Prenatal Depression and Infant Temperament: The Moderating Role of Placental Gene Expression

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Abstract

Prior research has demonstrated the link between maternal depression during pregnancy (i.e., prenatal depression) and increased neurodevelopmental dysregulation in offspring. However, little is known about the roles of key hypothalamic–pituitary axis regulatory genes in the placenta modulating this association. This study will examine whether placental gene expression levels of 11β-hydroxysteroid dehydrogenase type 2 (*HSD11B2*), glucocorticoid receptor (*NR3C1*), and mineralocorticoid receptor (*NR3C2*) can help elucidate the underlying mechanisms linking prenatal depression to infant temperament, particularly in infants with high negativity and low emotion regulation. Stored placenta tissues ($N = 153$) were used to quantify messenger ribonucleic acid levels of *HSD11B2*, *NR3C1*, and *NR3C2*. Assessments of prenatal depression and infant temperament at 6 months of age were ascertained via maternal report. Results found that prenatal depression was associated with increased Negative Affectivity ($p < .05$) after controlling for postnatal depression and psychosocial characteristics. Furthermore, the association between prenatal depression and Negative Affectivity was moderated by gene expression levels of *HSD11B2*, *NR3C1*, and *NR3C2* such that greater gene expression significantly lessened the association between prenatal depression and Negative Affectivity. Our findings suggest that

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CONFLICT OF INTEREST

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individual differences in placental gene expression may be used as an early marker of susceptibility or resilience to prenatal adversity.

Depression is a major stress-related disorder for women, with 10–25% of women experiencing depression during pregnancy (Field, Diego, & Hernandez-Reif, 2006; Marcus, Flynn, Blow, & Barry, 2003; Stowe, Hostetter, & Newport, 2005; de Tychey et al., 2005). Prenatal depression affects fetal activity and growth (Dieter et al., 2001), and infants of mothers who are depressed during pregnancy have been shown to exhibit increased levels of fear, stress, irritability, and reactivity (Davis, Glynn, Waffarn, & Sandman, 2011; Davis et al., 2004, 2007; Diego et al., 2004; Field, 2011; Gaynes et al., 2005; Zuckerman, Bauchner, Parker, & Cabral, 1990). Prior studies have also found that prenatal depression predicts developmental delays (Deave, Heron, Evans, & Emond, 2008), emotional and behavioral problems (Korhonen, Luoma, Salmelin, & Tamminen, 2012; Luoma et al., 2001, 2004), changes in cortical thickness (Sandman, Buss, Head, & Davis, 2015) in childhood and adolescence, and stress-related disease in adulthood (Barker, 2002; Kajantie, 2006).

Decades of interdisciplinary research have explored the underlying biological mechanisms that connect maternal depression, or exposure to prenatal stress, to offspring developmental outcomes. Much of this research has focused on glucocorticoid stress hormones such as cortisol as a possible component of the underlying mechanism. Highly stressed pregnant women may secrete a greater amount of cortisol compared to nonstressed pregnant women (Chrousos, 1992; Glover, O'Connor, & O'Donnell, 2010), although the evidence for this is mixed. As cortisol passes through the placenta to the fetus, increased levels have been strongly associated with depression in the general population (Knorr, Vinberg, Kessing, & Wetterslev, 2010; Pariante & Lightman, 2008) and in pregnant mothers (Field, Diego, Hernandez-Reif, et al., 2004; Field et al., 2006). The pathway lies in fetal overexposure to glucocorticoids that impact development of the central nervous system and the hypothalamic–pituitary (HPA) axis (Sandman, 2015; Sandman, Wadhwa, Chicz-DeMet, Porto, & Garite, 1999), which may set the child on a suboptimal neurodevelopmental trajectory (Davis et al., 2004).

The placenta plays a vital role in regulating the amount of glucocorticoids in circulation in the fetal environment (Moisiadis & Matthews, 2014; Seckl, 1998; Seckl & Holmes, 2007; Seckl & Meaney, 2004). The placental enzyme, 11β-HSD2, converts active cortisol to inactive cortisone (Benediktsson, Calder, Edwards, & Seckl, 1997). This enzyme is encoded by the *HSD11B2* gene. Higher 11β-HSD2 levels in the placenta create a barrier to the transfer of excessive glucocorticoids, thus protecting the fetus, while a relative deficiency of 11β-HSD2 allows greater passage of maternal glucocorticoids to the fetus. Greater placental *HSD11B2* DNA methylation has been associated with poor infant outcomes, such as lower birthweight, lower quality of movement, and lower muscle tone (Conradt, Lester, Appleton, Armstrong, & Marsit, 2013; Marsit, Maccani, Padbury, & Lester, 2012). DNA methylation is most frequently studied as a proxy measure of epigenetic regulation and is known to be associated with a reduction in gene expression (Marsit et al., 2012). However, one previous work by Räikkönen et al. (2015) found an inverse association where greater placental

HSD11B2 expression was correlated with infant dysregulated behavior, as measured by crying, feeding, spitting, bowel movement, sleeping, and predictability.

Among other important regulators of glucocorticoids in the placenta are the glucocorticoid receptors (GR; encoded by *NR3C1*) and mineralocorticoid receptors (MR; encoded by *NR3C2*), which modulate the actions of glucocorticoids on gene transcription (Conradt et al., 2015; Reynolds et al., 2015; Seckl, 1998; Seckl & Holmes, 2007; Seckl & Meaney, 2004). The activation of GR and MR inhibits HPA axis activity, which releases more cortisol through negative feedback inhibition in brain tissues such as the hippocampus (Matthews, 2002). GR deficiency in the placenta and insufficient placental glucocorticoid response may lead to impaired GR functions and thereby possibly contribute to the development of infant dysregulated behavior (Conradt et al., 2015; Paquette et al., 2015). Increased placental *NR3C1* methylation has been associated with decreased gene expression (Bromer, Marsit, Armstrong, Padbury, & Lester, 2013), poorer attention, greater cortisol stress reactivity, higher arousal, and decreased self-regulation in infants (Bromer et al., 2013; Conradt et al., 2015; Paquette et al., 2015). In contrast, some studies found that increased placental *NR3C1* expression, or decreased *NR3C1* methylation, was associated with adverse infant neurobehavioral outcomes, such as lower quality of movement, more lethargy, poorer attention, and decreased self-regulation (Räikkönen et al., 2015; Stroud et al., 2016). Finally, no association between placental MR (*NR3C2*) and infant neurobehavioral development has been noted. Similar to GR, MR is responsive to glucocorticoids and plays a significant role in glucocorticoid regulation. Prior research found that prenatal depression was associated with altered placental *NR3C2* gene expression (Reynolds et al., 2015), which suggests the involvement of MR in the molecular mechanisms that underlie the programming effects of prenatal depression in offspring development.

In one recent study, Conradt et al. (2013) examined whether placental *HSD11B2* and *NR3C1* methylation would interact with prenatal depression and anxiety in predicting infant neurobehavior between 37 and 41 weeks of age. They found that prenatal depression and anxiety alone did not predict infant neurobehavior, with the exception that prenatal depression was associated with lower muscle tone. However, when they interacted with DNA methylation they found that in the context of prenatal depression alone, greater *NR3C1* methylation on the CpG island (specifically in the region of CpG2) was associated with decreased infant self-regulation, lower muscle tone, and more lethargy. In addition, only in the context of prenatal anxiety, greater *HSD11B2* methylation on the CpG island (in the region of CpG4) conferred risk for lower muscle tone.

There are some limitations in Conradt et al.'s study. First, possible confounding factors (e.g., postnatal depression) have not been clearly specified. Second, placental DNA methylation of *HSD11B2* and *NR3C1* genes was conducted as markers for epigenetic vulnerabilities and the roles of the expression of those genes in the placenta were not evaluated. The relationship between DNA methylation and gene expression is not straightforward because gene expression is regulated by genetics and other epigenetic processes, such as histone modification and noncoding RNA (Jaenisch & Bird, 2003; Pastinen et al., 2004), and all of those functions collectively lead to the altered levels of gene expression (see Maccani &

Marsit, 2009 for a review). Consequently, to gain a more accurate evaluation of placental gene functioning, gene expression data (mRNA expression) must be provided.

Although there is evidence supporting the role of placental gene functions in regulating the relationship between prenatal depression and infant neurobehavior, no study has examined early temperament, which has been viewed as a precursor for subsequent mental health disorders (De Pauw & Mervielde, 2010; Hellemans, Sliwowska, Verma, & Weinberg, 2010). In the current study, we used gene expression data from placental tissue and hypothesized that prenatal maternal depression would be associated with infant temperament at 6 months, especially in areas related to negative affectivity and regulation. We predicted that prenatal depression would interact with the three key genes (*HSD11B2*, *NR3C1*, and *NR3C2*) involved in placental glucocorticoid metabolism or transfer to predict infant temperament. In particular, we hypothesized that the effect of prenatal depression on negative affectivity and dysregulation would be significantly stronger among infants with lower placental *HSD11B2*, *NR3C1*, and *NR3C2* expression and that greater expression would "protect" the infant from the deleterious effects of prenatal maternal depression, as evidenced by a lower association between maternal depression and infant temperament. As prior research suggested that both prenatal and postnatal maternal depression affect infant temperament (Davis et al., 2004), we also controlled for postnatal maternal depression.

METHOD

Participants

Data in this study came from a subsample of 153 mother–child dyads, whose placenta tissues were stored as a part of an ongoing prospective study of child development (see a detailed description PMID: 26418562). Participants were recruited at the prenatal obstetrics and gynecological clinics at Mount Sinai Hospital and New York Presbyterian Queens, NY, followed from their 2nd trimester through delivery, and then prospectively after birth. Exclusion criteria included HIV infection, maternal psychosis, maternal age <15 years, life-threatening maternal medical complications, and congenital/ chromosomal abnormalities in the fetus. The participants ($N = 153$) in the current study and those active participants of the parent study without placenta tissue ($N = 173$) were not significantly different across gestational age ($p = .411$), birthweight ($p = .168$), child gender ($p = .813$), maternal age ($p = .995$), marital status ($p = .385$), maternal education ($p = .265$), and race ($p = .086$).

Preterm infants born before 34 weeks' gestation were also excluded because of their risks for severe health and developmental problems (Crowther, Crosby, & Henderson-Smart, 2010; Loftin et al., 2010; Vohr, 2013). Infants were born with a mean gestational age of 39.1 ($SD = 1.84$) weeks (range 35.0–42.2 weeks) (Table 1 shows the demographic characteristics of the sample used in the current study).

This study was conducted according to the guidelines laid down in the Declaration of Helsinki. All mothers gave written informed consent before any assessment or data collection. All procedures involving human subjects in this study were approved by the Institutional Review Boards at the City University of New York, New York Presbyterian/ Queens, and the Icahn School of Medicine at Mount Sinai.

Measures

Maternal depression—The Edinburgh Postnatal Depression Scale (EPDS; Cox, Holden, & Sagovsky, 1987) was used to measure mother's depressive symptomatology during pregnancy and the postpartum period. The EPDS is a validated self-report questionnaire consisting of 10 question items. For each item, mothers reported how they felt in the past 7 days on a 4-point Likert scale from 0 to 3, based on levels of severity. Some items were reverse coded, and an aggregate sum score was generated. The EPDS is well validated and has acceptable reliability ranging from .79 to .86 (Kheirabadi, Maracy, Akbaripour, & Masaeli, 2012; Mazhari & Nakhaee, 2007; Montazeri, Torkan, & Omidvari, 2007; Small, Lumley, Yelland, & Brown, 2007), satisfactory sensitivity (78%), and specificity (75%) (Kheirabadi et al., 2012). EPDS has been used as a valid and reliable measure for depression during the prenatal and postnatal periods (Bolten et al., 2013; Luoma et al., 2001; Oberlander et al., 2008). Mothers completed the EPDS during their 2nd trimester and at 6 months postpartum. Forty-two (27%) mothers met criteria for clinical depression (10) during the prenatal period, and 28 (18%) met criteria during the postpartum period. In this study, the internal reliability (Cronbach's alpha) of prenatal and postnatal EPDS was .78 and .85, respectively.

Infant temperament—The Short Form of the Infant Behavior Questionnaire-Revised (IBQ-R; Garstein & Rothbart, 2003; Putnam, Helbig, Gartstein, Rothbart, & Leerkes, 2014) was used to measure infants' temperament at approximately 6 months. The IBQ-R is a parent report questionnaire, which is typically completed by the mother. It consists of 91 items about the frequency of their infant/child's specific behaviors. The 14 subscales include activity level, cuddliness, fear, sadness, high-intensity pleasure, low-intensity pleasure, approach, smiling and laughter, falling reactivity, duration of orienting, perceptual sensitivity, distress to limitations, vocal reactivity, and soothability. The IBQ-R has been found to form three hierarchical factors: Negative Affectivity, Regulatory Capacity/Orienting (Regulation), and Positive Emotionality/Surgency (Bayly & Gartstein, 2013; Gartstein, Bell, & Calkins, 2014). As prior evidence indicates that prenatal mood state is particularly associated with negative affectivity (Blair, Glynn, Sandman, & Davis, 2011; Pluess et al., 2011) and dysregulation (Babineau et al., 2015; Gutteling et al., 2005), we focused on the Negative Affectivity and Regulation factors, but not Positive Emotionality/Surgency. Negative Affectivity includes falling reactivity, fear, distress to limitations, and sadness subscales, with an internal reliability of .76. Regulation consists of low-intensity pleasure, cuddliness, duration of orienting, and soothability subscales, with an internal reliability of .82 (Gartstein & Rothbart, 2003).

Placenta sampling and gene expression profiling—Biopsies, free of maternal decidua, were collected from each placenta quadrant midway between the cord insertion and the placenta rim within an hour of delivery to maintain the optimal integrity of DNA and RNA (Diplas et al., 2009; Lambertini et al., 2008). Tissue was washed in cold sterile water, blotted in sterile gauze, snapfrozen in a liquid nitrogen tank for 24 hours, and stored in an ultra-freezer at −80°C until use. Frozen placenta tissues from each biopsy were ground into powder in a −80°C cooled TissueLyser II (Qiagen, Valencia, CA, USA) and mixed in equal

amounts to represent the whole placenta. DNA and RNA were isolated from powder in Maxwell 16 automated DNA/RNA extraction system (Promega, Madison, WI, USA).

Placental gene expression profiling was carried out using the NanoString™ technology with the nCounter Analysis System (Seattle, WA, USA). Briefly, 100 ng of RNA was incubated in the presence of reporter and capture probes overnight at 65°C. Following hybridization, unbound probes were removed, and the purified complexes were aligned and immobilized on imaging cartridges using an nCounter Prep Station II. Cartridges were then sealed and scanned in an nCounter Digital Analyzer for code count detection. The nanoString Norm package (Waggott et al., 2012) was used to normalize nCounter data. Code count data were first normalized against the geometric mean of spike-in controls and against the geometric mean of the housekeeping genes, GAPDH, RPL19, and RPLP0. The limit of detection (LOD) for each sample was set at two standard deviations above the mean of the included negative control probes. Expression below background threshold was set to the value of the LOD divided by the square root of 2 to maintain sample variability.

Missing data and outliers

Infant's birthweight and maternal postnatal depression variables were missing from two subjects. Little's MCAR tests indicated that data were missing completely at random ($p = .372$). No outliers (>3 SDs from the mean) and violation of normality were detected.

Statistical analysis

First, the unadjusted associations between the study variables were examined using Pearson correlation. Gender differences were examined by a series of independent sample t-tests. Using the PROCESS macro for SPSS (Hayes, 2013; Preacher & Hayes, 2004), which provides the model coefficient estimations using ordinary least squares regression, we tested the moderating effect of gene expression on the association between prenatal depression and infant temperament at 6 months. We computed the bootstrapped bias-corrected 95% confidence intervals by taking 10,000 bootstrapped samples (Hayes, 2013), with each continuous variable centered at its mean. Through this analysis, we were able to test the main effects of prenatal depression, gene expression, and their interaction effect, in predicting temperament (Negative Affectivity and Regulation). All interactions were further examined using the simple slope analysis procedure as implemented in the PROCESS macro (Aiken & West, 1991; Hayes, 2012). The interaction effect was probed to determine whether the simple slope of infant temperament on prenatal depression was statistically significant for higher (i.e., +1 SD) and lower (i.e., −1 SD) values of gene expression.

Covariates and cofounders

Possible infant (gender, gestational age at birth, and birthweight) and maternal characteristics (maternal education and welfare status) were further adjusted in the model. Prenatal maternal depression has been found to influence fetal growth in terms of gestational age and birthweight (Diego et al., 2004; Dieter et al., 2001; Field, Diego, Dieter, et al., 2004), and there are individual differences in infant behaviors with respect to psychosocial factors. Partially adjusted moderation analyses were controlled only for postnatal depression,

while fully adjusted moderation analyses were controlled for postnatal depression and all infant and maternal characteristics listed above.

RESULTS

Descriptive statistics

The correlation metrics and descriptive statistics are presented in Table 2. As seen, Negative Affectivity and Regulation were negatively correlated ($r = -.28$, $p < .001$). Prenatal and postnatal depression were both positively correlated with Negative Affectivity, but negatively correlated with Regulation. There were moderate correlations among the expression level of the three selected genes (*HSD11B2*, *NR3C1*, and *NR3C2*). Gene expression was associated with neither prenatal nor postnatal depression.

Boys exhibited lower scores than girls on Negative Affectivity (boys, mean $= 3.09$, $SD = 0.88$; girls, mean $= 3.41$, $SD = 0.89$, $p = .031$). Gender difference was not observed in Regulation, prenatal and postnatal depression, or gene expression measures.

Moderation effects of gene expression on temperament

Negative affectivity

HSD11B2: There was a significant main effect for prenatal depression on Negative Affectivity (p values $= .005$ and $.004$ in partially and fully adjusted analyses, respectively), whereas the main effect of *HSD11B2* on Negative Affectivity was not significant (see Table 3). There was a significant interaction between maternal depression and *HSD11B2* expression on Negative Affectivity ($p < .001$). Simple slope analysis showed that prenatal depression was only positively associated with Negative Affectivity at the levels of low *HSD11B2* expression ($p < .001$), but at the levels of high expression (see Figure 1a).

NR3C1: There was a significant main effect for prenatal depression on Negative Affectivity (p values $= .036$ and $.032$ in partially and fully adjusted analyses, respectively), whereas the main effect of *NR3C1* on Negative Affectivity was not significant. There was a significant interaction between maternal depression and *NR3C1* expression on Negative Affectivity (p values $= .041$ and $.025$ in partially and fully adjusted analyses, respectively). Simple slope analysis showed that prenatal depression was only positively associated with Negative Affectivity at the levels of low *NR3C1* expression (p values $= .006$ and $.004$ in partially and fully adjusted analyses, respectively), but not at the levels of high expression (see Figure 1b).

NR3C2: There was a significant main effect of prenatal depression on Negative Affectivity (p values $= .034$ and $.030$ in partially and fully adjusted analyses, respectively), whereas the main effect of *NR3C2* on Negative Affectivity was not significant. The interaction between maternal depression and *NR3C2* on Negative Affectivity was marginally significant or significant (p values $= .072$ and $.049$ in partially and fully adjusted analyses, respectively). Simple slope analysis showed that prenatal depression was only positively associated with Negative Affectivity at the levels of low *NR3C2* expression (p values $= .011$ and $.007$ in partially and fully adjusted analyses, respectively), but not at the levels of high expression (Figure 1c).

Regulation

Neither the main effects of prenatal depression and gene expression nor their interaction were significantly related to Regulation (see Table 4).

DISCUSSION

The current study has two main findings: (1) Prenatal depression was associated with increased Negative Affectivity at 6 months of age and (2) the association between prenatal depression and Negative Affectivity was moderated by the levels of *HSD11B2*, *NR3C1*, and *NR*3C2 gene expression, in which prenatal depression was linked to increased Negative Affectivity only at the lower *HSD11B2*, *NR3C1*, and *NR*3C2 gene expression levels. Our finding is consistent with previous studies that showed fetal exposure to maternal depression was conducive to programming effects, with downstream implications for infant temperament development. It also extends prior research by showing initial evidence that the impact of maternal depression may be alleviated by the level of gene expression in the placenta tissues.

Depression is the leading cause of disability worldwide (WHO, 2017) and is a significant public health concern. It has been widely speculated that children of mothers with higher prenatal depression are more likely to exhibit cognitive, behavioral, and emotional problems (Field, 2011) as a result of exposure to elevated maternal cortisol in the intrauterine environment. Our results show that greater maternal depression is independently associated with greater Negative Affectivity even after postnatal depression and other psychosocial characteristics were controlled for. This finding is consistent with prior research, which showed that prenatal maternal stress (e.g., depression, anxiety) predicted increased emotionality in offspring independent of postnatal maternal mood state (Davis et al., 2004, 2007; Huot, Brennan, Stowe, Plotsky, & Walker, 2004; O'Connor, Heron, Golding, Beveridge, & Glover, 2002).

We attempted to extend our understanding of whether the adverse effect of maternal depression during pregnancy on their offspring's temperament could be moderated by placental gene function. Beyond the effects of prenatal depression, postnatal depression, and background characteristics, placental *HSD11B2*, *NR3C1*, and *NR3C2* expression moderated the impact of exposure to prenatal depression. Greater prenatal depression and lower placental gene expression together appeared to confer risk for infants' negative temperament, whereas higher placental gene expression buffers the infant from the effect of prenatal depression. Lower expression of *HSD11B2*, *NR3C1*, and *NR3C2*, the key genes that metabolize and regulate glucocorticoids in the placenta, may contribute to levels of glucocorticoids exposure that may harm the fetus (Conradt et al., 2013; Marsit et al., 2012; Moisiadis & Matthews, 2014; Paquette et al., 2015). Specifically, lower placental *HSD11B2* expression may lead to a reduction in 11β-HSD2, thereby failing to create an effective barrier between mother and fetus by converting cortisol into cortisone, while lower *NR3C1* and *NR3C2* expression may result in decreased levels of GR and MR that may constrain glucocorticoid signaling in utero. While prior research has linked increased maternal cortisol to poor self-regulation and temperament problems among affected offspring (Buss et al., 2012; Davis et al., 2007; de Weerth, van Hees, & Buitelaar, 2003), it is also possible that

greater expression of *HSD11B2*, *NR3C1*, and *NR3C2* may protect against the impact of elevated levels of stress-induced glucocorticoids produced by the mother during pregnancy. Consequently, some infants may be less vulnerable to temperamental problems despite mother's prenatal depression.

Interestingly, neither prenatal depression and gene expression nor their interaction were related to Regulation. Negative Affectivity and Regulation represent different constructs of temperament (Bayly & Gartstein, 2013; Gartstein et al., 2014) as measured by the IBQ-R Negative Affectivity scale, which measures infants' response to distress, fear, crying, and sad mood. The development of these temperament traits may be more likely to be influenced by the dysregulated HPA axis functioning in offspring. The fetal HPA axis is developed and demonstrates enhanced activity during late gestation (Challis et al., 2001). The alternation in the development of the fetal HPA axis is subject to changes in fetal glucocorticoid exposure, which could be influenced by the changes in the placental *HSD11B2*, *NR3C1*, and *NR3C2* gene expression levels. In contrast, the IBQ-R Regulation scale measures infant temperament traits including pleasure related to low stimulus intensity, expression of enjoyment, duration of attention, and the ability to become calm when soothed by the caregiver. The development of emotion regulation in younger children is a complex phenomenon and is likely influenced by other neurobiological systems, such as the brain stem, limbic, and cortical systems (Geva & Feldman, 2008). Our findings suggest that infant's negative emotionality may be selectively affected by prenatal depression and further confirm that lower placental *HSD11B2*, *NR3C1*, and *NR3C2* levels are more likely to promote increased impaired emotionality but not problems with emotion regulation in infancy. However, the underlying mechanisms behind the differences between the two dimensions of temperament still need to be explored.

Prior literature suggests that gene expression itself might be susceptible to adverse environmental influences, particularly in the prenatal period, although we did not find direct associations between maternal depression and gene expression. Our findings indicate several inconsistences in the literature. Prenatal depression has been associated with increased *NR3C1* and *NR3C2* expression in the placenta (Räikkönen et al., 2015; Reynolds et al., 2015), but greater *NR3C1* methylation (i.e., lower expression) in cord blood (Conradt et al., 2013; Oberlander et al., 2008). No previous research has found a significant correlation between maternal depression and placental *HSD11B2* expression (O'Donnell et al., 2012; Ponder et al., 2011; Räikkönen et al., 2015; Reynolds et al., 2015), although lower expression has been associated with increased prenatal anxiety (O'Donnell et al., 2012).

It is worth noting that our results appear to be contrary to those of Räikkönen et al. (2015), where higher placental gene expression of *HSD11B2* and *NR3C1* (but not *NR3C2*) was associated with more difficulties in regulatory behaviors (i.e., crying, sleeping, feeding, spitting, bowel movement, sleeping, and predictability) in newborn infants around 15 days, and higher placental *NR3C1* gene expression partially mediated the association between prenatal depression and infant regulatory behaviors. Differences might stem from the fact that we measured temperament at 6 months using the IBQ-R, whereas Räikkönen et al. measured regulatory behaviors at 15 days using the Neonatal Perception Inventory. They suspected that greater expression of *NR3C1* might lead to placental glucocorticoid

oversensitivity, resulting in dysregulated infant behaviors. The investigation of placental gene expression of *HSD11B2*, *NR3C1*, *NR3C2* in relation to infant temperament has not been well explored. While the differences might be a result of the methodological differences between the two studies, future replication is necessary to increase understanding of the relationship between glucocorticoid metabolism in the placenta and emerging temperament in early childhood.

There are some limitations to the current study. First, both the measures of maternal prenatal depression and infant temperament relied on mothers' report. Future studies will benefit from assessments of infant temperament by multiple informants or via observation (Boyd, Zayas, & McKee, 2006; Edhborg, Lundh, Seimyr, & Widström, 2001; Pauli-Pott, Mertesacker, & Beckmann, 2004). Similarly, generalization of the findings for clinical-level depression may be limited as we relied on self-report depression symptomatology. The application of a more structured psychiatric interview (DSM-5) of depressive symptoms is warranted. Second, our sample was limited by the availability of placenta tissues. While key demographic characteristics between the infants with and without placenta tissues did not differ significantly, we acknowledge that this may have limited external validity. Furthermore, maternal depression was assessed only once, in mid-gestation. It is possible that mothers' depression fluctuated during pregnancy and its interaction with placental gene function would also be differentially associated with infant's temperament. Third, our study utilized a candidate gene approach and only examined three genes, while a genomewide analysis may offer new and more comprehensive insights. Fourth, given that the sample consisted of more families of low SES and minority status (Black and Hispanic), results may not generalize to families with higher economic resources or to other racial/ethnic groups (Blackmore et al., 1993; Lu & Halfon, 2003). Fifth, a very small proportion of our sample (2% or $n = 3$) used antidepressants during pregnancy. As there is a slight possibility that the association between prenatal depression and infant neurodevelopment may be influenced by antidepressant exposure (Casper et al., 2003; Weikum et al., 2013), the analyses were rerun again by excluding these three cases. Although the results showed no change, we have to remain cautious. Finally, placenta samples collected in the current study were obtained from pregnancies free of major obstetric complications, which may constrain the variances in both gene expression levels and infants' outcomes in an unknown fashion. Despite these limitations, the current study demonstrated that a greater level of maternal depression during pregnancy is associated with increased Negative Affectivity in infants. Furthermore, the negative effect of maternal depression on Negative Affectivity is present only among infants with lower placental *HSD11B2*, *NR3C1*, and *NR3C2* expression.

These findings support the concept that placental genes play a crucial role in regulating infant growth during early development. Understanding the effects of the expression of human placental genes can help uncover the role of prenatal depression in influencing infant development, thus contributing to preventive interventions for prenatal maternal depression to mitigate its negative effects on offspring development. Moving forward, a priority for researchers and clinicians alike should be working toward translating these findings into interventions to detect and prevent later psychopathology among high-risk infants. Our findings support the view that preventing early negative/ difficult temperament (e.g., greater negative affectivity) and future suboptimal neurobehavioral development characterized by

internalizing and externalizing behaviors (De Pauw & Mervielde, 2010; Hellemans et al., 2010) should involve interventions that begin during pregnancy. This information can aid in identifying offspring of depressed mothers. However, the clinical implications (i.e., incorporating gene expression in multidimensional risk indices) are still premature. Placental gene expression cannot be assessed when pregnancy continues, so studies must be undertaken using peripheral tissues. The circulating placental RNA (cpRNA) released from the placenta into the maternal bloodstream during pregnancy has been related to the gene expression levels in the placenta. As cpRNA may reflect changes in the placenta, it has been used as a noninvasive approach to examine placental functions for prenatal diagnosis (such as pre-eclampsia, preterm birth) when pregnancy continues (Tsui et al., 2004; Whitehead, Walker, & Tong, 2016). Although the degree of correlations in gene expression across different tissues (maternal blood versus placenta) remains in question, these studies suggest potential for the discovery of placental mRNA markers in the cpRNA that can be used for monitoring placental functions, particularly in modulating glucocorticoid circulation in utero. Finally, decreasing negative emotionality and/or increasing emotion regulation could lead to more positive socioemotional development in the child's life (Denham, Wyatt, Bassett, Echeverria, & Knox, 2009; Sanson, Hemphill, & Smart, 2004).

Acknowledgments

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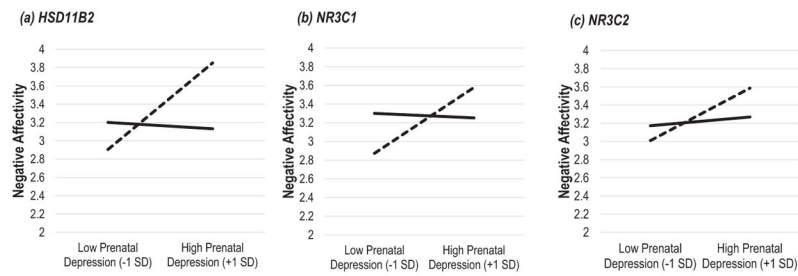
Figure 1.
Gene expression moderation of prenatal depression on Negative Affectivity. Solid line represents high gene expression (+1 SD), and dashed line represents low gene expression (−1 SD). Prenatal maternal depression is linked to higher levels of Negative Affectivity only among infants with the low levels of placental gene expression (*p* values < .001, =.004, and . 007 for *HSD11B2*, *NR3C1*, and *NR3C2*, respectively), but not high levels of gene expression (*p* values = .698, .817, and .589 for *HSD11B2*, *NR3C1*, and *NR3C2*, respectively). Figures are based on the fully adjusted analyses.

TABLE 1

Demographic Characteristics ($N = 153$)

Gestational age (weeks)	Mean (*SD*)	39.05 (1.84)
Birthweight (g)	<2,500, *N*(%)	7 (4.58)
	Mean (*SD*)	3,307.25 (482.94)
Child's sex	Boy, *N*(%)	86 (56.2)
	Girl, *N*(%)	67 (43.8)
Marital status	Married, *N*(%)	55 (35.9)
	Common law, *N*(%)	12 (7.8)
	Single, *N*(%)	84 (54.9)
	Divorced/separate/widowed, *N*(%)	2 (1.4)
On welfare	Yes, *N*(%)	117 (76.5)
	No, *N*(%)	36 (23.5)
Mother's education	Primary/some high school, *N*(%)	27 (17.6)
	High school degree/GED, *N*(%)	34 (22.2)
	Some college, *N*(%)	39 (25.5)
	Associate's degree, *N*(%)	19 (12.4)
	Bachelor's degree, *N*(%)	19 (12.4)
	Graduate-level degree, *N*(%)	15 (9.8)
Mother's race	White, *N*(%)	17 (11.1)
	Black, *N*(%)	38 (24.8)
	Hispanic, *N*(%)	80 (52.3)
	Asian, *N*(%)	11 (7.2)
	Others, *N*(%)	7 (4.6)
Maternal age	Mean (*SD*)	27.53 (5.8)
Use of antidepressant	Yes, *N*(%)	3 (2.0)
	No, *N*(%)	150 (98)
Negative affectivity	Mean (*SD*)	3.23 (0.89)
Regulation	Mean (*SD*)	5.42 (0.66)
HSD11B2	Mean (*SD*)	10.30 (1.76)
NR3C1	Mean (*SD*)	10.82 (0.45)
NR3C2	Mean (*SD*)	7.06 (0.68)
Prenatal depression	Mean (*SD*)	6.97 (5.27)
Postnatal depression	Mean (*SD*)	5.75 (5.51)

Note. SD, standard deviations.

TABLE 2

Unadjusted Associations Between Study Variables

	1	2	3	4	5	6	7
1. Negative affectivity	1						
2. Regulation	−.28[**]	1					
3. HSD11B2	−.14	.13	1				
4. NR3C1	.05	−.03	.19[**]	1			
5. NR3C2	−.08	−.11	.48[**]	.50[**]	1		
6. Prenatal depression	.32[**]	−.20[*]	.04	−.03	.00	1	
7. Postnatal depression	.40[**]	−.21[*]	−.01	−.02	.05	.50[**]	1

Note. Negative Affectivity and Regulation were measured by the Infant Behavior Questionnaire-Revised. Prenatal and postnatal depression was measured by the Edinburg Postnatal Depression Scale.

[*]
$p < .05,$

[**]
$p < .01.$

TABLE 3

Regression and Follow-Up Analyses: Predicting Negative Affectivity

Model 1—Postnatal depression adjusted

Regression model	β	t	p	95% CI
Postnatal depression	.30	3.63	<.001	.022, .075
HSD11B2	−.11	−1.50	.137	−.126, .017
Prenatal depression	.24	2.89	.005	.013, .070
HSD11B2 × prenatal depression	−.29	−3.67	<.001	−.042, −.013
Simple slope analyses for interaction				
Low *HSD11B2* (−1 *SD*)	.53	4.14	<.001	.047, .133
High *HSD11B2* (+1 *SD*)	−.04	−0.41	.684	−.041, .027
Regression model	**β**	**t**	**p**	**95% CI**
Postnatal depression	.31	3.60	<.001	.023, .078
NR3C1	.04	0.50	.621	−.220, .367
Prenatal depression	.18	2.12	.036	.002, .059
NR3C1 × prenatal depression	−.19	−2.06	.041	−.139, −.003
Simple slope analyses for interaction				
Low *NR3C1* (−1 *SD*)	.37	2.79	.006	.018, .107
High *NR3C1* (+1 *SD*)	−.01	−0.06	.954	−.041, .038
Regression model	**β**	**t**	**p**	**95% CI**
Postnatal depression	.32	3.71	<.001	.024, .080

Model 2—Fully adjusted

Regression model	β	t	p	95% CI
Postnatal depression	.31	3.69	<.001	.024, .078
Child gender	.18	2.59	.011	.078, .580
Gestational age	−.07	−0.95	.345	−.131, .046
Birthweight	−.08	−0.98	.331	−.0004, .0001
Maternal education	−.08	−0.80	.427	−.165, .070
Welfare status	−.17	−1.61	.110	−.822, .084
HSD11B2	−.12	−1.65	.101	−.132, .012
Prenatal depression	.25	2.91	.004	.013, .070
HSD11B2 × prenatal depression	−.28	−3.65	<.001	−.042, −.013
Simple slope analyses for interaction				
Low *HSD11B2* (−1 *SD*)	.53	4.15	<.001	.047, .133
High *HSD11B2* (+1 *SD*)	−.04	−0.39	.698	−.04, .027
Regression model	**β**	**t**	**p**	**95% CI**
Postnatal depression	.30	3.51	<.001	.022, .078
Child gender	.20	2.64	.009	.089, .627
Gestational age	−.03	−0.34	.733	−.110, .077
Birthweight	−.07	−0.89	.375	−.0004, .0002
Maternal education	−.06	−0.51	.608	−.155, .091
Welfare status	−.20	−1.78	.078	−.893, .046
NR3C1	.03	0.38	.705	−.238, .351
Prenatal depression	.18	2.16	.032	.003, .060
NR3C1 × prenatal depression	−.21	−2.27	.025	−.149, −.010
Simple slope analyses for interaction				
Low *NR3C1* (−1 *SD*)	.40	2.95	.004	.022, .112
High *NR3C1* (+1 *SD*)	−.03	−0.23	.817	−.044, −.035
Regression model	**β**	**t**	**p**	**95% CI**
Postnatal depression	.32	3.63	<.001	.024, .080

Model 1—Postnatal depression adjusted

Regression model	β	t	p	95% CI
NR3C2	−.07	−.86	.392	−.279, .110
Prenatal depression	.19	2.14	.034	.002, .060
NR3C2 × prenatal depression	−.12	−1.81	.072	−.064, .003
Simple slope analyses for interaction				
Low NR3C2 (−1 SD)	.31	2.59	.011	.012, .092
High NR3C2 (+1 SD)	.06	0.63	.533	−.023, .044

Model 2—Fully adjusted

Regression model	β	t	p	95% CI
Child gender	.19	2.56	.012	.077, .600
Gestational age	−.06	−0.72	.474	−.125, .059
Birthweight	−.07	−0.83	.410	−.0004, .0002
Maternal education	−.06	−0.51	.613	−.154, .091
Welfare status	−.19	−1.71	.089	−.878, .064
NR3C2	−.04	−0.58	.565	−.250, .137
Prenatal depression	.19	2.19	.030	.003, .061
NR3C2 × prenatal depression	−.13	−1.98	.049	−.067, −.0001
Simple slope analyses for interaction				
Low NR3C2 (−1 SD)	.32	2.72	.007	.015, .095
High NR3C2 (+1 SD)	.05	0.54	.589	−.024, .043

Note. At Model 1, adjusted for postnatal depression.

At Model 2, adjusted for postnatal depression, child gender, gestational age, birthweight, maternal education, and welfare status.

TABLE 4

Regression and Follow-Up Analyses: Predicting Regulation

Regression model	Model 1—Postnatal depression adjusted				Model 2—Fully adjusted			
	β	t	p	95% CI	β	t	p	95% CI
Postnatal depression	−.15	−1.63	.106	−.041, .004	−.14	−1.45	.148	−.040, .006
Child gender					.03	0.37	.715	−.176, .255
Gestational age					.05	0.63	.532	−.052, .100
Birthweight					−.05	−0.52	.606	−.0003, .0002
Maternal education					−.01	−0.07	.946	−.104, .098
Welfare status					.13	1.04	.298	−.183, .594
HSD11B2	.13	1.68	.095	−.009, .110	.11	1.33	.186	−.020, .103
Prenatal depression	−.16	−1.68	.094	−.044, .004	−.14	−1.42	.157	−.042, .007
HSD11B2 × prenatal depression	.04	0.42	.675	−.010, .015	.02	0.18	.859	−.012, .014
Simple slope analyses for interaction								
Low HSD11B2 (−1 SD)	−.19	−1.37	.173	−.060, .011	−.15	−1.05	.297	−.056, .017
High HSD11B2 (+1 SD)	−.12	−1.10	.275	−.043, .012	−.12	−1.06	.291	−.044, .013
Regression model	**β**	**t**	**p**	**95% CI**	**β**	**t**	**p**	**95% CI**
Postnatal depression	−.16	−1.72	.088	−.042, .003	−.14	−1.48	.141	−.041, .006
Child gender					.04	0.44	.658	−.170, .269
Gestational age					.04	0.45	.657	−.060, .095
Birthweight					−.05	−0.51	.611	−.0003, .0002
Maternal education					−.02	−0.17	.866	−.111, .093
Welfare status					.13	1.10	.274	−.174, .607
NR3C1	−.02	−0.31	.760	−.273, .200	−.03	−0.37	.713	−.290, .199
Prenatal depression	−.14	−1.53	.127	−.041, .005	−.12	−1.32	.189	−.040, .008
NR3C1 × prenatal depression	.04	0.40	.689	−.044, .066	.02	0.19	.847	−.052, .063
Simple slope analyses for interaction								
Low NR3C1 (−1 SD)	−.18	−1.27	.207	−.059, .013	−.14	−0.97	.333	−.056, .019
High NR3C1 (+1 SD)	−.10	−0.81	.422	−.045, .019	−.10	−0.80	.424	−.046, .020
Regression model	**β**	**t**	**p**	**95% CI**	**β**	**t**	**p**	**95% CI**
Postnatal depression	−.15	−1.66	.099	−.041, .004	−.13	−1.40	.164	−.040, .007

Model 1—Postnatal depression adjusted

Regression model	β	t	p	95% CI
NR3C2	−.09	−1.14	.258	−.246, .066
Prenatal depression	−.13	−1.43	.154	−.040, .006
NR3C2 × prenatal depression	−.02	−0.25	.804	−.030, .023
Simple slope analyses for interaction				
Low NR3C2 (−1 SD)	−.12	−0.90	.369	−.047, .017
High NR3C2 (+1 SD)	−.15	−1.41	.161	−.046, .008

Model 2—Fully adjusted

Regression model	β	t	p	95% CI
Child gender	.04	0.45	.653	−.167, .265
Gestational age	.05	0.57	.571	−.054, .098
Birthweight	−.05	−0.56	.573	−.0003, .0002
Maternal education	−.03	−0.24	.809	−.113, .088
Welfare status	.14	1.12	.263	−.167, .608
NR3C2	−.10	−1.24	.218	−.259, .060
Prenatal depression	−.11	−1.20	.231	−.038, .009
NR3C2 × prenatal depression	−.03	−0.45	.655	−.034, .021
Simple slope analyses for interaction				
Low NR3C2 (−1 SD)	−.08	−0.62	.539	−.043, .023
High NR3C2 (+1 SD)	−.15	−1.35	.181	−.046, .009

Note. At Model 1, adjusted for postnatal depression.

At Model 2, adjusted for postnatal depression, child gender, gestational age, birthweight, maternal education, and welfare status.