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SPECIAL ISSUE

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Prenatal stress enhances postnatal plasticity: The role of microbiota

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Abstract

Separate fields of inquiry indicate (a) that prenatal stress is associated with heightened behavioral and physiological reactivity and (b) that these postnatal phenotypes are themselves associated with increased susceptibility to both positive and negative environmental influences. Collectively, this work supports Pluess and Belsky's (*Psychopathology*, 2011, 23, 29) claim that prenatal stress fosters, promotes or "programs" postnatal developmental plasticity. Herein, we review animal and human evidence consistent with this hypothesis before advancing the novel idea that infant intestinal microbiota may be one candidate mechanism for instantiating developmental plasticity as a result of prenatal stress. We then review research indicating that prenatal stress predicts differences in infant intestinal microbiota; that infant intestinal microbiota is associated with behavioral and physiological reactivity phenotypes; and, thus, that prenatal stress may influence infant intestinal microbiota in a way that results in heightened physiological and behavioral reactivity and, thereby, postnatal developmental plasticity. Finally, we offer ideas for testing this claim and consider implications for intervention and use of probiotics during early infancy.

KEYWORDS

breastfeeding, developmental plasticity, gut microbiome, physiological dysregulation, prenatal stress, probiotics, temperament

1 | INTRODUCTION

A wealth of research indicates that prenatal stress predicts a number of altered and often deleterious child outcomes (for review, see Entringer, Buss, & Wadhwa, 2015; Glover, 2014; Tarabulsy et al., 2014; Van den Bergh, Mulder, Mennes, & Glover, 2005), including preterm birth and low birth weight (Wadhwa et al., 2002), deficiencies in intellectual and language functioning (Laplante et al., 2004), ADHD symptoms (Grossman et al., 2003), externalizing and anxiety problems (Glover, 2011), and motor and mental developmental disorders (Kofman, 2002; Tarabulsy et al., 2014). Although such human evidence suggests that prenatal stress *disrupts* "optimal" development, we present evidence for a different view on how and why prenatal stress has been repeatedly associated with impaired functioning.

Based on research on human infants showing (a) that prenatal stress is associated with heightened negative emotionality and physiological reactivity and (b) that these postnatal phenotypes are themselves associated with increased susceptibility to both positive *and* negative developmental experiences and environmental exposures postnatally, we argue that prenatal stress programs postnatal developmental plasticity, based on the hypothesis first advanced by Pluess and Belsky (2011). After this, we highlight changes in infant microbiota as one possible key biological mechanism by which prenatal stress might increase developmental plasticity. Finally, we consider implications of this claim for future research and, perhaps, intervention.

2 | PRENATAL STRESS AND BEHAVIORAL–PHYSIOLOGICAL DYSREGULATION

Prenatal stress, measured in a variety of ways, predicts greater behavioral and physiological dysregulation in infancy and childhood

(for reviews see Pluess & Belsky, 2011; Hartman & Belsky, 2018). Concerning behavioral dysregulation, prenatal stress is linked to increased displays of sadness, frustration, and fear, as well as a stable disposition of (negative) emotional reactivity (Huizink, De Medina, Mulder, Visser, & Buitelaar, 2002; Van den Bergh, et al., 2005). Maternal psychological stress measured at various times during pregnancy is associated with increased behavioral reactivity of 4-month-olds (Davis et al., 2004) and of toddlers (Lin et al., 2017), irregular sleeping and eating patterns of 6-month-olds, and heightened inhibition and negative emotionality of 5-year-olds (Martin, Noyes, Wisenbaker, & Huttenen, 1999), as well as more negatively emotional 6-month-olds (Nolvi et al., 2016). Furthermore, pregnant women exposed to a natural disaster—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 (even when controlling for postpartum depression and major life events; Laplante, Brunet, & King, 2015).

Such findings were confirmed in a recent meta-analysis showing that prenatal stress—indexed by maternal psychological distress, experience of major life events, and natural disaster exposure—is associated with greater child negative affectivity (Van Den Bergh et al., 2017). Although, there is some evidence to suggest elevated cortisol levels during pregnancy forecast infant negativity (e.g., Davis et al., 2007), another meta-analysis examining the association between maternal cortisol levels during pregnancy and infant behavioral negativity yielded mixed results (Zijlmans, Riksen-Walraven, de Vos, & de Weerth, 2015). Thus, it may be the case that maternal subjective experiences of stress during pregnancy are a better predictor of infant behavioral dysregulation than cortisol levels.

Concerning physiological functioning, prenatal stress is associated with dysregulation of the hypothalamic–pituitary–adrenal axis (HPA) in infants and children (Davis, Glynn, Waffarn, & Sandman, 2011; Field et al., 2004), effects which extend to even the first day of school (Gutteling, de Weerth, & Buitelaar, 2005). Notably, a natural experiment revealed that pregnant mothers positioned near the NYC terrorist attacks on 9/11 who subsequently developed post-traumatic stress disorder (PTSD) had infants with more dysregulated diurnal cortisol rhythms at one year of age than did other infants (Yehuda et al., 2005). However, it should be noted that some studies find no association or mixed findings between prenatal stress and physiological reactivity (Glover, O'connor, T. G., & O'donnell, K., 2010). Despite this, two meta-analyses revealed that dysregulation of child cortisol levels was predicted by (a) greater maternal cortisol during pregnancy (Zijlmans et al., 2015); and (b) a variety of stressors experienced prenatally, including substance abuse and maternal distress (Pearson, Tarabulsy, & Bussières, 2015). Such findings are consistent with rodent experiments indicating that prenatal stress (e.g., restraint stress, social stress) promotes higher baseline and reactive corticosterone levels in offspring (Maccari, Krugers, Morley-Fletcher, Szyf, & Brunton, 2014).

Regarding the literature just summarized, we would be remiss if we did not mention that some studies detect sex differences in the effects of prenatal stress on behavioral and physiological dysregulation (e.g., Braithwaite, Murphy, Ramchandani, & Hill, 2017). While not discussed in depth in this paper, it is likely that offspring sex plays a role in the mechanistic processes of prenatal programming (see Bale & Epperson, 2015 for review). Thus, future research should explore whether—and how—sex differences affects the developmental pathways highlighted herein. Additionally, it should be also noted that although prenatal stress can be indexed in numerous ways (e.g., maternal cortisol, psychological distress), in what follows, we often refer to prenatal stress as a general term under the assumption that these measures are interrelated and signify an overall more stressful prenatal state. Nevertheless, we return to this issue of whether various prenatal stress measures highlight differing effects on the fetus when discussing future research directions.

3 | POSTNATAL DEVELOPMENTAL PLASTICITY

The evidence just summarized becomes especially intriguing when juxtaposed to independent work showing that both developmental sequelae of prenatal stress just considered—negatively emotionality and physiological reactivity—are themselves associated with heightened postnatal plasticity (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van Ijzendoorn, 2011). That is, more negatively emotional and physiologically reactive children prove not just more adversely affected than others by negative environmental exposures (e.g., harsh parenting), but also benefit more from supportive contextual conditions (e.g., sensitive–responsive parenting; Belsky & Pluess, 2009, 2013; Belsky, Bakermans-Kranenburg, & Van Ijzendoorn, 2007). In fact, Slagt, Dubas, Deković, and Aken (2016) recent meta-analysis revealed that negative emotionality in infancy moderates effects of various environmental factors on a range of child-adjustment outcomes (e.g., social competence, cognitive development) in just such a "for-better-and-for-worse," differential-susceptibility-related manner (Belsky et al., 2007).

Turning to physiological reactivity, evidence indicates that elevated levels moderate effects of marital conflict on externalizing problems (Obradovic, Bush, & Boyce, 2011) and family adversity on school achievement (Obradovic, Bush, Stamperdahl, Adler, & Boyce, 2010)—also in a for-better-and-for-worse, differential-susceptibility-related manner. Additionally, evaluations of experimental interventions (e.g., Van den Berg & Bus, 2014) show that negatively emotional or physiologically reactive children benefit more, sometimes exclusively, from such efforts than do other children (for review, see Belsky & Pluess, 2013). In summary, then, both more physiologically and behaviorally reactive children repeatedly prove most vulnerable to the negative effects of contextual adversity *and* most likely to benefit from environmental support.

4 | PRENATAL PROGRAMMING OF POSTNATAL PLASTICITY

Consideration of research indicating (a) that prenatal stress is associated with elevated behavioral and physiological dysregulation and (b) that such phenotypic functioning is associated with heightened susceptibility to positive and negative environmental influences led Pluess and Belsky (2011) to hypothesize that prenatal stress fosters, promotes or "programs" postnatal developmental plasticity. If true, this hypothesis could account for many of the adverse, later developing phenotypes routinely associated with prenatal stress exposure. Perhaps the reason that prenatal stress is so often associated with problematic functioning in childhood and adolescence is because the very forces that engendered stress in pregnancy (e.g., poverty, marital conflict) continue postnatally for many whose prenatal experience fostered heightened developmental plasticity. Thus, when these children subsequently experience, postnatally, adversity that persists beyond pregnancy, they prove especially responsive to it.

When Pluess and Belsky (2011) first postulated their prenatal programming of postnatal plasticity hypothesis, they provided accompanying empirical evidence to support their claims. One relevant investigation relied on data from the large-scale NICHD Study of Early Child Care and Youth Development (NICHD Early Child Care Research Network, 2005). It linked low birth weight—which served as a proxy for heightened prenatal stress—to infant negative emotionality which, in turn, was associated with infants' enhanced susceptibility—in a for-better-and-for-worse manner—to effects of parenting 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—and especially girls—exposed to high levels of prenatal maternal 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. The same was not true of children whose mothers experienced little anxiety during pregnancy. Although these results are consistent with prenatal programming of postnatal plasticity, it should be noted that the sample size was small (N = 243) for detecting such an interactive effect and is thus in need of further replication. Despite this, in both cited works, regression slopes linking the environmental-exposure predictor with the measured outcome revealed that those exposed to high levels of prenatal stress manifest both the highest and lowest levels of all study members on the outcomes measured, depending on the quality of their postnatal care.

Further evidence of prenatal programming of postnatal plasticity comes from research comparing preterm and full-term babies. A substantial body of work indicates that psychosocial stress is an etiological risk factor in preterm birth (Shapiro, Fraser, Frasch, & Séguin, 2013)—even when controlling for other well-known risk factors (e.g., twin pregnancy, tobacco use, infection, premature contractions; Lilliecreutz, Larén, Sydsjö, & 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 examining 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 proved more developmentally responsive to their caregiving environment, evincing the greatest social and cognitive functioning when exposed to a high-quality caregiving environment yet the lowest social and cognitive functioning when they experienced a low-quality caregiving environment. Notably, caregiving quality did not predict the social and cognitive development of full-term infants. These findings are consistent with earlier work chronicling stronger associations between maternal responsiveness and cognitive growth in the case of preterm infants than full-term ones (Landry, Smith, Swank, Assel, & Vellet, 2001). In fact, an intervention designed to promote maternal responsiveness proved successful in doing so, but the benefits of being in the experimental rather than the control group were greater for preterm than full-term children (Landry, Smith, & Swank, 2006).

In addition to this human research, more support for the prenatal programming hypothesis comes from an animal experiment that we recently conducted (Hartman, Freeman, Bales, & Belsky, 2018). We chose prairie voles (*Microtus ochrogaster*) as experimental subjects because, unlike other common rodent models, they display attachment behavior to a pair-mate and biparental care of offspring. Furthermore, prairie voles naturally vary—in trait-like fashion across multiple litters—in the amount of care they display toward their newborn pups (Perkeybile, Griffin, & Bales, 2013). Whereas some engage in high levels of licking and grooming, others engage in very little. Thus, prairie voles are optimal for cross-fostering paradigms—that afford the contrasting effect of more and less "supportive" parenting—when testing hypotheses based on findings from human studies.

The study design involved, in its first stage, assigning pregnant voles on a random basis to a social stress or no-stress condition during the last week of pregnancy. We exposed those assigned to the experimental group to an unfamiliar and lactating—hence, aggressive—female vole for 10 min/day for five consecutive days, using a plexiglass divider to prevent physical harm. This paradigm is known to increase stress reactivity in offspring, both behaviorally and physiologically (Brunton & Russell, 2010). Control-condition voles remained undisturbed. The second stage of our investigation occurred postnatally when the offspring born to both experimental and control mothers were cross-fostered, again on a random basis, to either high- or low-quality rearing by unrelated parents. High-quality and low-quality parents were categorized using a standard method based on their natural levels of parenting behaviors (e.g., nursing, contact, licking, and grooming) displayed prior to the beginning of the experiment (Perkeybile et al., 2013).

In sum, the research used a 2 (Prenatal Stress: Yes vs. No) × 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 stress-induced 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 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 when exposed to low-quality rearing environments. In fact, in the case of voles in the control condition that were not prenatally stressed, postnatal rearing quality exerted no effect whatsoever on later reactivity.

5 | ALTERATIONS IN INFANT MICROBIOTA AS A POTENTIAL MECHANISM

Based on the research just presented, we contend that prenatal stress may increase developmental plasticity. But the question of how or by what mechanism such a process is instantiated remains of central developmental significance. One possible mechanism for how prenatal stress might increase plasticity is through changes in the composition of intestinal microbiota. Thus, in the following sections, we highlight the critical process of microbiota colonization, the relation between prenatal stress and infant microbiota, the association between infant microbiota and behavioral/physiological dysregulation, and other potential confounding/mediating factors for future research to consider.

5.1 | Microbiota: early colonization

Maturation of the immune system is heavily reliant on early intestinal microbial colonization, as it plays a large role in the developmental regulation of intestinal physiology. Gut microbiota has metabolic, trophic, and protective functions, serving as a barrier against pathogenic organisms, influencing homeostatic maintenance of the immune system and playing an important role in the digestion and metabolism of breast milk, colostrum, and formula (Guarner & Malagelada, 2003). Colonization starts with facultative anaerobes such as lactobacilli, coliforms, enterobacteria, and streptococci; these microbes are shortly followed by Bifidobacteria, bacteroides, clostridia, and eubacteria which become the dominant microbiota present in infant feces at 1–2 weeks of age (Roger, Costabile, Holland, Hoyles, & McCartney, 2010; Roger & McCartney, 2010). Lactobacilli, in particular, are one of the most prevalent bacteria within healthy mother's vaginal microbiome (Bailey, Lubach, & Coe, 2004). Importantly, disruptions in the colonization processes in early infancy increase the risk of disease later in life (Mshvildadze et al., 2010). In what follows, we describe two points in time that infant intestinal microbiota is initially seeded at birth and in utero.

5.1.1 | Transmission at birth

During pregnancy, Lactobacillus species are highly present in the composition of the vaginal microbiome, as both the diversity and richness of microbiota are reduced (Aagaard et al., 2012; Romero et al., 2014). For children born vaginally, the infant comes in contact with maternal vaginal microbiota during the birth process (Roger & McCartney, 2010) and there is a strong mother–infant association in fecal microbiota for the first 6 months following birth (Grönlund, Grzeskowiak, Isolauri, & Salminen, 2011). As demonstrated by several studies, mode of delivery has a substantial impact on the infant microbiome. Infants born vaginally have bacterial communities closely resembling those of their mother's vaginal microbiota, whereas infants born by cesarean have microbiota derived from their mother's skin and other environmental sources (e.g., hospital environment), thereby suggesting an alteration of typical mother-to-infant transmission of microbiota (Bäckhed et al., 2015; Biasucci et al., 2010; Cabrera-Rubio, Mira-Pascual, Mira, & Collado, 2016; Dominguez-Bello et al., 2010). Cesarean-born infants also show differences in gut microbiota diversity and the absence of crucial Bifidobacteria relative to vaginally born infants (Biasucci et al., 2010; Dominguez-Bello et al., 2010). Bifidobacteria are one of the first colonizers of newborn intestines and have been linked to early and beneficial immune responses in infants. This includes being more resistant to colonization by pathogens and better functioning gut barriers (Duranti et al., 2017; Huda et al., 2014; Zhang et al., 2016).

5.1.2 | In utero transmission

Although the uterine environment has long been thought to be sterile (Mackie, Sghir & Gaskins, 1999), recent evidence suggests that the infant gut may be seeded earlier than birth (Hu et al., 2013; Jiménez et al., 2008; Moles et al., 2013). Under this assumption of a "fetal microbiome," there are several ways bacterial colonization could occur, including entry through the mother's bloodstream, active transference of microbes from the gut or oral cavity by immune cells and in utero swallowing of amniotic fluid by the fetus (Jiménez et al., 2005; Moles et al., 2013; Wassenaar & Panigrahi, 2014). For example, Jiménez et al. (2005) orally inoculated a small group of pregnant mice with a bacterial strain isolated from human breast milk. This strain was later detected in the amniotic fluid of the inoculated animals but was not present in the control group. Despite this, evidence for fetal colonization is scarce and considered weak as studies often use molecular approaches with insufficient detection limits to examine low biomass microbial populations, lack controls for contamination and fail to provide sufficient evidence of bacterial viability (for recent review see Perez-Muñoz, Arrieta, Ramer-Tait, & Walter, 2017).

5.2 | Prenatal stress and microbiota

Stress during pregnancy is also associated with numerous maternal and infant health outcomes, including the dysregulation of the gut–brain axis; little is known, however, about the impact of stress on maternal bacterial communities and the later development of the infant microbiome (Shapiro et al., 2013). Using an animal model, Jasarevic, Howard, Misic, Beiting, and Bale (2017) relied upon high-resolution 16S rRNA marker gene sequencing to examine how stress during pregnancy affects maternal intestinal and vaginal microbiota as well as offspring intestinal microbiota shortly after birth and at weaning age. Across the prenatal period, maternal fecal communities were disrupted by stress; and chronic stress exposure produced long-term disruptions to vaginal bacterial community structure and composition. In offspring, prenatal stress exposure was associated with altered composition of early colonizers, lactobacillus and streptococcus, shortly after birth. Furthermore, at weaning, prenatal stress exposure was associated with sex-specific effects with prenatally stressed males exhibiting colitogenic microbiota typical of female offspring. The authors speculate that these perturbations in offspring microbiota may be due to a disrupted in utero environment driven by stress-altered maternal intestinal microbiota and also exposure to stress-altered vaginal microbiota during birth.

In addition to direct exposure of the infant to maternal microbiota, an indirect way in which prenatal stress might affect the developing fetal microbiome is through increased fetal exposure to cortisol. Research indicates that maternal cortisol may pass through the placenta leading to increased fetal cortisol levels (Duthie & Reynolds, 2013) and altered HPA development (Tollenaar, Beijers, Jansen, Riksen-Walraven, & De Weerth, 2011). Consequently, this heightened exposure to cortisol can also affect intestinal microbiome development. Specifically, cortisol disrupts intestinal barrier function and affects immune cells in the intestines, thereby likely influencing microbiome development (Cryan et al., 2012). Thus, prenatally stressed mothers may provide an altered microbiota profile to their infants via in utero exposures and the birth process which could be influential in the long term (Beijers, Buitelaar, & de Weerth, 2014).

Notably, several studies have linked prenatal stress to alterations in infant intestinal microbiota composition. For example, Bailey et al. (2004) found that prenatal stress exposure resulted in reduced overall concentrations of both Bifidobacteria and Lactobacilli in rhesus monkeys. The investigators concluded that moderate disturbance during pregnancy was enough to affect the intestinal microflora of the offspring. Conceivably, it also affected the (unmeasured) maternal microbiome, raising the possibility that alterations to the microbiome serve as a potential mechanism linking maternal condition and later infant health (Bailey et al., 2004; Shapiro et al., 2013). Another investigation, using mice, revealed that prenatal stress predicted adult offspring's intestinal microbiota as well as anxiety-like behavior (Gur et al., 2017). These findings extend to humans, as both mothers' subjective reports of stress and cortisol during pregnancy forecast differences in infant microbiota diversity which, in turn, is linked to infant health (Zijlmans et al., 2015).

Furthermore, preterm birth, highlighted previously as a marker of prenatal stress and associated with potential heightened plasticity, also predicts the developing infant's microbiome. Barrett et al. (2013) examined the composition of developing microbiome in a sample of preterm infants at 2–4 weeks. Despite large interindividual variation, they exhibited bacterial compositions lacking diversity and dominated by enterobacteriaceae, a potentially pathogenic bacterium. This contrasts with normal gestational-age infant's typical microbiome which is dominated by the presence of Bacteroides, Lactobacillus, and Bifidobacterium. Caution in embracing these findings is called for due to a small sample size and infants varying in antibiotic exposure. Of note, then, is that similar results emerged in independent work directly comparing infants of normal gestational age at birth and preterm infants (Moles et al., 2013); it found that preterm infants also had lower levels of Bifidobacteria. Thus, prenatal stress as indexed by preterm birth appears to affect infant microbiome composition. When considered in light of aforementioned research indicating that preterm infants appear more susceptible to effects of postnatal experiences than full-term ones, this evidence suggests, inferentially, that these changes in microbiota composition might play a role in promoting postnatal plasticity.

5.3 | Microbiota and infant behavioral/physiological dysregulation

Given the earlier claim that infant temperament and stress physiology are markers of developmental plasticity, it would seem especially notable that animal studies document a regulatory effect of the microbiome on activation of the HPA axis. More specifically, germ-free mice and rats evince elevated stress responses (see Sherwin, Rea, Dinan, & Cryan, 2016, for a review), but, intriguingly, if treated with probiotics, they manifest reduced anxiety- and depressive-like behavior (Bravo et al., 2011)—an effect which has been replicated in humans (Messaoudi et al., 2011).

Notably, microbiota patterns in humans are linked to negative temperament, such that lower diversity and stability of microbiota during the first weeks of life predicts 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. Apparently, then, variation in the microbiome is tied to differences in both behavioral and physiological dysregulation in children, the very phenotypic markers of enhanced developmental plasticity highlighted earlier.

6 | FUTURE DIRECTIONS AND CONSIDERATIONS

Given the evidence reviewed, there is a clear inferential basis for the claim that the microbiome may be one mechanistic pathway instantiating effects of prenatal stress on postnatal plasticity. After

all, prenatal stress affects infant intestinal microbiota which, in turn, influences environmental susceptibility, perhaps through behavioral/physiological reactivity. This, then, suggests that differential patterns of microbiota due to prenatal stress may not be inherently negative but instead a marker of increased susceptibility, for-better-and-for-worse, similar to physiological/behavioral dysregulation. How altered microbiota populations change over time when the infant is exposed to good- or poor-quality environments thus becomes a worthwhile avenue of future research. It may be the case that microbiota profiles of prenatally stressed infants change and adapt more to whatever postnatal environment they encounter compared to the microbiota profiles of nonprenatally stressed infants.

6.1 | Probiotic use

This line of reasoning also 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. Use of probiotics during both pregnancy and for infants and young children is on the rise in the United States (Thomas & Greer, 2010). In fact, there are increasing numbers of randomized control trials (RCTs) that select infants to receive probiotics or a placebo to test effects on health outcomes (Thomas & Greer, 2010). Thus, a potential future research direction would be to utilize this experimental data or collect data on how use of probiotics might affect infant behavioral/physiological dysregulation and even susceptibility to would-be rearing effects. The argument developed herein leads to the (inferential) prediction that infants who receive probiotics during early infancy will be less negatively emotional than others and, in turn, less susceptible to rearing effects. Thus, probiotic administration will reduce the influence of both supportive and unsupportive rearing conditions.

As for probiotic use during pregnancy, it is unclear whether this exposure would be associated with infant developmental plasticity. One might imagine that a mother consuming probiotics might be less stressed and therefore the fetus would be born less susceptible due to the reduction in stress; another possibility is that probiotics might alter the maternal microbiome which could be passed to the infant in utero and during the birth process. For reasons of uncertainty, then, this would also be a worthwhile avenue of research, enabling the determination of whether maternal use of probiotics during pregnancy influences infant behavioral/physiological reactivity and/or microbiota.

6.2 | Breastfeeding and infant microbiota

Breastfeeding is another important consideration when testing whether infant microbiota is a mechanism for prenatal programming of postnatal plasticity. It is well established that breastfeeding influences infant microbiota development, with those breast and formula fed showing marked differences in the composition of their gut microbiota. Bäckhed et al. (2015) assessed the gut microbiota of 98 mothers and infants, finding that exclusively formula-fed infants had more diverse gut microbiota dominated with Clostridia species typically found in adults, while exclusively breastfed infant's gut microbiota exhibited high proportions of Bifidobacterium and Lactobacillus. These scholars further suggested that the cessation of breastfeeding could be a major driver in the development of an adult microbiota, as results indicated that, at 12 months, the cessation of breastfeeding shifted the microbiota ecology of infants toward a more adult bacterial composition; infants who remained exclusively breastfed had bacterial communities that continued to be characterized by Bifidobacterium, Lactobacillus, and others. Thus, whether or not a mother chooses to breastfeed and how long she does so can have significant effects on infant microbiota development.

Given all that has been said through this point, it also seems noteworthy that mothers who are depressed during pregnancy—a form of prenatal stress—are less likely to breastfeed their babies and, if they do, tend to do so for a shorter duration than their nondepressed counterparts (Figueiredo, Canário, & Field, 2014). Conceivably, then, it may not be prenatal stress that affects infant microbiota but rather differences in the amount and duration of breastfeeding. There is also the possibility that breastfeeding reduces postpartum depression (Figueiredo et al., 2014), thereby altering the postnatal environment to which the infant is exposed. 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 influence of breastfeeding on infant microbiota composition and the quality of the postnatal environment.

It is unclear at this juncture whether engaging in breastfeeding has an active role in increasing or reducing an infant's plasticity. Some evidence suggests that breastfed infants have more difficult temperaments at three months of age than formula-fed ones or those on mixed diets (e.g., Lauzon-Guillain et al., 2012); this may indicate that breastfeeding promotes infant plasticity via difficult temperament. Furthermore, a study showed that cortisol measured across the first year of life was about 40% higher in breastfed than formula-fed infants (Cao et al., 2009), once again raising the possibility that breastfeeding may promote developmental plasticity via heightened physiological reactivity. Because studies of breastfeeding effects on infant development are correlational in nature, it will be difficult to determine whether breastfeeding has a causal effect on infant plasticity.

6.3 | Role of the immune system

Lastly, it will be important to consider the role of the child's immune system when examining intestinal microbiota as a mechanism for prenatal-stress-enhanced plasticity. Intestinal microbiota is a critical regulator of the development of the child's immune system and subsequent health (Matamoros, Gras-Leguen, Le Vacon, Potel, & De La Cochetiere, 2013). Bifidobacteria is one of the first colonizers of newborn intestines and is linked to early and beneficial immune responses in infants. This includes being more resistant to colonization by pathogens and better functioning gut barriers (Duranti et al., 2016; Huda et al., 2014; Zhang et al., 2016). Notably, the absence of

Bifidobacteria, coupled with an abundance of Clostridiales, is associated with systemic inflammation and lower vaccine response (Huda et al., 2014).

As stated previously, lower levels of Bifidobacteria in infants are themselves associated with greater prenatal stress (Bailey et al., 2004; Moles et al., 2013). Indeed, investigations have linked prenatal stress to changes in both mother and offspring immune systems (see Merlot, Couret, & Otten, 2008 for a review), as well as with child health (Mshvildadze et al., 2010). Given the documented alterations to the HPA system and changes in microbiota associated with prenatal stress, one might expect the child's immune system development to have a major influence on developmental plasticity. Therefore, it would be interesting to determine whether—and how—child immunity is involved in the proposed pathway of prenatal stress to infant microbiota to increased developmental plasticity.

6.4 | Types of prenatal stress

As stated previously, we have referred to prenatal stress as a general condition rather than distinguishing different measurements of prenatal stress (e.g., maternal cortisol, psychological distress). It remains possible, however, that prenatal psychosocial stress and cortisol may have differing effects on infant microbiota. Specifically, high maternal cortisol may result in increased bile acid production which could interfere with maternal microbiota development during pregnancy (Koren et al., 2012)—and thus affect the infant's microbiota colonization. On the other hand, psychosocial stress may be associated with other lifestyle factors such as diet. After all, psychosocial stress during pregnancy is associated with differential dietary patterns (Hurley, Caulfield, Sacco, Costigan, & Dipietro, 2005) which again may affect infant microbiota composition via changes in maternal microbiota.

In a study by Zijlmans et al. (2015), investigators examined the differential effects of maternal cortisol and psychosocial stress during the prenatal period on infant microbiota. They found that although cortisol and psychosocial stress were only moderately related, both predicted similar changes in infant microbiota. Furthermore, a composite of these two indices predicted the greatest change in microbiota while one or the other predicted only moderate changes, thus suggesting a possible dose-response effect of stress. Future research should continue to explore whether differing types of prenatal stress are associated with altered changes in maternal-infant microbiota transmission.

7 | CONCLUSION

We have outlined the claim that prenatal stress promotes postnatal plasticity by increasing susceptibility to environmental experiences and exposures (Pluess & Belsky, 2011). In addition to reviewing the Pluess and Belsky (2011) proposal and citing evidence consistent with it, we have extended their argument by hypothesizing that infant microbiota is a potential mechanism by which such enhanced plasticity could be instantiated. Specifically, we have called attention to how prenatal stress is associated with changes in infant microbiota composition and how microbiota composition is associated with two established markers of susceptibility—heightened behavioral and physiological reactivity. We have also considered future research directions, including ones that could evaluate whether use of probiotics could affect susceptibility to postnatal experiences, as well as the role of breastfeeding and the immune system. In so doing, we have sought to stimulate further research by encouraging other investigators to look at the potential "upside" of prenatal stress when infants experience supportive rearing milieus postnatally.

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