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Maternal Prenatal Distress and Child Cognitive Outcomes During the Preschool Years

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An abstract submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Psychology

2015

Abstract

Background: A great deal of animal research as well as available human research suggests that psychological distress experienced by the mother during gestation is associated with later neurodevelopmental deficits in offspring. However, most research investigating the outcomes associated with prenatal stress in humans has been conducted during infancy, leaving many questions unanswered regarding the long term effects of prenatal distress on child neurocognitive development. The current study examined the impact of maternal distress during pregnancy on neurocognitive outcomes in preschool age children, as well as potential mediators and moderators of this risk pathway. Specifically, children's hypothalamic-pituitary-adrenal axis functioning (i.e., cortisol reactivity) was examined as a mediator and parenting behaviors were examined as moderators. Methods: Mother-child dyads (*N*=162) were recruited from a longitudinal cohort of women who had previously participated in a study on maternal mood during pregnancy. Maternal distress during pregnancy was constructed as a latent variable, based on a combination of self-report and clinician rated measures collected throughout the course of pregnancy. During a follow-up visit, information was collected regarding mother's symptomatology since the child's birth and children's neurocognitive abilities. In addition, cortisol reactivity was assessed via saliva samples before and after a stressor task, and parenting behaviors were recorded during a parent-child interaction. Results: Maternal prenatal distress significantly predicted to children's lower general cognitive and expressive language abilities. This relationship was moderated by parent positive engagement such that the relationship was strongest for children whose mothers exhibited low levels of positive engagement and was not significant for mothers who exhibited high levels of positive engagement. Children's cortisol reactivity was not found to be a mediator. Conclusions: Prenatal maternal distress, measured in a multi-informant, comprehensive manner predicts to lower cognitive functioning in preschool aged children, particularly when mothers display low levels of positive parenting. The findings are discussed with regard to clinical implications and future research directions.

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The notion that the behaviors and emotional attitudes exhibited by the mother during pregnancy can affect the unborn child is an ancient concept held universally by cultures around the world (Ferreira, 1965). Writings dating from as early as the Old Testament and Hippocrates in 400 B.C. reference the impact of prenatal attitudes on the unborn child. Much more recently, scientific inquiry has turned to the effects of maternal distress on specific childhood outcomes (Bergman, Sarkar, O'Connor, Modi, & Glover, 2007; Davis & Sandman, 2010; Davis et al., 2007; Deave, Heron, Evans, & Emond, 2008; Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003; King & Laplante, 2005; Laplante et al., 2004; Lou et al., 1994; O'Connor, Heron, Glover, & Alspac Study Team, 2002; Talge, Neal, & Glover, 2007; Tarabulsy et al., 2014) and on the biological mechanisms (Field & Diego, 2008; Field et al., 2003; Lewinn et al., 2009) and psychosocial factors (Bergman, Sarkar, Glover, & O'Connor, 2008; 2010; Grant, McMahon, Reilly, & Austin, 2010) that might explain these outcomes. There remains a notable gap in this area of literature, however, regarding the potential effects of prenatal distress on neurocognitive outcomes during the preschool years. In addition, a better understanding of the pathways linking clinical levels of maternal prenatal distress and childhood outcomes is necessary to inform preventative interventions that may be applied in high-risk family contexts. The purpose of the current study, therefore, is to examine the relationship between prenatal distress and preschool cognitive outcomes, test potential mechanisms that might explain such an association, and explore the contexts in which such an association may be more or less evident. In particular I will focus on child hypothalamic-pituitary-adrenal (HPA) axis functioning in response to a stressor as a potential mediator and parenting behaviors as a potential moderator of the association

between maternal distress during pregnancy and child neurocognitive outcomes during the preschool years (ages 2 ½ - 5).

Prenatal Distress

The prenatal period is a time marked by rapid neurodevelopmental changes. As a result, the fetal brain is particularly vulnerable to environmental threats, such as maternal distress (Sandman, Davis, Buss, & Glynn, 2011a). Prenatal maternal distress is often operationalized in the literature as self-reports of daily hassles, negative life events during pregnancy, exposure to traumatic events, or presence of mood disorder symptomatology (Tarabulsy et al., 2014). Many studies exploring the effects of maternal prenatal distress utilize only one specific measure of distress. In addition, researchers often attempt to statistically control for one measure of distress, such as depression, while exploring the effect of another measure of distress, such as anxiety. However, given that varying forms of distress are often highly correlated (Goodman & Tully, 2008) the use of a single measure, or the statistical control of one measure while assessing the impact of another, may not be valid approaches to take when examining maternal prenatal distress and its association with child outcomes. Instead, the use of multiple measures of prenatal maternal distress, as well as statistical methods that recognize the underlying construct that these measures represent, allow for a higher level of internal validity, and potentially a greater ability to accurately assess the influence of maternal distress on child outcomes. This latent construct approach to the measurement of prenatal maternal distress will be utilized in the proposed study. However, because no studies in this area have utilized this latent construct method, the following review includes findings from studies that have

used more specific measures of maternal prenatal distress, as such a review is necessary to provide the groundwork for the proposed hypotheses.

Prenatal distress and the fetus. Fetal heart rate and fetal activity have both been employed as noninvasive measures of fetal responsiveness to maternal distress. Prenatal maternal depression and anxiety, both self-reported and clinician appraised, have been linked to fetal heart rate and activity levels (Kinsella & Monk, 2009). Near-term fetuses of women classified as having high anxiety or stress show increased fetal heart rate variability, more movement during active (REM) sleep, and a decreased amount of quiet (non-REM) sleep (Van den Bergh, Mulder, Mennes, & Glover, 2005). These same results have been noted during a laboratory stressor task (Monk et al., 2000), and in women experiencing depression during pregnancy (Allister, Lester, Carr, & Liu, 2001). The positive associations among prenatal distress, fetal heart rate, and fetal activity lend support for the idea that distress experienced prenatally may have an effect on fetal neurodevelopment and a wide variety of associated postnatal outcomes (DiPietro, Costigan, Pressman, & Doussard Roosevelt, 2000; Sandman, Davis, Buss, & Glynn, 2011b).

Prenatal distress and the neonatal period and infancy. One of the best replicated findings regarding prenatal distress and offspring outcomes is the association between prenatal anxiety or stress and obstetric complications, including premature birth and low birth weight for gestational age (Copper et al., 1996; Hedegaard, Henriksen, Sabroe, & Secher, 1993; Lou et al., 1994; Pagel, Smilkstein, Regen, & Montano, 1990). For example, using a prospective, population based design, Hedegaard et al. (1993) found a significant, positive association between self-reported general distress during the 3rd

trimester of gestation and an increased risk for pre-term delivery (before 37 weeks) in a sample of 8,719 women. Perceived stressors and mood disorder symptoms occurring during the 2nd trimester of gestation have also been linked with increased likelihood of premature birth and low birth weight (Copper et al., 1996; Dole, 2003). Notably, these adverse obstetric outcomes have been associated with later learning difficulties in childhood (Rice, Jones, & Thapar, 2007; Wadhwa, 2005). Further, a positive association has been consistently found between birth weight and later language and cognitive test scores in childhood (Shenkin, Starr, & Deary, 2004).

Prenatal distress itself, regardless of obstetric complications, has been associated with an array of deleterious outcomes in neonates and infants. For example, higher levels of maternal reported anxiety and depression during the 3rd trimester have been linked to increased mother reports of infant negative reactivity at two months postpartum, with the association between maternal prenatal depression and infant temperament remaining significant when postnatal maternal psychological distress was controlled (Davis et al., 2007). In addition, Field and colleagues (2003) found that neonates of mothers with high anxiety during the 2nd trimester of pregnancy had greater right frontal brain activation, an EEG pattern that has been related to negative affect in infancy through adulthood (Davidson, 1998). Bergman and colleagues (2007) used a laboratory assessment (Laboratory Temperament Assessment Battery—Locomotor Version), rather than maternal report, to measure child fearfulness in 14-19 month old infants. The authors found a significant positive relationship between maternal prenatal stressful life events and fearfulness in the infants, and that prenatal stress accounted for 10% of the fearfulness scores even after controlling for maternal postnatal stressful life events.

Prenatal distress has also been associated with suboptimal performance on standardized measures of cognitive functioning during infancy and toddlerhood (Davidson, 1998; Davis & Sandman, 2010; Huizink et al., 2003; Lou et al., 1994; Talge et al., 2007). In a recent meta-analysis, maternal prenatal stress and anxiety was found to have a small, but significant negative association with child cognitive development in 11 studies of children ranging from birth to 60 months (Tarabulsy et al., 2014). The Bergman (2007) study mentioned previously is one representative study included in this meta-analysis. In addition to examining child fearfulness, Bergman and colleagues also studied the relationship between retrospectively reported stressful life events experienced during pregnancy and infant cognitive outcomes (Bergman et al., 2007). A significant negative association was found between total number of stressful life events experienced prenatally and the child's Bayley Scales of Infant Development (BSID) mental development index (MDI) score; this relationship was also significant when looking at mothers' perception of the stressful events. Notably, the authors found that maternal prenatal stress accounted for 17% of the variance in cognitive abilities in 14-19 month old infants, and the results remained significant after controlling for postnatal stressful life events.

Prospective study designs reduce the bias that may hinder retrospective reporting. In a prospective study of 170 women, eight-month old infants whose mother's reported higher levels of daily hassles during early pregnancy or anxiety about giving birth at mid-pregnancy had, on average, a decline of eight points on the BSID MDI and psychomotor development (PDI) scales after controlling for postnatal maternal stress and depression (Huizink et al., 2003). Similarly, in a prospective study of 125 mothers and their

offspring, Bergman et al. (2010) found that maternal reported prenatal stressful life events assessed via self-reports at 17 weeks gestation inversely predicted BSID standard scores in children aged 17 months. This relationship was not observed for postnatal stressful life events. This association is also supported by results from the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective longitudinal cohort of mothers and their children where measures of depression and anxiety were collected throughout pregnancy and after birth. Results from the ALSPAC study indicate that mothers who experienced depressive symptoms at both 8 and 32 weeks (i.e., "persistent depression") of pregnancy were 50% more likely to have a child with a developmental delay at 18 months old as assessed via parental report (Deave et al., 2008).

Some studies have utilized disasters as "natural experiments," allowing researchers to examine the effect of disaster-related distress in a quasi-randomized sample (Glynn, 2001; Huizink et al., 2008; King & Laplante, 2005; Kinney, Miller, Crowley, Huang, & Gerber, 2008; Laplante et al., 2004). Project Ice Storm looks at the effects of exposure to the 1998 Quebec ice storm, one of the most costly natural disasters in Canadian history that left residents of Quebec without power for a few hours to more than six weeks during the coldest month of the year (Laplante et al., 2004). Researchers collected measures of self-reported objective and subjective stress experienced by women pregnant during the storm. Objective stress was measured using a questionnaire designed to address specific aspects of the Quebec ice storm, and based on categories of exposure used commonly in disaster research (King & Laplante, 2005). For example, women reported if they had been injured during the storm, experienced loss of personal income, the number of days they were without power, and if they spent time in a temporary

shelter. Subjective stress was assessed by the Impact of Event Scale-Revised (IES-R), a widely used measure of subjective reactions which includes items that address symptoms associated with posttraumatic stress disorder (e.g., intrusive thoughts, hyperarousal, avoidance). The authors found that higher levels of objective stress experienced by the mother during pregnancy were associated with lower levels of intellectual and language abilities in children at 2-years old. Specifically, prenatal stress exposure uniquely accounted for 11% of two-year olds' mental abilities and 12% of their language abilities. Overall, the current literature suggests that prenatal distress contributes to offspring outcomes in the weeks following birth and during infancy. However, less research has followed offspring longitudinally and examined the effect of prenatal distress on child outcomes later in development (Laplante et al., 2004).

Prenatal distress and preschool outcomes. The preschool years are a critical developmental period marked by significant gains in emotional, behavioral, and neurocognitive domains. Although still reliant on attachment to parents, preschoolers make considerable advances with regards to self-regulating impulses and behaviors (Davies, 2011). These gains may be attributed to neurocognitive developments in areas of the brain related to planning (e.g., the prefrontal cortex) and emotion (e.g., limbic structures) (Beauregard, Levesque, & Paquette, 2004). Normative developmental changes in the brain make it possible for preschoolers to inhibit impulses and utilize cognitive strategies and interpersonal coping skills to deal with feelings of distress. These abilities also allow preschoolers to better understand reality, thus reducing their reactivity to novel situations that previously caused anxious responses during infancy (Davies, 2011).

The majority of studies that have investigated the longer term outcomes (i.e., beyond infancy) of prenatal distress have tended to focus on emotional and behavioral sequelae. For example, results from the ALSPAC study indicate that maternal prenatal distress may be associated with child emotional and behavioral deficits during the preschool years (O'Connor et al., 2002). O'Connor and colleagues (2002) looked at prenatal anxiety and parent-reported behavior in preschool aged children (mean age 3.9 years). Mothers who scored in the top 15% for anxiety at either 18 or 32 weeks gestation were two to three times more likely to have a child who scored two standard deviations or more above the mean on parent-rated behavior and emotional problems. The results continued to be significant after adding postnatal anxiety into the model. In a follow-up study completed when the offspring were 81 months (6.75 years), the association between prenatal anxiety at 32 weeks gestation and mother reported emotional and behavioral problems remained significant, even after controlling for maternal postnatal anxiety at 8, 21, and 33 months (O'Connor, Heron, Golding, & Glover, 2003). Carter and colleagues (2001) also found a significant relationship between maternal prenatal depression and increased externalizing behaviors in 2 ½ year olds. These youth were also rated as lower on the Competency domain on the Infant-Toddler Social and Emotional Assessment (ITSEA), which measures competencies including attention and compliance. Notably, these results only remained significant for boys when the sample was divided by sex. Similar results were reported by Rodriguez and Bohlin (2005) who found that higher levels of perceived stress reported by pregnant women throughout gestation were associated with parent and teacher reported Attention Deficit Hyperactivity Disorder

(ADHD) symptoms in 7-year old boys, and that stress experienced in the 1st half of pregnancy accounted for 20% of the variance.

The preschool years are also marked by neurodevelopmental changes that lead to gains in cognitive abilities. Burgeoning brain development, maturity in thought, marked increase in vocabulary, and enhanced capacity to form memories occur in concert during this period (Davies, 2011; Lightfoot, Cole, & Cole, 2009). Developments specifically in the areas of the brain associated with language lead not only to maturation of language, but also increasing vocabulary which allows preschoolers to encode memories, an ability that they lacked during infancy (Fivush & Nelson, 2010; Simcock & Hayne, 2003). Advances in language coupled with repeated experiences increase the preschooler's ability to generalize and categorize new experiences based on old ones (Davies, 2011; Lightfoot et al., 2009). This increased ability to categorize and understand how a new experience is similar or different from a past experience enhances the child's understanding of reality and analytical thinking skills (Davies, 2011).

As mentioned, most studies investigating long term effects of maternal prenatal distress have focused on emotional and behavioral outcomes; there is much less literature investigating long term child neurocognitive outcomes. In one of the few studies of this type, Laplante and colleagues (2008) continued to follow offspring whose mothers experienced the 1998 Quebec ice storm, using standardized measures of cognitive abilities (Wechsler Preschool and Primary Scale of Intelligence-Revised; WPPSI-R) and language skills (Peabody Picture Vocabulary Test-Revised; PPVT-R) to assess functioning at age 5 ½ years. The results indicated negative relationships between levels of maternal reported objective stress during pregnancy and the youth's full scale IQ

(FSIQ), verbal intelligence scores, and language abilities. Youth whose mothers had experienced higher levels of objective stress prenatally had lower scores when compared with youth whose mothers had experienced low to moderate levels of objective stress; this relationship was not impacted by postnatal maternal psychological functioning. Recent findings from the same dataset have also indicated that subjective levels of maternal prenatal distress, measured by self-reports on the IES-R, were linked to decreased performance on tasks of motor functioning in 5 ½ year-old children (Cao, Laplante, Brunet, Ciampi, & King, 2012). These findings underscore the wide impact that distress during pregnancy may have on children's central nervous system and neurocognitive outcomes.

While the main findings from the Project Ice Storm study indicate that higher levels of prenatal distress are negatively related to cognitive outcomes in childhood, the authors also found that moderate levels of prenatal distress were positively associated with preschoolers' cognitive and language abilities (Laplante et al., 2008). Similar findings were reported by DiPietro et al. (2006) who found a significant, positive relationship between maternal reported stress and depression at mid-pregnancy (assessed at 24, 28, or 32 weeks gestation) and BSID scores in 2-year old children. This relationship remained significant even after controlling for maternal postnatal depression at 6 weeks and 24 months (concurrent depression).

It should be highlighted that both of the studies that noted positive associations between prenatal distress and child cognitive outcomes were composed of high-functioning, nonclinical samples; thus, perhaps in nonclinical samples, moderate levels of distress during pregnancy may be somewhat adaptive. However, clinical levels of

distress, even at moderate levels, may still be associated with detrimental child outcomes. The current study aims to add to the limited literature concerning cognitive outcomes during the preschool years and specifically explore the relationships between prenatal distress in a clinical sample of women, testing the primary hypothesis that maternal prenatal distress will be negatively associated with offspring cognitive functioning during the preschool period of development.

The Fetal Programming Hypothesis

The fetal programming hypothesis provides a context for the examination of HPA axis functioning as a potential mediator in the association between maternal prenatal distress and child neurocognitive outcomes. Fetal programming refers to the fetus' adaptations to the intrauterine environment and how these adaptations may be associated with postnatal development and outcomes (Talge et al., 2007). The theory uses the word 'programming' to describe the organizing and disorganizing influences of prenatal distress on later outcomes (Sandman, Davis, Buss, & Glynn, 2011a). Thus, according to this hypothesis, the relationship between the events experienced by the fetus prenatally and outcomes observed after birth is causal. It has been suggested that programming occurring during fetal development may have evolutionary significance; the offspring is "learning" about the outside world through its early environment and preparing itself for potentially similar experiences after birth (Sapolsky, 2004; Viltart & Vanbesien-Mailliot, 2007). This concept was first posited by Barker (1993), who observed that fetal malnutrition at different stages of gestation was linked to negative health outcomes in adulthood. Specifically, lower birth weight was associated with increased risk for cardiovascular disease and metabolic disorders, such as diabetes (Barker et al., 1993). In

this example, malnutrition experienced during gestation programmed the fetus's ability to metabolize glucose, and the fetus was unable to adjust to the improvement in his or her nutritional environment after birth (Barker, 1998). Evidence suggests that the psychological and physiological effects of distress experienced by the mother during pregnancy may also increase the risk for an array of negative health outcomes in offspring, such as cardiovascular disease, shortened lifespan, and asthma (Sandman, Davis, Buss, & Glynn, 2011a). As discussed below, it is hypothesized that the HPA axis may be the mechanism by which prenatal distress is transferred to the fetus, leading to negative outcomes for the child after birth.

When discussing the relationship between maternal distress and childhood outcomes it is crucial to consider shared genetic factors. For example, heritable factors may predispose the mother to having higher levels of distress and the child to certain negative outcomes. Parsing environmental and genetic factors in humans is difficult without experiments or genetically informative designs (Rutter, 2007). Animal research allows for random assignment to prenatal and postnatal environments, and studies using this method have offered evidence for fetal programming (Barbazanges, Piazza, Le Moal, & Maccari, 1996; Coe et al., 2003; Maccari et al., 1995; Schneider, Roughton, Koehler, & Lubach, 1999; Uno et al., 1994; Wakshlak & Weinstock, 1990). For example, Maccari and colleagues (1995) found that rat pups whose mothers underwent prenatal distress had higher levels of stress-induced corticosterone secretion and less hippocampal corticosterone receptors at 90-days old when compared to pups of dams who had not experienced prenatal distress. Wakshlak and Weinstock (1990) found increased timidity and emotionality in offspring of dams who had been exposed to prenatal stress when

compared to controls. Programming influences have also been noted in studies with humans who have been exposed to random traumatic events during pregnancy (Glynn, 2001; Huizink et al., 2008; Kinney et al., 2008; Laplante et al., 2004; 2008). Kinney and colleagues (2008) found a greater prevalence of autism spectrum disorders diagnosed in cohorts of women exposed to severe weather-related disasters during the middle to end of their pregnancies and, as discussed previously, researchers studying outcomes from the Project Ice Storm study observed decreases in cognitive and motor abilities in children whose mothers had experienced greater levels of objective and subjective stress during an ice storm while pregnant (Cao et al., 2012; Laplante et al., 2004; 2008). Further, in an examination of pregnant women using *in vitro* fertilization who were related or unrelated (i.e., egg and embryo donated and implanted) to their child, Rice and colleagues (2010) found that multiple child outcomes, including antisocial behavior, were related to prenatal distress in both sets of mothers (i.e., the outcomes were observed in both women who were related and unrelated to their child), suggesting that this association was not due to inherited factors. Thus, while genetic factors certainly play a role in child development, there is evidence that prenatal distress may also affect, or program, fetal development and result in particular child outcomes.

The Hypothalamic-Pituitary-Adrenal Axis

The HPA axis, the body's stress response system, is hypothesized to be a potential mechanism by which maternal distress affects fetal development. In normal development, physical or psychological stress activates the HPA axis, triggering the release of corticotrophin-releasing hormone (CRH) by the paraventricular nucleus of the hypothalamus (Jameison & Dinan, 2001). CRH circulates to the anterior pituitary where

adrenocorticotropic hormones (ACTH) are released (Jameison & Dinan, 2001; Sapolsky, 2004). ACTH enters the blood stream and triggers the adrenal cortex to release glucocorticoids, such as cortisol in humans and corticosterone in rats, and enable bodily responses necessary to react to oncoming stressors (Jameison & Dinan, 2001). As described in more detail below, maternal cortisol is not fully metabolized by the placenta; thus, increased stress experienced by the mother may result in increased fetal exposure of glucocorticoids (Challis et al., 2001; O'Connor et al., 2005; Wadhwa, Sandman, Chicz-Demet, & Porto, 1997).

Prenatal distress and the HPA axis. The literature regarding the influence of stress hormones on the developing human fetus is still quite limited. However, a substantial body of animal literature suggests that the endocrine system mediates the effect of maternal prenatal distress on fetal development (Sandman, Davis, Buss, & Glynn, 2011a; Sapolsky, 2004; Wadhwa, 2005). In particular, it has been suggested that the fetal HPA axis may be programmed by events occurring during gestation, leading to changes in the set point of the stress response system or permanent alterations in the developmental pattern or differentiation and proliferation within certain organ and tissues systems in the fetus (De Bruijn, Van Bakel, Wijnen, Pop, & Van Baar, 2009; Wadhwa, 2005).

During pregnancy, placental corticotrophin-releasing hormone (pCRH) activity is controlled by the maternal HPA axis (Wadhwa et al., 1997). Maternal prenatal distress increases the release of pCRH (Challis et al., 2001), and pCRH may activate the CRH receptors of the developing fetal hippocampus and limbic structures that contain an abundance of CRH receptors during pregnancy (Sandman et al., 1999). In addition to an

influx in circulating cortisol, increased maternal prenatal distress reduces the expression of 11 β-hydroxysteroid dehydrogenase type 2 (11β–HSD2), the glucocorticoid barrier enzyme that converts maternal cortisol into its inactive form when crossing the placenta (Challis et al., 2001; Sandman et al., 1999; Welberg, Seckl, & Holmes, 2001). A downregulation of 11β–HSD2 further increases fetal glucocorticoid exposure (Challis et al., 2001). Thus, it is hypothesized that increased stress experienced by the mother results in increased fetal exposure of glucocorticoids (Challis et al., 2001; O'Connor et al., 2005; Wadhwa et al., 1997), and it is suggested that this exposure to excess cortisol during pregnancy may lead to programming of the fetal HPA axis and brain areas that play a significant role in the HPA axis feedback.

Research from the animal literature offers insight into the potential neural changes that may result from fetal exposure to maternal distress and excess glucocorticoids. Evidence suggests that the hippocampus plays a central role in the regulation of the HPA axis (Buitelaar, Huizink, Mulder, de Medina, & Visser, 2003; Glover, O'Connor, & O'Donnell, 2010). Once maternal stress hormones have entered the fetal circulation they can have neurotoxic effects on hippocampal cells, thus leading to a downregulation of hippocampal glucocorticoid receptors (GRs), the receptors to which glucocorticoids bind (Sapolsky, 2004; Sapolsky, Uno, Rebert, & Finch, 1990). For example, pregnant rhesus monkeys injected with dexamethasone, a synthetic glucocorticoid, during gestation had an approximately 30% reduction in size and segmental volume of their hippocampus (Uno et al., 1994). Rhesus monkeys that were repeatedly exposed to unpredictable noise during gestation had reduced hippocampal volume and increased pituitary-adrenal axis activity (Coe et al., 2003). In addition, prenatally stressed rats have been found to have a

downregulation of GRs in the hippocampus, and similar changes were observed when rats were injected with glucocorticoids in the absence of stress (Barbazanges et al., 1996). Importantly, some GRs located in the hippocampus provide negative feedback for the HPA axis. Thus, a reduction or downregulation of GRs in the hippocampus results in less feedback inhibition and an overactivation of the HPA axis (De Kloet, Reul, De Ronde, Bloemers, & Ratka, 1986; Glover et al., 2010).

Though the hippocampus has received the majority of attention, other brain regions have also been implicated in the modulation of the HPA axis. For example, evidence indicates that the amygdala plays an important role in HPA axis regulation (Herman & Cullinan, 1997; Welberg & Seckl, 2001). Specifically, the amygdala has been shown to communicate HPA excitatory information, leading to appropriate cardiovascular and behavioral responses following stress (Herman & Cullinan, 1997). The prefrontal cortex (PFC) has also been identified as a neural structure underlying HPA axis activity (Pruessner et al., 2008). For example, the PFC has been implicated in both the excitatory and negative feedback processes, and damage to the PFC results in enhanced HPA activity in response to stress (Diorio, Viau, & Meaney, 1993). Further, reduced grey matter volume was observed in the PFC in school-age children whose mothers reported higher levels of pregnancy-related anxiety during mid-gestation (Buss, Davis, Muftuler, Head, & Sandman, 2010).

Research assessing the association between prenatal distress and HPA axis functioning in human offspring has typically examined cortisol levels in youth exposed to prenatal distress. Much of this research has been done with neonates and infants. For example, maternal depression and anxiety experienced during pregnancy have been

associated with increased cortisol in neonates approximately one week after birth (Diego, Field, & Hernandez-Reif, 2005; Lundy et al., 1999). One week old infants of mothers depressed during their 3rd trimester of pregnancy showed the same elevated cortisol pattern as their mothers (Lundy et al., 1999), and perinatal maternal depression was also associated with higher infant cortisol reactivity at six months of age (Brennan et al., 2008).

Several studies have also examined longer lasting alterations to the HPA axis in relation to prenatal distress. Guttelling and colleagues (2004) looked at maternal indicators of prenatal stress, including maternal cortisol levels during pregnancy, mothers' reports of daily hassles, and mothers' reports of pregnancy-related anxiety. They found a positive association between these indicators of maternal distress and preschool age children's (mean age 4.9 years) basal cortisol levels. These researchers also examined child cortisol levels in response to a potential stressor (i.e., vaccination). While no relationship was found between maternal cortisol and children's cortisol reactivity in response to a vaccination, the authors did find that 5-year old children of mothers who had higher levels of morning cortisol during pregnancy or higher levels of pregnancy-related anxiety had higher levels of basal cortisol on their first day of school when compared with children of mothers with lower levels of cortisol and anxiety during pregnancy (Gutteling, Weerth, & Buitelaar, 2005). de Bruijn and colleagues (2009) also found positive relationships between maternal emotional complaints during pregnancy (i.e., symptoms of depression and anxiety) and both basal cortisol levels and cortisol levels in response to a stressor in preschool aged children (mean age 3 years); however, these relationships were only significant for girls.

Similar findings have also been observed into adolescence. In a sample of 10-year old children from the ALSPAC study, maternal prenatal anxiety was positively associated with child cortisol levels at awakening and in the afternoon; however, maternal prenatal depression was not related to childhood cortisol (O'Connor et al., 2005). Huizink and colleagues (2008) examined a sample of adolescents (mean age 14 years) whose mothers had been exposed to the Chernobyl disaster in Finland during their pregnancy. The authors found that those youth whose mothers had experienced the stressor during their 2nd trimester had elevated cortisol levels when compared with nonexposed youth.

HPA Axis functioning and cognitive outcomes. Childhood cortisol levels have been associated with numerous behavioral and psychological outcomes. In infants, higher levels of cortisol have been linked to increased levels of irritability and difficulty with behavior regulation (measured by the Brazelton Neonatal Behavior Assessment Scale) (Field & Diego, 2008; Graham, Heim, Goodman, Miller, & Nemeroff, 1999). Cortisol dysregulation has also been related to externalizing disorders (van Goozen, Fairchild, Snoek, & Harold, 2007) and internalizing problems (Heim & Nemeroff, 2001; Kaufman & Charney, 2001) throughout childhood and adolescence.

Cortisol levels have also been associated with cognitive outcomes in childhood, though this literature is more limited. Increased concentrations of cortisol in the bloodstream during pregnancy have been linked to premature birth (de Weerth, van Hees, & Buitelaar, 2003) and low birth weight, both of which have been related to later cognitive and language deficits (Shenkin et al., 2004). Individuals with heightened levels of cortisol, such as those with Cushing Syndrome, also exhibit cognitive deficits (Starkman, Gebarski, Berent, & Schteingart, 1992); and, cognitive functioning improves

for these individuals when cortisol levels return to normal following treatment (Jameison & Dinan, 2001). Maternal cortisol levels during pregnancy have also been associated with cognitive outcomes in early childhood (Lewinn et al., 2009). For example, Lewinn and colleagues found a negative association between maternal prenatal cortisol levels and scores on standardized measures of intelligence when the offspring were 7-years old. Further, the authors found the same relationship when comparing the youth to their siblings; within sibling pairs, the child born when the mother had higher prenatal levels of cortisol performed worse on the cognitive tests.

It has been suggested that hyperactivity of HPA axis directly affects areas of the brain associated with cognitive functioning (Sohr-Preston & Scaramella, 2006). In addition to playing a critical role in the modulation of the HPA axis, the hippocampus is also essential for storing long term declarative memories (Squire & Zola-Morgan, 1991). Specifically, the GRs located in the hippocampus are important for the retention and consolidation of information (De Kloet, Oitzl, & Joëls, 2011). Notably, while short term cortisol increases in response to a stressor have been shown to enhance specific types of cognitive functioning, such as memory or anxiety of fear provoking events (Blair, Granger, & Peters Razza, 2005; Erickson, Drevets, & Schulkin, 2003), *consistently* elevated cortisol responses have been linked to impairments in verbal and declarative memory (Newcomer et al., 1999) and may interfere with the synaptic process of long-term potentiation involved in learning consolidation and executive functioning (Blair et al., 2005). In addition, the amygdala may mediate the association between stress on hippocampal long-term potentiation and memory processes (Kim, Lee, Han, & Packard, 2001). The PFC has also been shown to underlie higher level cognitive functioning

involved in executive functioning, such as planning, working memory, and attention (Casey, Giedd, & Thomas, 2000; Goldman-Rakic, 1987). Importantly, during early childhood, central components of the executive functioning system develop that form the foundation for the development of higher-level cognitive processes (Garon, Bryson, & Smith, 2008). Thus, there are several neural structures that may be particularly susceptible to fetal programming that may also implicate children's cognitive abilities.

Some researchers have suggested that maladaptive HPA axis activity leads to arousal in non-threatening situations, such as those involving learning (Sohr-Preston & Scaramella, 2006). Children who are overly aroused may have difficulties in the areas of focus and attention, which may in turn negatively impact their cognitive performance. In addition to examining links between maternal prenatal distress and child neurocognitive outcomes, the proposed study will build on previous literature to test whether child HPA axis dysregulation acts as a mediator in this relationship.

Parenting

Results from the animal literature suggest that a sensitive postnatal environment may ameliorate negative effects of prenatal distress on both biological and behavioral outcomes in the offspring. For example, rats whose mothers underwent prenatal distress via restraint procedures during their last week of pregnancy had higher levels of stress-induced corticosterone secretion and less hippocampal corticosterone receptors at 90-days old; however, these results were completely reversed when the offspring were adopted immediately after birth (Maccari et al., 1995). Of note, dams who adopted spent more time licking and picking up their pups than biological mothers. Similarly, Wakshlak and Weinstock (1990) randomly exposed pregnant dams to stress, in the form of

unpredictable noise and light bursts, throughout pregnancy. Offspring were then randomly assigned to neonatal "handling" or "nonhandling" groups, where the experimental group was handled for three minutes daily for 21 days. Again, prenatal stress was positively associated with increased timidity and emotionality in offspring, but results were reversed in offspring that underwent neonatal handling. Vallée and colleagues (1999) also found that rat pups whose mothers were exposed to prenatal distress had higher levels of circulating glucocorticoids and cognitive impairments (as assessed via maze procedures) throughout their lifespan. Again, postnatal handling acted as a protective factor as pups that underwent handling after birth did not exhibit HPA axis dysfunction or cognitive deficits later in life. The effect of "handling" per se was not entirely clear to the authors; however, it was hypothesized that the increased maternal care (e.g., licking, crouching over, picking up) that resulted from the handling procedures may have mediated the improvements observed in the rat pups (Vallée et al., 1999; Wakshlak & Weinstock, 1990).

Bergman and colleagues (2008) were the first to examine whether parenting might moderate the effect of prenatal stress on children's cognitive functioning. In this study, 123 female participants retrospectively reported stressful life events that they had experienced during pregnancy, and offspring fearfulness and mental development between 14-19 months postpartum were assessed. The authors used the Ainsworth Strange Situation Paradigm to assess mother-child attachment. The Strange Situation is a well-validated measure of parent-child relationship quality in infancy (Bergman et al., 2010). Children rated as being securely attached are believed to have experienced significantly more responsive and sensitive parenting than infants with insecure

attachment patterns (van Ijzendoorn, Schuengel, & Bakermans-Kranenburg, 2006). Given the limited research in humans, the authors tested alternative hypotheses regarding the moderating role of parenting. Based on the animal research, one hypothesis was that secure attachment would act as a protective factor against the adverse outcomes of prenatal distress. Less animal research has looked at the effect of poor postnatal rearing, but the authors suggested that the association between prenatal stress and later negative child outcomes might be exacerbated by less secure attachments. While the results did not indicate that attachment moderated the relationship between antenatal stress and cognitive outcomes, attachment did moderate the relationship between prenatal stress and infant fearfulness, such that the positive relationship between antenatal stress and infant fearfulness was stronger for infants with an insecure-ambivalent attachment. In a later study with the same sample, Bergman and colleagues (2010) found a negative relationship between maternal prenatal cortisol and cognitive development at 17 months, and that this association was stronger for infants with an insecure attachment and nearly nonexistent for youth with a secure attachment.

In the only other study examining the moderating role of caregiving on child cognitive outcomes, Grant et al. (2010) looked prospectively at prenatal stress in a group of pregnant women ($N = 77$) and their 7-month old infants. Prenatal anxiety was assessed during the 3rd trimester of pregnancy by a structured interview (Mini-Plus International Neuropsychiatric Interview). Maternal sensitivity was measured using the Global Rating Scales of Mother-Infant Interaction where a researcher, blind to mothers' diagnosis, viewed and rated videos of mother-infant interactions during a still-face paradigm. The still-faced procedure included free-play, a brief period of time where mothers left the

room, a face-to-face still-face episode, and resumption of free play. Results suggested that maternal sensitivity moderated the relationship between prenatal anxiety and infant mental development, such that maternal prenatal anxiety was associated with lower infant BSID MDI scores for women who were rated as low on sensitivity. Further, this interaction between maternal prenatal anxiety and postnatal sensitivity remained significant after controlling for postnatal anxiety and depression.

More research is needed to better understand how the postnatal caregiving environment might affect the relationship between prenatal distress and child cognitive outcomes during the preschool years. Language growth occurring during the preschool years leads to an increase in the variety of parent-child interactions, such as reading books and pretend play, both of which are associated with improved cognitive abilities in preschoolers (Sohr-Preston & Scaramella, 2006). The mixed findings from the extant literature may be explained by study design (retrospective versus prospective), diverse measures of maternal stress (cortisol versus self-report of life events versus diagnosis via a structured interview), and different techniques for assessing caregiving (attachment paradigm versus observation). The current study will use a well-validated measure of parent-child interactions (The Dyadic Parent-Child Interaction Coding System, 3rd Edition) (Eyberg, Nelson, Duke, & Boggs, 2009) and explore whether parenting behaviors moderate the relationship between clinical levels of maternal prenatal distress and child neurocognitive outcomes in the preschool phase of development.

Postnatal Distress

Of note, previous studies that have examined the association between maternal prenatal distress and child outcomes have frequently statistically controlled for maternal

postnatal distress. While this method allows for the statistical isolation of prenatal distress, given the high correlation between prenatal and postnatal psychopathology (Dipietro, Costigan, & Sipsma, 2008; Pesonen, Raikkonen, Strandberg, & Jarvenpaa, 2005), controlling for postnatal distress may lead to the spurious conclusion that prenatal distress is not associated with child outcomes when psychopathology is present at both prenatal and postnatal time points. To better understand the potential contribution of prenatal distress, the current study will conduct all analyses with and without postnatal and concurrent distress.

Rationale for the Proposed Study

The proposed study will contribute to the understanding of the relationship between prenatal distress and neurocognitive outcomes during the preschool years. While past studies have investigated the effects of specific forms of prenatal maternal distress (e.g., anxiety, depression, experiencing natural disaster), no published study we are aware of has looked at a combination of different types of distress that may be associated with longer lasting childhood outcomes. The current study takes advantage of the high intercorrelations between maternal distress measures completed during pregnancy by combining multiple measures of distress completed by different raters (mother, clinician, clinical interviewer) throughout pregnancy into a latent factor, thus reducing measurement error and providing a more comprehensive, "true" representation of maternal distress experienced during gestation. In addition, many studies examining prenatal distress have used samples of high-functioning women rather than clinical samples. As it has been suggested that pregnancy is a time marked by increased risk for developing a mental disorder or reexperiencing some form of psychopathology (Levey,

Ragan, Hower-Hartley, Newport, & Stowe, 2004) it is critical to explore the relationship between clinical levels of maternal distress and child outcomes. The proposed study aims to investigate both biological and psychosocial factors that might mediate or moderate the relationship between clinical levels of maternal prenatal distress and cognitive outcomes, and that have often been overlooked in the existing literature. A better understanding of this relationship and the factors that might affect this association will aid in the design of preventative measures that could reduce the risk for adverse cognitive outcomes during the preschool years and in later childhood.

Hypotheses

The goal of the proposed study is to explore the relationship between maternal prenatal distress and offspring neurocognitive outcomes, as well as the mediating role of childhood cortisol and the moderating role of parenting in this developmental risk process. The specific aims and hypotheses of the study are:

1. Examine the relationship between maternal prenatal distress in a clinical sample and offspring neurocognitive abilities in the preschool years. Based on animal models and theories regarding the programming effects of prenatal distress on child outcomes it is hypothesized that increased maternal prenatal distress will be associated with reduced levels of child neurocognitive functioning. The current study takes advantage of multiple clinician completed and self-report measures of maternal distress collected throughout pregnancy. Child neurocognitive functioning was assessed between the ages of 2 ½ and 5 years old using standardized tests measuring general cognitive abilities and expressive language.

2. Explore the mediating role of child HPA axis functioning on the relationship between maternal prenatal distress and child neurocognitive outcomes. Based on limited human literature, it is hypothesized that children's cortisol levels in response to a stressor will mediate the relationship between prenatal distress and neurocognitive outcomes such that increased maternal prenatal distress will be associated with high levels of offspring cortisol reactivity, which in turn will be associated with worse performance on measures of general cognitive abilities and language skills during the preschool years.

3. Explore the moderating role of parenting on the relationship between prenatal distress and child neurocognitive abilities. Although no research to date has examined how parenting behaviors might moderate this relationship in preschool aged children, based on the animal literature and extant human literature, it is hypothesized that the relationship between prenatal distress and neurocognitive abilities will be weaker for youth experiencing more positive parenting and stronger for youth experiencing more negative parenting.

Method

Participants

Participants in this study were women drawn from a cohort initially recruited and assessed by the Emory Women's Mental Health Program (WMHP) in the Department of Psychiatry at the Emory University School of Medicine. The final sample was composed of 162 women (Mean age=37 years) and their children (Mean Age=44 months, 49% female; see Table 1). Participants were included in the current analyses if they had completed at least two different types of prenatal measures of distress at some point during pregnancy.

The WMHP is a referral center for the treatment of mental disorders experienced during pregnancy and the postpartum. In addition to providing services to women currently experiencing psychological distress, the WMHP also provides care to women who have experienced symptoms prior to pregnancy or are at high-risk for experiencing distress. Thus, participants in the current study experienced varying levels of distress during pregnancy.

Procedure

Women were recruited as research participants prior to or during pregnancy at the WMHP. Psychological distress was evaluated throughout pregnancy using multiple measures at different time points. At study entry, a trained interviewer met with pregnant women and assessed current and lifetime diagnostic information using the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 2002). A subsample of the clinical interviews were double-coded to ensure adequate inter-rater reliability. On average, women who participated in the preschool follow-up study visited the WMHP five times during pregnancy. At the baseline visit and subsequent prenatal follow-up visits, participants met with a psychiatrist who assigned a Clinical Global Index (CGI) (Guy, 1976) score and a research assistant who administered the 17-item Hamilton Rating Scale for Depression (HRSD 17) (Hamilton, 1960). Participants also completed self-report forms assessing levels of stress (Perceived Stress Scale; PSS) (Cohen, Kamarck, & Mermelstein, 1983) and depression (Beck Depression Inventory; BDI) (Beck, Steer, & Brown, 1997).

The mothers and their children also participated in a postnatal follow-up study when children were between the ages of 2 ½-5 years old. Children's cortisol levels and

neurocognitive functioning, parent child interaction patterns, and mothers' current diagnostic information were assessed during this follow-up as detailed below.

Measures

Maternal prenatal distress. The current study used Structural Equation Modeling (SEM) techniques to construct a latent factor of maternal distress composed of different types of distress (depression, stress, and psychiatric functioning) obtained from a variety of sources (objective, subjective, and clinician-rated), at multiple time points in pregnancy. The latent factor approach provides a more comprehensive assessment of distress experienced by mothers during pregnancy and also minimizes errors associated with single measures. Additionally, 'area under the curve' (AUC) indices for each scale collected during pregnancy were computed to attempt to capture the cumulative exposure of distress experienced throughout pregnancy. By convention, the first visit was carried back to conception and the last measure forward to delivery to provide the AUC.

Two clinician rated measures of maternal distress were used in this study—the CGI (Guy, 1976) and the HRSD 17 (Hamilton, 1960). The CGI score was assigned by a study psychiatrist and based on a clinical interview reflecting current psychiatric symptom status. The CGI provides a global rating of the severity of the participant's disorder or symptoms, and thus provides a cross diagnosis assessment of severity of the symptoms. The CGI scale ranges from 1 (not at all ill) to 7 (extremely ill). The HRSD 17 is a 17-item scale that is completed by a trained clinical researcher in the context of a semi-structured interview to assess for symptoms of depression. The interviewer provides ratings on items including overall level of depression, feelings of worthlessness, suicide, guilt, insomnia, and physical symptoms in the preceding week. Scores on this scale range

from 0-81, with higher scores indicating more severe symptoms of depression. This scale has been shown to be a reliable and valid measure of depressive symptoms (Williams, 1988).

Mothers also completed two additional self-report measures of prenatal distress—the PSS (Cohen et al., 1983) and the BDI (Beck et al., 1997). The PSS is a 14-item self-report questionnaire that measures an individual's evaluation of the stressfulness of the situations in their lives over the past month. Questions ask about thoughts and feelings about situations such as something happening unexpectedly, ability to handle personal problems, and events occurring outside of "your" control. For each question, scores range from 0 (never) to 4 (very often). The PSS has been shown to have good reliability and validity across samples (Cohen et al., 1983). The BDI is a 21-item self-report scale assessing the intensity of depressive symptoms in the previous two weeks, with higher scores revealing more severe levels of depression symptoms. The symptoms listed and the time frame addressed are consistent with the DSM-IV. The BDI has high internal consistency, good test-retest reliability, and good construct, concurrent, and discriminate validity in clinical and nonclinical samples (Beck et al., 1997; Steer, Ball, Ranieri, & Beck, 1997; Whisman, Perez, & Ramel, 2000).

Maternal prenatal substance use. Information regarding alcohol and tobacco use during pregnancy was collected prospectively during pregnancy. Study psychiatrists met with participants every 4-6 weeks during their pregnancy and asked them to report on their substance use. Marijuana use during pregnancy (coded as present or absent) was self-reported during the preschool follow-up visit.

Maternal postnatal and concurrent distress. Postnatal maternal distress was

operationalized as the proportion of the child's life that mothers had experienced mental illness. To assess postnatal distress, participants were interviewed during the preschool follow-up visit using the SCID administered by either a PhD level psychologist or a trained graduate student. The SCID assesses for lifetime history and current presence of an Axis I disorder. The interviewer asks structured questions to determine the presence or absence of symptoms of each disorder. The SCID is often considered the "gold standard" for the assessment of Axis I pathology (Shear et al., 2000). Interrater reliability for the current study was well-established with kappas for each mood disorder diagnosis ranging from .78-.90.

In addition to assessing the presence of Axis I disorders, researchers assigned an overall rating of the patient's current functioning using the Global Assessment of Functioning (GAF) scale. During the follow-up visit mothers also completed a BDI to assess depressive symptoms experienced in the preceding two weeks. The availability of these concurrent measures of maternal distress allows for exploratory analyses concerning the specificity of the prenatal distress effect.

Child neurocognitive outcomes. Children underwent standardized testing with a trained researcher blind to maternal levels of prenatal distress. Neurocognitive abilities were assessed using the Differential Ability Scales (DAS), 2nd Edition (Elliott, 1990) and the Test of Early Language Development (TELD), 2nd Edition (Hresko, Reid, & Hammill, 1999). These tests are standardized measures with appropriate age norms used commonly in neuropsychological assessment. All testing was reviewed and checked by a PhD or master's level clinician.

The DAS is a commonly used measure of cognitive abilities that provides a composite measure of overall cognitive functioning (General Conceptual Ability; GCA). Children were administered the Early Years core subtests which tap verbal, nonverbal reasoning, and spatial abilities. The DAS has high internal consistency, good test-retest reliability, and good construct, concurrent, and discriminate validity in clinical and nonclinical samples (Elliott, 1990).

The TELD expressive language subtest was administered to measure expressive language skills. To assess language abilities, children were asked to name objects and actions, imitate sentences, and answer open-ended questions. The TELD has a high degree of internal consistency, alternate form reliability, and interrater reliability, as well as high content-description validity, criterion validity, and construct validity (Hresko et al., 1999).

Cortisol reactivity. Saliva samples were used to assess levels of children's cortisol levels in response to a stressor task. Saliva is a common, noninvasive method for assessing cortisol levels (Jessop & Turner-Cobb, 2008) that has been shown to provide a reliable measure of free (unbinded) cortisol (Kirschbaum & Hellhammer, 1989) and is highly correlated with serum levels of cortisol in children (Sannikka, Terho, Suominen, & Santti, 1983). Two saliva samples were collected from the child during the laboratory session: (1) a first sample collected from the child upon arrival to the laboratory; (2) a second sample collected 10-15 minutes after a laboratory stressor task. Cortisol collection was completed by having the child chew on a piece of a dental cotton covered in .025 grams of Kool-Aid^{tm} drink mix to stimulate saliva and increase cooperation (Gunnar &

Donzella, 2002). The saliva was then transferred from the cotton roll to a plastic vial via a syringe.

In order to measure cortisol reactivity, part of the Laboratory Temperament Assessment Battery (Lab-TAB)—Preschool Version (Goldsmith, Reilly, Longley, & Prescott, 1999) was used in an effort to elicit moderate levels of frustration or distress. The LabTAB is a set of standardized laboratory tasks designed to evoke certain emotions, and is a leading observational measure of childhood temperament used commonly in studies of young children (Shankman et al., 2005; Talge, Donzella, & Gunnar, 2008). Two components of the LabTAB were used in the current study. First, in the Attractive Toy in Transparent Box paradigm, the child was told that they could play with an attractive toy that was placed in a locked transparent box after they opened the box with a set of keys. However, the child was given the wrong set of keys and left alone for two minutes to attempt the impossible task of opening the box. Second, in the Impossibly Perfect Green Circles Paradigm, the child was asked by an experimenter to repeatedly draw circles in an effort to produce a "perfect" green circle. After each attempt, the experimenter pointed out a minor flaw (e.g., too pointy, too flat) and requested the child draw another circle. Cortisol samples were collected 10-15 minutes following the frustration tasks. All saliva samples were frozen and stored at -20°C until transferred to Yerkes National Primate Research Lab at Emory University for assay.

Parenting. The Dyadic Parent-Child Interaction Coding System, 3rd Edition (DPICS) (Eyberg et al., 2009) was used to code a 20-minute interaction between the mother and child in the laboratory. The DPICS is a widely used behavioral observation system with adequate reliability and validity (Eyberg et al., 2009). Half of the parent-

child interaction consisted of unstructured play where children and their mothers were provided a variety of age-appropriate toys and instructed to "play as they would at home." Following the unstructured play, mother-child dyads participated in structured play where they were asked to clean up the toys and work on a puzzle. Trained researchers, blind to maternal distress levels and child neurocognitive abilities, coded the interaction for parenting behaviors.

Specific parenting behaviors that were coded using the DPICS coding scheme included: direct commands, indirect commands, information questions, descriptive questions, neutral talk, reflections, negative talk, unlabeled praise, behavioral descriptions, and labeled praise (see Table 2). Interrater reliability ranged from .83-.99 for variables with adequate frequency. A principal component analysis (PCA) was completed using a Promax rotation. The PCA resulted in the identification of three factors (See Table 3). Factor 1 was composed of behaviors that are considered "Positive Engagement," including indirect commands, informational questions, descriptive questions, neutral talk, and reflections. Factor 2 was composed of behaviors considered "Negative Engagement," including negative talk and direct commands. Factor 3 was composed of behaviors considered "Positive Reinforcement," including labeled praise, unlabeled praise, and behavioral descriptions.

Determining Confounds

Confounds that have been associated with childhood outcomes were tested in preliminary analyses. Because the current study uses a clinical sample of women, many of the participants took psychotropic medication during pregnancy; thus, medication exposure was explored as a potential confound. Medication variables were computed by

multiplying number of drugs by number of weeks, adjusted for gestational age. In addition, given the age range of the youth who participated in the study (2 ½-5 years), some children had begun daycare or preschool, and others had not. Attending daycare or preschool may lead to an increased opportunity to practice skills tapped by the tests used in the neuropsychological assessment. Thus, whether the child has had exposure to a daycare/school was explored as a potential confound. Potential confounds that have been associated with cortisol reactivity were also examined in preliminary analyses, including time of cortisol collection, recent medication use, and children's sleep patterns.

Results

Structural equation modeling (SEM) techniques using the AMOS 18.0 program (Arbuckle, 2008) was used to test the relationship between the latent model of prenatal distress and child neurocognitive abilities, as well as the potential mediating effect of HPA axis dysregulation and the moderating role of parenting. Fit statistics and conventions recommended by Hu and Bentler (Kline, 2011) were used in all SEM analyses. To adjust for non-normality in the data, maximum likelihood estimation was used.

Preliminary analyses. Descriptive statistics for the prenatal distress measures are presented in Table 4. Bivariate correlations among the four measures of maternal prenatal distress were examined (see Table 5). Given theoretical support described previously, as well as the high correlations among the prenatal distress measures and minimal skew, it was considered justified to combine the prenatal measures into a latent construct of distress. The two cognitive outcomes measures (DAS GCA and TELD) were

positively correlated (r=.48, p<.001), but were examined in separate SEM models to assess for potential specific effects on language outcomes.

Measurement model. Prior to the inclusion of dependent variables, AMOS was used to examine the fit of the measurement model (See Figure 1). The structural model contained adequate fit statistics (χ^2(df=2)=3.47, p=0.18, CFI=.99, RMSEA(90%CI)=.06 (.00-.18)), further supporting the use of a latent model of maternal prenatal distress in the current analyses.

Covariates. First, prenatal medication exposure was examined as a potential covariate. Psychotropic medication in the current sample included serotonin reuptake inhibitors (SRI), antiepileptic drugs, antipsychotics, anxiolytics, hypnotics, and mood stabilizers. Several demographic confounds were also explored as potential covariates including child birth weight; child age; child gender; mother age; mother BDI score at the time of the preschool study; SES during pregnancy; prenatal alcohol, tobacco, and marijuana exposure; and whether children were participating in a structured early learning (SEL) setting (e.g., daycare, preschool).

Bivariate correlations between potential covariates and prenatal distress and neurocognitive measures were completed in SPSS (see Table 6). Covariates that were significantly associated with both the predictor and dependent variable, and did not negatively impact model fit, were included in final models. Based on these criteria, prenatal anxiolytic medication exposure, SES during pregnancy, prenatal tobacco exposure, marijuana use during pregnancy, and experience in a structured early learning setting were tested in SEM models predicting to DAS GCA. Prenatal tobacco exposure was examined in all analyses predicting to the TELD. Prenatal SRI exposure was not

correlated with prenatal distress (see Table 6); however, given recent findings using the present sample indicating that prenatal SRI exposure predicts TELD scores over and above maternal prenatal depression (Johnson, Smith, Newport, Stowe, Brennan, submitted), SRI exposure was included in secondary analyses predicting to expressive language performance.

The present study aimed to elucidate the unique effect of prenatal distress on child neurocognitive development. Prenatal, postnatal, and concurrent distress measures were highly correlated (see Table 5). To isolate prenatal distress from postnatal and concurrent distress, the proportion of time that mothers had experienced mental illness since the child's birth (i.e., postnatal distress), as well as current GAF and current BDI scores (i.e., concurrent distress) were included as covariates in secondary analyses.

Cortisol reactivity. Cortisol reactivity was calculated in two ways: (1) a difference score between the first ("baseline") and second cortisol samples, and (2) the second cortisol sample ("post-stressor cortisol"). Outliers, defined as greater than three standard deviations above or below the mean, were winsorized following the method of Tukey (1997). A natural logarithm transformation was done on the baseline, post-stressor, and difference score variables following the winsorizing procedures. Potential confounds with the difference score and post-stressor cortisol variables were explored (see Table 7). Mother's report of a child having a loose tooth on the day of testing as well as stimulant medication use were identified as potential covariates and examined in relevant models. Baseline cortisol was controlled in all cortisol analyses.

Hypothesis 1. To test the first hypothesis, that increased maternal prenatal distress would be associated with reduced neurocognitive functioning, scores on both of

the neurocognitive tests were entered as dependent variables in separate models (See Table 8). The structural model predicting to the DAS GCA (see Figure 2) had adequate fit (χ^2(df=20)=23.05, p=0.29, CFI=.99, RMSEA(90%CI)=.03(.00-.08)). Results indicated that greater levels of maternal prenatal distress significantly predicted to lower scores on the DAS (β=-.17, p=.04). In addition, when postnatal distress, concurrent GAF, and concurrent BDI were entered into the model separately and simultaneously as covariates, model fit remained strong and prenatal distress continued to significantly predict to lower DAS scores (see Table 8).

The structural model predicting to the TELD (see Figure 3) also contained adequate fit (χ^2(df=8)=10.27, p=0.25, CFI=.99, RMSEA(90%CI)=.04(.00-.11)). Results indicated that greater levels of maternal prenatal distress significantly predicted to lower standard scores on the TELD (β=-.22, p=.007). Model fit remained strong and prenatal distress continued to predict to lower scores on the TELD when including SRI exposure, postnatal distress, and concurrent distress as covariates independently and simultaneously (see Table 8).

Hypothesis 2. The second hypothesis was that cortisol reactivity would mediate the relationship between maternal prenatal distress and child neurocognitive outcomes. Two mediator variables were used: (1) the difference score between the two cortisol samples, and (2) the post-stressor cortisol sample. Two variables identified in preliminary analyses (child loose tooth and stimulant medication taken on the day of testing) were examined as potential covariates in relevant models. Model fit was stronger in all models when not including these variables as covariates; thus these variable were excluded from final analyses.

To establish mediation, the independent variable must by correlated with the mediator (Rucker, Preacher, Tormala, & Petty, 2011). A path model was constructed in AMOS to test whether prenatal distress predicted to child cortisol reactivity. Models contained adequate fit (difference score: χ^2(df=14)=15.02, p=0.34, CFI=.99, RMSEA(90%CI)=.02 (.00-.08); post-stressor cortisol: χ^2(df=9)=12.75, p=0.17, CFI=.99, RMSEA(90%CI)=.05(.00-.11)) and indicated that maternal prenatal distress did not significantly predict children's cortisol reactivity (difference score: β=.10, p=.13; post-stressor cortisol: β=.08, p=.34). In addition, a mediator must be related to the outcome variable. Regression analyses indicated that cortisol reactivity did not predict to DAS GCA (difference score: β =.07, t(94)=0.58, p=.56; post-stressor cortisol: β =.03, t(94)=0.24, p=.82) or standardized scores on the TELD (difference score: β =.01, t(131)=0.06, p=.95; post-stressor cortisol: β =-.04, t(132)=-0.44, p=.66). Thus, these non-significant associations indicate that child cortisol reactivity does not mediate the relationship between maternal prenatal distress and child neurocognitive outcomes.

Hypothesis 3. The third hypothesis was that parenting behaviors would moderate the relationship between maternal prenatal distress and child neurocognitive outcomes, such that the relationship between prenatal distress and cognitive abilities would be weaker for youth experiencing more positive parenting and stronger for youth experiencing more negative parenting. Estimated factor scores for the latent prenatal distress variable were computed in AMOS and exported to SPSS. Multiple regression were used to test this hypothesis in SPSS. As described above, a PCA completed on the parenting behaviors exhibited during the parent-child interaction component of the laboratory visit identified three factors: (1) Positive Engagement, (2) Negative

Engagement, and (3) Positive Reinforcement. Independent variables (prenatal distress and each of the parenting factor scores) were centered and distress X parenting interaction terms were computed. Total amount of talking done by mothers during the play session was entered into Block 1 for all analyses. Prenatal anxiolytic medication exposure, SES during pregnancy, experience in a structured early learning setting, tobacco exposure during pregnancy, and prenatal marijuana use were controlled and entered into Block 1 for analyses examining DAS GCA. Tobacco exposure during pregnancy was entered into Block 1 for analyses predicting to the TELD. Analyses with the TELD were run with and without prenatal SRI exposure included in Block 1. The centered maternal prenatal distress and parenting factor scores were entered into Block 2. Interaction terms were entered into Block 3.

Results are presented in Tables 9 and 10. Analyses revealed a significant interaction between maternal prenatal distress and mothers' Positive Engagement (β =.19, F=4.10, p=.045) in the prediction of DAS GCA. Results remained when including postnatal and concurrent distress as control variables (see Table 9). The Aiken and West (1991) method for probing significant interactions between continuous predictors was used to further examine this interaction. Using this procedure, simple slopes of the regression are plotted at different levels of the moderating variable. There was a significant, negative association between maternal prenatal distress and child performance on the DAS when mothers engaged in less Positive Engagement, b=-.23, t(114)=-2.68, p=.009. A significant relationship was not found between prenatal distress and DAS GCA at mean levels of Positive Engagement, b=-.09, t(114)=-1.54, p=.13, or one standard deviation above the mean b=.05, t(114)=0.50, p=.62. When controlling for

postnatal and concurrent distress, maternal prenatal distress was significantly associated with lower DAS GCA scores at one standard deviation below, b=-.32, t(114)=-3.44, p=.001, and mean levels of Positive Engagement, b=-.17, t(114)=-2.59, p=.01. Again, prenatal distress did not predict to DAS GCA scores at high levels of Positive Engagement, b=-.03, t(114)=-0.32, p=.75.

Of note, a trend level interaction was observed between maternal prenatal distress and mother Positive Reinforcement in the prediction of DAS GCA (β =.15, F=2.78, p=.10), and the strength of this interaction increased when postnatal and concurrent distress were included in the model (β =.18, F=3.75, p=.056). Using the Aiken and West (1991) method, prenatal distress predicted to significantly lower DAS scores one standard deviation below the mean of Positive Reinforcement, b=-.19, t(114)=-2.43, p=.02. Prenatal distress did not predict DAS scores at the mean (b=-.10, t(114)=-1.61, p=.11) or one standard deviation above the mean (b=-.002, t(114)=-0.03, p=.98). When controlling for postnatal and concurrent distress, maternal prenatal distress significantly predicted to lower scores on the DAS at the mean (b=-.18, t(112)=-2.61, p=.01) and one standard deviation below the mean of Positive Reinforcement (b=-.29, t(112)=-3.33, p=.001), while results remained nonsignificant for high levels of Positive Reinforcement (b=-.07, t(112)=-0.74, p=.46).

Similarly, a trend level interaction was found between Positive Reinforcement in the prediction of TELD scores when controlling for prenatal SRI exposure (β =.14, F=3.08, p=.08), and the strength of this interaction increased when postnatal and concurrent distress were included in the model (β =.15, F=3.74, p=.055) (see Table 10). Probing the interaction revealed a significant, negative association between maternal

prenatal distress and child performance on the TELD at one standard deviation below the mean, b=-.19, t(153)=-2.99, p=.003, and at mean levels of Positive Reinforcement, b=-.11, t(153)=-2.56, p=.01. No relationship was found between prenatal distress and TELD scores at high levels of Positive Reinforcement (b=-.04, t(153)=-0.68, p=.50). This pattern of results remained when controlling for postnatal and concurrent maternal distress.

Discussion

The purpose of the present study was to examine the relationship between clinical levels psychological distress experienced by women during pregnancy and neurocognitive abilities of their preschool-age children. In addition, the potential mediating role of children's cortisol reactivity and the moderating role of parenting behavior was evaluated in this risk pathway. Results indicated that increased maternal prenatal distress predicted to reduced neurocognitive abilities in preschool aged children. Cortisol reactivity was not identified as a mediator. However, parenting behaviors were found to moderate this relationship such that prenatal distress was only predictive of overall cognitive abilities in the context of low or mean levels of Positive Engagement and did not predict cognitive outcomes at high levels of Positive Engagement.

Prenatal Distress and Neurocognitive Abilities

The present results are consistent with findings from studies that have previously examined the prenatal distress-child neurocognitive outcomes relationship. The majority of these studies have been conducted with infants (Bergman et al., 2007; Davidson, 1998; Davis & Sandman, 2010; Huizink et al., 2003; Lou et al., 1994; Talge et al., 2007); fewer studies have looked at outcomes beyond the toddler-years (Carter et al., 2001; DiPietro et

al., 2006; Laplante et al., 2008; O'Connor et al., 2002; Rodriguez & Bohlin, 2005). The current study extends previous findings and suggests that, indeed, prenatal psychological distress can have longer term outcomes on offspring neurocognitive functioning.

The present study adds to the literature by utilizing a novel approach in the conceptualization of prenatal distress. Nearly all of studies composing the prenatal distress literature examine a single construct of distress, such as perceptions of stressful events (Bergman et al., 2007), daily hassles (Huizink et al., 2003), natural disasters (Laplante et al., 2004), or symptoms of depression (Deave et al., 2008). Replicating these previous associations with a latent factor suggests that this method is a viable option for future studies of prenatal distress. Furthermore, given the high comorbidity among types of psychological distress (Feldman et al., 2009; Goodman & Tully, 2008; Matthey, Barnett, Howie, & Kavanagh, 2003), it may be more ecologically valid to study a general construct of distress rather than statistically isolate one form of distress from another.

To our knowledge, this is the first study to examine the relationship between prenatal psychological distress and child cognitive abilities in clinically ill women (i.e., seeking treatment for psychological disorders during pregnancy); the vast majority of studies utilize community samples of healthy pregnant women (Bergman et al., 2008; Brouwers, van Baar, & Pop, 2001; Davis & Sandman, 2010; Grant et al., 2010; King & Laplante, 2005; Tarabulsy et al., 2014). Given that pregnancy is a timeframe when women are more susceptible developing or reexperiencing symptoms of a mental illness (Levey et al., 2004), more longitudinal studies with clinical samples are warranted.

Notably, some previous studies have used maternal cortisol levels during gestation as a proxy for maternal distress (Bergman et al., 2010; Gutteling et al., 2004;

Lewinn et al., 2009). Cortisol levels across pregnancy were available for 60 of the women in the current sample. Baseline cortisol levels in these women during the second and third trimester were significantly, positively associated with the latent model of prenatal distress (data not shown). Correlating a biological indicator with the psychological measures lends support for the validity of the latent distress variable. In addition, mothers' baseline cortisol levels during the second trimester were associated with lower scores on the DAS. However, these analyses should be interpreted cautiously due to the small sample size and given that relevant covariates (e.g., caffeine intake, sleep patterns, concurrent medication use) were not available for analyses. Future studies will likely want to continue investigating the relationship between maternal prenatal cortisol levels and psychological distress to better understand how physiological and psychological changes during gestation impact child development.

HPA Axis as a Mediator

Previous literature has suggested that the mechanism by which prenatal distress may influence offspring cognitive development is via alterations of the HPA axis (Sandman, Davis, Buss, & Glynn, 2011a; Sapolsky, 2004; Vallée et al., 1999; Wadhwa, 2005). The fetal programming hypothesis has frequently been used to explain the relationship between prenatal distress and child outcomes (De Bruijn et al., 2009; Sandman, Davis, Buss, & Glynn, 2011a; Sapolsky, 2004; Talge et al., 2007; Viltart & Vanbesien-Mailliot, 2007; Wadhwa, 2005). Specifically, it has been suggested that the fetal HPA axis may be programmed by experiences occurring during gestation, leading to changes in the set point of the HPA axis after birth (De Bruijn et al., 2009; Wadhwa, 2005).

In the current study, however, children's cortisol reactivity did not mediate the relationship between prenatal distress and child neurocognitive functioning. Furthermore, in follow-up analyses not presented above, maternal prenatal distress did not predict to children's baseline cortisol, and children's baseline cortisol did not predict to either of the neurocognitive measures. Given the increasing support in the animal (Coe et al., 2003; Sandman, Davis, Buss, & Glynn, 2011a; Sapolsky, 2004; Wadhwa, 2005) and human literature (Brennan et al., 2008; De Bruijn et al., 2009; Diego et al., 2005; Gutteling et al., 2004; Huizink et al., 2008; Lundy et al., 1999; O'Connor et al., 2005) for the fetal programming of the HPA axis, the lack of association between maternal prenatal distress and child cortisol was unexpected. Results were particularly surprising in light of an earlier follow-up study examining maternal depression and infant cortisol (of which a subset of participants from the present study completed) where peripartum exposure to maternal depression and comorbid maternal anxiety was strongly associated with infant cortisol reactivity (Brennan et al., 2008).

There are several potential explanations for the lack of findings with children's cortisol reactivity. First, literature regarding the association between cortisol reactivity and cognitive abilities is limited, with only a handful of studies indicating a significant association (Blair et al., 2005; Newcomer et al., 1999; Sohr-Preston & Scaramella, 2006). Second, the stressor paradigm used in the current study may not have elicited a sufficient level of frustration to generate a cortisol response. Notably, there is evidence suggesting that early childhood may be a developmental period marked by stress hyporesponsivity, a biological adaptation to protect the developing brain (Gunnar & Quevedo, 2007). Future

studies may want to explore a diurnal measure of cortisol to better capture potential fetal programming effects on children's HPA axis functioning.

It is also possible that the measure of biological change (i.e., cortisol reactivity) used in the present study was not sensitive enough to detect alterations due to fetal prenatal distress exposure. An alternative, albeit more complex, method for assessing the programming effects of maternal distress is studying changes to offspring brain morphology. The hippocampus, for example, has been suggested as a brain structure particularly susceptible to fetal programming influences due to excess cortisol (Sapolsky, 2004; Sapolsky et al., 1990; Teicher et al., 2003). Studies in primates (Coe et al., 2003; Uno et al., 1994) and rats (Barbazanges et al., 1996) have provided evidence that exposure to excess glucocorticoids during gestation results in reduced hippocampal volume in offspring. Significantly fewer human studies have studied changes in brain morphology as a result of prenatal distress. Using a prospective, community sample of women, Buss and colleagues (2010) found that maternal prenatal anxiety was associated with reduced gray matter volume in areas associated with executive functioning (e.g., the prefrontal cortex, the medial temporal lobe, the premotor cortex, the lateral temporal cortex, postcentral gyrus, and the cerebellum). In a separate study, the researchers found that higher levels of maternal cortisol during gestation were linked to a significant increase in right amygdala volume in 7-year-old girls, and amygdala size partially mediated the association between maternal prenatal cortisol and girls' affective problems (Buss et al., 2012). If possible, future studies would benefit from employing magnetic resonance imagining and voxel-based morphometry procedures to help elucidate the

potential neural mechanisms underlying the prenatal distress-child cognitive ability relationship.

Parenting as a Moderator

Results from the present study indicated that the relationship between maternal prenatal distress and child cognitive abilities can be influenced by the postnatal environment. Specifically, results suggested that higher levels of maternal Positive Engagement protected against reduced performance on the DAS. These results are consistent with animal studies, which have found that specific postnatal experiences can ameliorate the negative effects of stress during pregnancy (Maccari et al., 1995; Vallée et al., 1999; Wakshlak & Weinstock, 1990). To date, there are two human studies that that have examined mothers' parenting behaviors as a protective factor in the prenatal psychological distress-child cognitive outcomes relationship. Results from Bergman et al. (2008) did not indicate that parent-child attachment moderated the relationship between stressful life events experienced during pregnancy and toddlers' cognitive abilities. These non-significant findings may be partially explained by the use of retrospective reporting, focusing only on stressful life events, and examining parent-child attachment as a moderator (Bergman et al., 2008). In a prospective sample of pregnant women assessed for anxiety via a structured interview, Grant and colleagues (2010) found that prenatal stress interacted with parenting, such that prenatal anxiety predicting to reduced cognitive abilities for infants whose mothers were rated as being less sensitive. The current study extends the findings from Grant et al. (2010) in several ways including using a larger sample size (162 mother-child dyads versus 77), utilizing a broader measure of parenting behaviors (i.e., DPICS versus reactions to a still-face paradigm), and assessing older

children (preschool age versus infants). In addition, Grant et al. (2010) excluded mothers with chronic psychiatric illness. Thus, the current study adds to this literature by assessing the protective role of parenting in a sample of women, many of whom experienced clinical levels of psychological distress during pregnancy.

Given the limited literature in this area, conclusions should be drawn with caution; however, results from the current study in conjunction with those from the animal literature and Grant et al. (2010) suggest that specific types of parenting behaviors may reduce the negative association observed between prenatal psychological distress and child neurocognitive outcomes (Tarabulsy et al., 2014). Notably, this finding was significant even when postnatal and concurrent distress, which have been consistently linked to reduced child cognitive abilities (Feldman et al., 2009; Grace, Evindar, & Stewart, 2003; Hay et al., 2001; Hay, Pawlby, Waters, & Sharp, 2008; Tronick & Reck, 2009), were included in relevant models.

In the current study, prenatal distress did not predict to general cognitive abilities when mother's exhibited high levels of Positive Engagement. Specifically, Positive Engagement included verbal behaviors that reflect how parents can converse with their children including asking them questions and reflecting back information provided by the child. These behaviors align with features of "maternal sensitivity," such as coordinating voice and affect with children's signals (Feldman et al., 2009; NICHD, 1999). Maternal sensitivity has been found to affect the quality of parent-child interactions (Feldman et al., 2009; Grant et al., 2010; NICHD, 1999). More sensitive mothers may talk more with their children and encourage their children to speak (NICHD, 1999), resulting in increased opportunity and exposure to language (Feldman et al., 2009; NICHD, 1999;

Sohr-Preston & Scaramella, 2006). In addition, maternal sensitivity exhibited throughout early childhood has been identified as a strong predictor of verbal comprehension, expressive language, and school readiness, during the preschool years (Murray, Hipwell, Hooper, Stein, & Cooper, 1996; NICHD, 1999). Thus, mothers who exhibit more Positive Engagement with their children may provide an environment with increased opportunities to advance children's cognitive abilities, which may help to compensate for the vulnerabilities associated with exposure to prenatal psychological distress.

Parents' Positive Engagement may also impact children's cognitive abilities via indirect pathways. For example, certain parenting practices have been linked to children's emotion regulation skills, or one's ability to express and manage emotions (P. M. Cole, Martin, & Dennis, 2004; Morris, Silk, Steinberg, Myers, & Robinson, 2007). Specifically, it has been suggested that parents can help children develop emotion regulatory abilities by engaging in "emotion-coaching" techniques, including being aware of children's emotions and responding appropriately, as well as helping children verbally label their emotions (Gottman, Katz, & Hooven, 1997; Morris et al., 2007). These behaviors are similar to the verbal behaviors composing the Positive Engagement cluster in the present study. Furthermore, emotion regulatory abilities have been linked to memory abilities (Richards & Gross, 2000) and positively associated with academic success and performance on standardized measures of cognitive skills in young children (Graziano, Reavis, Keane, & Calkins, 2007).

Given the aforementioned studies suggesting a positive relationship between sensitive parenting and language development, it is interesting that a significant interaction was not observed when predicting to scores on the TELD. It may be that skills

tapped by the TELD were too narrow: the TELD specifically measures expressive language abilities while the DAS assesses verbal, nonverbal, and spatial competencies. Environments with high levels of Positive Engagement likely provide opportunities to enhance several types of cognitive abilities (e.g., nonverbal problem solving skills), not just language skills. In addition, the verbal cluster on the DAS is composed of both expressive and receptive tasks. While receptive language skills are certainly necessary to complete the TELD, scores are generated based on expressive language abilities. Furthermore, expressive language is an emerging skill for many preschool age children; thus, a relationship might become more apparent in an older sample.

Positive Engagement was the only significant moderator identified in the current analyses; however, there was a trend for an interaction for Positive Reinforcement when predicting to the DAS and TELD. The lack of significant findings may be attributed to a restriction in range as the behaviors that composed this factor (i.e., praise and behavioral descriptions) occurred with the lowest frequency. That these behaviors occurred less often in the current sample is not surprising as depressed women are more likely to engage in negative rather than positive parenting behaviors (Lovejoy, Graczyk, O'Hare, & Neuman, 2000).

However, contrary to the proposed hypothesis, Negative Engagement (i.e., negative talk and direct commands) was not found to be a significant moderator of the prenatal distress-child cognitive ability relationship. The role of negative parenting has received less attention than the effect of positive parenting in the animal literature, and no studies yet have supported this hypothesis in humans (Bergman et al., 2007; Grant et al., 2010). Some studies have suggested that prior risk exposure may increase one's

vulnerability to subsequent stressors (Brooks-Gunn, McCormick, Klebanov, & McCarton, 1998), and extreme negative parenting, such as abuse, has been related to poor cognitive abilities in children (DePrince, Weinzierl, & Combs, 2009). However, it may be that negative verbal behavior alone has little impact on the prenatal distress-child cognitive ability relationship.

Study Limitations

The current study had several notable limitations. Perhaps the most significant limitation was sample size. The recommended sample size for SEM is 200 (Kline, 2011); thus, future studies should aim to replicate these findings with a larger sample. In addition, the latent model of distress did not contain a specific measure of anxiety. Given the previous associations observed between prenatal anxiety and child outcomes (Field et al., 2003; Grant et al., 2010; O'Connor et al., 2002; 2003; Tarabulsy et al., 2014) not including a measure of anxiety may have reduced the validity of the latent model of distress. However, overall psychiatric functioning was assessed via the CGI; thus this measure should have captured any clinical levels of anxiety experienced by women during pregnancy. The current study also did not contain a control group. Though there was significant variability in the levels of distress experienced prenatally, all women in the study had at least a history of mental illness. A control group would have allowed for parsing the effect of current or past psychological distress from no history of distress on child neurocognitive functioning.

The current study was also limited in that it was unable to separate the role of environment from genetic factors, a common problem in human studies (Rutter, 2007).

Using random traumatic events as a stressor is one method that can help control for other maternal characteristics, and the current results are consistent with studies that have used such methods (Cao et al., 2012; Laplante et al., 2004; 2008). In one of the only studies of its kind documented in the literature, Rice and colleagues (2010) used a "prenatal cross-fostering" design in which pregnant mothers were related or unrelated to their child as a result of *in vitro* fertilization, and examined the link between prenatal maternal stress, current psychological distress, and offspring outcomes. Several child behavioral outcomes were related to prenatal distress in both sets of mothers (i.e., the outcomes were observed in both women who were related and unrelated to their child), suggesting that the associations were not due to inherited factors. Unfortunately, the current study design does not allow us to test what proportion of the variance might be accounted for by genetic factors. In addition, the study would have also benefited from collecting mother's IQ. Given the heritable nature of IQ, statistically controlling for mothers' IQ would have strengthened our ability to draw conclusions about the unique effect of prenatal distress on child cognitive outcomes.

There are several methodological concerns that directly impact the measure of parenting behaviors. Parenting behaviors were coded based on verbal behavior during a parent-child interaction conducted during a laboratory follow-up visit. Mothers may have been more or less likely to engage in certain behaviors as they were aware that they were being video recorded. For example, some of the behaviors that composed the Negative Engagement factor (e.g., negative talk) did not occur frequently. The low frequency of these behaviors may be attributed to the artificial environment in which dyads interacted.

Replication of the current findings is necessary with parenting behaviors collected in more naturalistic environments.

Lastly, the majority of the current sample was composed of moderate-to-high SES families. Low SES has been consistently linked to reductions in the quality of parent-child interactions (Dodge, Pettit, & Bates, 1994; Kotchick & Forehand, 2002; McLoyd, 1998); thus, the current study may not have tapped into the true effect of negative parenting behaviors on the prenatal distress-child neurocognitive relationship. Completing these analyses with a more economically diverse sample would increase the generalizability of the findings.

Study Strengths

The limitations reviewed above are offset by several strengths of the current study. First, a novel approach was taken in the operationalizing of maternal prenatal psychological distress. The extant distress literature has almost exclusively conceptualized distress as a single disorder or set of symptoms (e.g., anxiety) while controlling for comorbid symptoms (e.g., depression). Furthermore, many of the studies use self-report measures and retrospective reporting of symptoms. These methods are limited in that they provide an incomplete picture of the "true" level of distress experienced by the mother. In addition, these methods make it difficult to generalize findings to clinical settings where comorbidity is more the rule than the exception (Feldman et al., 2009; Goodman & Tully, 2008; Matthey et al., 2003). The measure of distress utilized in the current study took advantage of self-report and clinician administered measures assessing varying forms of distress at multiple time points throughout pregnancy. In addition, instead of taking an average score, the AUC was

calculated for each measure to provide a cumulative index of each aspect of distress. These AUC measures were used to construct a latent variable of distress in SEM. Thus, this latent variable provides a good measure of the unique levels of distress experience across pregnancy by each participant.

Another strength of the current study was that data were collected prospectively. All participants in the preschool follow-up study had previously provided data during their pregnancy. Each participant had attended multiple clinic visits during pregnancy and had met with a research assistant and psychiatrist, thus allowing for detailed information regarding distress levels and any medication changes.

To our knowledge, the current study was the first to examine the relationship between prenatal distress and child cognitive abilities in a clinically ill sample. This is particularly notable because many women experience clinical levels of distress throughout their lifetime, and pregnancy is not a protective factor against mental illness. Thus, the current study adds to the prenatal distress literature by indicating that clinical levels of psychiatric illness during pregnancy can have negative effects on child cognitive outcomes.

In that same vein, however, an additional strength of the current study was its examination of mediators and moderators of this relationship. In particular, very few studies have examined the potential role of parenting behavior in this risk pathway. The current study used a detailed coding scheme to analyze observed parenting behaviors and was able to identify specific behaviors that may serve as protective factors in the relationship between prenatal distress and child cognitive outcomes.

Clinical Implications

The findings from the current study have several important clinical implications for mothers and their children. First, the results underscore the importance of early intervention. Numerous studies have shown that prenatal distress predicts to reduced cognitive outcomes in infants; the current study adds to the literature by indicating that lower cognitive abilities may also present later in childhood. Thus, physicians and professionals working with clinically ill pregnant women will likely want to explain this risk to their patients so that they can seek early intervention for their children should they have concerns regarding their cognitive abilities.

Second, the present study showed that prenatal psychological distress predicts to lower cognitive abilities in preschoolers; however, engaging positively with children appears to reduce the likelihood of children exhibiting these negative outcomes. Furthermore, positive engagement was a protective factor even in the context of postnatal and concurrent maternal distress. Thus, the current findings suggest that if mothers can engage positively with their children, even when experiencing current symptomatology, the risk to their children can be reduced.

These findings could have a significant impact on intervention implementation. Toddler-Parent Psychotherapy (TPP) is one intervention that is designed to enhance the parent-child interaction through improving the communication between the mother and her child. Cicchetti, Rogosch, and Toth (2000) randomly assigned depressed women to receive TPP when their children were toddlers (mean age=20 months). At age three, children whose mothers had received TPP exhibited cognitive abilities that did not differ from those of healthy controls. Children of depressed mothers who did not received TPP displayed lower cognitive functioning. No studies that we are aware of have targeting

prenatally distressed women. Given the current findings, it may be beneficial to implement TPP or similar parenting interventions, even earlier than the toddler years. For example, psychiatrists and obstetricians may want to recommend TPP to their pregnant patients who are experiencing psychological distress to curb the potential negative cognitive outcomes before they develop.

Future Directions

While this study adds to the growing literature examining the association between maternal prenatal distress and child neurocognitive abilities, continued research is needed to replicate and extend these findings. In particular, further examination of potential moderators and mediators is needed to better understand if and how fetal programming may be affecting this relationship. For example, as discussed above, a better understanding of the neural mechanisms underlying the relationship between maternal prenatal distress and child cognitive abilities would help to explain this risk pathway. This may be achieved by conducting voxel-based morphometry to assess the morphology of certain brain structures that may be mediating the relationship between distress and child cognitive abilities.

Examination of additional moderators would also help to elucidate the circumstances in which the vulnerability for children of women who experienced distress during pregnancy is highest. As children age, peers gain a more influential role in their social interactions. It may be fruitful to explore similar analyses examining the role of peer interaction to see how other forms of social engagement impact cognitive outcomes. In addition, gender has previously been shown to moderate associations between prenatal distress and child outcomes (Carter et al., 2001; De Bruijn et al., 2009; Rodriguez &

Bohlin, 2005). The current study did not have an adequate sample size to thoroughly explore the potential effects of gender. Future studies with adequate sample sizes should examine whether prenatal distress differentially affects cognitive abilities in girls and boys.

One of the most unique features of the current study was its latent approach to the conceptualization of psychological distress. The field of psychology has long recognized the limitations associated with categorical approaches to diagnoses, and the recent publication of the updated *Diagnostic and Statistical Manual of Mental Disorders (DSM-V)* (American Psychiatric Association, 2013) reflects this dimensional diagnostic approach. As clinicians continue to utilize a more dimensional approach, research should also reflect this shift. Future psychological research would benefit from moving away from an emphasis on diagnostic categories (e.g., prenatal depression) towards a more dimensional, construct-based approach (e.g., prenatal distress).

Conclusion

It is well established, in both the animal and human literature, that maternal psychological distress during pregnancy can negatively impact a range of outcomes in their offspring. This study expanded the current literature by examining the relationship between maternal prenatal distress and child cognitive abilities during the preschool years, a period of development that has been the focus of fewer studies. A novel approach to the conceptualization of distress was used, where multiple measures of varying types of distress were completed by mothers and clinicians; collected throughout pregnancy; and combined into a latent variable using SEM. This latent approach was used to in an attempt to capture the impact of "true" distress during pregnancy on children's neurocognitive development. Results indicated that maternal prenatal distress

significantly predicted to children's overall cognitive functioning and their expressive language abilities. These findings remained significant when controlling for postnatal and concurrent distress, suggesting that the observed neurocognitive deficits were uniquely associated with prenatal distress. Furthermore, the association between distress and general cognitive functioning was moderated by maternal Positive Engagement: distress was most strongly predictive of general cognitive functioning in the context of lower Positive Engagement and did not predict cognitive abilities when mothers engaged in high levels of Positive Engagement. Findings from the current study have clinical implications, and suggest that parenting interventions should be targeted to women experiencing high levels of prenatal distress. In addition, this study reflects a shift in the field of psychology, away from a categorical conceptualization towards a more dimensional approach to understanding psychological disorders.

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Table 1

Sample Demographic Information

Variable		*Mean (SD)*	
Child Age		44 months (10.6)	
Mother Age		37.3 years (4.8)	
		% (*N*)	% (*N*)
Race/Ethnicity		Mother	Child
	African American	8 (13)	7.4 (12)
	Asian	1.9 (3)	0
	Biracial	0.6 (1)	8.6 (14)
	Caucasian	85.8 (139)	81.5 (132)
	Hispanic	2.5 (4)	1.2 (2)
	Missing	1.2 (2)	1.2 (2)
Marital Status			
	Married/Partnered	83.3 (135)	
	Divorced	6.8 (11)	
	Separated	3.1 (5)	
	Never Married	5.6 (9)	
	Missing	1.2 (2)	
Mother's Highest Level of Education			
	High School/GED	.6 (1)	
	Part College	9.9 (16)	
	Graduated 2-Year College	7.4 (12)	
	Graduate 4-Year College	35.2 (57)	
	Part Graduate/Professional School	3.7 (6)	
	Complete Graduate/Professional School	42 (68)	
	Missing	1.2 (2)	

Table 2

Brief Definitions and Examples of Parenting Verbal Behaviors Coded via the DPICS

Behavior	Feature of Behavior	Example
Negative Talk	Expresses disapproval of child or their activities or attributes	"You are being bad." "Stop whining."
Direct Commands	Contains an order	"Pick up the paper." "Be nice."
Indirect Commands	Suggests a behavior	"How about we sit down." "Will you tell me what this word is?"
Information Questions	Requests specific information	"What did the Easter Bunny bring you?" "Where are your toes?"
Descriptive Questions	Contains descriptive or reflective comment; only requires "yes" or "no" response	"Do you want to build a tower?" "Isn't that a silly cat?"
Neutral Talk	Introduces information but does not describe or evaluate child's behavior	"You used the blue crayon last time." "I want to play with you."
Reflections	Has the same meaning of child's statement	Child: "The car goes zoom zoom." Parent: "The car goes very fast."
Unlabeled Praise	Positive evaluation of child or nonspecific behavior	"Nice job." "I love you."
Behavioral Descriptions	Non-evaluative statement describing child's behavior	"You're building a house." "You drew a cat and gave it a long tail."
Labeled Praise	Positive evaluation of a specific behavior	"You sang that song beautifully." "Your drawing is pretty."

Table 3

Factor Loadings for Principal Components Analysis with Promax Rotation of Parenting Behaviors

	Positive Engagement	Negative Engagement	Positive Reinforcement
Negative Talk		.90	
Direct Commands		.87	
Indirect Commands	.45		
Information Questions	.83		
Descriptive Questions	.84		
Neutral Talk	.73		
Reflections	.58		
Unlabeled Praise			.59
Behavioral Descriptions			.54
Labeled Praise			.90

Table 4

Means and Standard Deviations of Study Measures

Measure	*Mean (SD)*
Prenatal CGI (AUC)	73.10 (31.6)
Prenatal BDI (AUC)	418.24 (329.18)
Prenatal HRSD17 (AUC)	414.03 (183.16)
Prenatal PSS (AUC)	981.89 (351.44)
Proportion of Child's Life Mother Experienced Active Mental Illness (Postnatal Distress)	.35 (.41)
Concurrent GAF	70 (12)
Concurrent BDI	7 (8.50)
DAS GCA	105.04 (13.83)
TELD	106.81 (13.62)
Baseline Cortisol[a]	-2.24 (.81)
Post-Stressor Cortisol[a]	-2.29 (.71)
Cortisol Difference Score[a]	2.30 (.02)

Note. "AUC" stands for "Area Under the Curve." [a]Values winsorized and log transformed.