dependent, meaning temporary or enduring. If it is enduring, there will always be time for the plasticity-enhanced child to regulate development in accordance with a stressful postnatal world. Recall that this was the very reason why we think that so much evidence exists linking prenatal stress with compromised development.

Now consider the case of the pregnant mother who experiences very little stress. It seems likely that this would be because she fits the environment well, has long done so, and expects to continue to do so well into the future. Under such conditions, it would seem advantageous for the fetus to canalize its development, based on maternal cues, earlier, in pregnancy, rather than later, following parturition.

In addition to this proposition, another possibility, suggested by D.W. Belsky (personal communication, January 26, 2018), is that prenatal stress decanalizes development, just as do some postnatal stressors (Burrows & Hannan, 2013; Chen, Nolte, & Schlotterer, 2015). The evolutionary reasoning behind this is that stress conveys to the developing organism that its otherwise canalized development is not likely to enable it to succeed (in reproductive-fitness terms), and so the likelihood of reproductive success might be increased if the organism deviated from its previous canalized path. One way of doing so could be to "take instructions" from the developmental environment and thus be particularly susceptible to postnatal experiences and exposures.

In conclusion, then, we have advanced—and extended—herein the claim that prenatal stress promotes developmental plasticity by increasing susceptibility to postnatal environmental experiences and exposures (Pluess & Belsky, 2011). In addition to reviewing the Pluess and Belsky (2011) proposal and citing new evidence consistent with it, we have considered how such enhanced plasticity might be instantiated, which children might be most susceptible to such prenatal-stress effects, and even why development may operate in the way we have hypothesized that it does. In so doing we have further developed a view of prenatal stress profoundly different from the prevailing one, which considers only adverse effects of such early life experience. It is our hope that the evidence and ideas advanced herein will stimulate further research by encouraging other investigators to look at the potential "upside" of prenatal stress when infants experience supportive rearing milieus postnatally. Even if more empirical support is needed, the work we have cited and the argument we have advanced has the potential to inform policy and intervention. Radically, one might even consider, should further support emerge for the view central to this report, promoting prenatal stress when there is every reason to believe that the postnatal environment will be highly supportive of developmental well-being.

At the same time, one should not lose sight of the developmental consequences of prenatal stress when the postnatal world remains highly stress inducing. Not only would the child exposed to such a "double whammy" be adversely affected by it, but because of his or her enhanced plasticity, this sequelae would be radically different from how this very child might have developed had the postnatal world

proved supportive. In such cases, the human capital development cost could be huge: a child highly susceptible to postnatal developmental exposures and experiences would have its development severely compromised rather than enhanced. Just imagine a world in which such children could experience just the opposite kind of life than many no doubt will.

References

Anderson, D. K., Rhees, R. W., & Fleming, D. E. (1985). Effects of prenatal stress on differentiation of the sexually dimorphic nucleus of the preoptic area (SDN-POA) of the rat brain. *Brain Research*, *332*, 113–118.

Aye, I. L., & Keelan, J. A. (2013). Placental ABC transporters, cellular toxicity and stress in pregnancy. *Chemico-Biological Interactions*, *203*, 456–466. doi:10.1016/j.cbi.2013.03.007

Babineau, V., Green, C. G., Jolicoeur-Martineau, A., Bouvette-Turcot, A. A., Minde, K., Sassi, R., . . . Lydon, J. (2015). Prenatal depression and 5-HTTLPR interact to predict dysregulation from 3 to 36 months–A differential susceptibility model. *Journal of Child Psychology and Psychiatry*, *56*, 21–29. doi:10.1111/jcpp.12246

Baibazarova, E., van de Beek, C., Cohen-Kettenis, P. T., Buitelaar, J., Shelton, K. H., & van Goozen, S. H. (2013). Influence of prenatal maternal stress, maternal plasma cortisol and cortisol in the amniotic fluid on birth outcomes and child temperament at 3 months. *Psychoneuroendocrinology*, *38*, 907–915. doi:10.1016/j.psyneuen.2012.09.015

Bailey, M. T., Lubach, G. R., & Coe, C. L. (2004). Prenatal stress alters bacterial colonization of the gut in infant monkeys. *Journal of Pediatric Gastroenterology and Nutrition*, *38*, 414–421. doi: 10.1097/00005176-200404000-00009

Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2015). The hidden efficacy of interventions: Gene × Environment experiments from a differential susceptibility perspective. *Annual Review of Psychology*, *66*, 381–409.

Barker, D. J. P. (1998). *Mothers, babies and health in later life*. Philadelphia, PA: Elsevier Health Sciences.

Bateson, P., Barker, D., Clutton-Brock, T., Deb, D., D'udine, B., Foley, R. A., . . . McNamara, J. (2004). Developmental plasticity and human health. *Nature*, *430*, 419–421. doi:10.1038/nature02725

Belsky, J. (1997). Variation in susceptibility to rearing influences: An evolutionary argument. *Psychological Inquiry*, *8*, 182–186. doi:10.1207/s15327965pli0803_3

Belsky, J. (2000). Conditional and alternative reproductive strategies: Individual differences in susceptibility to rearing experiences. In J. L. Rodgers, D. C. Rowe & W. B. Miller (Eds.), *Genetic influences on human fertility and sexuality: Theoretical and empirical contributions from the biological and behavioral sciences* (pp. 127–146). Boston: Springer.

Belsky, J. (2005). Differential susceptibility to rearing influences: An evolutionary hypothesis and some evidence. In B. Ellis & D. Bjorklund (Eds.), *Origins of the social mind: Evolutionary psychology and child development* (pp. 139–163). New York: Guildford Press.

Belsky, J. (2012). The development of human reproductive strategies: Progress and prospects. *Current Directions in Psychological Science*, *21*, 310–316. doi:10.1177/0963721412453588

Belsky, J., Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2007). For better and for worse: Differential susceptibility to environmental influences. *Current Directions in Psychological Science*, *16*, 300–304. doi:10.1111/j.1467-8721.2007.00525.x

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin*, *135*, 885. doi:10.1037/a0017376

Belsky, J., & Pluess, M. (2013). Beyond risk, resilience, and dysregulation: Phenotypic plasticity and human development. *Development and Psychopathology*, *25*, 1243. doi:10.1017/s095457941300059x

Belsky, J., Steinberg, L., & Draper, P. (1991). Childhood experience, interpersonal development, and reproductive strategy: An evolutionary theory of socialization. *Child Development*, *62*, 647–670. doi:10.1111/j.1467-8624.1991.tb01558.x

Bercik, P., Denou, E., Collins, J., Jackson, W., Lu, J., Jury, J., . . . Verdu, E. F. (2011). The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. *Gastroenterology*, *141*, 599–609. doi:10.1053/j.gastro.2011.04.052

Blakeley, P. M., Capron, L. E., Jensen, A. B., O'Donnell, K. J., & Glover, V. (2013). Maternal prenatal symptoms of depression and down regulation of placental monoamine oxidase A expression. *Journal of Psychosomatic Research*, *75*, 341–345. doi:10.1016/j.jpsychores.2013.07.002

Bloch, B., Guitteny, A. F., Chouham, S., Mougin, C., Roget, A., & Teoule, R. (1990). Topography and ontogeny of the neurons expressing vasopressin, oxytocin, and somatostatin genes in the rat brain: An analysis using radioactive and biotinylated oligonucleotides. *Cellular and Molecular Neurobiology*, *10*, 99–112. doi:10.1007/BF00733638

Bogdan, R., Agrawal, A., Gaffrey, M. S., Tillman, R., & Luby, J. L. (2014). Serotonin transporter-linked polymorphic region (5-HTTLPR) genotype and stressful life events interact to predict preschool-onset depression: A replication and developmental extension. *Journal of Child Psychology and Psychiatry*, *55*, 448–457. doi:10.1111/jcpp.12142

Börzsönyi, B., Demendi, C., Pajor, A., Rigó, J., Marosi, K., Ágota, A., . . . Joó, J. G. (2012). Gene expression patterns of the 11β-hydroxysteroid dehydrogenase 2 enzyme in human placenta from intrauterine growth restriction: The role of impaired feto-maternal glucocorticoid metabolism. *European Journal of Obstetrics and Gynecology and Reproductive Biology*, *161*, 12–17. doi:10.1016/j.ejogrb.2011.12.013

Boyce, W. T., Adams, S., Tschann, J. M., Cohen, F., Wara, D., & Gunnar, M. R. (1995). Adrenocortical and behavioral predictors of immune responses to starting school. *Pediatric Research*, *38*, 1009–1017. doi:10.1203/00006450-199512000-00030

Boyce, W. T., & Ellis, B. J. (2005). Biological sensitivity to context: I. an evolutionary–developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology*, *17*, 271–301. doi:10.1017/s0954579405050145

Bravo, J. A., Forsythe, P., Chew, M. V., Escaravage, E., Savignac, H. M., Dinan, T. G., . . . Cryan, J. F. (2011). Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proceedings of the National Academy of Sciences*, *108*, 16050–16055. doi:10.1073/pnas.1102999108

Brody, G. H., Miller, G. E., Yu, T., Beach, S. R., & Chen, E. (2016). Supportive family environments ameliorate the link between racial discrimination and epigenetic aging: A replication across two longitudinal cohorts. *Psychological Science*, *27*, 530–541. doi:10.1177/0956797615626703

Brunton, P. J., & Russell, J. A. (2010). Prenatal social stress in the rat programmes neuroendocrine and behavioural responses to stress in the adult offspring: Sex-specific effects. *Journal of Neuroendocrinology*, *22*, 258–271. doi:10.1111/j.1365-2826.2010.01969.x

Burrows, E. L., & Hannan, A. J. (2013). Decanalization mediating gene-environment interactions in schizophrenia and other psychiatric disorders with neurodevelopmental etiology. *Frontiers in Behavioral Neuroscience*, *7*, 157.

Bush, N. R., Allison, A. L., Miller, A. L., Deardorff, J., Adler, N. E., & Boyce, W. T. (2017). Socioeconomic disparities in childhood obesity risk: Association with an oxytocin receptor polymorphism. *JAMA Pediatrics*, *171*, 61–67.

Buss, C., Davis, E. P., Muftuler, L. T., Head, K., & Sandman, C. A. (2010). High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6–9-year-old children. *Psychoneuroendocrinology*, *35*, 141–153. doi:10.1016/j.psyneuen.2009.07.010

Canli, T., & Lesch, K. P. (2007). Long story short: The serotonin transporter in emotion regulation and social cognition. *Nature Neuroscience*, *10*, 1103–1109. doi:10.1038/nn1964

Carter, C. S. (2014). Oxytocin pathways and the evolution of human behavior. *Annual Review of Psychology*, *65*, 17–39. doi:10.1146/annurev-psych-010213-115110

Carter, C. S., Grippo, A. J., Pournajafi-Nazarloo, H., Ruscio, M. G., & Porges, S. W. (2008). Oxytocin, vasopressin and sociality. *Progress in Brain Research*, *170*, 331–336. doi:10.1016/s0079-6123(08)00427-5

Champoux, M., Bennett, A., Shannon, C., Higley, J. D., Lesch, K. P., & Suomi, S. J. (2002). Serotonin transporter gene polymorphism, differential early rearing, and behavior in rhesus monkey neonates. *Molecular Psychiatry*, *7*, 1058. doi:10.1038/sj.mp.4001157

Chen, F. R., Raine, A., Rudo-Hutt, A. S., Glenn, A. L., Soyfer, L., & Granger, D. A. (2015). Harsh discipline and behavior problems: The moderating effects of cortisol and alpha-amylase. *Biological Psychology*, *104*, 19–27. doi:10.1016/j.biopsycho.2014.11.005

Chen, J., Nolte, V., & Schlötterer, C. (2015). Temperature stress mediates decanalization and dominance of gene expression in Drosophila melanogaster. *PLOS Genetics*, *11*, e1004883.

Christian, L. M., Galley, J. D., Hade, E. M., Schoppe-Sullivan, S., Dush, C. K., & Bailey, M. T. (2015). Gut microbiome composition is associated with temperament during early childhood. *Brain, Behavior, and Immunity*, *45*, 118–127. doi:10.1016/j.bbi.2014.10.018

Cicchetti, D., Rogosch, F. A., & Thibodeau, E. L. (2012). The effects of child maltreatment on early signs of antisocial behavior: Genetic moderation by tryptophan hydroxylase, serotonin transporter, and monoamine oxidase A genes. *Development and Psychopathology*, *24*, 907–928. doi:10.1017/S0954579612000442

Conradt, E., Lester, B. M., Appleton, A. A., Armstrong, D. A., & Marsit, C. J. (2013). The roles of DNA methylation of NR3C1 and 11β-HSD2 and exposure to maternal mood disorder in utero on newborn neurobehavior. *Epigenetics*, *8*, 1321–1329. doi:10.4161/epi.26634

Conradt, E., Measelle, J., & Ablow, J. C. (2013). Poverty, problem behavior, and promise: Differential susceptibility among infants reared in poverty. *Psychological Science*, *24*, 235–242. doi:10.1177/0956797612457381

Conway, A., & Stifter, C. A. (2012). Longitudinal antecedents of executive function in preschoolers. *Child Development*, *83*, 1022–1036. doi:10.1111/j.1467-8624.2012.01756.x

Coussons-Read, M. E., Okun, M. L., & Nettles, C. D. (2007). Psychosocial stress increases inflammatory markers and alters cytokine production across pregnancy. *Brain, Behavior, and Immunity*, *21*, 343–350. doi:10.1016/j.bbi.2006.08.006

Cruceanu, C., Matosin, N., & Binder, E. B. (2017). Interactions of early-life stress with the genome and epigenome: From prenatal stress to psychiatric disorders. *Current Opinion in Behavioral Sciences*, *14*, 167–171. doi:10.1016/j.cobeha.2017.04.001

Davies, P. T., Sturge-Apple, M. L., & Cicchetti, D. (2011). Interparental aggression and children's adrenocortical reactivity: Testing an evolutionary model of allostatic load. *Development and Psychopathology*, *23*, 801–814. doi:10.1017/S0954579411000319

Davis, E. P., Glynn, L. M., Schetter, C. D., Hobel, C., Chicz-Demet, A., & Sandman, C. A. (2007). Prenatal exposure to maternal depression and cortisol influences infant temperament. *Journal of the American Academy of Child and Adolescent Psychiatry*, *46*, 737–746. doi:10.1097/chi.0b013e318047b775

Davis, E. P., Glynn, L. M., Waffarn, F., & Sandman, C. A. (2011). Prenatal maternal stress programs infant stress regulation. *Journal of Child Psychology and Psychiatry*, *52*, 119–129. doi:10.1111/j.1469-7610.2010.02314.x

Davis, E. P., & Pfaff, D. (2014). Sexually dimorphic responses to early adversity: Implications for affective problems and autism spectrum disorder. *Psychoneuroendocrinology*, *49*, 11–25. doi:10.1016/j.psyneuen.2014.06.014

Davis, E. P., & Sandman, C. A. (2010). The timing of prenatal exposure to maternal cortisol and psychosocial stress is associated with human infant cognitive development. *Child Development*, *81*, 131–148. doi:10.1111/j.1467-8624.2009.01385.x

Davis, E. P., Snidman, N., Wadhwa, P. D., Glynn, L. M., Schetter, C. D., & Sandman, C. A. (2004). Prenatal maternal anxiety and depression predict negative behavioral reactivity in infancy. *Infancy*, *6*, 319–331. doi:10.1207/s15327078in0603_1

Del Giudice, M., Barrett, E. S., Belsky, J., Hartman, S., Martel, M. M., Sangenstedt, S., & Kuzawa, C. W. (2018). Individual differences in developmental plasticity: A role for early androgens? *Psychoneuroendocrinology*, *90*, 165–173.

Demendi, C., Börzsönyi, B., Pajor, A., Rigó, J., Nagy, Z. B., Szentpéteri, I., & Joó, J. G. (2012). Abnormal fetomaternal glucocorticoid metabolism in the background of premature delivery: Placental expression patterns of the 11β-hydroxysteroid dehydrogenase 2 gene. *European Journal of Obstetrics and Gynecology and Reproductive Biology*, *165*, 210–214. doi:10.1016/j.ejogrb.2012.08.009

Devlin, A. M., Brain, U., Austin, J., & Oberlander, T. F. (2010). Prenatal exposure to maternal depressed mood and the MTHFR C677T variant affect SLC6A4 methylation in infants at birth. *PLOS ONE*, *5*, e12201. doi:10.1371/journal.pone.0012201

DeVries, G. J., Buijs, R. M., van Leeuwen, F. W., Caffe, A. R., & Swaab, D. F. (1985). The vasopressinergic innervation of the brain in normal and castrated rats. *Journal of Comparative Neurology*, *233*, 236–254. doi:10.1002/cne.902330206

de Weerth, C., Fuentes, S., Puylaert, P., & de Vos, W. M. (2013). Intestinal microbiota of infants with colic: Development and specific signatures. *Pediatrics*, *131*, e550–e558. doi: 10.1542/peds.2012-1449

de Weerth, C., van Hees, Y., & Buitelaar, J. K. (2003). Prenatal maternal cortisol levels and infant behavior during the first 5 months. *Early Human Development*, *74*, 139–151. doi:10.1016/s0378-3782(03)00088-4

Dich, N., Doan, S. N., & Evans, G. W. (2015). Children's emotionality moderates the association between maternal responsiveness and allostatic load: Investigation into differential susceptibility. *Child Development*, *86*, 936–944. doi:10.1111/cdev.12346

DiPietro, J. A., Novak, M. F., Costigan, K. A., Atella, L. D., & Reusing, S. P. (2006). Maternal psychological distress during pregnancy in relation to child development at age two. *Child Development*, *77*, 573–587. doi:10.1111/j.1467-8624.2006.00891.x

Dix, T., & Yan, N. (2014). Mothers' depressive symptoms and infant negative emotionality in the prediction of child adjustment at age 3: Testing the maternal reactivity and child vulnerability hypotheses. *Development and Psychopathology*, *26*, 111–124. doi:10.1017/S0954579413000898

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2011). Differential susceptibility to the environment: An evolutionary–neurodevelopmental theory. *Development and Psychopathology*, *23*, 7–28. doi:10.1017/S0954579410000611

Ellis, B. J., Shirtcliff, E. A., Boyce, W. T., Deardorff, J., & Essex, M. J. (2011). Quality of early family relationships and the timing and tempo of puberty: Effects depend on biological sensitivity to context. *Development and Psychopathology*, *23*, 85–99. doi:10.1017/S0954579410000660

Entringer, S., Buss, C., & Wadhwa, P. D. (2015). Prenatal stress, development, health and disease risk: A psychobiological perspective—2015 Curt Richter Award Paper. *Psychoneuroendocrinology*, *62*, 366–375. doi:10.1016/j.psyneuen.2015.08.019

Essex, M. J., Armstrong, J. M., Burk, L. R., Goldsmith, H. H., & Boyce, W.T. (2011). Biological sensitivity to context moderates the effects of the early teacher–child relationship on the development of mental health by adolescence. *Development and Psychopathology*, *23*, 149–161. doi:10.1017/s0954579410000702

Field, T., Diego, M., Dieter, J., Hernandez-Reif, M., Schanberg, S., Kuhn, C., . . . Bendell, D. (2004). Prenatal depression effects on the fetus and the newborn. *Infant Behavior and Development*, *27*, 216–229. doi:10.1016/s0163-6383(04)00012-8

Figueiredo, B., Canário, C., & Field, T. (2014). Breastfeeding is negatively affected by prenatal depression and reduces postpartum depression. *Psychological Medicine*, *44*, 927–936.

Frankenhuis, W. E., & Del Giudice, M. (2012). When do adaptive developmental mechanisms yield maladaptive outcomes? *Developmental Psychology*, *48*, 628.

Gaspar, P., Cases, O., & Maroteaux, L. (2003). The developmental role of serotonin: News from mouse molecular genetics. *Nature Reviews Neuroscience*, *4*, 1002–1012. doi:10.1038/nrn1256

Gitau, R., Adams, D., Fisk, N. M., & Glover, V. (2005). Fetal plasma testosterone correlates positively with cortisol. *Archives of Disease in Childhood—Fetal and Neonatal Edition*, *90*, F166–F169.

Gitau, R., Cameron, A., Fisk, N. M., & Glover, V. (1998). Fetal exposure to maternal cortisol. *Lancet*, *352*, 707–708. doi:10.1016/S0140-6736(05)60824-0

Glover, V. (2011). Annual Research Review: Prenatal stress and the origins of psychopathology: An evolutionary perspective. *Journal of Child Psychology and Psychiatry*, *52*, 356–367. doi:10.1111/j.1469-7610.2011.02371.x

Glover, V. (2014). Maternal depression, anxiety and stress during pregnancy and child outcome; what needs to be done. *Best Practice & Research: Clinical Obstetrics & Gynaecology*, *28*, 25–35. doi:10.1016/j.bpobgyn.2013.08.017

Glover, V., Bergman, K., Sarkar, P., & O'Connor, T. G. (2009). Association between maternal and amniotic fluid cortisol is moderated by maternal anxiety. *Psychoneuroendocrinology*, *34*, 430–435.

Gluckman, P. D., Hanson, M. A., Spencer, H. G., & Bateson, P. (2005). Environmental influences during development and their later consequences for health and disease: Implications for the interpretation of empirical studies. *Proceedings of the Royal Society of London B: Biological Sciences*, *272*, 671–677. doi:10.1098/rspb.2004.3001

Green, C. G., Babineau, V., Jolicoeur-Martineau, A., Bouvette-Turcot, A. A., Minde, K., Sassi, R., . . . Steiner, M. (2017). Prenatal maternal depression and child serotonin transporter linked polymorphic region (5-HTTLPR) and dopamine receptor D4 (DRD4) genotype predict negative emotionality from 3 to 36 months. *Development and Psychopathology*, *29*, 901–917. doi:10.1017/S0954579416000560

Grossman, A. W., Churchill, J. D., McKinney, B. C., Kodish, I. M., Otte, S. L., & Greenough, W. T. (2003). Experience effects on brain develop-

ment: Possible contributions to psychopathology. *Journal of Child Psychology and Psychiatry*, *44*, 33–63. doi:10.1111/1469-7610.t01-1-00102

Grundwald, N. J., Benítez, D. P., & Brunton, P. J. (2016). Sex-dependent effects of prenatal stress on social memory in rats: A role for differential expression of central vasopressin-1a receptors. *Journal of Neuroendocrinology*, *28*. doi:10.1111/jne.12343

Gueron-Sela, N., Atzaba-Poria, N., Meiri, G., & Marks, K. (2015). The caregiving environment and developmental outcomes of preterm infants: Diathesis stress or differential susceptibility effects? *Child Development*, *86*, 1014–1030. doi:10.1111/cdev.12359

Gur, T. L., Shay, L., Palkar, A. V., Fisher, S., Varaljay, V. A., Dowd, S., & Bailey, M. T. (2017). Prenatal stress affects placental cytokines and neurotrophins, commensal microbes, and anxiety-like behavior in adult female offspring. *Brain, Behavior, and Immunity*, *64*, 50–58. doi:10.1016/j.bbi.2016.12.021

Gutteling, B. M., de Weerth, C., & Buitelaar, J. K. (2005). Prenatal stress and children's cortisol reaction to the first day of school. *Psychoneuroendocrinology*, *30*, 541–549. doi: 10.1016/j.psyneuen.2005.01.002

Hankin, B. L., Nederhof, E., Oppenheimer, C. W., Jenness, J., Young, J. F., Abela, J. R. Z., . . . Oldehinkel, A. J. (2011). Differential susceptibility in youth: Evidence that 5-HTTLPR × Positive Parenting is associated with positive affect "for better and worse." *Translational Psychiatry*, *1*, e44. doi:10.1038/tp.2011.44

Hartman, S., Freeman, S. M., Bales, K. L., & Belsky, J. (2018). Prenatal stress as a risk—and opportunity—factor. *Psychological Science*, *29*, 572–580.

Hartman, S., Sung, S., Simpson, J. A., Schlomer, G. L., & Belsky, J. (2017). Decomposing environmental unpredictability in forecasting adolescent and young adult development: A two-sample study. *Development and Psychopathology*. Advance online publication.

Henry, C., Kabbaj, M., Simon, H., Moal, M., & Maccari, S. (1994). Prenatal stress increases the hypothalamo-pituitary-adrenal axis response in young and adult rats. *Journal of Neuroendocrinology*, *6*, 341–345. doi:10.1111/j.1365-2826.1994.tb00591.x

Hompes, T., Izzi, B., Gellens, E., Morreels, M., Fieuws, S., Pexsters, A., . . . Verhaeghe, J. (2013). Investigating the influence of maternal cortisol and emotional state during pregnancy on the DNA methylation status of the glucocorticoid receptor gene (NR3C1) promoter region in cord blood. *Journal of Psychiatric Research*, *47*, 880–891. doi:10.1016/j.jpsychires.2013.03.009

Huizink, A. C., De Medina, P. G. R., Mulder, E. J., Visser, G. H., & Buitelaar, J. K. (2002). Psychological measures of prenatal stress as predictors of infant temperament. *Journal of the American Academy of Child & Adolescent Psychiatry*, *41*, 1078–1085.

Jaffee, S. R., & Price, T. S. (2007). Gene–environment correlations: A review of the evidence and implications for prevention of mental illness. *Molecular Psychiatry*, *12*, 432–442. doi:10.1038/sj.mp.4001950

Jansson, T., & Powell, T. L. (2007). Role of the placenta in fetal programming: Underlying mechanisms and potential interventional approaches. *Clinical Science*, *113*, 1–13. doi:10.1042/CS20060339

Johansson, A., Bergman, H., Corander, J., Waldman, I. D., Karrani, N., Salo, B., . . . Westberg, L. (2012). Alcohol and aggressive behavior in men—Moderating effects of oxytocin receptor gene (OXTR) polymorphisms. *Genes, Brain and Behavior*, *11*, 214–221. doi:10.1111/j.1601-183X.2011.00744.x

Kertes, D. A., Kamin, H. S., Hughes, D. A., Rodney, N. C., Bhatt, S., & Mulligan, C. J. (2016). Prenatal maternal stress predicts methylation of genes regulating the hypothalamic–pituitary–adrenocortical system in mothers and newborns in the Democratic Republic of Congo. *Child Development*, *87*, 61–72. doi:10.1111/cdev.12487

Khashan, A. S., Abel, K. M., McNamee, R., Pedersen, M. G., Webb, R. T., Baker, P. N., . . . Mortensen, P. B. (2008). Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. *Archives of General Psychiatry*, *65*, 146–152. doi:10.1001/archgenpsychiatry.2007.20

Kim, S., & Kochanska, G. (2012). Child temperament moderates effects of parent–child mutuality on self-regulation: A relationship-based path for emotionally negative infants. *Child Development*, *83*, 1275–1289. doi:10.1111/j.1467–8624.2012.01778.x

Kim, S. J., Young, L. J., Gonen, D., Veenstra-vanderWeele, J., Courchesne, R., Courchesne, E., . . . Insel, T. R. (2002). Transmission disequilibrium testing of arginine vasopressin receptor 1A (AVPR1A) polymorphisms in autism. *Molecular Psychiatry*, *7*, 503. doi:10.1038/sj.mp.4001125

Kochanska, G., Kim, S., Barry, R. A., & Philibert, R. A. (2011). Children's genotypes interact with maternal responsive care in predicting children's competence: Diathesis–stress or differential susceptibility? *Development and Psychopathology*, *23*, 605–616. doi:10.1017/S0954579411000071

Kofman, O. (2002). The role of prenatal stress in the etiology of developmental behavioural disorders. *Neuroscience and Biobehavioral Reviews*, *26*, 457–470. doi:10.1016/S0149-7634(02)00015-5

Lakatos, K., Nemoda, Z., Birkas, E., Ronai, Z., Kovacs, E., Ney, K., . . . Gervai, J. (2003). Association of D4 dopamine receptor gene and serotonin transporter promoter polymorphisms with infants' response to novelty. *Molecular Psychiatry*, *8*, 90–97. doi:10.1038/sj.mp.4001212

Landry, S. H., Smith, K. E., & Swank, P. R. (2006). Responsive parenting: Establishing early foundations for social, communication, and independent problem-solving skills. *Developmental Psychology*, *42*, 627. doi:10.1037/0012-1649.42.4.627

Landry, S. H., Smith, K. E., Swank, P. R., Assel, M. A., & Vellet, S. (2001). Does early responsive parenting have a special importance for children's development or is consistency across early childhood necessary? *Developmental Psychology*, *37*, 387. doi:10.1037/0012-1649.37.3.387

Laplante, D. P., Barr, R. G., Brunet, A., Du Fort, G. G., Meaney, M. L., Saucier, J. F., . . . King, S. (2004). Stress during pregnancy affects general intellectual and language functioning in human toddlers. *Pediatric Research*, *56*, 400–410. doi:10.1203/01.PDR.0000136281.34035.44

Laplante, D. P., Brunet, A., & King, S. (2015). The effects of maternal stress and illness during pregnancy on infant temperament: Project Ice Storm. *Pediatric Research*, *79*, 107–113. doi:10.1038/pr.2015.177

Laplante, D. P., Brunet, A., Schmitz, N., Ciampi, A., & King, S. (2008). Project Ice Storm: prenatal maternal stress affects cognitive and linguistic functioning in $5\frac{1}{2}$-year-old children. *Journal of the American Academy of Child & Adolescent Psychiatry*, *47*, 1063–1072. doi:10.1097/CHI.0b013e31817eec80

Laurent, H. K., Leve, L. D., Neiderhiser, J. M., Natsuaki, M. N., Shaw, D. S., Harold, G. T., & Reiss, D. (2013). Effects of prenatal and postnatal parent depressive symptoms on adopted child HPA regulation: Independent and moderated influences. *Developmental Psychology*, *49*, 876. doi:10.1037/a0028800

Lee, P. R., Brady, D. L., Shapiro, R. A., Dorsa, D. M., & Koenig, J. I. (2007). Prenatal stress generates deficits in rat social behavior: Reversal by oxytocin. *Brain Research*, *1156*, 152–167. doi:10.1016/j.brainres.2007.04.042

Lilliecreutz, C., Larén, J., Sydsjö, G., & Josefsson, A. (2016). Effect of maternal stress during pregnancy on the risk for preterm birth. *BMC Pregnancy and Childbirth*, *16*, 5. doi:10.1186/s12884-015-0775-x

Lucassen, P. J., Bosch, O. J., Jousma, E., Krömer, S. A., Andrew, R., Seckl, J. R., & Neumann, I. D. (2009). Prenatal stress reduces postnatal neurogenesis in rats selectively bred for high, but not low, anxiety: Possible key role of placental 11β-hydroxysteroid dehydrogenase type 2. *European Journal of Neuroscience*, *29*, 97–103. doi:10.1111/j.1460-9568.2008.06543.x

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*, 434–445. doi:10.1038/nrn2639

Maccari, S., Krugers, H. J., Morley-Fletcher, S., Szyf, M., & Brunton, P. J. (2014). The consequences of early-life adversity: Neurobiological, behavioural and epigenetic adaptations. *Journal of Neuroendocrinology*, *26*, 707–723. doi:10.1111/jne.12175

Martin, R. P., Noyes, J., Wisenbaker, J., & Huttenen, M. O. (1999). Prediction of early childhood negative emotionality and inhibition from maternal distress during pregnancy. *Merrill Palmer Quarterly*, *45*, 370–391. doi:10.1353/mpq.2008.0013

Mason, W. A., & Mendoza, S. P. (1998). Generic aspects of primate attachments: Parents, offspring and mates. *Psychoneuroendocrinology*, *23*, 765–778. doi:10.1016/S0306-4530(98)00054-7

McGowan, P. O., Suderman, M., Sasaki, A., Huang, T. C., Hallett, M., Meaney, M. J., & Szyf, M. (2011). Broad epigenetic signature of maternal care in the brain of adult rats. *PLOS ONE*, *6*, e14739. doi:10.1371/journal.pone.0014739

Merlot, E., Couret, D., & Otten, W. (2008). Prenatal stress, fetal imprinting and immunity. *Brain, Behavior, and Immunity*, *22*, 42–51. doi:10.1016/j.bbi.2007.05.007

Messaoudi, M., Lalonde, R., Violle, N., Javelot, H., Desor, D., Nejdi, A., . . . Cazaubiel, J. M. (2011). Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. *British Journal of Nutrition*, *105*, 755–764. doi:10.1017/S0007114510004319

Meyer-Lindenberg, A., Kolachana, B., Gold, B., Olsh, A., Nicodemus, K. K., Mattay, V., . . . Weinberger, D. R. (2009). Genetic variants in AVPR1A linked to autism predict amygdala activation and personality traits in

healthy humans. *Molecular Psychiatry*, *14*, 968–975. doi:10.1038/mp.2008.54

Miyagawa, K., Tsuji, M., Fujimori, K., Saito, Y., & Takeda, H. (2011). Prenatal stress induces anxiety-like behavior together with the disruption of central serotonin neurons in mice. *Neuroscience Research*, *70*, 111–117.

Moore, S. R., & Depue, R. A. (2016). Neurobehavioral foundation of environmental reactivity. *Psychological Bulletin*, *142*, 107. doi:10.1037/bul0000028

Mueller, B. R., & Bale, T. L. (2008). Sex-specific programming of offspring emotionality after stress early in pregnancy. *Journal of Neuroscience*, *28*, 9055–9065.

NICHD Early Child Care Research Network. (2005). *Child care and child development: Results of the NICHD Study of Early Child Care and Youth Development*. New York: Guilford Press.

Oberlander, T. F., Weinberg, J., Papsdorf, M., Grunau, R., Misri, S., & Devlin, A. M. (2008). Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics*, *3*, 97–106. doi:10.4161/epi.3.2.6034

Obradović, J., Bush, N. R., & Boyce, W. T. (2011). The interactive effect of marital conflict and stress reactivity on externalizing and internalizing symptoms: The role of laboratory stressors. *Development and Psychopathology*, *23*, 101–114. doi:10.1017/s0954579410000672

Obradović, J., Bush, N. R., Stamperdahl, J., Adler, N. E., & Boyce, W. T. (2010). Biological sensitivity to context: The interactive effects of stress reactivity and family adversity on socioemotional behavior and school readiness. *Child Development*, *81*, 270–289. doi:10.1111/j.1467-8624.2009.01394.x

Obradović, J., Portilla, X. A., & Ballard, P. J. (2016). Biological sensitivity to family income: Differential effects on early executive functioning. *Child Development*, *87*, 374–384. doi:10.1111/cdev.12475

O'Connor, T. G., Heron, J., Golding, J., Beveridge, M., & Glover, V. (2002). Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. *British Journal of Psychiatry*, *180*, 502–508. doi:10.1192/bjp.180.6.502

O'Connor, T. G., Heron, J., Golding, J., & Glover, V. (2003). Maternal antenatal anxiety and behavioural/emotional problems in children: A test of a programming hypothesis. *Journal of Child Psychology and Psychiatry*, *44*, 1025–1036. doi:10.1111/1469-7610.00187

O'Donnell, K. J., Jensen, A. B., Freeman, L., Khalife, N., O'Connor, T. G., & Glover, V. (2012). Maternal prenatal anxiety and downregulation of placental 11β-HSD2. *Psychoneuroendocrinology*, *37*, 818–826. doi:10.1016/j.psyneuen.2011.09.014

Olofsdotter, S., Åslund, C., Furmark, T., Comasco, E., & Nilsson, K. W. (2017). Differential susceptibility effects of oxytocin gene (OXT) polymorphisms and perceived parenting on social anxiety among adolescents. *Development and Psychopathology*. Advance online publication. doi:10.1017/S0954579417000967

Pärtty, A., Kalliomäki, M., Endo, A., Salminen, S., & Isolauri, E. (2012). Compositional development of Bifidobacterium and Lactobacillus microbiota is linked with crying and fussing in early infancy. *PLOS ONE*, *7*, e32495. doi:10.1371/journal.pone.0032495

Peña, C. J., Monk, C., & Champagne, F. A. (2012). Epigenetic effects of prenatal stress on 11β-hydroxysteroid dehydrogenase-2 in the placenta and fetal brain. *PLOS ONE*, *7*, e39791. doi:10.1371/journal.pone.0039791

Penders, J., Thijs, C., Vink, C., Stelma, F. F., Snijders, B., Kummeling, I., . . . Stobberingh, E. E. (2006). Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics*, *118*, 511–521.

Perkeybile, A. M., Griffin, L. L., & Bales, K. L. (2013). Natural variation in early parental care correlates with social behaviors in adolescent prairie voles (Microtus ochrogaster). *Frontiers in Behavioral Neuroscience*, *7*, 21. doi:10.3389/fnbeh.2013.00021

Pitzer, M., Jennen-Steinmetz, C., Esser, G., Schmidt, M. H., & Laucht, M. (2011). Differential susceptibility to environmental influences: The role of early temperament and parenting in the development of externalizing problems. *Comprehensive Psychiatry*, *52*, 650–658. doi:10.1016/j.comppsych.2010.10.017

Pluess, M., & Belsky, J. (2011). Prenatal programming of postnatal plasticity. *Development and Psychopathology*, *23*, 29–38. doi:10.1017/s0954579410000623

Pluess, M., & Belsky, J. (2013). Vantage sensitivity: Individual differences in response to positive experiences. *Psychological Bulletin*, *139*, 901. doi:10.1037/a0030196

Pluess, M., Velders, F. P., Belsky, J., van IJzendoorn, M. H., Bakermans-Kranenburg, M. J., Jaddoe, V. W., . . . Tiemeier, H. (2011). Serotonin transporter polymorphism moderates effects of prenatal maternal anxiety on infant negative emotionality. *Biological Psychiatry*, *69*, 520–525. doi:10.1016/j.biopsych.2010.10.006

Poehlmann, J., Hane, A., Burnson, C., Maleck, S., Hamburger, E., & Shah, P. E. (2012). Preterm infants who are prone to distress: Differential effects of parenting on 36-month behavioral and cognitive outcomes. *Journal of Child Psychology and Psychiatry*, *53*, 1018–1025. doi:10.1111/j.1469-7610.2012.02564.x

Ponder, K. L., Salisbury, A., McGonnigal, B., Laliberte, A., Lester, B., & Padbury, J. F. (2011). Maternal depression and anxiety are associated with altered gene expression in the human placenta without modification by antidepressant use: Implications for fetal programming. *Developmental Psychobiology*, *53*, 711–723. doi:10.1002/dev.20549

Poulin, M. J., Holman, E. A., & Buffone, A. (2012). The neurogenetics of nice: Receptor genes for oxytocin and vasopressin interact with threat to predict prosocial behavior. *Psychological Science*, *23*, 446–452. doi:10.1177/0956797611428471

Prichard, Z. M., Mackinnon, A. J., Jorm, A. F., & Easteal, S. (2007). AVPR1A and OXTR polymorphisms are associated with sexual and reproductive behavioral phenotypes in humans. *Human Mutation*, *28*, 1150. doi:10.1002/humu.9510

Radtke, K. M., Ruf, M., Gunter, H. M., Dohrmann, K., Schauer, M., Meyer, A., & Elbert, T. (2011). Transgenerational impact of intimate partner violence on methylation in the promoter of the glucocorticoid receptor. *Translational Psychiatry*, *1*, e21. doi:10.1038/tp.2011.21

Räikkönen, K., Pesonen, A. K., O'reilly, J. R., Tuovinen, S., Lahti, M., Kajantie, E., . . . Reynolds, R. M. (2015). Maternal depressive symptoms during pregnancy, placental expression of genes regulating glucocorticoid and serotonin function and infant regulatory behaviors. *Psychological Medicine*, *45*, 3217–3226 doi:10.1017/S003329171500121X.

Raver, C. C., Blair, C., & Willoughby, M. (2012). Poverty as a predictor of 4-year-olds' executive function: New perspectives on models of differential susceptibility. *Developmental Psychology*, *49*, 292. doi:10.1037/a0028343

Reynaert, M. L., Marrocco, J., Mairesse, J., Lionetto, L., Simmaco, M., Deruyter, L., . . . Morley-Fletcher, S. (2016). Hedonic sensitivity to natural rewards is affected by prenatal stress in a sex-dependent manner. *Addiction Biology*, *21*, 1072–1085. doi:10.1111/adb.12270

Rice, F., Harold, G. T., Boivin, J., Hay, D. F., van Den Bree, M., & Thapar, A. (2009). Disentangling prenatal and inherited influences in humans with an experimental design. *Proceedings of the National Academy of Sciences*, *106*, 2464–2467.

Rice, F., Harold, G. T., Boivin, J., van den Bree, M., Hay, D. F., & Thapar, A. (2010). The links between prenatal stress and offspring development and psychopathology: Disentangling environmental and inherited influences. *Psychological Medicine*, *40*, 335–345. doi:10.1017/S0033291709005911

Rioux, C., Castellanos-Ryan, N., Parent, S., Vitaro, F., Tremblay, R. E., & Séguin, J. R. (2016). Differential susceptibility to environmental influences: Interactions between child temperament and parenting in adolescent alcohol use. *Development and Psychopathology*, *28*, 265–275. doi:10.1019/S0954579415000437

Roisman, G. I., Newman, D. A., Fraley, R. C., Haltigan, J. D., Groh, A. M., & Haydon, K. C. (2012). Distinguishing differential susceptibility from diathesis–stress: Recommendations for evaluating interaction effects. *Development and Psychopathology*, *24*, 389–409. doi:10.1017/S0954579412000065

Rothbart, M. K., & Bates, J. E. (2006). Temperament. In W. Damon, R. Lerner, & N. Eisenberg (Eds.), *Handbook of child psychology: Vol. 3. Social, emotional, and personality development* (6th ed., pp. 99–166). New York: Wiley.

Rubin, D. M., O'Reilly, A. L., Luan, X., & Localio, A. R. (2007). The impact of placement stability on behavioral well-being for children in foster care. *Pediatrics*, *119*, 336–344.

Saxbe, D. E., Margolin, G., Spies Shapiro, L. A., & Baucom, B. R. (2012). Does dampened physiological reactivity protect youth in aggressive family environments? *Child Development*, *83*, 821–830. doi:10.1111/j.1467-8624.2012.01752.x

Seckl, J. R., & Holmes, M. C. (2007). Mechanisms of disease: Glucocorticoids, their placental metabolism and fetal "programming" of adult pathophysiology. *Nature Clinical Practice Endocrinology & Metabolism*, *3*, 479–488. doi:10.1038/ncpendmet0515

Shapiro, G. D., Fraser, W. D., Frasch, M. G., & Séguin, J. R. (2013). Psychosocial stress in pregnancy and preterm birth: Associations and mechanisms. *Journal of Perinatal Medicine*, *41*, 631–645. doi:10.1515/jpm-2012-0295

Sharp, H., Hill, J., Hellier, J., & Pickles, A. (2015). Maternal antenatal anxiety, postnatal stroking and emotional problems in children: Outcomes predicted from pre- and postnatal programming hypotheses. *Psychological Medicine*, *45*, 269–283. doi:10.1017/S0033291714001342

Sherwin, E., Rea, K., Dinan, T. G., & Cryan, J. F. (2016). A gut (microbiome) feeling about the brain. *Current Opinion in Gastroenterology*, *32*, 96–102. doi:10.1097/MOG.0000000000000244

Simcock, G., Elgbeili, G., Laplante, D. P., Kildea, S., Cobham, V., Stapleton, H., . . . King, S. (2017). The effects of prenatal maternal stress on early temperament: The 2011 Queensland Flood Study. *Journal of Developmental & Behavioral Pediatrics*, *38*, 310–321. doi:10.1097/DBP.0000000000000444

Slagt, M., Dubas, J. S., Deković, M., & van Aken, M. A. (2016). Differences in sensitivity to parenting depending on child temperament: A meta-analysis. *Psychological Bulletin*, *142*, 1068–1110. doi:10.1037/bul0000061

St.-Pierre, J., Laurent, L., King, S., & Vaillancourt, C. (2016). Effects of prenatal maternal stress on serotonin and fetal development. *Placenta*, *48*, S66–S71. doi:10.1016/j.placenta.2015.11.013

Swenson, R. R., Beckwith, B. E., Lamberty, K. J., Krebs, S. J., & Tinius, T. P. (1990). Prenatal exposure to AVP or caffeine but not oxytocin alters learning in female rats. *Peptides*, *11*, 927–932. doi:10.1016/0196-9781(90)90011-s

Tabak, B. A., Meyer, M. L., Castle, E., Dutcher, J. M., Irwin, M. R., Han, J. H., . . . Eisenberger, N. I. (2015). Vasopressin, but not oxytocin, increases empathic concern among individuals who received higher levels of paternal warmth: A randomized controlled trial. *Psychoneuroendocrinology*, *51*, 253–261. doi:10.1016/j.psyneuen.2014.10.006

Takahashi, L. K., & Kalin, N. H. (1991). Early developmental and temporal characteristics of stress-induced secretion of pituitary-adrenal hormones in prenatally stressed rat pups. *Brain Research*, *558*, 75–78. doi:10.1016/0006-8993(91)90715-8

Tribollet, E., Goumaz, M., Raggenbass, M., Dubois-Dauphin, M., & Dreifuss, J. J. (1991). Early appearance and transient expression of vasopressin receptors in the brain of rat fetus and infant. An autoradiographical and electrophysiological study. *Developmental Brain Research*, *58*, 13–24. doi:10.1016/0165-3806(91)90232-8

Unternaehrer, E., Bolten, M., Nast, I., Staehli, S., Meyer, A. H., Dempster, E., . . . Meinlschmidt, G. (2016). Maternal adversities during pregnancy and cord blood oxytocin receptor (OXTR) DNA methylation. *Social Cognitive and Affective Neuroscience*, *11*, 1460–1470. doi:10.1093/scan/nsw051

van den Berg, H., & Bus, A. G. (2014). Beneficial effects of BookStart in temperamentally highly reactive infants. *Learning and Individual Differences*, *36*, 69–75. doi:10.1016/j.lindif.2014.10.008

van den Bergh, B. R., Mulder, E. J., Mennes, M., & Glover, V. (2005). Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: Links and possible mechanisms. A review. *Neuroscience and Biobehavioral Reviews*, *29*, 237–258. doi:10.1016/j.neubiorev.2004.10.007

van den Bergh, B. R., van Calster, B., Smits, T., van Huffel, S., & Lagae, L. (2008). Antenatal maternal anxiety is related to HPA-axis dysregulation and self-reported depressive symptoms in adolescence: A prospective study on the fetal origins of depressed mood. *Neuropsychopharmacology*, *33*, 536–545. doi:10.1038/sj.npp.1301450

van den Hove, D. L. A., Lauder, J. M., Scheepens, A., Prickaerts, J. H. H. J., Blanco, C. E., & Steinbusch, H. W. M. (2006). Prenatal stress in the rat alters 5-HT 1A receptor binding in the ventral hippocampus. *Brain Research*, *1090*, 29–34. doi:10.1016/j.brainres.2006.03.057

van de Weil, N., van Goozen, S. H., Matthys, W., Snoek, H., & van Engeland, H. (2004). Cortisol and treatment effect in children with disruptive behavior disorders: A preliminary study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *43*, 1011–1018. doi:10.1097/01.chi.0000126976.56955.43

van IJzendoorn, M. H., Belsky, J., & Bakermans-Kranenburg, M. J. (2012). Serotonin transporter genotype 5HTTLPR as a marker of differential susceptibility? A meta-analysis of child and adolescent gene-by-environment studies. *Translational Psychiatry*, *2*, e147. doi:10.1038/tp.2012.73

van Waes, V., Darnaudery, M., Marrocco, J., Gruber, S. H., Talavera, E., Mairesse, J., . . . Maccari, S. (2011). Impact of early life stress on alcohol consumption and on the short- and long-term responses to alcohol in adolescent female rats. *Behavioural Brain Research*, *221*, 43–49. doi:10.1016/j.bbr.2011.02.033

Wadhwa, P. D., Glynn, L., Hobel, C. J., Garite, T. J., Porto, M., Chicz-DeMet, A., . . . Sandman, C. A. (2002). Behavioral perinatology: Biobehavioral processes in human fetal development. *Regulatory Peptides*, *108*, 149–157. doi:10.1016/S0167-0115(02)00102-7

Walum, H., Westberg, L., Henningsson, S., Neiderhiser, J. M., Reiss, D., Igl, W., . . . Lichtenstein, P. (2008). Genetic variation in the vasopressin receptor 1a gene (AVPR1A) associates with pair-bonding behavior in humans. *Proceedings of the National Academy of Sciences*, *105*, 14153–14156. doi:10.1073/pnas.0803081105

Watson, E. D., & Cross, J. C. (2005). Development of structures and transport functions in the mouse placenta. *Physiology*, *20*, 180–193. doi:10.1152/physiol.00001.2005

Whitaker-Azmitia, P. M., Druse, M., Walker, P., & Lauder, J. M. (1996). Serotonin as a developmental signal. *Behavioural Brain Research*, *73*, 19–29. doi:10.1016/0166-4328(96)00071-X

Wigger, A., Sánchez, M. M., Mathys, K. C., Ebner, K., Frank, E., Liu, D., . . . Landgraf, R. (2004). Alterations in central neuropeptide expression, release, and receptor binding in rats bred for high anxiety: Critical role of vasopressin. *Neuropsychopharmacology*, *29*, 1–14. doi:10.1038/sj.npp.1300290

Wroble-Biglan, M. C., Dietz, L. J., & Pienkosky, T. V. (2009). Prediction of infant temperament from catecholamine and self-report measures of maternal stress during pregnancy. *Journal of Reproductive and Infant Psychology*, *27*, 374–389.

Yehuda, R., Engel, S. M., Brand, S. R., Seckl, J., Marcus, S. M., & Berkowitz, G. S. (2005). Transgenerational effects of posttraumatic stress disorder in babies of mothers exposed to the World Trade Center attacks during pregnancy. *Journal of Clinical Endocrinology and Metabolism*, *90*, 4115–4118. doi:10.1210/jc.2005-0550

Zijlmans, M. A., Korpela, K., Riksen-Walraven, J. M., de Vos, W. M., & de Weerth, C. (2015). Maternal prenatal stress is associated with the infant intestinal microbiota. *Psychoneuroendocrinology*, *53*, 233–245. doi:10.1016/j.psyneuen.2015.01.006

Zuckerman, M. (1999). *Diathesis-stress models*. Washington, DC: American Psychological Association.

Zuena, A. R., Mairesse, J., Casolini, P., Cinque, C., Alemà, G. S., Morley-Fletcher, S., . . . Nicoletti, F. (2008). Prenatal restraint stress generates two distinct behavioral and neurochemical profiles in male and female rats. *PLOS ONE*, *3*, e2170. doi:10.1371/journal.pone.0002170