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Biological embedding of perinatal social relationships in infant stress reactivity

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Whereas significant advances have been made in understanding how exposure to early adversity ‘gets under the skin’ of children to result in long term changes in developmental outcomes, the processes by which positive social relationships become biologically embedded remain poorly understood. The aim of this study was to understand the pathways by which maternal and infant social environments become biologically embedded in infant cortisol reactivity. 272 pregnant women and their infants were prospectively assessed during pregnancy and at 6 months postpartum. In serial mediation analyses, higher perceived social support from partners during pregnancy was associated with lower infant cortisol reactivity or larger decreases in cortisol in response to a stressor at 6 months of age via lower self-reported prenatal maternal depression and higher mother-infant interaction quality. The findings add to our understanding of how perinatal social relationships become biologically embedded in child development.

Key words: Biological embedding; social support; mother-infant interaction quality; cortisol reactivity

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Early life exposures have extraordinary potency to direct developmental trajectories because they calibrate the function of the stress response systems, which regulate a wide range of adaptive functions (Del Giudice, Ellis, & Shirtcliff, 2011). This process of adaptive calibration is a form of non-genomic microevolution that allows for rapid adaptation of development to match the local conditions of the social and physical environment. Considerable support for this proposal has been generated by the rapidly growing field of developmental neuroscience, which is demonstrating that environments and exposures become biologically embedded at the cellular and systems levels. Biological embedding refers to the process by which experiences, particularly during sensitive periods of development, alter brain and biological development (Hertzman & Boyce, 2010). For example, studies of children receiving institutionalized care clearly demonstrate that biological and cognitive development are strongly influenced by social context and the detrimental effects of early adversity may be reversed by the introduction of high quality caregiving environments (Johnson et al., 2010; Miller & Hendrie, 2000; van IJzendoorn, Bakermans-Kranenberg, & Juffer, 2007; Zeanah et al., 2003). Whereas significant advances have been made in understanding how exposure to early adversity ‘gets under the skin’ of children to result in long term changes in developmental outcomes, the processes by which positive social relationships become biologically embedded remain poorly understood. Here we examine whether social relationships during pregnancy are associated with the postpartum relationship between a mother and her infant and, together how these social relationships become embedded in infant cortisol reactivity – an early measure of biobehavioral self-regulation.

Biological Embedding of the Infant HPA Axis

The primary function of the hypothalamic-pituitary-adrenal (HPA) axis is the distribution of energetic resources across biological systems in response to environmental conditions, such as

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stress. The HPA axis is a key biobehavioral regulation system that integrates information about the external environment with internal states and therefore is one of the systems by which biological embedding is believed to occur (Del Giudice et al., 2011). For this reason, the HPA axis is believed to mediate many effects of the environment on children's development. Early-life experience, and exposure to adversity in particular, has an enduring effect on development through calibration of the HPA axis (McEwan, 2012), and the social environment can exacerbate or ameliorate the effects of early life experiences (Boyce & Ellis, 2005). The effect of cortisol on developing brain structures and neural networks may be especially impactful during sensitive periods of development such as in early infancy (Gunnar & Quevedo, 2008). Over the long-term, frequent over-activation of the HPA axis and elevated circulating levels of cortisol have the ability to shape children's developmental trajectories and increase the likelihood of poor outcomes, such as altered cognition and memory (Heffelfinger & Newcomer, 2001; Stark et al., 2006), and behavioral problems (Bagner, Sheinkopf, Vohr, & Lester, 2010; Granger, Weisz, & Kauneckis, 1994; Susman, Dorn, InoffGermain, Nottelmann, & Chrousos, 1997). Among children and adolescents, elevated cortisol reactivity to stress has been associated with internalizing disorders such as depression and anxiety (Granger et al., 1994; Luby et al., 2003; Natsuaki et al., 2009; Poon, Turpyn, Hansen, Jacangelo, & Chaplin, 2016) and the available evidence suggests that elevated cortisol reactivity presages an increased risk for developmental psychopathology (Charil, Laplante, Vaillancourt, & King, 2010; Lupien, McEwan, Gunnar, & Heim, 2009). Thus, poorly regulated cortisol reactivity in infancy may be an early risk factor for future psychopathology.

The fundamentally social nature of the HPA axis is shown by the fact that, at least in older children and adults, social-evaluative threat is one of the most reliable stimuli to solicit an

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HPA axis response (Seeman & McEwan, 1996). Even in infancy the HPA axis is sensitive to the quality of the social environment and disturbances in parental care can disrupt normal regulation of the neuroendocrine system (Gunnar & Quevedo, 2008). Interactions between a mother and infant are among the most significant of early environmental influences and the quality of interactions between mothers and infants plays a key role in the biological embedding of social relationships into regulation of the infant HPA axis reactivity (Gunnar & Donzella, 2002). High quality mother-infant interactions (e.g., contingent and appropriate responses to infant cues) buffer child HPA axis activation (Ahnert, Gunnar, Lamb, & Barthel, 2004; Albers, Riksen-Walraven, Sweep, & de Weerth, 2008; Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996). In contrast, when the quality of maternal-infant interactions is low (e.g., low maternal sensitivity or insecure attachment), HPA axis reactivity may be exaggerated and prolonged (Albers et al., 2008; Blair et al., 2008; Blair, Granger, Willoughby, & Kivlighan, 2006). This biological embedding of parent-infant interactions within the infant HPA axis represents a potential pathway by which both supportive and challenging social relationships affect child developmental outcomes and risk for psychopathology.

The Role of the Maternal Social Environment during Pregnancy

Just as the postnatal social environment plays a significant role in shaping the developmental adaptations made by the infant in early life, the prenatal social environment plays a significant role in the adaptations mothers make to pregnancy and parenting. Pregnancy instigates significant life changes that require major psychosocial and emotional adjustments, which can be a significant source of both joy and distress (Da Costa, Larouche, Drista, & Brender, 1999). Effective psychosocial support during pregnancy may promote more positive adaptations by reducing experiences of psychological distress, such as depression (Elsenbruch et

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al., 2007; Westdahl et al., 2007), and encouraging women to engage in healthy behaviors during pregnancy (Cameron, Wells, & Hobfoll, 1996), such as smoking cessation, better diet, and attendance at medical appointments. Not surprisingly, pregnant women in supportive relationships give birth to healthier infants (Campos et al., 2008) whereas women who have poor social support have an increased risk of adverse birth outcomes including reduced birthweight (Elsenbruch et al., 2007). Supportive relationships during pregnancy may also protect the developing fetus from the negative effects of prenatal stress by reducing the impact of life-stress on emotional well-being, for example depression, (Glazier, Elgar, Goel, & Holzapfel, 2004) and by reducing maternal cortisol elevations consequent to experiences of psychological distress (Giesbrecht, Poole, Letourneau, Campbell, & Kaplan, 2013). Taken together, these studies suggest that social support may be an important protective factor that promotes maternal health with downstream effects on the health of the baby.

Prenatal social support also plays a role in promoting the emerging mother-infant relationship by improving maternal mental health. Preparations for caregiving begin prenatally and include neurocognitive changes that take place during pregnancy. These neurocognitive changes function to encourage tendencies toward maternal behaviors that facilitate high quality interactions between mothers and infants (Feldman, Weller, Zagoory-Sharon, & Levine, 2007; Glynn & Sandman, 2011; Swain, 2011). Emerging evidence suggests that prenatal depression may disrupt the neurocognitive changes that facilitate high quality caregiving. Specifically, prenatal depression has been associated with a substantial reduction in women's attentional biases toward infant distress signals (Pearson, Cooper, Penton-Voak, Lightman, & Evans, 2010) and heightened avoidant and reduced comforting response toward distressed infant stimuli during pregnancy (Macrae et al., 2015), as well as lowered postnatal responsiveness towards the

infant (Pearson et al., 2012). Because social support has been associated with reduced maternal depression during pregnancy, and depression may disrupt the prenatal neurocognitive adaptations that occur to promote high quality mother-infant interactions, it is possible that social support may indirectly promote the mother-infant relationship via reductions in prenatal maternal depression.

Current Study

Our overall aim was to determine how the maternal and infant social environments contribute to the development of infant HPA axis regulation. We reasoned that because maternal prenatal social support is associated with lower depression during pregnancy and depression may interfere with maternal preparations for high-quality infant interactions, maternal prenatal social support may be a protective factor for infant stress regulation. Therefore, we set out to determine whether prenatal social support is indirectly associated with the regulation of infant stress response via maternal depression and caregiving. Two specific hypotheses were tested. First, we hypothesized that prenatal maternal social support enhances the quality of postnatal maternal-infant interactions by reducing prenatal maternal depression (Figure 1 Model 1). Second, we further hypothesized that the pathway from higher prenatal social support to lower maternal depression and subsequently to higher quality of postnatal maternal-infant social interactions would be associated with lower infant HPA axis reactivity (Figure 1 Model 2). To test these hypotheses, we conducted a prospective cohort study in a relatively low sociodemographic risk Canadian sample of maternal-infant pairs in which we assessed women's perception of social support received from partners and self-reported depressive symptoms during pregnancy and maternal-infant interaction quality and infant HPA axis reactivity at 6-months postpartum.

Methods

Participants

Participants were 294 women enrolled in an ongoing prospective cohort study, the Fetal Programming study, which is a community sample of volunteers recruited from prenatal clinics in 2011 and 2012. Women were included if they had a singleton pregnancy, were less than 22 weeks of gestation at the first study visit, and were 18 years of age or older. Women were excluded if they smoked or consumed alcohol during pregnancy, were being treated with a synthetic glucocorticoid, or had known fetal complications at time of study entry. The study time points were as follows: Time 1 (T1; 6-22 weeks gestation), Time 2 (T2; 27-37 weeks gestation), and Time 3 (T3; 6 months postnatal). 5 participants miscarried and 17 participants dropped out of the study, therefore the final study sample comprises the 272 mother-infant dyads that completed the postnatal assessment. Of note, all women enrolled in the current study reported being in a heterosexual, romantic relationship. Gestational age (GA) at each time point in pregnancy was determined based on last reported menstrual period and confirmed by at least one ultrasound. Prior to data collection, participants provided informed consent to the procedures, which were approved by the University of Calgary Conjoint Health Research Ethics Board.

Descriptive information for the study sample is shown in Table 1. The study sample represents a relatively low sociodemographic risk population of women and infants as the majority were mature (mean age 32.8), married or in common-law relationships, White, had university-level education, and had middle to upper-middle class household annual income. Although the study sample underrepresents young (i.e., under 20) and low-income pregnant women, as compared to a nationally representative sample (Leung, McDonald, Kaplan, Giesbrecht, & Tough, 2013; Public Health Agency of Canada Team, 2009), the sample is largely consistent with the sociodemographics of families living within the recruitment region (Calgary,

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Canada) and may be comparable to low sociodemographic risk families living in Canada and other first world countries.

Data Collection

Maternal perceived social support and symptoms of depression were assessed at each time point (T1-T3) using standardized questionnaires. At the postnatal assessment (T3), mothers and infants completed an observational measure of maternal-infant interaction quality and infants underwent a battery of frustration tasks. Saliva samples were collected from the infants at baseline and 20 minutes post-frustration to assess infant cortisol reactivity.

Measures

Social Support Effectiveness. Women's perception of social support received from their romantic partner was assessed via the Social Support Effectiveness Questionnaire (SSEQ; Rini, Dunkel Schetter, Hobel, Glynn, & Sandman, 2006), a 35-item measure of emotional, informational, task, and negative support received over the previous 3 months. Within each domain, women were asked to rate on a 5-point scale: a) how well the quantity of support received from her partner matched the amount she wanted, b) whether she wished the support had differed somehow, c) how skillful her partner was at providing support, d) how often it was difficult to solicit support, and e) if her partner offered support without being asked. Women also rated negative support, or the extent to which a respondent perceived her partner's support as negatively infringing on her own efficacy/self-esteem. Internal consistency of the SSE is strong (Cronbach $\alpha = .87$), and it has previously been used to distinguish levels of social support in samples of pregnant women (Giesbrecht et al., 2013; Rini et al., 2006; Stapleton et al., 2012). Total scores of the scale can range from 0 to 80, with higher scores indicating more effective support.

Maternal Depression Symptoms. Self-report of maternal depression symptoms was assessed using the 10 item Edinburgh Depression Scale (EDS; Cox, Holden, & Sagovsky, 1987). This instrument has been validated by standardized psychiatric interviews with large samples and has well documented reliability and validity among both pregnant and postpartum women (Affonso, De, Horowitz, & Mayberry, 2000; Bergink et al., 2011; Cox et al., 1987; Jomeen & Martin, 2007). The EDS was created to counter the limitations of other well-established depression scales, which tend to be falsely elevated in pregnant women based on somatic symptoms such as weight gain and fatigue. Items were rated on a 4-point scale to produce a summative score ranging from 0 to 30, with higher scores indicating more depressive symptoms. Although we measured depression twice across pregnancy, we were not specifically interested in examining the discrete onset of maternal depression or the differences in early versus late pregnancy depression. Rather, there is evidence that the severity of maternal depression is an important predictor of poor child outcomes (Brennan et al., 2000; Deave, Heron, Evans, & Emond, 2008) as well as the quality of mother-infant interactions (Teti, Gelfand, Messinger, & Russell, 1995). Thus, we used a prenatal depression severity score, which was defined as the highest EDS score reported during pregnancy (Brennan et al., 2000). In order to adjust for any potential effect of timing, we controlled for the gestational age (GA) when the highest EDS score was reported.

Maternal-Infant Interaction Quality. The quality of mother-infant interactions was assessed using the Parent Child Interaction Teaching Scale (PCITS; Oxford & Finlay, 2013), which is a standardized observational measure of maternal-infant interaction. The PCITS assessment involved video-recorded observation of mothers teaching their infant a new task; afterward, behaviors were coded according to the PCITS manual (Oxford & Finlay, 2013).

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Maternal behaviors assessed included maternal sensitivity to infant cues, response to child's distress, social-emotional growth fostering, and cognitive growth fostering activities. Infant behaviors assessed included the clarity of infant cues and responsiveness to caregiver. Together, these subscales provide an overall measure of maternal-infant interaction quality, which was used in the analyses. Total scores of the scale can range from 0 to 73, with higher values indicating higher quality mother-infant interactions. The data were coded by a single coder blinded to the study objectives and prenatal exposures. The coder was trained by a PCITS instructor and then successfully achieved inter-rater reliability greater than 90% agreement with an expert coder, which is the standard established for research reliability on this measure. The coder recoded a random 10% of video recordings twice and intra-rater reliability was excellent ([ICC] $ICC = .98$). The trained coder was recertified for research reliability by a PCITS instructor before and during the course of the study to maintain reliability and avoid coder drift.

Infant HPA Reactivity. Infant HPA axis reactivity was assessed after exposure to a standardized stressor. The stressor involved the toy retraction, toy barrier, and arm restraint tasks from the Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith & Rothbart, 1996), which elicit cortisol responses in infants (Laurent, Ablow, & Measelle, 2012). Because there is a short delay between exposure to a stressor and peak HPA axis response, whole saliva was collected from under the tongue at baseline and 20 minutes post stressor (Kirschbaum & Hellhammer, 1999) using a synthetic swab (Salimetrics Children's Swab, Salimetrics, State College, PA) which has been validated for the collection of cortisol (Bright, Frick, Out, & Granger, 2014). To avoid saliva contamination, participants were asked to refrain from feeding their infant in the 30 minutes prior to coming to the lab or during the laboratory procedure. In cases where feeding occurred within the 30 minutes before sample collection water was used the

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rise the infant's mouth and then samples were collected 10 minutes after rinsing. We obtained sufficient saliva samples from all infants in the current study. Saliva samples were stored at -60°C until they were shipped frozen to Salimetrics, State College, PA. All samples were assayed for salivary cortisol using the Salimetrics enzyme immunoassay. It has a lower limit of sensitivity of 0.007 µg/dl, standard curve range from 0.012 to 3.0 µg/dl, and average intra- and inter-assay coefficients of variation 3.5% and 5.1%, respectively. Method accuracy, determined by serial dilution are 100.8% and 91.7%. A random 10% of samples were assayed in duplicate to confirm reliability; the intra-assay coefficient of variation was 3.5%. Mean values from duplicate samples were used for analysis. The final distribution of infant cortisol values was positively skewed, as is typical for such measures, and thus were natural log transformed prior to analysis (Gunnar & Talge, 2008). Infant cortisol reactivity was calculated as area under the curve increase (AUCi) from baseline to post-stress (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). 2 infants had AUCi values that were identified as univariate outliers (z-scores exceeded 3.29) which we adjusted according to recommendations (Tabachnick & Fidell, 2012). Overall, 54% of infants (n = 146) demonstrated an increase from baseline cortisol levels to post stressor, and the average AUCi was positive ($M = .78$, $SD = 5.4$), indicating that on average infants had an increase in cortisol in response to the frustration stressor. Such variability in HPA axis reactivity is typical of infants at 6 months of age (See Gunnar & Quevedo, 2008 for a review).

Covariates. As described above, the GA when a woman reported the highest depression score was included as a covariate in the statistical models in order to account for any effect of exposure timing. In order to rule out any other potential confounders as the basis for any observed effects, and based upon previous findings we evaluated a number of other potential covariates for inclusion in the analyses. Family characteristics such as family income, marital

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status, ethnicity, maternal education, infant sex, and parity were investigated for inclusion in the statistical models. Infant GA at birth has been associated with both mother-infant relationships (Wille, 1991) and infant cortisol (Elhassan, Miller, Vazquez, & Lumeng, 2015; Grunau et al., 2007), and maternal postpartum depression has been associated with reduced mother-infant interaction quality (Beck, 1995; Crnic, Greenberg, Ragozin, Robinson, & Basham, 1983; Shin, Park, & Mi, 2006), thus these variables were also investigated for inclusion in the statistical models. In addition, given the diurnal rhythm exhibited by cortisol, we examined time of day when infant cortisol reactivity was measured as a variable for inclusion as a covariate.

Data Analytic Strategy

Preliminary analyses were conducted using SPSS 22.0 software (IBM Inc, 2013) and involved conducting bivariate correlations between primary study variables of interest. Tests of the hypotheses were conducted using Hayes' PROCESS macro (Hayes, 2012), which implements a product of coefficients approach to mediation analyses (Preacher, Rucker, & Hayes, 2007). We employed an empirical bias-corrected bootstrapping procedure, which involved obtaining 10,000 artificial samples drawn with replacement from the existing data and reduces Type-1 error rates by using resampling methods (Fritz & MacKinnon, 2007; MacKinnon, Lockwood, & Williams, 2004). For hypothesis 1 (Figure 1 Model 1: Social Support → Prenatal Depression → Interaction Quality) and 2 (Figure 1 Model 2: Social Support → Prenatal Depression → Interaction Quality → Infant Cortisol), the indirect paths of interest (i.e., mediation paths) were examined to address each hypothesis. We derived parameter estimates and confidence intervals (CI) for all indirect paths. For all hypothesized indirect (mediation) effects, we examined the 95% CIs for the indirect effects to determine if the hypothesized mediation paths were significant. This approach accounts for the possibility of non-normality and/or

asymmetry for the indirect effect (Hayes & Preacher, 2013). Mediation is supported when the CIs do not contain zero. All models included covariates as described below.

Results

Preliminary Analyses

Descriptive statistics for the primary study variables are shown in Table 1. Bivariate correlations were conducted between all major study variables to better understand the relationships between the variables of interest. Higher perceived social support in early pregnancy was associated with lower self-reported depression severity during pregnancy, $r(266) = -.443, p < .001$. Higher severity of self-reported depressive symptoms during pregnancy was associated with lower mother-infant interaction quality at 6 months, $r(266) = -.121, p = .048$. Mother-infant interaction quality was negatively associated with infant cortisol reactivity, whereby lower quality interactions were associated with higher infant cortisol reactivity, $r(269) = -.168, p = .005$. Prenatal social support was not associated with postpartum mother-infant interaction quality, $r(268) = -.015, p = .812$. Neither prenatal social support, $r(269) = .065, p = .288$, nor prenatal depression severity, $r(267) = .045, p = .457$, were associated with infant cortisol reactivity in bivariate analyses.

Bivariate correlations (not shown) were also used to understand the relationship between potential covariates (i.e., family income, marital status, maternal education, ethnicity, infant sex, parity, infant GA at birth, maternal postpartum depression) and the primary study variables. Prenatal depression severity was associated with income, $r(260) = -.255, p < .001$, marital status, $r(262) = -.196, p = .001$, maternal education, $r(260) = -.184, p = .003$, ethnicity, $r(262) = .128, p = .038$, and postpartum depression, $r(267) = .534, p < .001$. Mother-infant interaction quality was associated with income, $r(260) = .137, p = .026$, and ethnicity, $r(262) = -.180, p = .003$. Time of

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day when infant cortisol reactivity was measured was not associated with infant cortisol reactivity, $r(270) = .030, p = .620$. Thus, only income, marital status, maternal education, ethnicity, and maternal postpartum depression, were included as additional covariates in the final mediation models.

Hypothesis 1: Effects of social support on maternal depression and maternal-infant interaction

To test hypothesis 1 we were interested in paths a_i and b_i (Figure 1 Model 1). Specifically, path a_i shows that women reporting higher perceived social support from partners in early pregnancy reported fewer prenatal depression symptoms, $B = -.092, p < .001$, and path b_i shows that lower self-reported prenatal depression severity was associated with higher maternal-infant interaction quality, $B = -.277, p = .045$. The direct effect of prenatal social support on maternal-infant interaction (path c') was not significant, $B = -.040, p = .329$, however the test for the indirect effect of Social Support $\rightarrow$ Prenatal Depression $\rightarrow$ Interaction Quality, was significant, $B = .025, 95\% \text{ CI } [.005, .060]$. These findings indicate that perceived partner support during pregnancy has a positive indirect association with maternal-infant interaction quality via its association with lower self-reported maternal depression severity during pregnancy but that perceived social support is not associated with maternal-infant interaction when the effects of prenatal depression are removed. Complete model results, including all covariates, are reported in supplementary Table S1.

Hypothesis 2: Effects of social support on infant cortisol reactivity

To test hypothesis 2 we were interested in examining paths a_1 and d_{21} (which are the same as paths a_i and b_i in the previous model) and path b_2 (Figure 1 Model 2), which is the direct effect of maternal-infant interaction on infant cortisol reactivity. Path b_2 shows that higher

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maternal-infant interaction quality was associated with lower infant cortisol reactivity or larger decreases in cortisol in response to the frustration stressor, $B = -.127$, $p = .005$. The direct effect of prenatal social support on infant cortisol reactivity (path c') was not significant, $B = .025$, $p = .401$. However, the serial indirect effect of Social Support $\rightarrow$ Prenatal Depression $\rightarrow$ Interaction Quality $\rightarrow$ Infant Cortisol was significant, $B = -.003$, 95% CI $[-.011, -.001]$, indicating that perceived partner social support in early pregnancy is associated with lower self-reported prenatal depression severity, lower depression severity is associated with higher maternal–infant interaction quality, and higher maternal-infant interaction quality is associated with lower infant cortisol reactivity or larger decreases in cortisol. Model 2 includes tests for two other indirect effects, neither of which is of interest to the test for hypothesis 2: Social Support $\rightarrow$ Prenatal Depression $\rightarrow$ Infant Cortisol, and Social Support $\rightarrow$ Interaction Quality $\rightarrow$ Infant Cortisol. Neither was significant. Complete model results, including all covariates, are reported in supplementary Table S2.

Reverse Causality Analysis

In order to evaluate the support for our proposed model, we tested an alternate path model in which prenatal depression was a predictor of perceived social support; see Model 3: Prenatal Depression $\rightarrow$ Social Support $\rightarrow$ Interaction Quality $\rightarrow$ Infant Cortisol, Figure S1. Higher prenatal depression severity was associated with lower social support, $B = -1.03$, $p < .001$, however prenatal social support was not associated with mother-infant interaction quality, $B = -.040$, $p = .329$, and the overall indirect effect was not significant, $B = -.005$, 95% CI $[-.026, .003]$. Thus, the reverse causality model was not supported.

Discussion

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The current study set out to investigate a potential pathway by which perinatal maternal and infant social relationships may become biologically embedded in the infant HPA axis in a relatively low sociodemographic risk sample of maternal-infant pairs. Specifically, we examined the pathways by which women's perceived social support from partners during pregnancy is associated with infant HPA axis reactivity. The data support a role for both maternal depression during pregnancy and maternal-infant interaction in the postpartum. Using a longitudinal path modeling approach, we demonstrated that women who report high levels of partner support received in early pregnancy experienced lower levels of self-reported depression symptoms prenatally, which was subsequently associated with higher quality of observed mother-infant interactions at 6-months of age and lower infant cortisol reactivity or larger decreases in cortisol in response to a stressor. The findings from the present study add to our understanding of how social relationships may modulate infant stress reactivity, and specifically how partner social support during early pregnancy may support high quality mother-infant relationships via improved prenatal maternal mental health. These findings are consistent with the hypothesis that social relationships become biologically embedded in children's development (Boyce & Ellis, 2005; Hertzman & Boyce, 2010) and specifically that positive social relationships are associated with reduced HPA axis reactivity in infants. To our knowledge, this is the first study to demonstrate support for the downstream effects that social support provided during pregnancy has on infant stress reactivity, and by extension these findings have implications for children's future risk for adverse developmental outcomes and psychopathology (Bagner et al., 2010; Granger et al., 1994; Heffelfinger & Newcomer, 2001; Luby et al., 2003; Natsuaki et al., 2009; Poon et al., 2016; Susman et al., 1997).

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The finding that high quality mother-infant interactions are associated with lower infant cortisol reactivity or larger decreases in cortisol in response to a stressor is consistent with a large body of previous literature (e.g. see Gunnar & Quevedo, 2008 for a review). Nevertheless, previous studies have focused on the effect of *postpartum* social support on maternal caregiving behavior (Crnic et al., 1983; Shin et al., 2006); much less is known about how social support provided *during pregnancy* may shape maternal-infant interactions and stress biology in infants. The current study demonstrated that women who reported higher perceived social support from partners in early pregnancy reported fewer depressive symptoms during the prenatal period, which is consistent with previous studies (Elsenbruch et al., 2007; Seguin et al., 1995). However, we further showed that fewer self-reported prenatal depressive symptoms was subsequently associated with higher quality mother-infant interactions in the postpartum. Thus, we demonstrated that the association between perceived partner support and the mother-infant relationship may begin *during pregnancy*. Although the extension of previous postpartum findings to the prenatal period is not surprising, the associations with perceived social support during pregnancy suggest important new pathways by which social relationships may become biologically embedded in child development. Social support during pregnancy may help to regulate the maternal HPA axis with downstream effects on the development of the fetal HPA axis. It is known, for example, that prenatal social support dampens HPA axis responses to everyday stressors in pregnant women (Giesbrecht et al., 2013), and this may be a factor involved in both reducing symptoms of maternal depression and in regulating the development of the fetal HPA axis.

Another potential pathway is through a process referred to as ‘maternal programming’ (Glynn & Sandman, 2011) which involves subtle neurocognitive and psychological changes that

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take place to facilitate bonding and the development of sensitive maternal behaviors that promote high quality postnatal interactions with infants (Leerkes, 2010; Pearson, Lightman, & Evans, 2011; Redshaw & Martin, 2013; Swain, Lorberbaum, Kose, & Strathearn, 2007). For instance, studies that have compared pregnant women to non-pregnant controls have shown that pregnancy is associated with attentional biases towards distressed faces (Pearson et al., 2011; Roos et al., 2012) and an enhanced ability to encode emotional facial expressions (Pearson, Lightman, & Evans, 2009). These neurocognitive changes have been associated with both mothers' self-reported quality of relationships with their infants after birth (Pearson et al., 2011) and with objective measures of maternal sensitivity (Leerkes, 2010). Magnetic resonance imaging studies have also identified structural changes that occur in new mothers' brains, which include increases in gray matter volume in regions associated with maternal motivation and caregiving behaviors (Kim et al., 2010). Postpartum mothers also demonstrate reward-related neural activity in response to infant stimuli (Strathearn, Li, Fonagy, & Montague, 2008), whereby infant cues provide motivation for maternal care behavior and promote mother-infant bonding (Swain et al., 2014).

The same neural networks that underpin these maternal behaviors are also implicated as dysfunctional in depression (Moses-Kolko, Horner, Phillips, Hipwell, & Swain, 2014; Pearson et al., 2010). Therefore, prenatal depression may hinder these neurocognitive changes from occurring during pregnancy, but social support may be a protective factor for the maternal neurocognitive adaptations that occur during pregnancy to prepare a woman to be a competent caregiver in the postpartum. Prenatally depressed women have substantially reduced attentional biases towards infant distress signals in comparison to non-depressed women (Pearson et al., 2010) and have lower postnatal responsiveness towards their infant (Pearson et al., 2012), which

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may contribute to lower quality interactions with their infants. Accordingly, prenatal social support may play a role in both the ‘maternal programming’ process that occurs in expectant mothers and consequently the ‘fetal programming’ of the infant HPA axis.

It is well-known that the early life social environment is related to long-term developmental outcomes. For this reason, biological embedding of social support in the infant HPA axis is an important protective factor for the developmental success of children. HPA axis reactivity is an important early indicator of biobehavioral self-regulation, with dysregulated HPA axis reactivity predicting altered cognition and memory (Heffelfinger & Newcomer, 2001; Stark et al., 2006) and behavioral problems (Bagner et al., 2010; Granger et al., 1994; Susman et al., 1997). Elevated cortisol reactivity to stress has been associated with internalizing disorders such as depression and anxiety in children and adolescents (Luby et al., 2003; Natsuaki et al., 2009; Poon et al., 2016) and thus poorly regulated cortisol reactivity in infancy may be an early risk factor for future psychopathology. As such, our findings indicate that effective partner support provided during pregnancy may be protective for child developmental outcomes.

Previous research has often ignored or failed to include the prenatal period when examining the impact of social support and maternal depression on infant development, despite mounting evidence that pregnancy represents an important preparatory period to enable a mother to be sensitive to the needs of her infant from the moment of birth as well as a sensitive period for development of the infant HPA axis. Our prospective investigation of prenatal psychosocial processes that are involved in the biological embedding of infant cortisol reactivity is a unique and significant strength of the current study.

Nevertheless, there are limitations that warrant consideration. First, the study sample consisted primarily of married, White women with middle class socioeconomic status, which

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may limit the generalizability of the study results to higher-risk populations. Although the sample was largely representative of the composition of families in the recruitment region (Calgary, Canada), the sample underrepresents mothers who are young and low income and as such, the findings may not be generalizable to higher sociodemographic risk or non-White populations. The fact that we are able to detect these associations in a relatively low sociodemographic risk group, with all of the protective advantages implied, speaks both to the power of perinatal social relationships and to the possibility that even among otherwise low-risk samples, these experiences have the ability to affect developmental outcomes. Furthermore, the findings highlight the need to examine these associations in higher sociodemographic risk groups where the severity of depression is likely higher and the quality of maternal-infant interaction may be lower.

Second, we did not enroll women who reported consuming tobacco, non-prescription drugs, or alcohol during pregnancy, which may have excluded women with the least social support, as women in the general population who receive the least effective social support also tend to engage in the poorest health behaviors during pregnancy (Hobel, Goldstein, & Barrett, 2008; Hoffman & Hatch, 1996). Third, although we test indirect (or mediation) models and made an effort to maintain a temporal sequence of the variables, the results are nevertheless observational and the associations cannot be interpreted causally. For instance, although there is evidence that social support prospectively predicts depressive symptoms (Kendler, Myers, & Prescott, 2005; Stice, Ragan, & Randall, 2004), it is possible that depressed individuals elicit or perceive less effective social support than nondepressed individuals (Stice et al., 2004; Stice, Rohde, Gau, & Ochner, 2011), which implies the opposite directionality of that proposed in the current study. However, when we tested for this possibility in the reverse causality analysis we

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found that the alternate pathway in which prenatal depression was a predictor of perceived social support was not supported, which provides greater confidence in our proposed cascade of effects. Fourth, we note that although it is impractical to assess infant cortisol reactivity on multiple days, it is possible to assess basal cortisol on multiple days and doing so would increase confidence in the laboratory measure of baseline cortisol as a representative basal sample. Finally, it is important to note that this study focused exclusively on romantic partner support. Although this type of support is thought to be one of the most significant sources of support during adulthood and particularly during pregnancy (Rini et al., 2006), it is only one important source. In addition, other support sources, such as family support, may have greater importance in other cultural contexts (Campos et al., 2008). Studies examining the impact of other sources of prenatal social support and social network size on infant development are needed to understand whether the effects found in the current study are unique to partner support or social support in general.

The present study found evidence for an indirect association between prenatal social support and infant cortisol reactivity via maternal depression and the mother-infant relationship, and therefore is consistent with the notion that social relationships are biologically embedded in infant development. Infant cortisol reactivity is an early indicator of biobehavioral self-regulation and poorly regulated cortisol reactivity has been associated with adverse outcomes including reduced cognition and memory (Heffelfinger & Newcomer, 2001; Stark et al., 2006), poor self-control (Granger et al., 1994), behavioral problems (Bagner et al., 2010; Granger et al., 1994; Susman et al., 1997), and increased risk for internalizing/externalizing disorders and psychopathology (Luby et al., 2003; Natsuaki et al., 2009; Poon et al., 2016). Thus, the findings provide initial support for the downstream effects that prenatal partner social support has on

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infant development and highlight the importance of examining psychosocial factors during the prenatal period. Further research is needed to determine whether social support is also a protective factor for the neurocognitive ‘maternal programming’ that takes place during pregnancy to support high quality caregiving, and how these adaptations contribute to the quality of interactions between mothers and their infants. Given that perceived social support is a potentially modifiable intervention target, this study provides justification for future research to focus on prenatal social support interventions and especially whether increasing the effectiveness of social support during pregnancy improves the wellbeing of women and stress regulation in children.

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Tables

Table 1

Descriptive statistics for the study sample (n=272).

	%	M (SD)	Range
Maternal Age (years)		32.8 (3.9)	20.3 – 43.7
Infant GA at Birth (weeks)		39.2 (1.7)	29.4 – 42.0
Birth Weight (grams)		3349 (552)	1200 – 5210
Perceived Social Support		58.3 (13.3)	17 – 80
Prenatal Depression Severity		7.0 (4.5)	0 – 22
Mother-Infant Interaction Quality		52.7 (7.9)	30 – 70
Infant Cortisol Baseline (LN ug/dL)		.18 (.12)	.04 – 1.2
Infant Cortisol Reactivity (LN AUCi)		.78 (5.4)	-10.3 – 19.1
Preterm birth (<37 weeks gestation)	5.8		
Infant Sex			
Male	52.2		
Female	47.8		
Married Or Common Law	98.1		
Maternal Education			
University Degree Or Higher	89.5		
Less Than High School Diploma	1.5		
Ethnicity			
White	80.3		
Asian	6.2		
Latin American	4.1		
Chinese	3.7		
Other	5.5		
Annual Household Income			
More Than \$100,000/Year	55.1		
\$70,000 – \$100,000	24.3		
\$40,000 – \$70,000	12.0		
Less Than \$40,000/Year	8.6		
Parity			
Primiparous	48.1		
Multiparous	51.9		

BIOLOGICAL EMBEDDING OF PERINATAL SOCIAL RELATIONSHIPS

Figures

Model 1:

Model 2:

Figure 1. Longitudinal path models examining the relations between prenatal social support, prenatal depression severity, maternal-infant interaction quality, and infant cortisol reactivity. Unstandardized estimates are displayed. Significant paths are represented by solid lines, non-significant paths are represented by dashed lines.