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Prenatal maternal cortisol concentrations predict neurodevelopment in middle childhood

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Abstract

Glucocorticoids (cortisol in humans) are the end product of the hypothalamic-pituitary-adrenocortical (HPA) axis and are proposed as a key mechanism for programming fetal brain development. The present prospective longitudinal study evaluates the association between prenatal maternal cortisol concentrations and child neurodevelopment. Participants included a low risk sample of 91 mother-child pairs. Prenatal maternal plasma cortisol concentrations were measured at 19 and 31 gestational weeks. Brain development and cognitive functioning were assessed when children were 6–9 years of age. Structural magnetic resonance imaging scans were acquired and cortical thickness was determined. Child cognitive functioning was evaluated using standardized measures (Wechsler Intelligence Scale for Children IV and Expressive Vocabulary Test, Second Edition). Higher maternal cortisol concentrations during the third trimester were associated with greater child cortical thickness primarily in frontal regions. No significant associations were observed between prenatal maternal cortisol concentrations and child cortical thinning. Elevated third trimester maternal cortisol additionally was associated with enhanced child cognitive performance. Findings in this normative sample of typically developing children suggest that elevated maternal cortisol during late gestation exert lasting benefits for brain development and cognitive functioning 6–9 years later. The benefits of fetal exposure to higher maternal cortisol during the third trimester for child neurodevelopment are consistent with the role cortisol plays in maturation of the human fetus. It is plausible that more extreme elevations in maternal cortisol concentrations late in gestation, as well as exposure to pharmacological levels of synthetic glucocorticoids, may have neurotoxic effects on the developing fetal brain.

Keywords

Cortisol; Glucocorticoids; Prenatal; Fetal; Brain; MRI

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1. Introduction

The human brain develops as a result of a carefully orchestrated sequence of events beginning in the embryonic period and continuing into adulthood. These developmental progressions are sculpted by early environmental influences with both salutary and detrimental effects. Since Hebb's discovery that rats reared in complex environments showed superior learning compared with standard laboratory-reared rats, substantial evidence has confirmed that early "enrichment" can exert profound and lasting benefits for the developing brain (Cymerblit-Sabba et al., 2013; Hebb, 1947). Studies of early enrichment have focused almost exclusively on the postnatal period (Greenough et al., 1987). However, the maturational changes occurring during the fetal period including neurogenesis, migration, differentiation and synaptogenesis by far outpace any other period of the lifespan (Huttenlocher, 1994; Levitt, 2003). Thus, the fetal period is the time of the lifespan that is maximally susceptible to environmental influences (Lebel et al., 2015; Stroud et al., 2014). A large body of research has evaluated the mechanisms by which postnatal enrichment benefits brain and behavioral development. The mechanisms by which in utero experiences can promote neurodevelopment remain poorly understood.

Glucocorticoids, cortisol in humans, are the end product of the hypothalamic-pituitary-adrenocortical (HPA) axis. Glucocorticoids exert a wide array of metabolic, endocrine, and immune effects and are proposed as a key mechanism for programing fetal brain development. Glucocorticoids pass through the blood–brain barrier and exert a range of effects on the developing fetal brain (Meyer, 1983; Moisiadis and Matthews, 2014) including neurogenesis, axonal and dendritic development, synaptogenesis, remodeling of axons, and myelination (Huang et al., 2001; McCabe et al., 2001; Meyer, 1983; Moisiadis and Matthews, 2014). These effects are greatest in regions that contain the highest levels of glucocorticoid receptors, such as the amygdala, hippocampus and prefrontal cortex (PFC) (McEwen et al., 2015; Moisiadis and Matthews, 2014). Although much attention has been paid to the neurotoxic effects of exposure to high levels of both synthetic and endogenous glucocorticoids (Coe and Lubach, 2005; Davis et al., 2013, 2009; Giesbrecht et al., 2016a; Khalife et al., 2013; LeWinn et al., 2009), clearly glucocorticoids play a necessary role in the promotion of normative brain development (Drake et al., 2007; Trejo et al., 2000) and the necessary role of glucocorticoids for fetal organ maturation has been widely recognized in the obstetric literature (Jobe et al., 2003; Jobe and Soll, 2004; Waffarn and Davis, 2012).

Maternal cortisol increases 3–5 fold normatively over the course of human gestation (Sandman et al., 2006), maternal cortisol crosses the placenta (Giesbrecht et al., 2016b) and maternal plasma cortisol and fetal cortisol levels are strongly correlated (Gitau et al., 1998). Exposure to maternal cortisol promotes maturation of fetal organ systems, including the fetal lungs and the central nervous system (CNS) (Drake et al., 2007; Trejo et al., 2000). Normal fetal development and maturation are dependent on an optimal increase in maternal cortisol late in gestation, which promotes both fetal development (Glynn and Sandman, 2012) and infant cognitive functioning (Davis and Sandman, 2010). Consistent with these findings in humans, experimental manipulations with rodents illustrate that exposure to moderate increases in glucocorticoids early in the postnatal period (analogous to the late prenatal period in humans in terms of brain maturity) (Avishai-Eliner et al., 2002) show persisting

improvements on cognitive tasks assessing learning and memory, as well as increased neural plasticity (Catalani et al., 2002; Scaccianoce et al., 2001; Trejo et al., 2000). Because cortisol is a signal potentially indicating environmental risk, the idea that cortisol may facilitate neural maturation and may have associated cognitive benefits is not inconsistent with evidence that even modestly elevated cortisol predicts greater sensitivity or reactivity to the environment (Davis et al., 2011; Davis and Pfaff, 2014; Davis and Sandman, 2012; Edelmann et al., 2016; O'Connor et al., 2013). The beneficial neurodevelopmental effects of exposure to elevated maternal cortisol late in gestation contrast with the negative effects of fetal exposure to excess cortisol early in gestation (Bergman et al., 2010; Buss et al., 2012; Davis and Sandman, 2010) or exposure to high concentrations of endogenous and synthetic glucocorticoids (Davis et al., 2013; Khalife et al., 2013; LeWinn et al., 2009; Uno et al., 1994). Thus, a nuanced understanding of the potential salutary and detrimental effects of maternal cortisol on fetal brain development requires consideration of both gestational timing and level of exposure.

The persisting effects of higher cortisol concentrations late in gestation on child brain development and cognitive functioning have not been examined. This prospective longitudinal study includes a population of healthy pregnant women and their typically developing children and was designed to test the hypothesis that in this normative sample elevated levels of endogenous maternal cortisol in later gestation would enhance child cortical development and cognitive functioning. Based on prior studies with infants (Davis and Sandman, 2010) and on rodent models (Catalani et al., 2002; Scaccianoce et al., 2001; Trejo et al., 2000), we predicted that in a low risk sample, in contrast to elevated maternal cortisol concentrations earlier in gestation, higher maternal cortisol concentrations late in gestation would exert global benefits on the brain and cognitive development. To test this hypothesis, we evaluated the relation between prenatal maternal cortisol assessed during mid and late gestation and child outcomes.

2. Methods

2.1. Participants

English-speaking, healthy adult pregnant women with singleton pregnancies were initially recruited by the 19th gestational week. Subjects were excluded if they had (i) tobacco, alcohol, or other drug use in pregnancy, (ii) uterine or cervical abnormalities, or (iii) presence of any conditions associated with dysregulated neuroendocrine function.

The present sample included 91 mother-child pairs assessed when children (42 girls) were 6–9 years of age (M = 7.4years). Table 1 displays descriptive information for the study sample. Mothers gave informed consent and children gave informed assent for all aspects of the protocol, which was approved by the Institutional Review Board for protection of human subjects. Every participant had a stable neonatal course (Median Apgar = 9, Range 8 to 10) and were without neonatal illness, congenital, chromosomal, or genetic anomalies. None of the children had evidence of intraventricular hemorrhage (determined by ultrasound), periventricular leukomalacia, and/or low-pressure ventriculomegaly in the newborn period. Further, all participants had normal neurological findings (determined by neuroradiological review of MRI scans), including normal ventricle size, at assessment.

2.2. Background information

2.2.1. Sociodemographic and maternal characteristics—Sociodemographic characteristics including household income and maternal education were determined by standardized maternal interview. Maternal depressive symptoms at the time of child assessment were evaluated with the Beck Depression Inventory (Beck et al., 1996). These measures serve as indicators of the quality of the postnatal environment, which also influences neurodevelopmental trajectories, and were considered as covariates in the statistical analyses. Maternal anxiety and depressive symptoms were evaluated at 19 and 31 gestational weeks using the State Anxiety Inventory (STAI) (Spielberger, 1983) and the Center for Epidemiologic Studies Depression Sale (CES-D) (Radloff, 1977).

2.2.2. Prenatal and neonatal medical characteristics—Gestational age was determined by a combination of last menstrual period and early uterine size, and was confirmed by obstetric ultrasonographic biometry before 20 weeks (O'Brien et al., 1981). An extensive structured medical interview was conducted by a research nurse at both prenatal visits to assess maternal health and pregnancy related complications. Additionally, maternal and infant medical records were reviewed to assess pregnancy complications and birth outcome. These two sources were used to derive a well-established index characterizing prenatal obstetric risk and this index was considered in covariate analyses (Hobel, 1982). Ninety-four percent of the women had one or fewer medical risks during their pregnancy. The sum of medical risk factors was calculated as an indicator of current risk conditions.

2.3. Prenatal maternal assessments

2.3.1. Prenatal maternal plasma cortisol—Plasma cortisol was included as an index of total maternal adrenal output that is strongly correlated (r = 0.62) with fetal venous blood cortisol levels (Gitau et al., 1998). Plasma cortisol has been related to fetal venous (Gitau et al., 1998) and amniotic fluid (Sarkar et al., 2007) cortisol concentrations and thus is a good indicator of fetal exposure. Approximately 35% of free cortisol is converted to cortisone during passive diffusion into saliva and thus salivary cortisol is a less direct measure of fetal exposure. For these reasons, we elected to evaluate plasma cortisol (Nicolson, 2008). Maternal blood samples were collected during the course of gestation at 19.4 ± 1.0 and 30.8 ± 0.7 gestational weeks. All maternal blood samples were collected at least one hour after the participant had eaten (time of day M = 13:34 ± 1:33). A 20-ml blood sample was drawn using antecubital venipuncture into EDTA vacutainers. All samples were centrifuged at 2000 × *g* for 15 min; plasma was then extracted and stored in polypropylene tubes at −70 °C until assayed.

Plasma cortisol levels were determined with a competitive binding, solid-phase, enzyme-linked immunosorbent assay (IBL America, Minneapolis, MN). Plasma samples (20 μl) and enzyme conjugate (200 μl) were added to the antibody-coated microtiter wells, thoroughly mixed, and incubated for 60 min at room temperature. Each well was washed three times with wash solution (400 μl per well) and struck to remove residual droplets. Substrate solution (100 μl) was added to each well and incubated for 15 min at room temperature. The absorbance units were measured at 450 nm within 10 min after the stop solution (100 μl) had

been added. The assay had less than 9% cross-reactivity with progesterone and less than 2% cross-reactivity with five other naturally occurring steroids. The inter-assay and intra-assay coefficients of variance are reported as less than 8%, and the minimum detectable level of the assay was 0.25 μg/dL. All statistical analyses were performed with cortisol concentrations that were log transformed (because cortisol data were skewed) and adjusted for time of sample collection and gestational week at assessment.

2.4. Child assessments

2.4.1. MRI acquisition—Structural MRI scans were acquired using a 3-T Philips Achieva system. To minimize head motion, padding was placed around the head. Ear protection was given to all children. To further increase compliance and reduce motion, children were fitted with headphones and allowed to watch a movie of their choice while in the scanner. Following the scanner calibration scans, a high resolution T1 anatomical scan was acquired in the sagittal plane with 1 mm^3 isotropic voxel dimensions. An Inversion-Recovery Spoiled Gradient Recalled Acquisition (IR-SPGR) sequence with the following parameters were applied: Repetition rate (TR) = 11 ms, Echo Time (TE) = 3.3 ms, Inversion Time (TI) = 1100 ms, Turbo Field Echo factor (TFE) = 192, Number of slices: 150, no SENSE acceleration, Flip angle = 18°. Acquisition time for this protocol was seven minutes.

2.4.2. Image processing—Cortical surface reconstruction was performed with the FreeSurfer image analysis software suite (http://surfer.nmr.mgh.harvard.edu/). See Muftuler et al. (2011) for preprocessing and analysis details. Procedures for the measurement of cortical thickness have been validated with histological analysis (Rosas et al., 2002) and manual measurements (Salat et al., 2004). The cortical surface images generated by the FreeSurfer software were visually inspected for errors in segmentation and corrections were made as needed.

After False Discovery Rate (FDR) corrections, the number of vertices was determined in each significant area in each region of the brain. The number of significant vertices for each area was added and divided by the total number of vertices (X 100) in that area to provide the percentage of the vertices that were significantly thicker in association with prenatal maternal cortisol. The same procedure was computed for the number of significant vertices in each lobe. For hemispheric and whole brain percentages, the procedure was the same except the total number of subcortical vertices was subtracted from the total. Data from 7 children were excluded from analyses due to motion artifact. Thus, 84 participants were included in analyses of imaging data.

Primary regions in which prenatal maternal cortisol concentrations were associated with cortical thickness were evaluated as regions of interest to determine associations with child cognitive functioning. For each region of interest, the average thickness in millimeters was extracted for each subject from the statistical cortical parcellation file created by FreeSurfer during the segmentation process. This file contains the average thickness in millimeters of the distance between the white matter and the pial surface. Parcellation is based on the Desiken/Killiany Atlas (Desikan et al., 2006).

2.4.3. Behavioral assessments—Children's *general intelligence* was assessed using the Perceptual Reasoning Index (PRI) of the Wechsler Intelligence Scale for Children (WISC-IV), a measure of non-verbal and fluid reasoning. The PRI is relatively language free and two of its subscales (Matrix Reasoning and Block Design) have been shown to be excellent indicators of general intelligence (Wechsler, 2002). Expressive language was evaluated using the Expressive Vocabulary Test, Second Edition (EVT-2) (Williams, 2007). The EVT-2 uses both labeling and synonym items to assess expressive vocabulary in children and adults ages 2.5–90+ without relying on reading or writing. The EVT-2 has been shown to have good validity, internal reliability (α= 0.94 through α = 0.97 for children ages 6–9 years), and excellent stability (r = 0.95) (Williams, 2007).

2.5. Data analysis

Preliminary analyses were performed using Pearson correlations and *t*-tests to determine whether sociodemographic (i.e., race/ethnicity, maternal marital status, maternal education, and household income), maternal (i.e., concurrent depressive symptoms) or neonatal (i.e., gestational age at birth, birth order) characteristics were associated with child behavioral measures. Only household income was significantly associated with child behavior. Higher household income was associated with better performance on the EVT and WISC (r = 0.24 and r = 0.40, $p < 0.05$). Thus household income was included as a covariate in behavioral analyses. As described above child gestational age at birth and maternal depressive symptoms were additionally included as covariates in child behavioral analyses to evaluate the specificity of prenatal influences independent of birth outcome or current maternal psychological well-being.

We tested the hypothesis that 3rd trimester elevations in maternal cortisol concentrations would be associated with cortical thickness and behavior. To test this hypothesis, first we compared the association between child cortical thickness and maternal cortisol at mid pregnancy (19 gestational weeks) with maternal cortisol late in pregnancy (31 gestational weeks). We then contrasted these two gestational periods to test whether the associations between cortisol and child neurodevelopment changed with advancing gestation. Associations between prenatal maternal cortisol and child cortical thickness were analyzed at each node on the cortical surface using the Monte Carlo method with 10,000 permutations. Spatially normalized cortical thickness maps of each subject were entered into a regression model. For imaging analyses age of the child at testing, sex, and handedness were additionally included as covariates. Associations were considered to be statistically significant at $p < 0.05$ after the False Discovery Rate (FDR) correction for multiple comparisons as recommended by Genovese and colleagues (Genovese et al., 2002). Significant findings (regions of interest) were evaluated separately for males and females to evaluate sex differences.

The relation between child behavioral outcomes and maternal cortisol at 19 and 31 gestational weeks was evaluated using partial correlations to adjust for confounding factors. In cases where cortisol was significantly related to cognitive outcomes we evaluated whether cortical thickness (identified regions of interest based on analyses described above) mediated

the relation between prenatal cortisol and cognitive functioning using the Preacher and Hayes test of indirect effects (Preacher et al., 2006, 2007).

3. Results

3.1. Maternal cortisol

As expected, maternal cortisol concentrations increased from 13.5 (SD = 5.9) υg/dl at 19 gestational weeks to 22.5 (SD = 12.9) υg/dl at 31 gestational weeks ($p < 0.001$). (Fig. 1 illustrates the distribution of log transformed cortisol data). Maternal cortisol levels at 19 and 31 gestational weeks were not significantly correlated ($r = 0.08$, $p = 0.45$). Consistent with prior published research (de Weerth and Buitelaar, 2005; Petraglia et al., 2001), prenatal maternal cortisol concentrations were not significantly associated with maternal anxiety ($r = -0.05$ to -0.02, p's > 0.60) or depressive symptoms ($r = -0.02$ to 0.14, p's > 0.30).

3.2. Prenatal maternal cortisol and child cortical thickness

Overall the cortex was 9.4% thicker in children exposed as fetuses to higher levels of maternal cortisol in late gestation (31 gestational weeks). As shown in Fig. 2 and Table 2, the positive associations between child cortical thickness and prenatal maternal cortisol were present across the whole brain, with the strongest associations in left frontal cortical regions. Elevated prenatal maternal cortisol was most strongly associated with cortical thickness bilaterally in the rostral middle frontal, lateral orbital frontal, and pars triangularis as well as in the left, superior frontal, caudal middle frontal, parsopercularis and parsorbitalis, paracentral and precentral (see Table 3). The magnitude of the association did not significantly differ for males and females. Analyses are presented separately for males and females in the supplement. Elevated maternal cortisol at 19 gestational weeks only modestly predicted child cortical thickness, predominantly in the occipital lobe. Higher maternal cortisol concentrations were not significantly associated with child cortical thinning during either mid or late gestation (see Table 2).

3.3. Prenatal maternal cortisol and child behavioral assessments

Higher maternal cortisol concentrations at 31 gestational weeks was associated with enhanced child performance on the WISC (partial $r = 0.22$, $p < 0.05$) and the EVT (partial $r = 0.24$, $p < 0.05$) after adjusting for covariates (gestational age at delivery, maternal depressive symptoms and household income). Tests of indirect effects showed that child cortical thickness did not mediate the effect of maternal cortisol concentrations in late pregnancy on child cognitive performance. Maternal cortisol at 19 gestational weeks was not significantly associated with child WISC (partial $r = 0.0$, $p = 0.99$) or EVT (partial $r = 0.05$, $p = 0.62$).

4. Discussion

We present evidence in a typically developing and low risk sample of mother-child dyads that higher maternal cortisol concentrations in late gestation are associated with greater child cortical thickness, primarily in frontal regions, and enhanced cognitive performance 6–9

years later. These findings provide support for the hypothesis that maternal cortisol influences fetal brain development with subsequent consequences for child neurodevelopment. In this low risk cohort of children, there was no evidence that the cortex was thinner in association with higher prenatal maternal cortisol concentrations in late gestation. Further, we did not observe significant sex differences in the relation between maternal cortisol and child cortical thickness.

The present study suggests that elevations in maternal cortisol later in gestation promotes maturation of the fetal brain and has beneficial effects on child neurodevelopment that persist for at least 6–9 years after birth. As expected, maternal cortisol increased significantly from 19 to 31 gestational weeks. Placental hormones, including placental CRH, play a key role in determining the magnitude of this increase. Not surprisingly given the dynamic changes in cortisol across gestation, maternal cortisol concentrations at these two time points were not significantly correlated, and only elevations at 31 gestational weeks predicted child outcomes. These findings are highly consistent with the role cortisol plays in maturation of the human fetus (Drake et al., 2007; Trejo et al., 2000). Early in gestation, maternal cortisol concentrations are relatively low and the fetus is largely protected from maternal cortisol by the placental enzyme 11β-HSD2. Later in pregnancy, when elevated cortisol is necessary for fetal maturation, fetal exposure to maternal cortisol is facilitated by a decline in 11β-HSD2 activity which allows a greater proportion of maternal cortisol to cross the placental barrier (Giannakoulpoulous et al., 1994; Murphy et al., 2006). The observed benefits of elevated maternal cortisol during the third trimester are consistent with our prior evidence linking elevated 3rd trimester maternal cortisol to fetal neurodevelopment (Glynn and Sandman, 2012) and to enhanced cognitive functioning at one year of age (Davis and Sandman, 2010) and experimental animal models showing that moderate increases in glucocorticoids facilitate brain development resulting in enhanced cognitive functioning (Casolini et al., 1997; Catalani et al., 2002; Scaccianoce et al., 2001). Our findings in a normative sample of children provide evidence that optimal physiological elevations in maternal cortisol towards the end of gestation influence maturation of the fetal nervous system leading to persisting benefits for brain development and cognitive performance. These findings highlight the importance of considering both timing and magnitude of gestational exposure because fetal exposure to elevated cortisol concentrations early in gestation or extreme levels later in gestation may have neurotoxic effects (Davis and Sandman, 2010; Davis et al., 2013; Khalife et al., 2013; LeWinn et al., 2009).

Consistent with several prior published studies (de Weerth and Buitelaar, 2005; Petraglia et al., 2001), in this low risk cohort of pregnant women, interindividual variation in cortisol concentrations could not be explained by levels of maternal anxiety and depression. It is unknown during pregnancy, a time of dramatic changes in the psychobiological stress systems, what mediators may act as sensors and transducers of maternal psychosocial state that effect offspring neurodevelopmental trajectories. Plausible candidate mediators include inflammatory processes and stress-associated alterations of placental functioning.

The present findings suggest that the trajectory of fetal brain development adapts to even relatively subtle variations in maternal signals such as cortisol. Timing of exposure, the concentration of maternal cortisol and the schedule of neurological development contribute

to the consequences for neurodevelopment. Because the human brain develops in a specific sequence during gestation it is differentially susceptible to environmental signals during sensitive or critical periods such as neurogenesis (earlier in gestation) and synaptogenesis (later in gestation). We can speculate from the published literature that the human fetus may be more vulnerable to negative effects of normal variations in maternal cortisol early in gestation (Buss et al., 2012; Davis and Sandman, 2010; Glynn and Sandman, 2012), but that exposure to high levels later in gestation also may induce neurotoxicity with detrimental long-term consequences. For instance, in contrast to the results reported here for naturally occurring levels of endogenous cortisol in a low risk sample, exposure to pharmacological concentrations of synthetic glucocorticoid treatment during the third trimester is associated with cortical thinning (Davis et al., 2013). Further, both synthetic glucocorticoids (Khalife et al., 2013) and endogenous cortisol in a high risk sample (LeWinn et al., 2009) are associated with inattention and poor cognitive performance.

Elevated third trimester concentrations of maternal cortisol were associated with greater child cortical thickness throughout the cortex. Within these global effects there is evidence for greater susceptibility of frontal, particularly prefrontal, regions to cortisol exposure that is plausibly related to the distribution of glucocorticoid receptors in the brain. Prefrontal regions including the orbital frontal, dorsolateral frontal cortex and frontal pole were thicker among children of mothers with higher cortisol concentrations during late gestation. High concentrations of glucocorticoid receptors are observed in frontal cortical regions (Mychasiuk et al., 2012). These data are consistent with the possibility that fetal exposure to normative increases in maternal cortisol concentrations later in gestation may promote brain maturation in regions that are rich in glucocorticoid receptors, such as the frontal cortex. Greater cortical thickness may reflect the density of connections between neurons, increased dendritic arbor of neurons or increased myelination of axons that lie within gray matter, each of which is related to enhancements in information processing that may benefit cognitive functioning (Jacobs et al., 2001a). Although the mechanisms remain unknown, animal models indicate that prenatal glucocorticoid exposure influences myelination (Antonow-Schlorke et al., 2009; Raschke et al., 2008) and perinatal exposure to physiologic increases in glucocorticoids stimulates the production of nerve growth factor (NGF) (Scaccianoce et al., 2001) perhaps contributing to the observed associations with cortical thickness.

The prefrontal cortex (PFC) broadly plays a critical role in a higher order cognitive functions including cognitive control/executive functions such as working memory, reasoning, problem solving, planning and inhibitory control (Miller and Cohen, 2001; Ramnani and Owen, 2004). The involvement of the PFC, especially highly affected regions such as the dorsolateral PFC (Cameron et al., 2015; Leon-Dominguez et al., 2015), in executive functions may account for the association between prenatal maternal cortisol and both verbal and non-verbal measure of cognitive ability. Tests of indirect effects indicated that cortical thickness did not underlie the observed association between prenatal maternal cortisol and child cognitive functioning. It is plausible that cortisol might influence neural systems that underlie cognitive functioning in ways that are not detected by the current behavioral tasks. Evaluation of additional behavioral functions as well as other neural measures (e.g., network connectivity) (Kim et al., 2016) in future research may elucidate the ways that cortisol influences behavior via alterations in neural development. The present findings may serve as

a guide for areas of the brain to examine more closely in future studies evaluating either connectivity or brain activation.

Although the strongest associations were observed in frontal regions, associations in additional cortical regions with prenatal maternal cortisol were also observed. The observed association between prenatal maternal cortisol and thickness in occipital and temporal regions including the fusiform gyrus and inferior temporal gyrus suggest that processes related to visual recognition, including face recognition, may be influenced by gestational cortisol exposure (Anzellotti and Caramazza, 2014).

One strength of the study is that mother-child pairs were assessed using a prospective and serial longitudinal design beginning during the fetal period. The assessment of maternal cortisol during gestation, in addition to evaluation of both child cognitive performance and brain anatomy circumvents methodological issues related to shared methods variance (i.e., mother's reporting on their own stress and on child behavior) that are prevalent in the existing literature. Because this study relied on naturally occurring variations in maternal cortisol, rather than experimental manipulations, it is not possible to separate the effects of prenatal maternal cortisol from the consequences of other factors that might contribute to this association including genetic factors or postnatal experiences. Study designs involving children conceived by in vitro fertilization who were not genetically related to their mothers, research on monozygotic twins who differ as to whether they share a placenta or not, as well as studies of synthetic glucocorticoid administration provide strong evidence that the fetal environment contributes to subsequent child development beyond effects of genetics (Davis et al., 2013; Jacobs et al., 2001b; Lewis et al., 2011; Melnick et al., 1978). Further, although aspects of the postnatal environment such as maternal depression and SES do not account for the observed association, we cannot rule out the possibility that postnatal experiences, including maternal behavior, may contribute to our finding (Glynn et al., 2016). We assessed plasma maternal cortisol because it is strongly correlated with fetal cortisol concentrations (Gitau et al., 1998). Because it is not feasible to collect repeated blood samples across the day in healthy ambulatory pregnant women, a limitation of this approach is that cortisol was evaluated at a single time point during the day. Although all analyses adjusted for time of day, studies with repeated assessments may provide a more robust index of maternal cortisol. However, despite the limitation of an assessment at one time during the day, we observed the predicted association between third trimester maternal cortisol and child brain and behavioral development. This study assessed the consequences of prenatal maternal cortisol for child brain and behavioral development in a low risk and normative sample of mothers and children. Thus, findings suggest that in normative samples higher maternal cortisol concentrations late in gestation benefit child neurodevelopment. Future research should examine higher risk samples to determine the effects of more extreme elevations in prenatal maternal cortisol concentrations.

Glucocorticoids play a central role in regulation of fetal brain development. Maternal cortisol crosses the placenta and maternal and fetal cortisol levels are strongly correlated (Gitau et al., 1998). Fetal exposure to optimal levels of maternal cortisol may benefit neurodevelopment resulting in greater cortical thickness and advanced cognitive development. The present findings are consistent with what is known about the role of

cortisol in fetal maturation. Although the majority of psychological research has focused on the negative impact of high levels of cortisol, it is well known in the medical literature that cortisol plays a central role in the promotion of normative fetal development including maturation of vital systems such as the lungs and CNS (Jobe et al., 2003; Jobe and Soll, 2004; Waffarn and Davis, 2012). The present findings in conjunction with our prior research linking higher 3rd trimester maternal cortisol to fetal maturation and infant cognitive development (Davis and Sandman, 2010; Glynn and Sandman, 2012) and experimental animal research demonstrating that perinatal exposure to increased glucocorticoids benefit neurodevelopment (Casolini et al., 1997; Catalani et al., 2002; Scaccianoce et al., 2001) are consistent with what is known about the role of cortisol in promoting fetal development and provide evidence that moderate elevations in cortisol late in gestation may be a signal that promotes neurodevelopment.

All authors have participated in the research and article preparation. EPD and CAS conceived and designed the study and acquired the data. CB, EPD, CAS, and KH analyzed the data. All authors contributed to the interpretation of the data, drafted or revised the manuscript, and have approved the final article.

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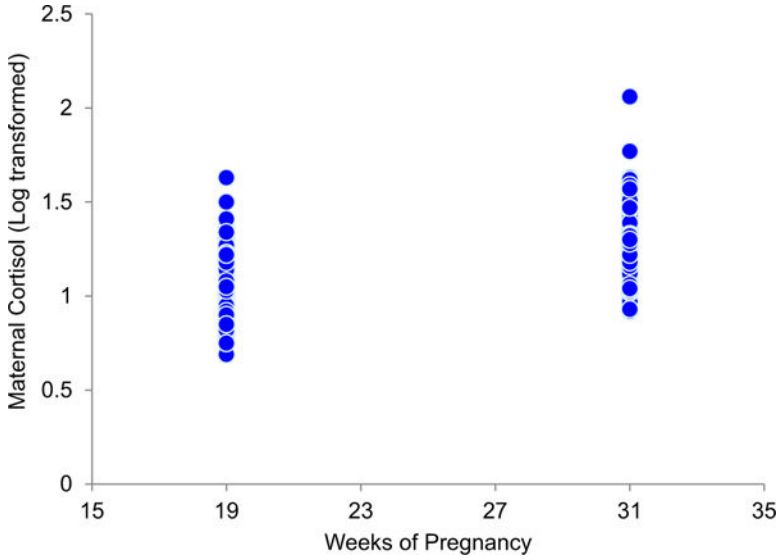

Fig. 1.

Distribution of prenatal maternal cortisol at 19 and 31 gestational weeks. Note that graph depicts log transformed cortisol data.

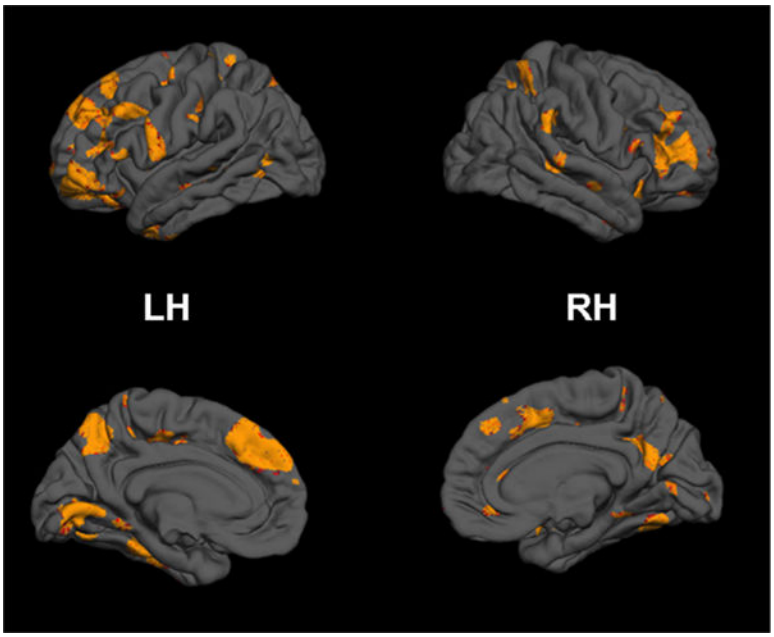

Fig. 2.

Orange overlays indicate associations between child cortical thickness and prenatal maternal cortisol at 31 gestational weeks that are significant after false discovery rate correction. LH, left hemisphere; RH, right hemisphere. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Sample characteristics.

Maternal Characteristics	
Age at Child Assessment (*M* ± SD)	37.8 ± 6.7
Cohabitating with Child's Father (%)	88
Household Income ($) (*M* ± SD)	82,000 (29,000)
Education (%)	
High School or Less	38
Associates Degree	17
Bachelors Degree	25
Graduate Degree	20
BDI[a] (*M* ± SD)	6.1 ± 6.9
Child Characteristics	
Sex (% Female)	46
Ethnicity (%)	
Non-Hispanic White	40
Hispanic	25
Asian	8
Multi-Ethnic	22
Other	5
Gestational Age at Birth (*M* ± SD)	39.1 ± 1.5
Birth Weight (g)	3487.2 ± 609.1
WISC-IV, PRI (*M* ± SD)	110.1 ± 15.4 (males = 113.4 ± 17.4 females = 107.1 ± 13.4)
EVT-2 (*M* ± SD)	107.7 ± 13.4 (males = 108.0 ± 13.4 females = 107.4 ± 13.7)

[a] *Abbreviations*: BDI, Beck Depression Inventory; WISC-IV, Wechsler Intelligence Scale for Children; EVT-2; PRI, Perceptual Reasoning Index, Expressive Vocabulary Test, Second Edition.

Table 2

Percentage of child cortical structures that are thicker (top) or thinner (bottom) based on prenatal maternal cortisol concentrations at 19 and 31 gestational weeks. The results are presented for the total region as well as the left and right hemisphere.

	19 Gestational Weeks			31 Gestational Weeks		
	Total	**LH**	**RH**	**Total**	**LH**	**RH**
Elevated Prenatal Maternal Cortisol and Child Cortical *Thickening*						
Frontal	4	5	3	14	18	9
Temporal	3	3	3	8	9	7
Parietal	2	1	3	7	6	7
Occipital	9	10	9	6	10	2
Cingulate	1	0	2	2	2	3
Elevated Prenatal Maternal Cortisol and Child Cortical *Thinning*						
Frontal	2	3	1	0	0	1
Temporal	1	1	1	0	0	0
Parietal	2	3	1	1	1	1
Occipital	0	0	0	3	3	2
Cingulate	3	2	4	2	0	2

Table 3

Elevated prenatal maternal cortisol at 31 gestational weeks is associated with child cortical thickening in the frontal lobe.

	Percent of Structure Left Hemisphere	Percent of Structure Right Hemisphere
Frontal	18	9
Medial Orbital Frontal	6	4
Lateral Orbital Frontal	16	14
Superior Frontal	23	8
Rostral Middle/Dorsolateral Prefrontal	42	28
Caudal Middle Frontal	22	0
Frontal Pole	10	0
Pars Triangularis	11	27
Parsorbitalis	45	0
Parsopercularis	37	8
Precentral	16	0
Paracentral	18	0