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Research paper

Prenatal SSRI antidepressant use and maternal internalizing symptoms during pregnancy and postpartum: Exploring effects on infant temperament trajectories for boys and girls

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ABSTRACT

Background: The severity and treatment of depression/anxiety during pregnancy and postpartum has important implications for maternal and child well-being. Yet, little is known about prenatal SSRI use and early child socioemotional development. This study explores effects of prenatal SSRI exposure, and pre- and postnatal internalizing symptoms on trajectories of infant temperament, identifying potential differences for boys and girls.
Methods: Using latent growth models, sex differences in infant temperament trajectories from 3- to 10-months were examined in relation to prenatal and postpartum internalizing symptoms and prenatal SSRI exposure among 185 mother-infant dyads.
Results: For girls, prenatal internalizing symptoms were associated with greater initial distress to limitations, and lower duration of orienting, smiling/laughter, and soothability. Postnatal symptoms predicted slower decreases in girls' duration of orienting. SSRI exposure predicted decreases in distress to limitations and slower increases in smiling and laughter. For boys, maternal internalizing symptoms did not generally affect temperament profiles. SSRI exposure was associated with higher initial activity level and slower declines in distress to limitations.
Limitations: Only parent-report indicators of infant temperament across 10 months of infancy were provided. Maternal internalizing symptoms were measured at discrete times during pregnancy and postpartum, with no analysis of changes in symptoms across time.
Conclusions: Prenatal SSRI treatment, and both prenatal and postpartum internalizing symptoms, exert unique effects on infant temperament. Overall, the present study suggests sex-dependent fetal programming effects that should be further evaluated in future research. Results have implications for perinatal mental health treatment and perceived impacts on child socioemotional development.

1. Introduction

Maternal anxiety and mood disorders/symptoms present during pregnancy and shortly after birth coincide with rapid periods of development, wherein the fetal and infant brain and nervous system are particularly vulnerable to the influence of early experiences (Johnson et al., 2013). Well-replicated findings indicate prenatal anxiety and depression are associated with a wide range of neonatal and infant outcomes, including risk for pre-term birth and low birth weight (Dunkel Schetter and Tanner, 2012; Field, 2017; Grote et al., 2010), changes in cortisol levels among neonates (Field et al., 2004; Lundy et al., 1999; Romero-Gonzalez et al., 2018) and infant behavioral difficulties (Kingston et al., 2012). In the postpartum period, maternal distress not only has direct implications for infant development (Kingston et al., 2012), but can also affect dyadic relationships between the mother and child (e.g., bonding disturbance, less sensitive parenting; Muzik et al., 2017). Because of the stability of internalizing symptoms from pre- to postpartum (e.g., Dietz et al., 2007), it is particularly important to treat mental health concerns during pregnancy, as effective treatment may have important implications for the well-being of women, children, and their families.

Within emerging Developmental Origins of Health and Disease

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(DOHaD) literature (Wadwha et al., 2009; Gluckman et al., 2011), there is a growing emphasis on associations between prenatal stress—including depression and anxiety as responses to stress—and early development, using 'fetal programming' models. In general, fetal programming refers to various prenatal changes to maternal physiology (e.g., in response to stress, disease, substance use), which can alter offspring phenotypes and affect development across the lifespan (Glover, 2011; Hochberg et al., 2011). Despite forthcoming evidence for programming effects, there is significant heterogeneity in outcomes, wherein certain children are adversely affected, whereas others do not appear to experience long-term consequences (Glover, 2011). Sex-based differences may in part account for this variability in child outcomes associated with prenatal exposure to maternal distress (Sandman et al., 2013; Sutherland and Brunwasser, 2018). More specifically, accumulating evidence suggests that in the face of prenatal stress exposure (i.e., maternal depression, anxiety, and physiological stress response), girls are more likely to develop increased physiological and temperamental reactivity, as well as risk for internalizing behaviors (e.g., anxiety; Costello et al., 2007; Hamada and Matthews, 2018; Sandman et al., 2013; Tibu et al., 2014; Van den Bergh et al., 2007; Van Lieshout and Boylan, 2010). Comparatively, boys are more likely to experience reductions in reactivity and risk for later externalizing behaviors (e.g., aggression; Hamada and Matthews, 2018; Li et al., 2010; Rodriguez and Bohlin, 2005; Sandman et al., 2013; Tibu et al., 2014). Given these now replicated patterns, researchers have increasingly underscored the importance of evaluating sex-based differences within prenatal programming models (Sandman et al., 2013; Sutherland and Brunwasser, 2018). Although a number of prenatal exposures have been implicated in shaping offspring social-emotional development, and temperament in particular (Gartstein and Skinner, 2018), maternal internalizing symptoms and selective serotonin reuptake inhibitor (SSRI) medications utilized to treat these difficulties are especially critical to examine, due to the number of affected individuals (Bennett et al., 2004; Cooper et al., 2007).

The current study was therefore undertaken with two specific aims: (1) to investigate trajectories of infant temperament in association with pre- and postnatal maternal internalizing symptoms and prenatal exposure to SSRIs; and (2) to explore whether infant sex moderates the developmental associations between pre- and postnatal maternal mental health factors and the development of infant temperament. Given high rates of co-morbidity between pre- and postnatal depression and anxiety (O'Hara and McCabe, 2013), and in accordance with the developmental literature examining cumulative risk models (Gray et al., 2017; Sheinkopf et al., 2007), maternal symptoms of anxiety and depression were examined as an internalizing symptom composite, calculated during pregnancy and postpartum. Associations between pre- and postnatal internalizing symptoms, prenatal SSRI exposure, and growth in infant temperament across the first year of life were specifically of interest, as early-emerging socioemotional development has important implications for a host of developmental outcomes, and may be an early risk phenotype for subsequent child psychopathology (Gartstein et al., 2016b), with growth parameters demonstrating unique predictive value (Gartstein et al., 2010; Gartstein and Hancock, 2016).

1.1. Infant temperament

According to Rothbart's psychobiological model, temperament encompasses individual differences in reactivity and self-regulation, observed across domains of affect, activity, and attention (Rothbart and Bates, 2006). As a constitutionally-based construct, temperament has a biological basis, including genetic (Posner et al., 2007) and epigenetic mechanisms (Gartstein and Skinner, 2018; Monk et al., 2012). Temperament *reactivity* includes individual differences in responsivity to internal and external changes, including affect, motor activity, and attentional responses; whereas *self-regulation* and its components (e.g., soothability) serve to modulate reactivity (Rothbart and Bates, 2006; Rothbart and Derryberry, 1981; Strelau, 1983). Because of its observable manifestations and biological basis, temperament can be measured via behavioral and/or physiological markers (e.g., cortisol reactivity and electroencephalogram indicators; Rothbart and Bates, 2006; Gartstein et al., 2016b), with the former approach utilized in this study.

Sex-based differences in temperament are well-documented, and begin as early as infancy. Existing research indicates that girls tend to demonstrate more fearful or inhibited behaviors, compared to more frequent/intense approach-related behaviors reported for boys (e.g., activity, high intensity pleasure; Campbell and Eaton, 1999; Gartstein and Rothbart, 2003; Kivijärvi et al., 2005; Martin et al., 1997; Rothbart, 1988). Meta-analytic findings support large sex differences in a number of temperament domains across childhood, including higher effortful control among girls (e.g., inhibitory control, perceptual sensitivity), and higher surgency among boys (e.g., activity level, high-intensity pleasure; Else-Quest et al., 2006). Moreover, sex differences in temperament trajectories across the first year of life have been reported, especially for approach- and avoidance-related dimensions, with boys starting higher and increasing on the former and girls on the latter (Gartstein and Hancock, 2019; Gartstein et al., 2018). It is possible that this documented and early appearing variability in temperament development between girls and boys is in part a function of differential prenatal exposure effects.

Despite overall evidence for relative stability of temperament (Rothbart et al., 2001), temperament is prone to changes in expression (Rothbart et al., 2000) and undergoes rapid development in infancy. More recent theoretical models and empirical evidence point to significant developmental transitions across temperament domains, that in turn predict important developmental outcomes (Bridgett et al., 2013; Gartstein et al., 2010; Rothbart et al., 2011). Prior research supports considerable growth across infancy (Braungart-Rieker et al., 2010; Bridgett et al., 2013); Thomas et al., 2018), for example, with high initial levels and steeper increases in infant fear predicting greater toddler anxiety (Gartstein et al., 2010). Importantly, more recent work demonstrates these trajectories are largely non-linear in nature (Gartstein and Hancock, 2019). Thus, results of growth-focused investigations indicate that changes in fine-grained temperament dimensions across infancy form meaningful developmental patterns, potentially predictive of important outcomes, such as emerging symptoms of child psychopathology and parenting behaviors. Addressing factors that affect the developmental trajectories of infant temperament represents an area of research with the potential to produce targets for early clinical intervention and prevention efforts.

1.1.1. Prenatal mental health

Findings specific to effects of prenatal depression and anxiety on infant temperament outcomes have been somewhat equivocal; however, there is substantial empirical support for associations between mothers' prenatal psychological distress (e.g., depression, anxiety, and stress) and having an infant with higher negative emotionality and lower self-regulatory abilities (Erickson et al., 2017; Korja et al., 2017). Sex-dependent programming effects are starting to be explored in the context of prenatal programming models of early temperament development. In a recent review, Sutherland and Brunwasser (2018) identified several studies that supported the association between maternal prenatal distress and higher negative emotionality/reactivity among girls, but decreased reactivity among boys (Braithewaite et al., 2017a, 2017b), with one study reporting that prenatal exposure to stress from a natural disaster predicted increased irritability among boys only (Simcock et al., 2017). In their summary of the existing research, Sutherland and Brunwasser (2018) subsequently called for ongoing attention to sex-specific associations between prenatal maternal distress and infant temperament.

1.1.2. Postnatal mental health

Maternal symptoms of depression and anxiety in the postnatal period can also affect early childhood socioemotional development, and temperament in particular, as the postnatal caregiving environment can either exacerbate or mitigate effects of prenatal stress (Bergman et al., 2008; Bergman et al., 2010; Thomas et al., 2017). Although a comprehensive review of the literature describing associations between postnatal maternal mental health and child temperament development is beyond the scope of this study, research generally indicates maternal postpartum anxiety predicts more difficult temperament across the first few years of life (McMahon et al., 2001; Mednick, 1996), and infants born to postnatally depressed mothers are moderately more likely to exhibit less social engagement and more fearful behavior (Kingston et al., 2012).

Unfortunately, firm conclusions regarding links between pre- and postnatal mental health and infant temperament development are limited by differences across studies in the timing of temperament measurements (Erickson et al., 2017). Among the few longitudinal studies addressing temperament growth, links between infant temperament trajectories and maternal characteristics in the postpartum period have been identified. For example, maternal self-reported depression scores at 3.5 months postpartum predicted accelerated growth in infant fear reactivity between 4 and 12 months (Gartstein et al., 2010). Thus, there is a need to account for postpartum depression and anxiety symptoms in the context of efforts aimed at furthering our understanding of prenatal maternal mental health contributions to changes in temperament development across infancy, addressing whether temperament trajectory effects are sex-dependent.

1.2. Prenatal SSRI use

Given potential implications of effectively treating maternal mental health concerns for women and their children, determining safe and effective pre- and postnatal treatment options has paramount importance. Although psychotherapy typically represents a first-line treatment option, SSRI use is considered appropriate for treatment of moderate-to-severe mental health issues during this period (Alwan et al., 2016; Muzik et al., 2011; Smith et al., 2009). Increases in antidepressant use during pregnancy appear to be driven by SSRI medications, with prior estimates within the U.S. indicating a rise in antidepressant use from 5.7% of pregnant women in 1999 to 13.4% of pregnant women in 2003 (Cooper et al., 2007). While SSRIs are prescribed with the expectation that they will confer a benefit to the mother—and by extension to her infant and child—such effects have not been widely demonstrated (Weikum et al., 2013), and developmental concerns remain regarding the safety of SSRI use among pregnant women and breastfeeding mothers. In particular, studies have linked prenatal SSRI exposure with increased relative risk of negative birth and neonatal outcomes (Grigoriadis, 2014; Roca et al., 2011) and disturbances in early childhood behavior, neurodevelopment, and physiological stress reactivity (Hanley et al., 2013; Oberlander et al., 2008; Zeskind and Stephens, 2004).

Nevertheless, in their recent review of the safety of prenatal SSRI use, Alwan and colleagues (2016) underscored difficulties in separating effects of prenatal SSRI use from the underlying depression and other associated risk factors. For instance, prenatal SSRI use could be a marker of more severe or persistent depression (Oberlander and Zwaigenbaum, 2017), with observed effects that may be attributed to associations between higher maternal stress and fetal programming (Gartstein and Skinner, 2018; Glover, 2011; Hochberg et al., 2011). Nevertheless, SSRI exposure is also capable of directly shaping brain development via altered levels of the key neurotransmitter serotonin (5HT) during developmentally sensitive periods. Unique effects of prenatal SSRI medication on fetal development can be expected, as serotonin has a critical neurotrophic role in the maturation of the central nervous system, considered with respect to infant temperament in the present study. Notably, emerging research indicates that alternations to prenatal serotonin levels can have variable developmental consequences depending on postnatal factors (Brummelte et al., 2017), with maternal postpartum internalizing symptoms considered herein.

Given the developmental complexities and empirical challenges, there is a need for additional research, including randomized controlled trials, to better understand the implications of prenatal SSRI use; however, logistical, medical and ethical barriers are profound (Muzik and Hamilton, 2016). Pending future research, current best practice recommendations indicate that decisions regarding psychotherapy vs. medication use in pregnancy and postpartum should operate on an individualized basis, wherein factors affecting the mother and her child are carefully considered via a personalized analysis of risks and benefits (Alwan et al., 2016; Muzik and Hamilton, 2016). The current study therefore addresses effects of maternal internalizing symptomatology (both pre- and postnatally) and prenatal SSRI use, in order to explore unique associations with early temperament development among offspring, considering sex-dependent consequences.

1.2.1. Prenatal SSRI exposure and temperament development

Current understanding of the relationship between prenatal SSRI use and child temperament development is limited, and only select studies have explored SSRI effects independent of maternal mood symptoms. Within two broader studies of child development following prenatal use of the SSRI fluoxetine, Nulman and colleagues failed to demonstrate associations between prenatal fluoxetine exposure and child temperament outcomes during the toddler and preschool years (Nulman et al., 1997, 2002). More recently, Lupattelli et al. (2018) investigated prenatal SSRI use and developmental outcomes among 4,128 Norwegian preschool-age children, exploring potential effects of the timing of prenatal exposure (i.e., early-, mid-, or late-pregnancy). Results indicated that SSRI exposure at any time during pregnancy was not associated with child temperament trajectories between 1.5 and 5 years of age (Lupattelli et al., 2018).

Effects of prenatal SSRI exposure have been noted earlier in development; however, specific exploration of temperament outcomes in infancy has been limited. For example, stress responses in three-month-old infants indexed by evening basal cortisol levels, were lower in SSRI-exposed infants relative to their non-exposed counterparts, after controlling for maternal mood and breastfeeding status (Oberlander et al., 2008). In sum, despite preliminary indications that prenatal SSRI use does not exert unique effects on early temperament development in children, there is a general dearth of research, especially in infancy. To our knowledge, this study is the first to explore sex-based differences in developmental trajectories of infant temperament, as influenced by unique contributions of maternal pre- and postnatal internalizing symptoms and SSRI exposure during pregnancy.

2. Current study

The present study was undertaken to distinguish between prenatal SSRI exposure and maternal depression/anxiety (internalizing) symptoms across prenatal and postpartum periods, exploring their effects on infant temperament development during the first year of life for boys and girls. Specifically, Latent Growth Curve modelling enabled us to investigate patterns or trajectories of mother-reported temperament across three time points throughout infancy (i.e., 3, 6, and 10 months of age), as predicted by (a) mood/anxiety symptoms during the third trimester of pregnancy and three months postpartum and (b) any prenatal exposure to SSRIs. Given the accumulating evidence of sex-dependent prenatal programming effects, developmental models were examined separately for boys and girls, in order to discern potential sex differences in growth patterns related to maternal symptomatology and SSRI use.

Although prior studies have not considered these specific temperament assessment points, general expectations regarding trajectories can

be articulated. First, we anticipated that maternal internalizing symptoms, both prenatally and during the postpartum period, would be associated with initial levels and growth trajectories of infant temperament. For girls, we hypothesized that higher levels of prenatal and postpartum internalizing symptoms would in turn contribute to higher initial levels and increases in infant negative emotionality, and fear in particular, across the first year of life. Inverse relationships were anticipated for positive emotionality/surgency (i.e., smiling/laughter, activity level) and emerging regulatory abilities (i.e., duration of orienting and soothability), so that lower levels of pre- and postnatal internalizing symptomatology would be associated with higher initial levels and increases over time. For boys, we hypothesized a different pattern of influence, consistent with existing literature. It was expected that elevated maternal pre- and postnatal internalizing symptoms would be associated with lower initial levels and decreases in infant negative emotionality, and lower levels/slower growth in regulatory abilities, but higher levels and greater increases for positive emotionality/surgency attributes.

Prior research investigating the effects of prenatal SSRI exposure on the development of infant temperament has been limited in scope in terms of time of assessment and use of physiological markers, with studies conducted with older children yielding equivocal results. Nonetheless, given that *in utero* SSRI exposure may dampen infant physiological reactivity (Oberlander et al., 2008), higher initial levels and trajectories of increases in infant activity level, fear, distress to limitations, and smiling/laughter were expected for non-exposed infants. Sex differences have not been examined with respect to prenatal SSRI exposure and influences on infant temperament, thus specific a-priori hypotheses could not be formulated for our examination of infant sex as a moderator of SSRI effects.

3. Methods

3.1. Participants

Following approval from the University of British Columbia Research Ethics Board, Children's and Women's Health Center of British Columbia Research Review Committee, and informed consent, second-trimester pregnant women (n = 191), were recruited for a study examining prospective relationships between prenatal SSRI use and child outcomes, residing in or near the metropolitan area of Vancouver, Canada. The final sample included 185 mother-infant dyads (6 mothers withdrew before delivery); 185 delivered, 159 were available at 3 months and 163 were available at 6 months. Variations in participation at each time point occurred due to maternal withdrawal, as well as mothers availability limited to contact via mail (hence the difference between the 3 and 6 month cohorts). During pregnancy, participants reported on their demographic characteristics (Table 1) and SSRI medication use across pregnancy. Participants were all Caucasian and generally college-educated. Self- and clinician-reported indicators of depression and anxiety were obtained in the third trimester (33–36 weeks). Birth outcomes data, along with postpartum symptoms of anxiety and depression, were collected at 3 months postpartum. Mothers reported on the infant's temperament when children were 3, 6, and 10 months of age.

3.2. Measures

3.2.1. Maternal internalizing symptoms

Depressive symptoms were measured during pregnancy (33–36 weeks gestation) and postpartum (3–6 months) via the Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987), a 10-item self-report indicator with demonstrated reliability and validity both prenatally (Murray and Cox, 1990) and postpartum (Cox et al., 1987). Items on the EPDS are rated on a 4-point Likert-type scale, with higher scores indicating greater depressive symptomatology. Clinician-based indicators of anxiety and depression were also determined by trained research assistants using the Hamilton Rating Scales for Anxiety (HAMA; Hamilton, 1959) and Depression (HAMD; Hamilton, 1960). The 21-item HAMD has previous reliability in the assessment of depression during pregnancy and postpartum (Ji et al., 2011). Both measures are rated on a 5-point Likert-type scale, with higher scores indicating greater symptom severity. In the present sample, the EPDS, HAMA, and HAMD demonstrated strong intercorrelations (range 0.75 – 0.89; M = 0.82) and were thus combined, computing a sum of standardized scale scores, to create a multi-informant 'Internalizing Symptom Composite' used as general marker of anxiety and depression-related distress in both pregnancy and postpartum. Similar approaches to composite internalizing symptoms are described elsewhere (Gartstein et al., 2016a; Oddi et al., 2013; Potapova et al., 2014), and are consistent with a cumulative risk perspective (Gray et al., 2017; Sheinkopf et al., 2007).

Table 1
Demographic characteristics of mothers and infants (using cohort available at 3 months postpartum; n = 159).

Variable	*SSRI exposed mean (SD)*	*Non-exposed mean (SD)*
Maternal age at birth	32.5 (5.4)	34.1 (4.9)
Maternal education (years)	16.4 (3.4)	18.1 (3.3)
Prenatal internalizing symptoms	33.9 (18.2)	19.7 (17.5)
Postnatal internalizing symptoms	26.3 (16.3)	15.4 (14.1)
Prenatal SSRI exposure (days)	238 (65.8)	N/A
Gestational age at birth	39.1 (1.5)	39.9 (1.5)
Birth weight (grams)	3294 (479)	3530 (493)
5-min APGAR (%)		
0–8	7.3	19.3
9–10	92.7	80.7
Parity (% primiparous)	60.4	60.6
Breastfeeding (% feeding done via breastmilk)	60.1	67.6
Girl Infant (%)	56.0	52.7
	Frequency	*Percentage*
SSRI use (n = 62)	76	39.8
Paroxetine	18	11.5
Venlafaxine	13	8.4
Citalopram	12	7.3
Sertraline	9	6.3
Fluoxetine	9	5.8
Escitalopram	1	0.5

Note. SSRI = Selective Serotonin Reuptake Inhibitor; Data presented are based on participants at the 3-month time point, as this marks the initial measurement point for the outcome variables of interest (i.e., infant temperament scales).

3.2.2. SSRI exposure

Prenatal SSRI use was assessed during the 3rd trimester via maternal self-report. Within the entire sample, 76 participants (39.8%) were prescribed an SSRI antidepressant medication during pregnancy. Average length of prenatal SSRI exposure was approximately 236 days. The most commonly reported SSRI was Paroxetine (28.9%) followed by Venlafaxine (21.1%) and Citalopram (18.4%). In the current study, prenatal SSRI exposure was measured as a binary variable (i.e., infants with preantal exposure to any SSRI medication use vs. those without any exposure), and was also measured continuously in days of prenatal exposure.

3.2.3. Infant behavior questionnaire (IBQ)

Infant temperament was assessed at 3, 6, and 10 months using the Infant Behavior Questionnaire (Rothbart, 1981), a 94-item parent-report measure. Items are rated on a 7-point Likert-type scale indicating frequency of occurrence for various temperament characteristics in the past week, or two weeks for less frequent events (e.g., encounters with unfamiliar adults). Items were summed to form six temperament

subscales: activity level, distress to limitations, duration of orienting, fear, smiling/laughter, and soothability. Indicators of internal consistency for the IBQ range from 0.67 to 0.84 (Rothbart, 1981). Parent-report temperament measures are recognized for their ability to provide data on infant behavior across settings (Gartstein et al., 2012), with IBQ items constructed to minimize "global judgments" of infant behaviors that may introduce bias (Garstein and Rothbart, 2003; Rothbart, 1981).

3.3. Analytic design

Relations between infant temperament variables and potential covariates were explored through use of bivariate correlations and t-tests. Specific covariates included maternal education and birth-related variables: parity, gestational age (GA) at birth, APGAR score, birthweight, as well as the breastfeeding status. Covariates were retained in subsequent growth curve models if these demonstrated a significant association with the fine-grained temperament outcomes of interest. Next, latent growth curve models were analyzed in Mplus 8 (Muthén and Muthén, 2018), with robust full information maximum likelihood estimation used to accommodate missing data and potential nonnormality (e.g., Enders, 2013). Specifically, for each IBQ scale, just-identified conditional spline (piecewise growth) models examining change from 3 to 6 months and 6 to 10 months were fit to the data for boys and girls separately, with predictors of the 3-month starting point and of the change across the two intervals (slope). The model was just-identified, and hence fit perfectly by default, because (1) three time points are always perfectly captured by an intercept and two unconstrained segments, and (2) each model's predictors were allowed to relate to all three growth elements (i.e., the intercept, the slope of the first segment, and the slope of the second segment). Growth patterns for each of the fine-grained temperament domains are illustrated in Fig. 1.

Hypothesized predictors of temperament growth patterns included prenatal and postpartum internalizing symptoms, as well as prenatal SSRI exposure, across all models, and control variables deemed relevant based on previously described bivariate analyses. With regard to prenatal SSRI exposure, this predictor was analyzed both as a dichotomy (not exposed vs. exposed), labeled as the *binary model*, and as the actual number of days of SSRI exposure (0 for those not exposed and >0 for those exposed), referred to as the *prenatal SSRI exposure index*. The value of internalizing variables, covariates, and SSRI variables in predicting aspects of temperament growth was assessed within the boys' and girls' models separately, and the difference in magnitude of each predictor's path across boys' and girls' models was tested using bootstrapping with 1000 bootstrap resamples. This approach addresses the extent to which sex moderates predictors' relevance, while dealing with potential nonnormality in the test of the difference between predictor paths across sex.

4. Results

Demographic variables and descriptive statistics are provided in Table 1. Among the considered covariates, GA at birth was positively associated with 3-month smiling/laughter scores, whereas parity was negatively associated with 6-month duration of orienting and 10-month activity level. Therefore, GA was retained for the smiling/laughter analyses and parity was included in the duration of orienting and activity level analyses. No other covariates were included in the growth curve models, given the lack of significant bivariate associations with fine-grained temperament variables across the three time points considered in this study (see Table 2). Zero-order correlations and mean differences associated with hypothesized predictors (i.e., pre- and postnatal internalizing symptoms, prenatal SSRI use, and infant sex) are also provided in Tables 2 and 3.

4.1. Growth curve temperament models

4.1.1. SSRI binary models

Separate spline models for infant temperament trajectories among boys and girls, as predicted by the prenatal SSRI exposure binary variable (i.e., exposed vs. not exposed), pre and postnatal maternal internalizing symptoms, and any relevant covariates, are presented in Table 4a. Overall, growth models demonstrated unique patterns of change for boys and girls. For boys, prenatal SSRI exposure was significantly associated with steeper increases in activity level and more gradual decreases in distress to limitations from 3–6 months (slope 1). Higher levels of prenatal internalizing symptoms predicted lower initial levels of activity level, whereas greater postnatal internalizing symptoms were significantly associated with slower increases in fear from 3–6 months (slope 1), and dampened decreases in soothability from 6–10 months (slope 2).

Among girls, prenatal SSRI exposure was similarly associated with distress to limitations slopes from 3–6 months; however, SSRI exposure predicted steeper decreases in distress to limitations (slope 1). Greater prenatal maternal internalizing symptoms predicted higher initial levels of distress to limitations, as well as lower initial levels of duration of orienting, smiling/laughter, and soothability. In the postnatal period, higher maternal internalizing symptoms were associated with slower decreases in girls' duration of orienting from 6–10 months (slope 2).

4.1.1.1. Significant sex differences. Statistically significant differences across the binary SSRI sex-specific models are denoted in Table 4a. Differences based on infant sex emerged for numerous temperament intercepts, as well as temperament slopes from 3–6 months. Compared to models for girls, prenatal maternal internalizing symptoms predicted significantly higher initial levels for boys across the following temperament domains: activity level, smiling/laughter, duration of orienting, and soothability—with the latter two intercepts demonstrating trend-level effects for boys, but not girls. Prenatal internalizing symptoms also predicted slower growth in boys' 3–6 month slopes for duration of orienting and smiling/laughter, when compared to girls. In addition, prenatal SSRI exposure predicted significantly steeper growth in activity level, as well as slower decreases in distress to limitations from 3 to 6 months among boys; for girls, SSRI exposure was associated with less growth in activity level (trend-level effect) and faster declines in distress to limitations. There were no significant sex differences in the infant fear models, temperament slopes from 6–10 months across all domains, nor any temperament trajectories associated with postnatal internalizing symptoms.

4.1.2. SSRI exposure index models

Results of the second set of spline models, wherein SSRI exposure was operationalized as an exposure index variable (i.e., number of days exposed prenatally), are presented in Table 4b. For boys, the only statistically significant results emerged for infant smiling/laughter, wherein slower decreases in boys' smiling/laughter from 6–10 months (slope 2) were predicted by postnatal maternal internalizing symptoms. Within the girls' exposure index models, several findings were consistent with those of the binary SSRI model results. In particular, higher prenatal maternal internalizing symptoms were once again associated with significantly higher initial levels of distress to limitations among girls, as well as lower initial levels of duration of orienting, smiling/laughter, and soothability. Furthermore, higher postnatal maternal internalizing symptoms were associated with dampened declines in girls' duration of orienting from 6–10 months (slope 2). Results for SSRI exposure index revealed that girls with longer duration of prenatal exposure demonstrated more gradual growth in smiling/laughter from 6 to 10 months (slope 2).

4.1.2.1. Significant sex differences. Statistically significant differences

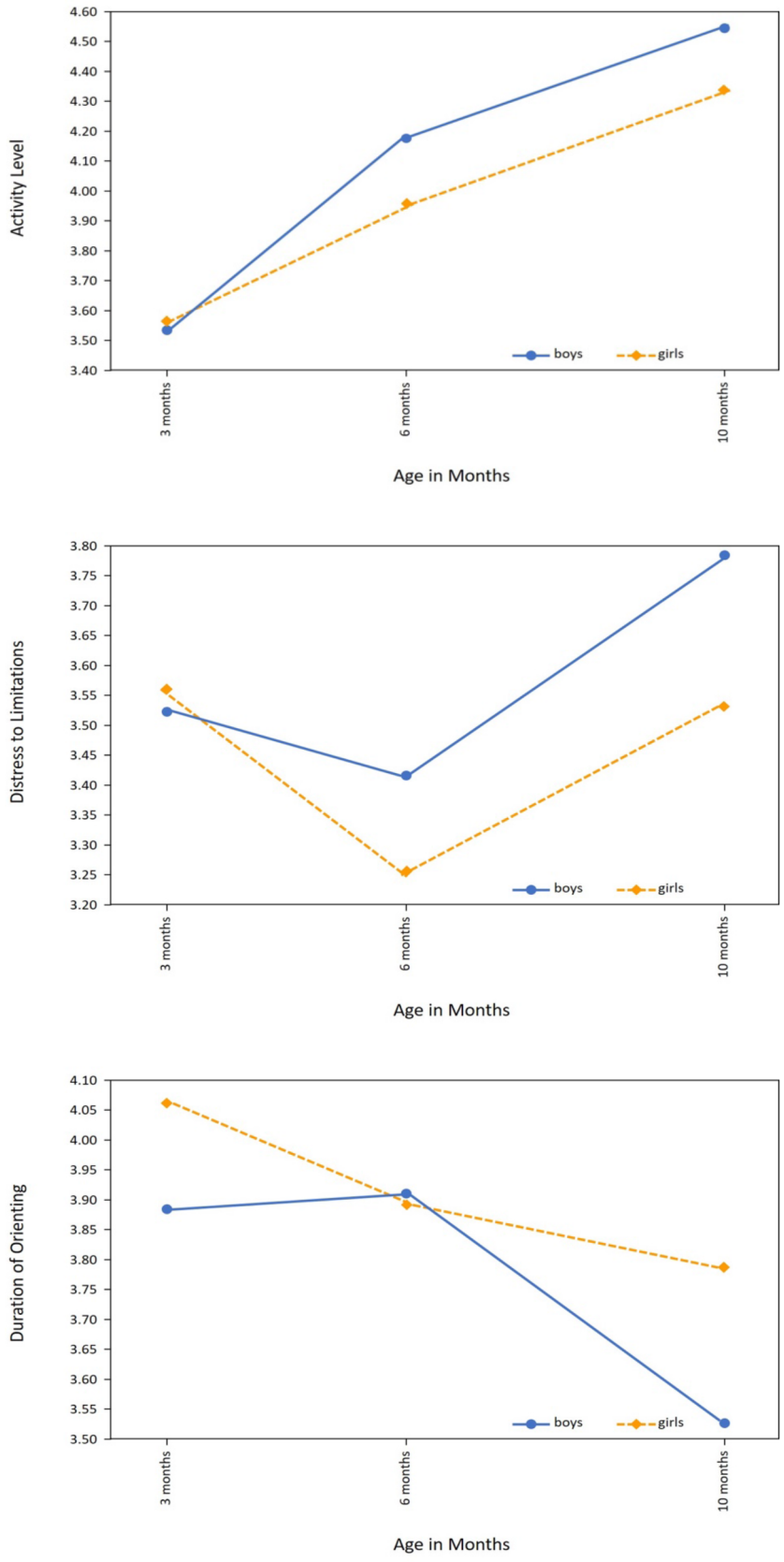
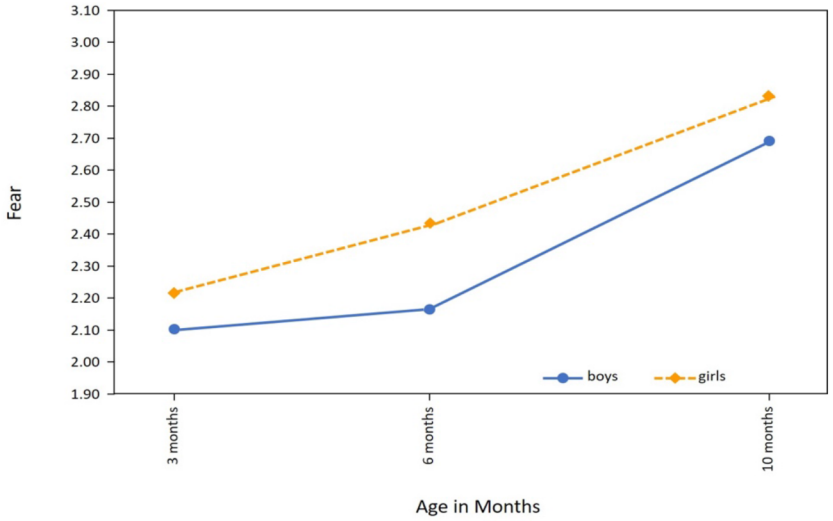
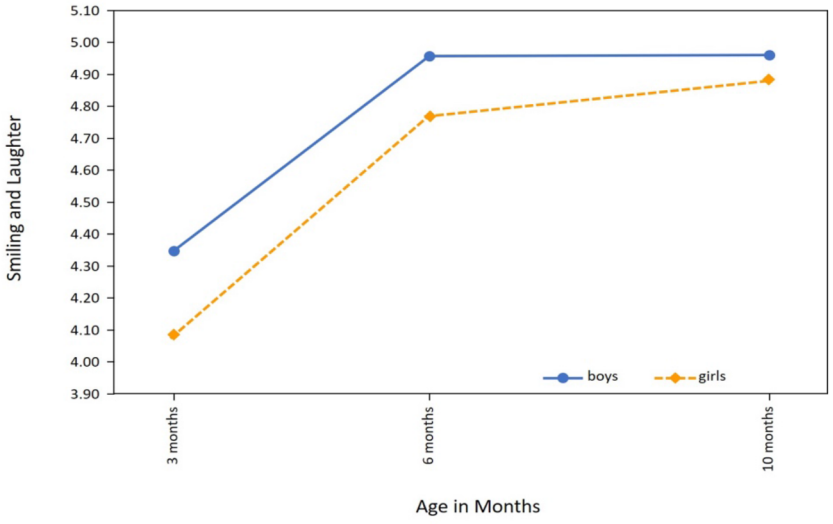


Fig. 1a. Growth trajectories reflecting patterns of change in fine-grained temperament dimensions of activity levels, distress to limitations, and duration of orienting across 3, 6 and 10 months for boys and girls.





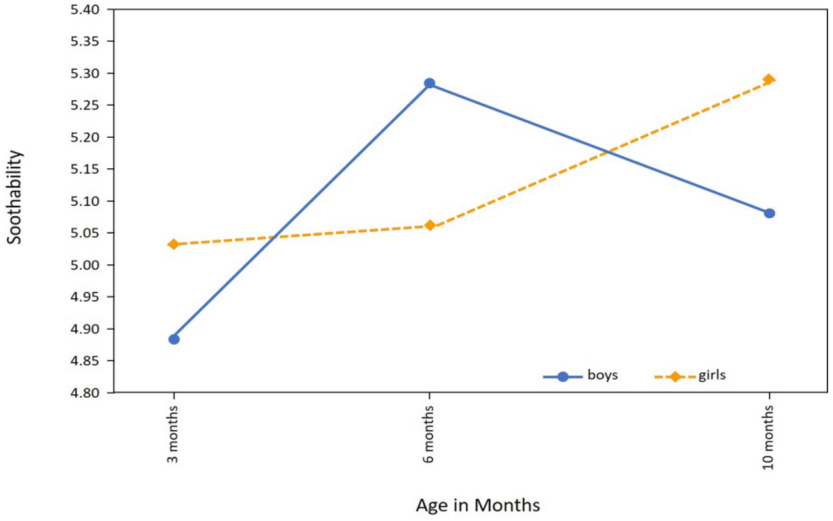


Fig. 1b. Growth trajectories reflecting patterns of change in fine-grained temperament dimensions of fear, smiling/laughter, and soothability across 3, 6 and 10 months for boys and girls.

Table 2
Bivariate correlation coefficients for fine-grained temperament dimensions, covariates, and predictors (i.e., maternal pre- and postnatal internalizing symptoms, and prenatal SSRI exposure).

3-month variables	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
1. Activity Level	–	0.16*	0.37**	0.35**	0.14	−0.01	−0.02	0.00	−0.01	0.13	0.09	−0.11	0.08	0.04	−0.03
2. Smiling/Laughter	0.16*	–	−0.10	−0.23**	0.31**	0.43**	0.10	0.21**	0.08	−0.01	0.02	−0.01	−0.16	−0.22**	0.02
3. Fear	0.37**	−0.10	–	.473**	−0.08	−0.14	0.02	0.00	0.07	0.06	0.06	−0.12	0.28**	0.26**	−0.03
4. Distress to Limitations	0.35**	−0.23**	0.47**	–	−0.11	−0.25**	−0.08	−0.08	−0.05	0.02	0.02	−0.13	0.25**	0.22**	−0.12
5. Soothability	0.14	0.31**	−0.08	−0.11	–	0.28**	0.06	−0.06	−0.04	−0.07	−0.04	0.04	−0.12	−0.1	0.08
6. Duration of Orienting	−0.01	0.43**	−0.14	−0.25**	0.28**	–	−0.04	0.13	0.08	−0.09	0.03	−0.02	−0.19*	−0.17*	−0.17
7. Maternal Education	−0.02	0.10	0.02	−0.08	0.06	−0.04	–	0.08	0.09	0.06	−0.166*	−0.157*	−0.24**	−0.023**	0.16
8. Gestational Age	0.00	0.21**	0.00	−0.08	−0.06	0.13	0.08	–	0.58**	0.20**	−0.01	0.02	−0.14	−0.09	0.17
9. Birth Weight	−0.01	0.08	0.07	−0.05	−0.04	0.08	0.09	0.58**	–	0.15*	0.05	−0.06	−0.03	−0.05	0.25*
10. APGAR	0.13	−0.01	0.06	0.02	−0.07	−0.09	0.06	0.20**	0.15*	–	0.10	0.04	−0.025	−0.04	0.01
11. Parity	−0.11	−0.01	−0.12	−0.13	0.04	−0.02	−0.157*	0.02	−0.06	0.04	–	0.02	−0.23**	−0.08	−0.03
12. Breastfeeding Status	0.09	0.02	0.06	0.02	−0.04	0.03	−0.17*	−0.01	0.05	0.10	0.02	–	0.17*	0.11	−0.07
13. Pre- Internalizing	0.08	−0.16	0.28**	0.25**	−0.12	−0.19*	−0.24**	−0.14	−0.03	−0.025	−0.23**	0.17*	–	0.61**	−0.29*
14. Post- Internalizing	0.04	−0.22**	0.26**	0.22**	−0.10	−0.17*	−0.023**	−0.09	−0.05	−0.04	−0.08	0.11	.61**	–	−0.05
15. SSRI Exposure (days)	−0.03	0.02	−0.03	−0.12	0.08	−0.17	0.16	0.17	0.25*	0.01	−0.03	−0.07	−0.29*	−0.05	–

6-month variables	1	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
1. Activity Level	–	0.37**	0.38**	0.57**	0.36**	0.31**	−0.02	−0.04	0.00	0.14	−0.10	−0.02	0.08	0.06	0.06
2. Smiling/Laughter	0.37**	–	0.07	0.14	0.52**	0.47**	0.07	0.01	−0.02	0.04	−0.15	−0.08	−0.11	−0.14	0.18
3. Fear	0.38**	0.07	–	0.53**	.18*	0.15	−0.06	−0.03	−0.02	−0.01	−0.13	−0.01	0.23**	0.09	−0.18
4. Distress to Limitations	0.57**	0.14	0.53**	–	0.23**	0.14	−0.10	−0.06	0.05	0.02	−0.19*	0.02	0.12	0.06	−0.10
5. Soothability	0.36**	0.52**	0.18*	0.23**	–	0.40**	0.07	−0.09	0.01	−0.02	−0.10	−0.02	0.02	0.03	0.25*
6. Duration of Orienting	0.31**	0.47**	0.15	0.14	0.40**	–	0.03	−0.02	−0.12	0.01	−0.05	0.03	−0.08	−0.05	−0.06
7. Maternal Education	−0.02	0.07	−0.06	−0.10	0.07	0.03	–	0.08	0.09	0.06	−0.16*	−0.17*	−0.14	−0.09	0.17
8. Gestational Age	−0.04	0.01	−0.03	−0.06	−0.09	−0.02	0.08	–	0.58**	0.20**	0.02	−0.01	−0.03	−0.05	0.25*
9. Birth Weight	0.00	−0.02	−0.02	0.05	0.01	−0.12	0.09	0.58**	–	0.15*	−0.06	0.05	−0.03	−0.04	0.01
10. APGAR	0.14	0.04	−0.01	0.02	−0.02	0.01	0.06	0.20**	0.15*	–	0.04	0.10	−0.24**	−9.23**	0.16
11. Parity	−0.10	−0.15	−0.13	−0.19*	−0.10	−0.05	−0.16*	0.02	−0.06	0.04	–	0.02	−0.23**	−0.08	−0.03
12. Breastfeeding Status	−0.02	−0.08	−0.01	0.02	−0.02	0.03	−0.17*	−0.01	0.05	0.10	0.02	–	.17*	0.11	−0.07
13. Pre- Internalizing	0.08	−0.11	0.23**	0.12	0.02	−0.08	−0.14	−0.03	−0.03	−0.24**	−0.23**	.17*	–	0.61**	−0.29*
14. Post- Internalizing	0.06	−0.14	0.09	0.06	0.03	−0.05	−0.09	−0.05	−0.04	−9.23**	−0.08	0.11	.61**	–	−0.05
15. SSRI Exposure (days)	0.06	0.18	−0.18	−0.10	0.25*	−0.06	0.17	0.25*	0.01	0.16	−0.03	−0.07	−0.29*	−0.05	–

10-month variables	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
1. Activity Level	–	0.28*	0.01	0.32**	0.00	−0.05	−0.12	−0.08	−0.05	−0.02	−0.10	−0.22*	0.05	0.05	0.08
2. Smiling/Laughter	0.28*	–	−0.23*	−0.17	0.34**	0.29**	0.03	−0.12	0.03	0.18	0.08	−0.02	0.07	0.22	0.22
3. Fear	0.01	−0.23*	–	0.47**	−0.11	0.08	−0.10	0.06	0.01	−0.05	0.14	0.00	0.16	0.06	−0.41*
4. Distress to Limitations	0.32**	−0.17	0.44**	–	−0.11	−0.20	−0.02	0.16	−0.02	−0.13	0.10	−0.14	0.22*	0.18	−0.29
5. Soothability	0.00	0.34**	−0.11	−0.11	–	0.15	−0.02	−0.14	0.01	0.10	0.11	0.13	0.1	0.29*	0.24
6. Duration of Orienting	−0.05	0.29**	0.08	−0.20	0.15	–	0.20	0.00	0.00	0.00	0.13	0.18	−0.03	0.059	0.01
7. Maternal Education	−0.12	0.03	−0.10	−0.02	−0.02	0.20	–	0.58**	0.20**	0.08	−0.01	0.02	−0.14	−0.09	0.17
8. Gestational Age	−0.08	−0.12	0.06	0.16	−0.14	0.00	0.58**	–	0.15*	0.09	0.05	−0.06	−0.03	−0.05	0.25*
9. Birth Weight	−0.05	0.03	0.01	−0.02	0.01	0.00	0.20**	0.15*	–	0.06	0.10	0.04	−0.03	−0.04	0.01
10. APGAR	−0.02	0.18	−0.05	−0.13	0.10	0.00	0.08	0.09	0.06	–	−0.17*	−0.16*	−0.24**	−0.23**	0.16
11. Parity	−0.22*	−0.02	0.00	−0.14	0.13	0.18	0.02	−0.06	0.04	−0.16*	–	0.02	−0.23**	−0.08	−0.03
12. Breastfeeding Status	−0.10	0.08	0.14	0.10	0.11	0.13	−0.01	0.05	0.10	−0.17*	0.02	–	.17*	0.11	−0.07
13. Pre- Internalizing	0.05	0.07	0.16	0.22*	0.10	−0.03	−0.14	−0.03	−0.03	−0.24**	−0.23**	.17*	–	0.61**	−0.29*
14. Post- Internalizing	0.05	0.22	0.06	0.18	0.29*	0.059	−0.09	−0.05	−0.04	−0.23**	−0.08	0.11	0.61**	–	−0.05
15. SSRI Exposure (days)	0.08	0.22	−0.41*	−0.29	0.24	0.01	0.17	0.25*	0.01	0.16	−0.03	−0.07	−0.29*	−0.05	–

Note.
* $p \leq 0.05$.
** $p \leq 0.01$.

across the SSRI exposure index models for boys and girls are denoted in Table 4b. Sex differences emerged across the initial levels of duration of orienting, smiling/laughter, and soothability. Specifically, for each of these temperament domains, higher levels of prenatal maternal internalizing symptoms were associated with significantly lower initial temperament levels among girls but not boys. Similar to the binary models, sex differences in effects of prenatal internalizing effects on temperament trajectories from 3–6 months were identified, wherein higher prenatal internalizing symptoms were associated with slower growth in 3–6 month slopes for duration of orienting and smiling/laughter only for boys. An additional significant sex difference emerged for trajectories of smiling/laughter from 6–10 months. Notably, longer duration of prenatal SSRI exposure was associated with a dampened decline in smiling/laughter from 6–10 months among boys, as compared to slower 6–10 month smiling/laughter growth among exposed girls. There were no statistically significant differences in the exposure index models for the temperament domains of activity level, distress to limitations, or fear.

Table 3
Independent samples t-tests for infant sex and the binary SSRI exposure variable: Differences across groups at 3, 6, and 10 months for each fine-grained temperament dimension.

	Boys (n = 69)		Girls (n = 90)		
3-month outcome variables	M	SD	M	SD	*t*-test
1. Activity Level	3.52	0.78	3.57	0.75	−0.45
2. Smiling/Laughter	4.33	1.08	4.11	1.00	1.28
3. Fear	2.08	0.75	2.22	0.77	−1.15
4. Distress to Limitations	3.54	0.72	3.57	0.88	−0.28
5. Soothability	4.97	0.75	5.04	0.77	−0.61
6. Duration of Orienting	3.89	1.09	4.08	1.00	−1.11
	Boys (n = 73)		Girls (n = 91)		
6-month outcome variables	M	SD	M	SD	*t*-test
1. Activity Level	4.15	0.82	3.97	0.91	1.30
2. Smiling/Laughter	4.95	0.83	4.76	0.97	1.28
3. Fear	2.16	0.74	2.43	0.76	−2.30*
4. Distress to Limitations	3.38	0.86	3.26	0.82	0.92
5. Soothability	5.25	0.74	5.05	1.05	1..45
6. Duration of Orienting	3.92	0.94	3.88	1.06	0.24
	Boys (n = 39)		Girls (n = 44)		
10-month outcome variables	M	SD	M	SD	*t*-test
1. Activity Level	4.50	0.72	4.30	0.88	1.18
2. Smiling/Laughter	4.96	0.76	5.05	0.78	−0.53
3. Fear	2.68	0.68	2.67	0.74	0.50
4. Distress to Limitations	3.67	0.86	3.39	0.90	1.44
5. Soothability	5.16	0.93	5.40	0.84	−1.22
6. Duration of Orienting	3.57	0.88	3.94	1.05	−1.69
	Exposed (n = 62)		Non-Exposed (n = 97)		
3-month outcome variables	M	SD	M	SD	*t*-test
1. Activity Level	3.48	0.70	3.59	0.80	0.88
2. Smiling/Laughter	4.00	0.98	4.33	1.06	1.93
3. Fear	2.25	0.81	2.09	0.73	−1.27
4. Distress to Limitations	3.62	0.73	3.52	0.86	−0.78
5. Soothability	5.04	0.84	4.99	0.71	−0.40
6. Duration of Orienting	3.87	1.03	4.08	1.04	1.23
	Exposed (n = 66)		Non-Exposed (n = 98)		
6-month outcome variables	M	SD	M	SD	*t*-test
1. Activity Level	3.99	0.94	4.08	0.83	0.67
2. Smiling/Laughter	4.76	0.99	4.91	0.85	1.01
3. Fear	2.34	0.79	2.29	0.74	−0.44
4. Distress to Limitations	3.27	0.91	3.34	0.79	0.49
5. Soothability	5.13	1.07	5.15	0.83	0.16
6. Duration of Orienting	3.93	0.96	3.88	1.03	−0.31
	Exposed (n = 31)		Non-Exposed (n = 52)		
10-month outcome variables	M	SD	M	SD	*t*-test
1. Activity Level	4.28	0.97	4.46	0.70	0.92
2. Smiling/Laughter	5.11	0.76	4.85	0.78	−0.94
3. Fear	2.63	0.62	2.71	0.77	0.52
4. Distress to Limitations	3.52	0.78	3.52	0.95	0.03
5. Soothability	5.39	0.94	5.23	0.86	−0.80
6. Duration of Orienting	3.89	0.84	3.70	1.06	−0.87

Note.
* $p \leq 0.05$.

5. Discussion

Using growth curve modeling, we investigated the impact of pre- and postnatal maternal depression and anxiety symptoms, and prenatal SSRI exposure, on initial levels of infant temperament as well as changes in temperament patterns/trajectories across the first year of life. Importantly, we considered infant sex as a moderator of these effects, in light of emerging evidence that fetal programming is likely sex-dependent, with developmental consequences differing for boys and girls (Hamada and Mathews, 2018; Sandman et al., 2013; Sutherland and Brunwasser, 2018). A number of significant differences in the patterns following exposure to maternal internalizing symptoms and SSRI use emerged. Overall, SSRI exposure appeared to be more detrimental with respect to temperament development sequelae for boys, whereas the presence of greater maternal internalizing symptomatology resulted in more negative consequences for girls.

For boys, SSRI exposure reflected in the binary group membership variable (i.e., exposed vs. non-exposed) was associated with higher initial levels of activity level and slower decreases in distress to limitations from 3 to 6 months, which may reflect a risky temperament constellation, as greater activity and anger/frustration have been linked with externalizing problems (see e.g., Nigg, 2006). On the other hand,

Table 4a
Fine-grained infant temperament dimensions predicated by covariates, maternal pre/postpartum internalizing symptoms, and prenatal SSRI exposure.

SSRI Binary Models: Boys	Path Coefficients (Standardized)		
Variables	Intercept (SE)	Slope 1 (SE)	Slope 2 (SE)
Activity Level			
Parity	0.11 (0.14)	-0.04 (0.13)	**-0.38^ (0.18)**
Prenatal SSRI Exposure (Y/N)	-0.21 (0.13)	**0.28* (0.13)**	0.01 (0.17)
Prenatal Internalizing Symptoms	**0.36** (0.13)**	-0.16 (0.15)	-0.31 (0.21)
Postnatal Internalizing Symptoms	-0.10 (0.17)	-0.01 (0.13)	0.14 (0.17)
Distress to Limitations			
Parity	**-0.20^ (0.11)**	0.00 (0.12)	-0.01 (0.15)
Prenatal SSRI Exposure (Y/N)	-0.13 (0.12)	**0.26* (0.11)**	-0.10 (0.17)
Prenatal Internalizing Symptoms	0.01 (0.14)	0.00 (0.15)	0.24 (0.21)
Postnatal Internalizing Symptoms	0.15 (0.15)	-0.08 (0.15)	-0.14 (0.18)
Duration of Orienting			
Prenatal SSRI Exposure (Y/N)	0.12 (0.13)	0.03 (0.13)	-0.12 (0.18)
Prenatal Internalizing Symptoms	0.10 (0.14)	**-0.24^ (0.13)**	**0.39^ (0.20)**
Postnatal Internalizing Symptoms	-0.24 (0.16)	0.19 (0.17)	0.06 (0.20)
Fear			
Prenatal SSRI Exposure (Y/N)	0.12 (0.12)	-0.03 (0.13)	-0.08 (0.16)
Prenatal Internalizing Symptoms	0.20 (0.14)	0.15 (0.11)	-0.29 (0.20)
Postnatal Internalizing Symptoms	0.14 (0.13)	**-0.24* (0.12**	0.09 (0.14)
Smiling/Laughter			
Gestational Age	**0.37* (0.17)**	-0.29 (0.18)	-0.15 (0.15)
Prenatal SSRI Exposure (Y/N)	0.00 (0.14)	0.11 (0.16)	0.17 (0.15)
Prenatal Internalizing Symptoms	0.18 (0.14)	**-0.26^ (0.14)**	0.11 (0.22)
Postnatal Internalizing Symptoms	-0.21 (0.15)	0.21 (0.16)	**0.31^ (0.17)**
Soothability			
Prenatal SSRI Exposure (Y/N)	0.10 (0.13)	0.01 (0.13)	0.00 (0.14)
Prenatal Internalizing Symptoms	0.14 (0.16)	-0.03 (0.16)	-0.22 (0.26)
Postnatal Internalizing Symptoms	-0.15 (0.13)	0.18 (0.15)	**0.44* (0.17)**

SSRI Binary Models: Girls	Path Coefficients (Standardized)		
Variables	Intercept (SE)	Slope 1 (SE)	Slope 2 (SE)
Activity Level			
Parity	0.09 (0.12)	0.05 (0.14)	0.28 (0.16)
Prenatal SSRI Exposure (Y/N)	-0.09 (0.12)	-0.18 (0.13)	**-0.31^ (0.17)**
Prenatal Internalizing Symptoms	-0.20 (0.14)	0.15 (0.17)	0.20 (0.26)
Postnatal Internalizing Symptoms	**0.27^ (0.15)**	0.09 (0.15)	-0.31 (0.26)
Distress to Limitations			
Parity	-0.08 (0.10)	-0.01 (0.11)	0.13 (0.24)
Prenatal SSRI Exposure (Y/N)	-0.06 (0.11)	**-0.22* (0.11)**	-0.01 (0.20)
Prenatal Internalizing Symptoms	**0.34* (0.15)**	-0.12 (0.17)	0.06 (0.32)
Postnatal Internalizing Symptoms	-0.04 (0.18)	-0.04 (0.18)	-0.01 (0.31)
Duration of Orienting			
Prenatal SSRI Exposure (Y/N)	**-0.20^ (0.11)**	0.14 (0.11)	-0.02 (0.15)
Prenatal Internalizing Symptoms	**-0.38** (0.15)**	0.20 (0.15)	-0.39 (0.27)
Postnatal Internalizing Symptoms	0.19 (0.19)	-0.07 (0.14)	**0.63* (0.24)**
Fear			
Prenatal SSRI Exposure (Y/N)	-0.20 (0.12)	-0.02 (0.12)	0.07 (0.16)
Prenatal Internalizing Symptoms	0.23 (0.16)	0.00 (0.20)	0.01 (0.26)
Postnatal Internalizing Symptoms	0.20 (0.13)	-0.13 (0.19)	-0.05 (0.23)
Smiling/Laughter			
Gestational Age	-0.06 (0.12)	-0.02 (0.11)	-0.10 (0.16)
Prenatal SSRI Exposure (Y/N)	-0.07 (0.11)	0.04 (0.12)	-0.07 (0.18)
Prenatal Internalizing Symptoms	**-0.33* (0.15)**	0.26 (0.17)	0.03 (0.31)
Postnatal Internalizing Symptoms	0.08 (0.17)	-0.14 (0.18)	0.23 (0.25)
Soothability			
Prenatal SSRI Exposure (Y/N)	0.07 (0.13)	-0.10 (0.13)	0.09 (0.16)
Prenatal Internalizing Symptoms	**-0.46* (0.19)**	0.28 (0.19)	0.05 (0.20)
Postnatal Internalizing Symptoms	0.23 (0.19)	-0.09 (0.18)	-0.02 (0.21)

Note. Slope 1 = change in temperament from 3–6 months. Slope 2 = change in temperament from 6–10 months. Dark-shaded values represent paths significantly different by infant sex ($p < .05$); light-shade ($p < .10$). ^$p \leq 0.10$; *$p \leq 0.05$; **$p \leq 0.01$.

Table 4b
Fine-grained infant temperament dimensions predicated by covariates, maternal pre/postnatal internalizing symptoms, and prenatal SSRI exposure.

SSRI Exposure Index Models: Boys	Path Coefficients (Standardized)		
Variables	Intercept (SE)	Slope 1 (SE)	Slope 2 (SE)
Activity Level			
Parity	0.13 (0.16)	-0.07 (0.15)	-0.39 (0.21)
Prenatal SSRI Exposure (Days)	-0.06 (0.22)	0.02 (0.31)	0.10 (0.35)
Prenatal Internalizing Symptoms	0.27 (0.22)	-0.08 (0.23)	-0.28 (0.25)
Postnatal Internalizing Symptoms	-0.08 (0.22)	0.00 (0.18)	0.11 (0.20)
Distress to Limitations			
Parity	-0.09 (0.18)	-0.14 (0.19)	0.16 (0.30)
Prenatal SSRI Exposure (Days)	0.42 (0.36)	-0.47 (0.34)	0.52 (0.49)
Prenatal Internalizing Symptoms	0.14 (0.18)	-0.11 (0.23)	0.36 (0.32)
Postnatal Internalizing Symptoms	0.09 (0.18)	0.01 (0.21)	-0.18 (0.29)
Duration of Orienting			
Prenatal SSRI Exposure (Days)	-0.25 (0.20)	-0.15 (0.23)	0.20 (0.50)
Prenatal Internalizing Symptoms	-0.00 (0.17)	**-0.33^ (0.17)**	0.47 (0.30)
Postnatal Internalizing Symptoms	-0.16 (0.19)	0.23 (0.19)	0.00 (0.27)
Fear			
Prenatal SSRI Exposure (Days)	-0.04 (0.28	-0.13 (0.31)	0.65 (0.37)
Prenatal Internalizing Symptoms	0.22 (0.18)	0.09 (0.17)	-0.17 (0.24)
Postnatal Internalizing Symptoms	0.17 (0.15)	-0.19 (0.17)	-0.12 (0.22)
Smiling/Laughter			
Gestational Age	0.24 (0.19)	-0.29 (0.20)	-0.37 (0.15)
Prenatal SSRI Exposure (Days)	0.18 (0.21)	0.06 (0.16)	0.51 (0.19)
Prenatal Internalizing Symptoms	0.22 (0.16)	-0.23 (0.14)	0.13 (0.15)
Postnatal Internalizing Symptoms	**-0.28^ (0.16)**	0.27 (0.17)	**0.33* (0.14)**
Soothability			
Prenatal SSRI Exposure (Days)	0.12 (0.28)	0.25 (0.27)	0.23 (0.39)
Prenatal Internalizing Symptoms	0.21 (0.21)	0.12 (0.21)	-0.17 (0.36)
Postnatal Internalizing Symptoms	-0.17 (0.15)	0.11 (0.19)	**0.43^ (0.20)**

SSRI Exposure Index Models: Girls	Path Coefficients (Standardized)		
Variables	Intercept (SE)	Slope 1 (SE)	Slope 2 (SE)
Activity Level			
Parity	0.10 (0.13)	0.05 (0.15)	0.20 (0.20)
Prenatal SSRI Exposure (Days)	0.18 (0.27)	0.15 (0.20)	-0.18 (0.36)
Prenatal Internalizing Symptoms	-0.17 (0.16)	0.11 (0.18)	0.19 (0.30)
Postnatal Internalizing Symptoms	0.26 (0.19)	0.07 (0.16)	**-0.47^ (0.26)**
Distress to Limitations			
Parity	-0.10 (0.10)	-0.05 (0.12)	0.12 (0.24)
Prenatal SSRI Exposure (Days)	-0.07 (0.18)	-0.07 (0.22)	-0.48 (0.34)
Prenatal Internalizing Symptoms	**0.33* (0.16)**	-0.17 (0.20)	0.01 (0.33)
Postnatal Internalizing Symptoms	-0.01 (0.16)	-0.09 (0.20)	0.02 (0.31)
Duration of Orienting			
Prenatal SSRI Exposure (Days)	-0.28 (0.23)	0.27 (0.24)	0.25 (0.26)
Prenatal Internalizing Symptoms	**-0.48** (0.16)**	**0.27^ (0.16)**	-0.33 (0.26)
Postnatal Internalizing Symptoms	0.11 (0.18)	0.01 (0.15)	**0.60* (0.22)**
Fear			
Prenatal SSRI Exposure (Days)	0.11 (0.17)	-0.13 (0.24)	**-0.52^ (0.21)**
Prenatal Internalizing Symptoms	0.20 (0.17)	-0.03 (0.22)	-0.03 (0.28)
Postnatal Internalizing Symptoms	0.15 (0.15)	-0.15 (0.21)	-0.06 (0.25)
Smiling/Laughter			
Gestational Age	-0.6 (0.12)	-0.03 (0.14)	-0.04 (0.19)
Prenatal SSRI Exposure (Days)	0.10 (0.19)	0.19 (0.16)	**-0.69* (0.27)**
Prenatal Internalizing Symptoms	**-0.35* (0.17)**	0.27 (0.20)	-0.01 (0.34)
Postnatal Internalizing Symptoms	0.10 (0.21)	-0.07 (0.20)	0.09 (0.23)
Soothability			
Prenatal SSRI Exposure (Days)	0.10 (0.18)	0.16 (0.17)	-0.07 (0.37)
Prenatal Internalizing Symptoms	**-0.46* (0.19)**	0.26 (0.20)	0.07 (0.25)
Postnatal Internalizing Symptoms	0.30 (0.22)	-0.07 (0.20)	-0.03 (0.22)

Note. Slope 1 = change in temperament from 3–6 months. Slope 2 = change in temperament from 6–10 months. Dark-shaded values represent paths significantly different by infant sex ($p < .05$); light-shade ($p < .10$). ^$p \leq 0.10$; *$p \leq 0.05$; **$p \leq 0.01$.

prenatal maternal internalizing symptoms were associated with lower initial activity levels. Postpartum internalizing symptoms were associated with slower increases in fearfulness from 3 to 6 months and more gradual declines in soothability between 6 and 10 months of age. Significant differences between models developed for boys and girls were more limited in the context of the SSRI exposure index analyses (i.e., days-of-exposure during pregnancy). Specifically, a relationship between postpartum internalizing symptoms and slower decreases in smiling and laughter between 6 and 10 months of age was noted only for boys, controlling for all other predictors. Although findings obtained in the context of analyses conducted with the binary SSRI exposure variable and the SSRI exposure index were not identical, both can provide a potentially important window into fetal programming effects. These discrepant effects are not surprising, given the considerable difference in the SSRI exposure quantification among these two operationalizations. Overall, a greater number of significant effects was noted using the binary SSRI exposure variable (exposed vs. non-exposed), likely as a function of the SSRI exposure index distribution in the present sample (i.e., a considerable range, yet majority of cases with a greater number of exposure days; Table 1). The observed pattern of results provides indication of sex-dependent prenatal SSRI exposure effects that require additional research.

Current results are also notable for a differentiated pattern of temperament development for girls, and a number of potentially risky effects associated with maternal internalizing symptoms that were identified. As expected, prenatal maternal anxiety and depression were linked with greater initial levels of distress to limitations, along with lower duration of orienting, smiling/laughter, and soothability. In addition, higher postnatal maternal symptoms predicted slower decreases in duration of orienting, which likely bodes risk rather than protection. Normative decreases in infant duration of orienting during the 2nd half of the first year of life have been previously described (Gartstein and Hancock, 2019; Ruff and Rothbart, 1996) and linked with a greater flexibility in shifting eye gaze (Johnson et al., 1991). Such changes in duration of orienting are understood as a function of advances in attentional skills and underlying maturation of the frontal brain regions (Posner et al., 2012). Shorter orienting reactions may also be indicative of faster habituation and greater processing speed (Colombo et al., 1991; Gartstein et al., 2013), whereas longer duration of orienting has been previously linked to suboptimal social-emotional development (e.g., lowered joint attention in novel contexts, associations with subsequent autism spectrum disorder symptoms; Todd and Dixon, 2010; Zwaigenbaum et al., 2005). For girls, the overall effects of pre- and postnatal internalizing symptoms were consistent across the SSRI model operationalizations (i.e., models with the binary SSRI indicator, and those relying on the SSRI exposure index measured in terms of the number of days prenatal medication use). However, SSRI exposure effects on girls' temperament development were mixed across model types. When considered as a dichotomized variable, prenatal SSRI exposure was associated with faster decreases in girls' distress to limitations. As a continuous variable, greater number of days of SSRI exposure were associated with slower increases in smiling and laughter from 6 to 10 months of age. This pattern of dampened smiling/laughter growth for girls prenatally exposed to longer maternal SSRI use emerges in the context of prior literature on infant temperament growth, wherein smiling/laughter demonstrates a steadily increasing trajectory across the first year, which did not vary by sex within a normative sample (Gartstein and Hancock, 2019).

The cumulative pattern of temperament development effects reported in the current study is partially consistent with our hypotheses and the existing literature. That is, hypotheses were largely confirmed that girls were more susceptible to higher levels of prenatal and postpartum internalizing symptoms, showing greater initial levels/increases in infant negative emotionality across 3 and 6 months. Although fear-related effects were not observed, prenatal maternal anxiety and depression contributed to higher initial levels of distress to limitations. Inverse relationships between maternal internalizing symptoms, positive emotionality/surgency (i.e., smiling/laughter, activity level) and regulatory capacity (i.e., duration of orienting and soothability) were also hypothesized, and lower initial duration of orienting, smiling/laughter, and soothability were noted for girls whose mothers reported higher levels of symptomatology during pregnancy. With respect to postnatal symptoms, an associated slower decline in duration of orienting for girls is notable as a potential marker of future adversity, and is unique to this indicator of internalizing symptoms, as prenatal anxiety and depression, as well as SSRI exposure were considered in this model. Our findings parallel results reported by Nolvi et al. (2018), wherein a significant negative effect of maternal postnatal general anxiety was noted on executive function test performance at 8 months of age, but only for girls. Similar to previously described developmental interpretations, it may be that effects of prenatal exposures manifest at younger ages in girls compared to boys, and/or boys who survive prenatal adversity are less susceptible to subsequent contextual stressors (Nolvi et al., 2018; Sandman et al., 2013).

One of the primary study goals was to add to the limited literature examining associations between prenatal SSRI exposure and infant temperament. In order to address concerns about the importance of differentiating effects of SSRI exposure from the underlying psychological distress (Alwan et al., 2016), prenatal exposure to SSRIs was examined in the context of prenatal and postpartum internalizing symptoms. Results of this study indicate that prenatal SSRI exposure, and both prenatal and postpartum maternal internalizing symptoms exert unique effects on infant temperament. Effects of SSRI exposure were circumscribed for boys and girls, but warrant attention nonetheless. The present findings are partially consistent with an earlier report based on a physiological marker (i.e., cortisol reactivity), which indicated that prenatal SSRI exposure was associated with decreased reactivity among 3-month old infants (Oberlander et al., 2008). That is, for girls, faster declines in distress to limitations and slower growth for smiling and laughter were noted, indicative of dampened reactivity. This pattern of results may be suggestive of an SSRI exposure-related "buffering" effect, or reflect potentially problematic hypo-reactivity for girls—both possibilities that require further study. Furthermore, potential buffering effects may be indirect, wherein mothers treated with SSRI medications present with more positive *perceptions* of their daughters, as temperament was measured via parent-report.

The observed pattern of prenatal internalizing symptom effects on riskier temperament trajectories for girls is consistent with the existing literature, and specifically studies demonstrating that pre- and postnatal symptoms of depression and anxiety increase the risk of a temperament profile characterized by higher negative emotionality and less advanced regulatory abilities (Erickson et al., 2017; Kingston et al., 2012; Korja et al., 2017). Given replicated findings that such infant temperament profiles confer risk for behavior problems later in childhood (De Pauw and Mervielde, 2010), maternal depression in the postpartum period (Beck, 2001), and impairments in mother-infant interactions (Boivin et al., 2005; Nolvi et al., 2016), understanding interrelationships between infant temperament and maternal mental health during pregnancy and shortly after birth has widespread implications. It is critical to discern the nature of greater vulnerability in girls, for whom effective treatment and targeted clinical interventions reducing maternal symptoms of anxiety and depression may be particularly important (for review, see Letourneau et al., 2017). Furthermore, effects observed for prenatal anxiety and depression emerged above and beyond postpartum internalizing symptoms and likely reflect an element of fetal programming associated with prenatal exposure to maternal mood disturbances (see de Weerth, 2018). This study provided a more developmentally sensitive assessment of changes in infant temperament in association with pre- and postnatal maternal mental health and *in utero* SSRI exposure compared to previous investigations, with results providing partial support for our hypotheses.

Several additional implications may be gleaned from the current

findings. First, studies focusing exclusively on negative emotionality or temperament "difficulty" may not fully capture the effects of maternal mental health on infant temperament outcomes. Historically, temperament research has focused on "difficult temperament" (Britton, 2011; Cutrona and Troutman, 2014; Denis et al., 2012), which combines negative emotionality and regulatory capacity (Thomas and Chess, 1977). Such lack of differentiation across temperament constructs obscures critical distinctions, such as the ones elucidated in the present study. Our results further underscore the importance of examining independent contributions to temperament reactivity *and* regulation, as unique relationships emerged for these temperament domains in their association with pre-and postnatal internalizing symptoms and prenatal SSRI exposure.

Additionally, our results support the importance of measuring maternal mental health symptoms during both pregnancy and postpartum. Given the strength of associations between prenatal and postpartum psychological distress (Meltzer-Brody and Jones, 2015), concerns about collinearity in statistical analyses are relevant, and there are considerable differences in decisions made with respect to exploration of independent effects for pre and postnatal symptoms (see Korja et al., 2017; van der Wal et al., 2007). Within the current study, an examination of unique effects of prenatal and postpartum internalizing symptoms ultimately contributed to our understanding of how the timing of maternal mental health symptoms may affect different domains of temperament. Effects of prenatal vs. postpartum internalizing symptoms are also important, given the emerging literature on the time course of depression during pregnancy and postpartum. More specifically, previous research suggests that there are distinct classes and unique patterns of adversity between mood symptoms that emerge in pregnancy only, postpartum only, or persist from pregnancy into the first year life (Fredriksen et al., 2017; Lusby et al., 2016).

6. Limitations

There are several limitations of the current study that warrant attention. First, temperament indicators were based on maternal reports, and future research should explore differential effects of SSRI use and internalizing symptoms during pregnancy and postpartum in association with observed infant temperament and physiological markers. Additional limitations include the measurement of maternal internalizing symptoms during pregnancy and postpartum, without exploration of changes in maternal symptomatology over time (see e.g., Park et al., 2018). Specifically, prenatal programming effects may differ as a function of the timing and duration of exposure, and our study was limited to measures of depression and anxiety during the third trimester. Future modeling of maternal symptoms in relation to infant temperament outcomes in parallel process models could help further our understanding of meaningful patterns, informing treatment of maternal child health concerns. In addition, maternal internalizing symptoms and SSRI exposure could be associated with indirect effects on infant temperament (e.g., via mother-infant interactions), and future attention to parenting and the postpartum environmental context (e.g., using a mediational framework) is warranted. Similarly, the current study did not address whether mothers maintained, discontinued, or initiated SSRI use in the postpartum period. Despite the focus prenatal programming effects, future research should attend to SSRI use across pregnancy and postpartum, as the impact of postnatal maternal SSRI use on dyadic interactions and parenting behaviors may also have important implications for trajectories of temperament development. Finally, although infant temperament can be considered a risk phenotype for future child emotional and behavioral problems, no distal outcomes beyond 10 months of age were captured. As such, it is unclear in the current sample whether the higher-risk temperament profiles associated with pre- and postnatal internalizing symptoms for girls, and SSRI exposure for boys, are related to ongoing developmental difficulties.

7. Conclusion

In summary, the present study provides additional insight into unique effects of prenatal SSRI exposure, and prenatal and postpartum internalizing symptoms, on developmental trajectories of infant temperament across the first year of life, identifying potentially important differences for boys and girls. As expected, prenatal internalizing symptoms were associated with greater initial distress to limitations, along with lower duration of orienting, smiling/laughter, and soothability for girls, with postnatal symptoms also predicting slower decreases in duration of orienting. SSRI effects for girls contributed to dampened reactivity: faster decreases in distress to limitations and slower increases in smiling and laughter, possibly suggesting an SSRI exposure-related "buffering" or developmental benefit; alternatively, results may also reflect hypo-reactivity that could bode subsequent developmental adversity—to be determined in future research. For boys, maternal internalizing symptoms did not consistently translate into a risky temperament profile; however, SSRI exposure was associated with higher initial activity level and slower declines in distress to limitations, potentially indicative of behavioral risk. Overall, the present study contributes to a growing body of research, suggesting sex-dependent fetal programming effects that warrant further empirical inquiry.

Contributors

Oberlander and Grunau were responsible for the original research concept and design. Brain and Oberlander oversaw the acquisition of data. Specific study hypotheses, design, and statistical analyses were completed by Erickson and Gartstein. Hancock was responsible for the analytic design, with additional support from Erickson and Gartstein. Erickson wrote the first draft of the manuscript. All authors were involved in critically reading, writing, and revising the manuscript.

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Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.08.003.

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