Published in final edited form as:

Stress. 2011 November ; 14(6): 665–676. doi:10.3109/10253890.2011.623250.

Maternal pregnancy-specific anxiety is associated with child executive function at 6–9 years age

C. BUSS¹, E. P. DAVIS^{1,2}, C. J. HOBEL³, and C. A. SANDMAN²

¹Department of Pediatrics, University of California Irvine, Orange, USA

²Department of Psychiatry and Human Behavior, University of California Irvine, Orange, USA

³Department of Obstetrics and Gynecology, Cedars Sinai Medical Center, Los Angeles, USA

Abstract

Because fetal brain development proceeds at an extremely rapid pace, early life experiences have the potential to alter the trajectory of neurodevelopment, which may increase susceptibility for developmental and neuropsychiatric disorders. There is evidence that prenatal maternal stress and anxiety, especially worries specifically related to being pregnant, influence neurodevelopmental outcomes. In the current prospective longitudinal study, we included 89 women for whom serial data were available for pregnancy-specific anxiety, state anxiety, and depression at 15, 19, 25, 31, and 37 weeks gestation. When the offspring from the target pregnancy were between 6 and 9 years of age, their executive function was assessed. High levels of mean maternal pregnancy-specific anxiety over the course of gestation were associated with lower inhibitory control in girls only and lower visuospatial working memory performance in boys and girls. Higher-state anxiety and depression also were associated with lower visuospatial working memory performance. However, neither state anxiety nor depression explained any additional variance after accounting for pregnancy-specific anxiety. The findings contribute to the literature supporting an association between pregnancy-specific anxiety and cognitive development and extend our knowledge about the persistence of this effect until middle childhood.

Keywords

Anxiety; depression; executive function; pregnancy; programming; sex differences

Introduction

The Developmental Origins of Health and Disease (Barker 1998) or Fetal Programming (Lucas 1991) hypothesis predicts that exposure to adverse conditions during critical periods of development has life-long consequences with implications for health and well-being (Gluckman and Hanson 2006). One key assumption of the programming hypothesis is that biological systems undergoing rapid developmental changes are especially vulnerable to organizing and disorganizing influences (Seckl and Meaney 2004).

© Informa Healthcare USA, Inc.

Correspondence: C. Buss, Department of Pediatrics, University of California Irvine, 333 The City Blvd. W, Suite 1200, Orange, CA 92868, USA. Tel: + 1 714 940 1924. Fax: + 1 714 940 1939. cbuss@uci.edu.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

The immature brain can be considered “under construction” (Connors et al. 2008) with the development of the human central nervous system following a protracted, neatly orchestrated chain of specific ontogenetic events including neuron proliferation, migration, differentiation, synaptogenesis, myelination, and neural pruning. Because of these rapid developmental changes during the prenatal period, early life experiences have the potential to alter the trajectory of neurodevelopment, which may increase susceptibility for developmental and neuropsychiatric disorders (Andersen 2003).

Growing evidence suggests that abnormal development of the brain during gestation contributes to a range of psychopathological conditions that are manifested throughout the entire lifespan (Rees et al. 2008). A common phenotype of these disorders is impaired cognitive function (Arnsten 2009; Douglas and Porter 2009) with impaired executive function being among the premorbid cognitive deficits preceding onset of these disorders (Kates 2010). Several classes of prenatal factors have been implicated as adversely affecting brain development including premature birth (Huppi et al. 1998; Peterson et al. 2000; Peterson et al. 2003; Beauchamp et al. 2008; Davis et al. 2011a), exposure to obstetric risk conditions such as infection (Brown et al. 2009; Sorensen et al. 2009), maternal undernutrition (Hulshoff Pol et al. 2000), and unhealthy maternal behaviors such as smoking, alcohol, or drug use (Sowell et al. 2008; Lotfipour et al. 2009; Thompson et al. 2009). Little is known about the consequences of brain development of fetal exposure to prenatal maternal psychosocial stress. We recently presented the first evidence in humans for region-specific gray matter volume reductions in 6- to 9-year-old children whose mothers reported high levels of pregnancy-specific anxiety at 19 weeks gestation (Buss et al. 2010).

A growing number of prospective studies demonstrate that prenatal psychological distress is associated with cognitive impairments during infancy (Huizink et al. 2002, 2003; Van den Bergh and Marcoen 2004), childhood (Niederhofer and Reiter 2004), and adolescence (Mennes et al. 2006; van den Bergh et al. 2006; Mennes et al. 2009). However, not all studies have demonstrated an association between maternal anxiety/stress and subsequent infant outcome (Van den Bergh 1990; Brouwers et al. 2001; DiPietro et al. 2006), and it is possible that generalized self-report measures of psychological distress do not adequately characterize stress that is unique during pregnancy. As reviewed elsewhere (Sandman et al. 2011; Wadhwa et al. 2011), evidence is emerging that measures of pregnancy-specific stress are better than the measures of generalized psychological distress for predicting developmental outcomes including preterm delivery (Wadhwa et al. 1993; DiPietro et al. 2004; Roesch et al. 2004; Kramer et al. 2009), fetal behavior (DiPietro et al. 2002), infant cognitive and motor development (Huizink et al. 2002, 2003; Buitelaar et al. 2003; DiPietro et al. 2006; Davis and Sandman 2010), infant emotional regulation (DiPietro et al. 2006; Blair et al. 2011), and child brain morphology (Buss et al. 2010).

The objective of the current research is to test in a prospective longitudinal study the associations between maternal pregnancy-specific anxiety, general state anxiety and depression, measured repeatedly over the course of gestation, and cognitive performance in their 6- to 9-year-old children. Because there is substantial evidence from animal and human studies that there are different developmental consequences resulting from a variety of prenatal environmental exposures based on the offspring's sex (Weinstock 2007; Weinberg et al. 2008; Wynne et al. 2011; Zohar and Weinstock 2011), the consequences of prenatal stress exposure in interaction with child sex were assessed.

We hypothesized that higher maternal anxiety and depression during pregnancy would be associated with poorer child cognitive performance with stronger effects for pregnancy-specific anxiety than for general anxiety or depression.

Materials and methods

Participants

This is a prospective longitudinal study of children 6–9 years of age born to women who were recruited early in gestation when pregnant for study participation between 1998 and 2002 and were assessed prospectively throughout their pregnancy. All methods and procedures were approved by the Institutional Review Board of the participating institutions and all mothers provided written informed consent and all children provided informed assent. Initial prenatal recruitment criteria were as follows: study participants were English-speaking adult women (>18 years age) with singleton, intrauterine pregnancies. Exclusion criteria were tobacco, alcohol, or other drug use in pregnancy; uterine or cervical abnormalities; or presence of any condition potentially associated with dysregulated neuroendocrine function such as endocrine, hepatic or renal disorders, or corticosteroid medication use. While not an exclusion criterion, none of the women in this sample were treated for any psychiatric disorders. Eighty-nine children, whose mothers had been recruited before 15 weeks gestation were included in the current study. Among these 89 children were two siblings; thus one mother was enrolled in the study with two subsequent pregnancies and consequently two children for the follow-up study.

Assessments in pregnant women.—For all pregnant women, gestational age (GA) was determined by best obstetric estimate with a combination of last menstrual period and early uterine size, and was confirmed by obstetric ultrasonographic biometry before 20 weeks using standard clinical criteria (O'Brien et al. 1981). Obstetric risk was defined as the presence of certain medical conditions in the index pregnancy or previous pregnancies (e.g. vaginal bleeding, pregnancy-induced hypertension, preeclampsia, infection; Hobel 1982). Risk conditions were determined through interview and extensive medical chart review. The sum of medical risk factors was calculated as an indicator of the presence of any current risk conditions. Information on birth outcomes was retrieved from medical charts after delivery. Sociodemographic characteristics and birth outcomes are summarized in Table I.

Maternal psychological state—The maternal psychosocial state was assessed over the course of gestation on average at 15 (± 1.04 , SD), 19 (± 0.7), 25 (± 0.87), 31 (± 0.7), and 37 (± 0.7) weeks gestation. Information on maternal depression was collected at all time points except 15 weeks gestation. Moreover, maternal depression was assessed at 8.2 (± 2.9 , SD) weeks postpartum (range: 5–19 weeks) and concurrently with the child's cognitive testing.

Pregnancy-specific anxiety—The 10-item pregnancy-related anxiety scale assesses a woman's pregnancy-specific fears and concerns. Answers were given on a four-point scale and included items such as: "I am fearful regarding the health of my baby," "I am concerned or worried about losing my baby," and "I am concerned or worried about developing medical problems during my pregnancy." The final score on this measure could range from 10 to 40. This reliable measure (Cronbach's $\alpha = 0.75$ – 0.85) was specifically developed for use in pregnancy research (Rini et al. 1999).

State anxiety—The 10-item state anxiety subscale of the state-trait anxiety inventory (STAI, Spielberger 1983) was used to measure momentary generalized anxiety. Responses were made using a four-point Likert scale ranging from 1 (not at all) to 4 (very much) and scores could range from a minimum of 10 to a maximum of 40. The STAI has good internal consistency with a Cronbach's α coefficient of 0.92 (Spielberger 1983).

Depression—Prenatal and postpartum maternal depression was evaluated using the short form of the Center for Epidemiological Studies Depression (CESD) Inventory (Santor and

Coyne 1997). Responses to each of the nine items were recorded on a four-point Likert scale with a range of 0–3. The final score could range from 0 to 27, with a higher score indicating greater impairment. This measure has been used extensively and published studies demonstrate both internal consistency ($\alpha = 0.84$) and validity of this measure (Santor and Coyne 1997).

Maternal concurrent depression at the time of the child's neurocognitive assessment (6–9 years) was evaluated with the Beck Depression Inventory (BDI) (Beck et al. 1996). Responses to each of the 21 items were recorded on a four-point Likert scale with a range of 0–3. The final score could span from 0 to 63, with a higher score indicating higher depression.

Maternal intelligence measures—Mothers were administered the perceptual reasoning index (PRI) of the Wechsler adult intelligence scale Fourth Edition (WAIS-IV) during the same session that the children's executive function was assessed. The subscales of this index contribute to the estimate of performance intelligence quotient (IQ). This information may be important because maternal measures of performance IQ are the best predictors of both intellectual and linguistic abilities of children (Sommer et al. 2000).

Assessments in children—All children in the study were born after 34 gestational weeks (mean $\pm$ SD: 39.2 ± 1.6 weeks, 11% born preterm, Table I), had a stable neonatal course (all Apgar scores >8), and no emotional or physical conditions were reported in a structured interview using the MacArthur Health and Behavior Questionnaire (Armstrong and Goldstein 2003) at the ages of 6–9 years (mean $\pm$ SD: 7.4 ± 0.9 years), when they underwent cognitive testing.

Cognitive assessments—Working memory and inhibitory control, representing core executive function domains, were assessed in all children.

Flanker task—The Flanker task (Eriksen and Eriksen 1974) measures inhibitory control and requires the ability to resolve conflicts when competing information is present. The participants viewed five arrows and were instructed to press a left or right response button based on the direction of the center arrow (target). They were instructed to ignore the surrounding arrows, which were either congruent or incongruent with the center arrow. This task consisted of 24 congruent trials and 24 incongruent trials. Each set of arrows was presented until the child responded (maximum of 5000 ms) with a 750-ms inter-trial interval. Before the actual task commenced, 20 practice trials were completed. These consisted of eight trials where only the middle arrow was presented and 12 trials for which all five arrows were presented in six congruent and six incongruent trials. Child-handedness was not relevant for this task because an equal number of target stimuli pointed to the left and right and therefore the right and left hands were equally engaged. Speed and accuracy were combined by dividing the mean reaction time by the correct responses. As reviewed by Mullane et al. (2008), this is the preferred way for assessing performance efficiency. We therefore calculated the average ratio (mean reaction time/number of correct responses) for congruent and incongruent trials, with a higher score indicating poorer performance. These measures of performance efficiency were not normally distributed (kurtosis >5) and were therefore logtransformed. As a measure of inhibitory control, performance on congruent and incongruent trials was compared (Rueda et al. 2004; Fan et al. 2008) by subtracting performance efficiency on incongruent trials from that on congruent trials. This measure was the outcome variable for inhibitory control that was used in all analyses with higher scores reflecting less efficient interference control. In addition, the association between prenatal predictors and reaction time as well as the type of errors (false alarms vs. missed trials) was analyzed. One child failed to complete the Flanker task.

Sequential memory test—The sequential memory test, based on the Corsi block-tapping test (Busch et al. 2005), assessed children's capacity for holding a visuospatial sequence in working memory and involves active rehearsal and controlled attention (Klingberg 2006). At the start of the task, squares on a computer monitor changed color for 1000 ms, one at a time, in a certain sequence. The child was then asked to reproduce the sequence by touching the squares in the order that they changed color. Child handedness was determined with the Edinburgh Inventory (Oldfield 1971) and children were required to use their dominant hand to reproduce the sequence.

The length of the sequence increased with accurate performance but did not increase beyond 6. The test commenced after two correctly answered practice trials (one sequence of 2 and one sequence of 3) and was terminated after two consecutive errors. Maximum sequence length was recorded as the measure of performance on this task, 6 being the highest score that could be achieved. Two children failed to complete the sequential memory task.

Statistical analyses

Confounding variables—Correlational analyses identified maternal (race/ethnicity, obstetric risk, parity, age at delivery, postpartum and concurrent depression, and WAIS PRI score) and child (GA at birth, sex, age at assessment) variables that might be associated with maternal prenatal psychological state or child cognitive performance. The following variables were associated with either maternal prenatal psychological state or child cognitive performance (all $p < 0.05$): Hispanic ethnicity, number of obstetric risk factors, postpartum (assessed at 5–19 weeks) and concurrent (assessed at the child's neurocognitive assessment) depression, maternal WAIS PRI scores, child age at assessment. Because of the shared variance between postpartum and concurrent maternal depression, only one measure of maternal depression was included as a covariate. Concurrent maternal depression was included as a covariate in all analyses because it was associated with the children's Flanker performance ($p = 0.05$), while maternal depression assessed at 8 weeks postpartum was not significantly associated with child cognitive performance.

Despite the non-significant association of length of gestation with prenatal maternal state and child cognitive outcome, all analyses were performed with and without the 10 children who were born between 34 and 37 weeks GA to rule out the possibility that the findings were determined by these preterm born children. Excluding the 10 children did not significantly change the results; therefore, all analyses are presented including these cases.

Prenatal maternal psychosocial state and child cognitive performance—First, the association between accumulative exposure of maternal prenatal anxiety and depression over the course of gestation and offspring executive function was assessed with hierarchical linear regression models. Hierarchical linear growth curve models were conducted to identify specific sensitive periods during gestation when maternal psychosocial state was significantly associated with child cognitive performance and to test whether the trajectory of change in maternal psychosocial state over the course of gestation was associated with child cognitive outcomes.

Hierarchical linear regression analyses—Hierarchical linear regression analyses were performed to assess the association between average pregnancy anxiety and depression and child executive function. Separate models tested the association between prenatal predictors and the two measures of executive function (interference control on the Flanker task and longest sequence on the sequential memory task). Relevant covariates (Hispanic ethnicity, number of obstetric risk factors, concurrent maternal depression, maternal WAIS PRI scores, child age at assessment) were entered in the first step. Maternal prenatal anxiety

measures and depression, child sex, and the interaction term between maternal psychosocial state and sex were entered in step 2 resulting in three models for each of the two cognitive outcomes, one for pregnancy-specific anxiety, one for state anxiety, and one for depression. A final model was implemented to determine which of the three measures of maternal psychosocial state was the strongest predictor of child executive function; for this purpose, pregnancy-specific anxiety, state anxiety, and depression were entered step-wise. Standardized β coefficients for each of the predictors entered in step 2 and F values for the full models are reported.

Hierarchical linear modeling—Hierarchical linear modeling (HLM) growth curve analyses (Raudenbush and Liu 2001) were performed to test whether the trajectory of change in maternal prenatal maternal psychosocial state over the course of gestation as well as levels at specific time points during gestation were associated with children's cognitive performance. Two-level models evaluated differences in maternal prenatal psychological state in association with the offspring's cognitive performance. For this purpose prenatal maternal psychological state, measured repeatedly over the course of gestation, was modeled on level 1. Quadratic modeling of prenatal maternal psychological state proved to be superior to linear modeling (all $p < 0.001$). Age-residualized scores of performance on cognitive tasks and significant time-invariant covariates (Hispanic ethnicity, number of obstetric risk factors, concurrent maternal depression, and maternal WAIS PRI scores) were included in the model on level 2. Standard coefficients (b_0) and standard errors are reported for intercept (specific time points during gestation) and overall slope differences (b_2) in maternal prenatal psychological state in association with child executive function.

Results

Maternal psychosocial state over the course of gestation

Table I shows pregnancy-specific anxiety, state anxiety, and depression scores at each pregnancy visit. With advancing GA, pregnancy-specific anxiety scores as well as state anxiety scores significantly decreased (pregnancy-specific anxiety: $F_{(3.3,208)} = 4.8$, $p < 0.001$, state anxiety: $F_{(2.6,158)} = 11.26$, $p < 0.001$). Maternal depression scores did not significantly change over the course of gestation ($F_{(2.9,183)} = 0.91$, $p = 0.44$). Spearman's ρ correlation coefficients suggested significant rank stability in pregnancy-specific anxiety, state anxiety, and depression scores over the course of gestation (pregnancy-specific anxiety: $r = 0.50$ – 0.80 , all $p < 0.001$; state anxiety: $r = 0.28$ – 0.56 , all $p < 0.05$; depression: $r = 0.59$ – 0.71 , all $p < 0.001$). Furthermore, as expected pregnancy-specific anxiety, state anxiety, and depression scores were significantly correlated (pregnancy-specific anxiety and state anxiety: $r = 0.53$, $p < 0.001$; pregnancy-specific anxiety and depression: $r = 0.45$, $p < 0.001$; state anxiety and depression: $r = 0.68$, $p < 0.001$). Neither pregnancy-specific anxiety nor state anxiety or depression scores differed based on fetal sex (all $p > 0.2$).

Maternal prenatal psychological state and child's cognitive performance

Performance on the Flanker and sequential memory tasks is summarized in Table II.

Average maternal psychosocial state and child's cognitive performance—

After statistically co-varying Hispanic ethnicity, number of obstetric risk factors, concurrent maternal depression, maternal WAIS PRI scores, and child age at assessment, higher mean pregnancy-specific anxiety was significantly associated with less efficient conflict processing on the Flanker task ($\beta = 0.40$, $p < 0.01$; $F_{(8,79)} = 3.17$, $p < 0.01$). Furthermore, child sex was significantly associated with conflict processing ($\beta = 1.13$, $p < 0.05$) and the interaction between pregnancy-specific anxiety and sex was also significant ($\beta = -1.14$, $p < 0.05$). Post hoc analyses stratified by child sex showed that pregnancy-specific anxiety

predicted conflict processing in girls ($\beta = 0.43, p < 0.01; F_{(6,42)} = .92, p < 0.05$) but not in boys ($\beta = -0.18, p = 0.33; F_{(6,32)} = 1.86, p = 0.12$, Figure 1). Follow-up analyses showed that the lower performance (assessed by the ratio of mean reaction time and number of correct responses) in girls whose mothers presented with high pregnancy-specific anxiety was a function of slower reaction times (congruent: $\beta = 0.25, p = 0.06$, incongruent: $\beta = 0.33, p = 0.01$) and was not related to a higher number of missed trials ($p > 0.2$) or a higher number of false alarms ($p > 0.10$).

Neither prenatal maternal state anxiety ($\beta = -0.023, p = 0.86$) nor prenatal maternal depression scores ($\beta = -0.05, p = 0.76$) were associated with conflict processing. The non-significant interactions between child sex and prenatal maternal state anxiety ($\beta = 0.87, p = 0.28$) and prenatal maternal depression ($\beta = 0.43, p = 0.32$) indicated that this applied to boys and girls.

Furthermore, higher average pregnancy-specific anxiety ($\beta = -0.47, p < 0.01; F_{(8,78)} = 4.4, p < 0.001$), higher maternal prenatal state anxiety ($\beta = -0.28, p < 0.05; F_{(8,78)} = 3.5, p < 0.01$), and higher maternal prenatal depression scores ($\beta = -0.42, p = 0.01; F_{(8,78)} = 3.7, p = 0.001$) were associated with lower performance on the sequential memory task. These effects were not sex-specific as indicated by the non-significant interaction between prenatal maternal psychosocial state and child sex (pregnancy-specific anxiety: $\beta = 0.59, p = 0.22$; state anxiety: $\beta = -0.27, p = 0.72$; depression: $\beta = 0.27, p = 0.51$). Higher maternal anxiety and depression scores were associated with poorer performance both in boys and girls. When mean pregnancy-specific anxiety, mean state anxiety, and mean depression scores were entered step-wise on level 2, only mean pregnancy-specific anxiety was a significant predictor of sequential memory performance ($\beta = -0.36, p = 0.001; F_{(6,80)} = 5.6, p < 0.001$, Figure 2) indicating that maternal prenatal state anxiety and depression did not contribute to the prediction of cognitive performance in this multivariate model.

Because pregnancy-specific anxiety was identified as the strongest predictor of inhibitory control and spatial working memory performance, subsequent models only included pregnancy-specific anxiety as a predictor.

Time-specific effects of pregnancy-specific anxiety on child's cognitive performance

—Because the interaction between pregnancy-specific anxiety and child sex was a significant predictor of Flanker performance but not for performance in the sequential memory task, for the Flanker task HLM analyses were performed stratified by sex and for the sequential memory task, analyses were performed for the whole group. For the results of these HLM analyses, standard coefficients and standard errors are reported for the association between pregnancy-specific anxiety and child cognitive performance.

Flanker task—In females, high pregnancy-specific anxiety at 15 weeks ($b_0 = 14.22 \pm 5.54, p = 0.01$), 19 weeks ($b_0 = 13.27 \pm 4.07, p < 0.01$), and 25 weeks gestation ($b_0 = 10.59 \pm 3.52, p < 0.01$) was associated with a higher score on the inhibitory control measure indicating less efficient conflict processing. No significant association between performance on the Flanker task and pregnancy-specific anxiety at either 31 weeks ($b_0 = 6.43 \pm 4.63, p = 0.17$) or 37 weeks ($b_0 = 1.57 \pm 9.20, p = 0.87$) gestation was observed. The trajectory of pregnancy-specific anxiety change over the course of gestation was not associated with performance on the Flanker task ($b_2 = -0.0164 \pm 0.040, p = 0.68$, Figure 3A).

In males, neither the trajectory of change in pregnancy-specific anxiety over the course of gestation ($b_2 = 0.039 \pm 0.065, p = 0.55$) nor levels of pregnancy-specific anxiety at any given time point during pregnancy (b_0 's: -0.98 to -7.4 , all $p = 0.82$ – 0.10) were associated with performance of congruent trials of the Flanker task (Figure 3B).

Sequential memory task—High levels of maternal pregnancy-specific anxiety at each time point in gestation were associated with lower performance on the sequential memory task (15 weeks: $b_0 = -2.29 \pm 0.59$, $p < 0.001$; 19 weeks: $b_0 = -1.49 \pm 0.51$, $p < 0.01$; 25 weeks: $b_0 = -0.94 \pm 0.48$, $p = 0.05$; 31 weeks: $b_0 = -1.17 \pm 0.43$, $p < 0.01$; and 37 weeks: $b_0 = -2.31 \pm 0.66$, $p = 0.001$). Furthermore, the overall rate of change of pregnancy-specific anxiety over the course of gestation was associated with performance on the sequential memory task ($b_2 = -0.01 \pm 0.005$, $p < 0.01$, Figure 4), reflecting the larger effects of high pregnancy-specific anxiety on performance on this task in early and late gestation than in mid gestation.

Discussion

During gestation, maternal anxiety or worry that is specific to pregnancy predicted impaired executive function among 6- to 9-year-old offspring. Confidence in these data is increased because associations were observed among healthy typically developing children and cannot be explained by obstetric complications or postnatal influences including maternal depression. Maternal prenatal pregnancy-specific anxiety was identified as a stronger predictor of executive function in the offspring than maternal prenatal state anxiety or depression. These results are consistent with observations that pregnancy-specific anxiety is a more sensitive predictor of the offspring's developmental outcomes than general anxiety (Wadhwa et al. 1993; DiPietro et al. 2002; Huizink et al. 2003; Roesch et al. 2004; DiPietro et al. 2006; Davis and Sandman 2010; Blair et al. 2011). This may be explained by stress related to events, beliefs, or fears proximal to pregnancy being more novel, relevant, and distressing to the pregnant woman and therefore more consequential to the fetus. However, this conclusion is based on results from step-wise regression analyses. This statistical approach has been criticized as exploratory and because model building is based solely on p values (Steyerberg et al. 2000). However, this method is appropriate as applied in the current study because it was used to test and confirm the *a priori* hypothesis that pregnancy-specific anxiety would be a stronger predictor of child cognitive performance than maternal state anxiety or depression. Confidence in this conclusion is supported by previous studies from several laboratories, including ours (Wadhwa et al. 1993; DiPietro et al. 2002; Huizink et al. 2003; Roesch et al. 2004; DiPietro et al. 2006; Davis and Sandman 2010; Blair et al. 2011), which indicate that pregnancy-specific anxiety is a significant and stronger predictor of infant and child neurodevelopmental outcomes.

Executive functions are orchestrated by activity within the prefrontal cortex (Diwadkar et al. 2000). We recently reported an association between high maternal pregnancy-specific anxiety and reduced prefrontal cortical volumes among a small subgroup of this sample (Buss et al. 2010). These findings from structural magnetic resonance imaging (MRI) are consistent with findings from studies in animals documenting effects of prenatal stress on the development of prefrontal cortical structures (Kinnunen et al. 2003; Fumagalli et al. 2004; Michelsen et al. 2007; Jutapakdeegul et al. 2010). Taken together it may be concluded that the effects of pregnancy-specific anxiety on executive function may be mediated by its effect on the prefrontal cortex.¹

The findings indicate that high pregnancy-specific anxiety was associated with lower visuospatial working memory performance in boys and girls, but inhibitory control was impaired in association with higher pregnancy-specific anxiety only in girls. The visuospatial working memory performance in girls was affected by high levels of

¹Because MRI scans were only obtained in a subgroup of the cohort included in the analyses for the current report, a lack of power prevented us from testing direct mediational effects of pregnancy-specific anxiety on executive function by affecting prefrontal cortical volumes.

pregnancy-specific anxiety at each time point assessed during gestation, while the impairment of inhibitory control with higher pregnancy-specific anxiety was only significant between 15 and 25 weeks gestation but not in later gestation. The question arises whether those brain regions distinctly underlying visuospatial working memory performance but not inhibitory control are more susceptible to prenatal adverse influences than brain regions that orchestrate inhibitory control. Besides the frontoparietal network generally involved in executive functions (Baddeley 1998; Diwadkar et al. 2000), the hippocampus is specifically involved in visuospatial working memory performance (Toepfer et al. 2011). Interestingly, the hippocampus is a brain region that is considered to be especially susceptible to adverse prenatal effects (Lemaire et al. 2000; Coe et al. 2003; Song et al. 2008; Jia et al. 2009). It is plausible that programming effects on the hippocampus account for the stronger effects of high pregnancy-specific anxiety on visuospatial working memory performance.

Furthermore, the finding that inhibitory control was impaired in female but not in male offspring that were born to mothers who experienced high pregnancy-specific anxiety may indicate sexually dimorphic vulnerability to programming influences. There is some evidence suggesting sexually dimorphic developmental consequences resulting from a variety of prenatal environmental exposures (Weinstock 2007; Weinberg et al. 2008; Wynne et al. 2011; Zohar and Weinstock 2011). It has been hypothesized that the sex-specific susceptibility to environmental insults may be due to the greater plasticity of the female placenta (Clifton 2010), or it may be related to a more rapid developmental trajectory in females (Nathanielsz et al. 2003; Buss et al. 2009). A clear understanding of the differential susceptibility of male and female fetuses to prenatal influences has not yet emerged but the current findings emphasize the importance of considering fetal sex in order to understand the prenatal influences on the developing brain.

The HLM analyses exploring sensitive periods during gestation confirmed that elevated pregnancy-specific anxiety only impaired inhibitory control in females. Furthermore, this association was significant from early until mid gestation (15–25 weeks) but not in late gestation (31–37 weeks). This pattern is consistent with the results from our MRI study (Buss et al. 2010), where we reported pronounced reductions in prefrontal cortical gray matter volume only when pregnancy-specific anxiety levels were high in early but not in late gestation. The effect of timing may also be related to the fact that different brain regions have a unique timetable for development and therefore specific periods of neural vulnerability. This possibility has been supported by observations in rhesus monkeys, where prenatal exposure to the same stressor had greater effects on postnatal motor development if it occurred earlier in gestation, when neuronal migration was at its peak, than if it occurred in mid- to late gestation, when synaptogenesis was at its peak (Schneider et al. 1999). It is important to acknowledge that the observed consequences of prenatal programming not only depend on the timing of the insult and the brain region of interest but also on the stage of assessment. Studies on postnatal brain development clearly have shown regional and temporal patterns of dynamic maturational change continuing through childhood and adolescence, with sex-specific maturational patterns (Giedd et al. 2009; Muftuler et al. 2011). This implies that what we observed and reported here in children of this age range may not be final. It is possible that at a later maturational stage, prenatal stress exposure will confer a different pattern of neurocognitive impairment, and potentially more similar effects in boys and girls. Therefore, following these children into adolescence and adulthood will provide valuable information on the persistence of prenatal stress effects on the developing brain.

The precise mechanism of how maternal psychological stress is transduced from the pregnant mother to the fetus is not known but likely involves a complex interaction between the maternal environment, placental changes, and epigenetic programming of the fetus.

Variation in concentrations of stress-sensitive hormones (placental Corticotropin-releasing hormone, cortisol) during pregnancy predicts fetal as well as infant behavioural neurodevelopmental outcomes (Sandman et al. 1999; de Weerth et al. 2003; Huizink et al. 2003; Davis et al. 2005, 2007, 2011b; Gutteling et al. 2005; Class et al. 2008; Ellman et al. 2008; Davis and Sandman 2010). Potential mechanisms by which maternal stress and associated increases in placental CRH and cortisol may produce longlasting changes in brain function have been suggested from animal models and may include epigenetic alterations (Oberlander et al. 2008), changes in neurotransmitter levels (Roceri et al. 2002; Pickering et al. 2006), adult neurogenesis (Coe et al. 2003; Fujioka et al. 2006; Lemaire et al. 2006) as well as cell growth and survival (Roceri et al. 2002; Van den Hove et al. 2006).

It cannot be ruled out that the effects of high pregnancy-specific anxiety on cognitive performance are moderated by postnatal exposures. There is evidence that the quality of parental sensitivity and parent-child bonding affect the neurodevelopmental outcomes in the offspring and moderate the impact of prenatal influences (Buss et al. 2007; Bergman et al. 2008, 2010; Grant et al. 2010). A limitation of the current study is that we did not collect data on parent-child interactions for the assessment of their quality. Importantly though, maternal depression, which has been shown to be associated with mother-child bonding (Edhborg et al. 2011), was controlled for in all analyses and it can be concluded that the detrimental effects of high levels of maternal pregnancy-specific anxiety on executive function reported here are not explained by maternal depressive symptoms.

The finding that associations between pregnancy-specific anxiety and child executive function can be observed among a group of low-risk women that did not smoke or consume alcohol and had a slightly higher than average socioeconomic status, strengthens the results of the study because such additional risk factors by themselves and in interaction with the mother's psychosocial state could affect fetal brain development. While the cohort of the current study may not be representative of the general population and the results of the current study may therefore not be generalizable, it is reasonable to assume that the results of the current study are conservative estimates of the effects of high maternal pregnancy-specific anxiety can exert on the developing brain and that with additional risk factors, the effects observed in this cohort could be potentiated.

Neuropsychiatric disorders have been associated with adverse conditions during fetal life (Watson et al. 1999; Brown and Susser 2002; Connors et al. 2008; Khashan et al. 2008). In our healthy, typically developing children, high levels of pregnancy-specific anxiety were associated with relatively impaired executive function, which is among the pre-morbid cognitive deficits preceding the onset of these disorders (Kates 2010). Therefore, high levels of maternal pregnancy-specific worries and beliefs throughout gestation may increase susceptibility for adverse neurodevelopmental and neuropsychiatric outcomes in children, especially among girls. Clinical assessments of anxiety currently do not consider pregnancy-specific anxiety. However, the current findings as well as previously published evidence for high maternal pregnancy-specific anxiety affecting neurodevelopmental outcomes (Huizink et al. 2002, 2003; Buitelaar et al. 2003; DiPietro et al. 2006; Buss et al. 2010; Davis and Sandman 2010) suggests that a focus on women's pregnancy-specific worries may be a target for early identification of risk for impaired neurodevelopment in the offspring and could guide intervention strategies.

Acknowledgments

This research was supported by National Institute of Health grants NS-41298, HD-51852 and HD28413 to CAS, MH-091351 to CB and by Miriam Jacobs Endowed Chair to CJH. We gratefully acknowledge contributions made by staff of our Research Laboratory for data collection, especially Christina Canino and Cheryl Crippen. We also thank the mothers and children who participated.

References

- Andersen SL. Trajectories of brain development: Point of vulnerability or window of opportunity? *Neurosci Biobehav Rev.* 2003; 27:3–18. [PubMed: 12732219]
- Armstrong JM, Goldstein LH. Manual for the MacArthur health and behavior questionnaire (HBQ 1.0). MacArthur Foundation Research Network on Psychopathology and Development, University of Pittsburgh. 2003
- Arnsten AF. Toward a new understanding of attention-deficit hyperactivity disorder pathophysiology: An important role for prefrontal cortex dysfunction. *CNS Drugs.* 2009; 23(Suppl 1):33–41. [PubMed: 19621976]
- Baddeley A. Recent developments in working memory. *Curr Opin Neurobiol.* 1998; 8:234–238. [PubMed: 9635207]
- Barker DJ. In utero programming of chronic disease. *Clin Sci (Lond).* 1998; 95:115–128. [PubMed: 9680492]
- Beauchamp MH, Thompson DK, Howard K, Doyle LW, Egan GF, Inder TE, Anderson PJ. Preterm infant hippocampal volumes correlate with later working memory deficits. *Brain.* 2008; 131:2986–2994. [PubMed: 18799516]
- Beck, AT.; Steer, RA.; Brown, GK. Manual for Beck depression inventory II (BDI-II). Psychology Corporation; San Antonio, TX: 1996.
- Bergman K, Sarkar P, Glover V, O'Connor TG. Quality of child–parent attachment moderates the impact of antenatal stress on child fearfulness. *J Child Psychol Psychiatry.* 2008; 49:1089–1098. [PubMed: 19017025]
- Bergman K, Sarkar P, Glover V, O'Connor TG. Maternal prenatal cortisol and infant cognitive development: Moderation by infant–mother attachment. *Biol Psychiatry.* 2010; 67:1026–1032. [PubMed: 20188350]
- Blair M, Glynn LM, Sandman CA, Davis EP. Prenatal maternal anxiety and early childhood temperament. *Stress.* 2011; 14:644–651. [PubMed: 21790468]
- Brouwers EP, Van Baar AL, Pop VJ. Maternal anxiety during pregnancy and subsequent infant development. *Infant Behav Dev.* 2001; 24:95–106.
- Brown AS, Deicken RF, Vinogradov S, Kremen WS, Poole JH, Penner JD, Kochetkova A, Kern D, Schaefer CA. Prenatal infection and cavum septum pellucidum in adult schizophrenia. *Schizophr Res.* 2009; 108:285–287. [PubMed: 19135339]
- Brown AS, Susser ES. In utero infection and adult schizophrenia. *Ment Retard Dev Disabil Res Rev.* 2002; 8:51–57. [PubMed: 11921387]
- Buitelaar JK, Huizink AC, Mulder EJ, de Medina PG, Visser GH. Prenatal stress and cognitive development and temperament in infants. *Neurobiol Aging.* 2003; 24(Suppl 1):S53–S60. discussion S67–58. [PubMed: 12829109]
- Busch RM, Farrell K, Lisdahl-Medina K, Krikorian R. Corsi block-tapping task performance as a function of path configuration. *J Clin Neuropsychol.* 2005; 27:127–134.
- Buss C, Davis EP, Class QA, Gierczak M, Pattillo C, Glynn LM, Sandman CA. Maturation of the human fetal startle response: Evidence for sex-specific maturation of the human fetus. *Early Hum Dev.* 2009; 85:633–638. [PubMed: 19726143]
- Buss C, Davis EP, Muftuler LT, Head K, Sandman CA. High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6-9-year-old children. *Psychoneuroendocrinology.* 2010; 35:141–153. [PubMed: 19674845]
- Buss C, Lord C, Wadiwalla M, Hellhammer DH, Lupien SJ, Meaney MJ, Pruessner JC. Maternal care modulates the relationship between prenatal risk and hippocampal volume in women but not in men. *J Neurosci.* 2007; 27:2592–2595. [PubMed: 17344396]
- Class QA, Buss C, Davis EP, Gierczak M, Pattillo C, Chicx-DeMet A, Sandman CA. Low levels of corticotropin-releasing hormone during early pregnancy are associated with precocious maturation of the human fetus. *Dev Neurosci.* 2008; 30:419–426. [PubMed: 19127063]
- Clifton VL. Review: Sex and the human placenta: Mediating differential strategies of fetal growth and survival. *Placenta.* 2010; 31:S33–S39. [PubMed: 20004469]

- Coe CL, Kramer M, Czeh B, Gould E, Reeves AJ, Kirschbaum C, Fuchs E. Prenatal stress diminishes neurogenesis in the dentate gyrus of juvenile rhesus monkeys. *Biol Psychiatry*. 2003; 54:1025–1034. [PubMed: 14625144]
- Connors SL, Levitt P, Matthews SG, Slotkin TA, Johnston MV, Kinney HC, Johnson WG, Dailey RM, Zimmerman AW. Fetal mechanisms in neurodevelopmental disorders. *Pediatr Neurol*. 2008; 38:163–176. [PubMed: 18279750]
- Davis EP, Buss C, Muftuler LT, Head K, Hasso A, Wing DA. Children's brain development benefits from longer gestation. *Front Psychol*. 2011a; 2:1–7. [PubMed: 21713130]
- Davis EP, Glynn LM, Dunkel Schetter C, Hobel C, Chicx-Demet A, Sandman CA. Corticotropin-releasing hormone during pregnancy is associated with infant temperament. *Dev Neurosci*. 2005; 27:299–305. [PubMed: 16137987]
- Davis EP, Glynn LM, Schetter CD, Hobel C, Chicx-Demet A, Sandman CA. Prenatal exposure to maternal depression and cortisol influences infant temperament. *J Am Acad Child Adolesc Psychiatry*. 2007; 46:737–746. [PubMed: 17513986]
- Davis EP, Glynn LM, Waffarn F, Sandman CA. Prenatal maternal stress programs infant stress regulation. *J Child Psychol Psychiatry*. 2011b; 52:119–129. [PubMed: 20854366]
- Davis EP, Sandman CA. The timing of prenatal exposure to maternal cortisol and psychosocial stress is associated with human infant cognitive development. *Child Dev*. 2010; 81:131–148. [PubMed: 20331658]
- de Weerth C, van Hees Y, Buitelaar JK. Prenatal maternal cortisol levels and infant behavior during the first 5 months. *Early Hum Dev*. 2003; 74:139–151. [PubMed: 14580753]
- DiPietro JA, Ghera MM, Costigan K, Hawkins M. Measuring the ups and downs of pregnancy stress. *J Psychosom Obstet Gynaecol*. 2004; 25:189–201. [PubMed: 15715018]
- DiPietro JA, Hilton SC, Hawkins M, Costigan KA, Pressman EK. Maternal stress and affect influence fetal neurobehavioral development. *Dev Psychol*. 2002; 38:659–668. [PubMed: 12220045]
- DiPietro JA, Novak MF, Costigan KA, Atella LD, Reusing SP. Maternal psychological distress during pregnancy in relation to child development at age two. *Child Dev*. 2006; 77:573–587. [PubMed: 16686789]
- Diwadkar VA, Carpenter PA, Just MA. Collaborative activity between parietal and dorso-lateral prefrontal cortex in dynamic spatial working memory revealed by fMRI. *Neuroimage*. 2000; 12:85–99. [PubMed: 10875905]
- Douglas KM, Porter RJ. Longitudinal assessment of neuropsychological function in major depression. *Aust N Z J Psychiatry*. 2009; 43:1105–1117. [PubMed: 20001409]
- Edhborg M, Nasreen HE, Kabir ZN. Impact of postpartum depressive and anxiety symptoms on mothers' emotional tie to their infants 2–3 months postpartum: A population-based study from rural Bangladesh. *Arch Womens Ment Health*. 2011; 14:307–316. [PubMed: 21626173]
- Ellman LM, Schetter CD, Hobel CJ, Chicx-Demet A, Glynn LM, Sandman CA. Timing of fetal exposure to stress hormones: Effects on newborn physical and neuromuscular maturation. *Dev Psychobiol*. 2008; 50:232–241. [PubMed: 18335490]
- Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perceptual Psychol*. 1974; 16:143–149.
- Fan J, Hof PR, Guise KG, Fossella JA, Posner MI. The functional integration of the anterior cingulate cortex during conflict processing. *Cereb Cortex*. 2008; 18:796–805. [PubMed: 17652463]
- Fujioka A, Fujioka T, Ishida Y, Maekawa T, Nakamura S. Differential effects of prenatal stress on the morphological maturation of hippocampal neurons. *Neuroscience*. 2006; 141:907–915. [PubMed: 16797130]
- Fumagalli F, Bedogni F, Perez J, Racagni G, Riva MA. Corticostriatal brain-derived neurotrophic factor dysregulation in adult rats following prenatal stress. *Eur J Neurosci*. 2004; 20:1348–1354. [PubMed: 15341606]
- Giedd JN, Lalonde FM, Celano MJ, White SL, Wallace GL, Lee NR, Lenroot RK. Anatomical brain magnetic resonance imaging of typically developing children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 2009; 48:465–470. [PubMed: 19395901]
- Gluckman PD, Hanson MA. The consequences of being born small—an adaptive perspective. *Horm Res*. 2006; 65(Suppl 3):5–14. [PubMed: 16612108]

- Grant KA, McMahon C, Reilly N, Austin MP. Maternal sensitivity moderates the impact of prenatal anxiety disorder on infant responses to the still-face procedure. *Infant Behav Dev.* 2010; 33:453–462. [PubMed: 20554325]
- Gutteling BM, de Weerth C, Buitelaar JK. Prenatal stress and children's cortisol reaction to the first day of school. *Psychoneuroendocrinology.* 2005; 30:541–549. [PubMed: 15808923]
- Hobel, CJ. Identification of the patient at risk. In: Schwartz, RH.; Schneider, J., editors. *Perinatal medicine: Management of the high risk fetus and neonate.* Williams & Wilkins; Baltimore: 1982.
- Huizink AC, de Medina PG, Mulder EJ, Visser GH, Buitelaar JK. Psychological measures of prenatal stress as predictors of infant temperament. *J Am Acad Child Adolesc Psychiatry.* 2002; 41:1078–1085. [PubMed: 12218429]
- Huizink AC, Robles de Medina PG, Mulder EJ, Visser GH, Buitelaar JK. Stress during pregnancy is associated with developmental outcome in infancy. *J Child Psychol Psychiatry.* 2003; 44:810–818. [PubMed: 12959490]
- Hulshoff Pol HE, Hoek HW, Susser E, Brown AS, Dingemans A, Schnack HG, van Haren NE, Pereira Ramos LM, Gispén-de Wied CC, Kahn RS. Prenatal exposure to famine and brain morphology in schizophrenia. *Am J Psychiatry.* 2000; 157:1170–1172. [PubMed: 10873931]
- Huppi PS, Warfield S, Kikinis R, Barnes PD, Zientara GP, Jolesz FA, Tsuji MK, Volpe JJ. Quantitative magnetic resonance imaging of brain development in premature and mature newborns. *Ann Neurol.* 1998; 43:224–235. [PubMed: 9485064]
- Jia N, Yang K, Sun Q, Cai Q, Li H, Cheng D, Fan X, Zhu Z. Prenatal stress causes dendritic atrophy of pyramidal neurons in hippocampal CA3 region by glutamate in offspring rats. *Dev Neurobiol.* 2009; 70:114–125. [PubMed: 19950194]
- Jutapakdeegul N, Afadl S, Polaboon N, Phansuwan-Pujito P, Govitrapong P. Repeated restraint stress and corticosterone injections during late pregnancy alter GAP-43 expression in the hippocampus and prefrontal cortex of rat pups. *Int J Dev Neurosci.* 2010; 28:83–90. [PubMed: 19782125]
- Kates WR. Investigating the cognitive antecedents of schizophrenia. *Am J Psychiatry.* 2010; 167:122–124. [PubMed: 20123918]
- Khashan AS, Abel KM, McNamee R, Pedersen MG, Webb RT, Baker PN, Kenny LC, Mortensen PB. Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. *Arch Gen Psychiatry.* 2008; 65:146–152. [PubMed: 18250252]
- Kinnunen AK, Koenig JJ, Bilbe G. Repeated variable prenatal stress alters pre- and postsynaptic gene expression in the rat frontal pole. *J Neurochem.* 2003; 86:736–748. [PubMed: 12859686]
- Klingberg T. Development of a superior frontal-intraparietal network for visuo-spatial working memory. *Neuropsychologia.* 2006; 44:2171–2177. [PubMed: 16405923]
- Kramer MS, Lydon J, Seguin L, Goulet L, Kahn SR, McNamara H, Genest J, Dassa C, Chen MF, Sharma S, Meaney MJ, Thomson S, Van Uum S, Koren G, Dahhou M, Lamoureux J, Platt RW. Stress pathways to spontaneous preterm birth: The role of stressors, psychological distress, and stress hormones. *Am J Epidemiol.* 2009; 169:1319–1326. [PubMed: 19363098]
- Lemaire V, Koehl M, Le Moal M, Abrous DN. Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. *Proc Natl Acad Sci USA.* 2000; 97:11032–11037. [PubMed: 11005874]
- Lemaire V, Lamarque S, Moal ML, Piazza PV, Abrous DN. Postnatal stimulation of the pups counteracts prenatal stress-induced deficits in hippocampal neurogenesis. *Biol Psychiatry.* 2006; 59:786–792. [PubMed: 16460692]
- Lotfipour S, Ferguson E, Leonard G, Perron M, Pike B, Richer L, Seguin JR, Toro R, Veillette S, Pausova Z, Paus T. Orbitofrontal cortex and drug use during adolescence: Role of prenatal exposure to maternal smoking and BDNF genotype. *Arch Gen Psychiatry.* 2009; 66:1244–1252. [PubMed: 19884612]
- Lucas A. Programming by early nutrition in man. *Ciba Found Symp.* 1991; 156:38–50. discussion 50–35. [PubMed: 1855415]
- Mennes M, Stiers P, Lagae L, Van den Bergh B. Long-term cognitive sequelae of antenatal maternal anxiety: Involvement of the orbitofrontal cortex. *Neurosci Biobehav Rev.* 2006; 30:1078–1086. [PubMed: 16780948]

- Mennes M, Van den Bergh B, Lagae L, Stiers P. Developmental brain alterations in 17 year old boys are related to antenatal maternal anxiety. *Clin Neurophysiol.* 2009; 120:1116–1122. [PubMed: 19433367]
- Michelsen KA, van den Hove DL, Schmitz C, Segers O, Prickaerts J, Steinbusch HW. Prenatal stress and subsequent exposure to chronic mild stress influence dendritic spine density and morphology in the rat medial prefrontal cortex. *BMC Neurosci.* 2007; 8:107. [PubMed: 18093285]
- Muftuler LT, Davis EP, Buss C, Head K, Hasso AN, Sandman CA. Cortical and subcortical changes in typically developing preadolescent children. *Brain Res.* 2011; 1399:15–24. [PubMed: 21640983]
- Mullane JC, Corkum PV, Klein RM, McLaughlin E. Interference control in children with and without ADHD: A systematic review of Flanker and Simon task performance. *Child Neuropsychol.* 2008; 15:321–342. [PubMed: 18850349]
- Nathanielsz PW, Berghorn KA, Derks JB, Giussani DA, Docherty C, Unno N, Davenport A, Kutzlers M, Koenen S, Visser GH, Nijland MJ. Life before birth: Effects of cortisol on future cardiovascular and metabolic function. *Acta Paediatr.* 2003; 92:766–772. [PubMed: 12894758]
- Niederhofer H, Reiter A. Prenatal maternal stress, prenatal fetal movements and perinatal temperament factors influence behavior and school marks at the age of 6 years. *Fetal Diagn Ther.* 2004; 19:160–162. [PubMed: 14764962]
- O'Brien GD, Queenan JT, Campbell S. Assessment of gestational age in the second trimester by real-time ultrasound measurement of the femur length. *Am J Obstet Gynecol.* 1981; 139:540–545. [PubMed: 7193418]
- Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics.* 2008; 3:97–106. [PubMed: 18536531]
- Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia.* 1971; 9:97–113. [PubMed: 5146491]
- Peterson BS, Anderson AW, Ehrenkranz R, Staib LH, Tageldin M, Colson E, Gore JC, Duncan CC, Makuch R, Ment LR. Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. *Pediatrics.* 2003; 111:939–948. [PubMed: 12728069]
- Peterson BS, Vohr B, Staib LH, Cannistraci CJ, Dolberg A, Schneider KC, Katz KH, Westerveld M, Sparrow S, Anderson AW, Duncan CC, Makuch RW, Gore JC, Ment LR. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. *JAMA.* 2000; 284:1939–1947. [PubMed: 11035890]
- Pickering C, Gustafsson L, Cebere A, Nylander I, Liljequist S. Repeated maternal separation of male Wistar rats alters glutamate receptor expression in the hippocampus but not the prefrontal cortex. *Brain Res.* 2006; 1099:101–108. [PubMed: 16784730]
- Raudenbush SW, Liu X. Effect of study duration, frequency of observation, and sample size on power in studies of group differences in polynomial change. *Psychol Methods.* 2001; 6:387–401. [PubMed: 11778679]
- Rees S, Harding R, Walker D. An adverse intrauterine environment: Implications for injury and altered development of the brain. *Int J Dev Neurosci.* 2008; 26:3–11. [PubMed: 17981423]
- Rini CK, Dunkel-Schetter C, Wadhwa PD, Sandman CA. Psychological adaptation and birth outcomes: The role of personal resources, stress, and sociocultural context in pregnancy. *Health Psychol.* 1999; 18:333–345. [PubMed: 10431934]
- Roceri M, Hendriks W, Racagni G, Ellenbroek BA, Riva MA. Early maternal deprivation reduces the expression of BDNF and NMDA receptor subunits in rat hippocampus. *Mol Psychiatry.* 2002; 7:609–616. [PubMed: 12140784]
- Roesch SC, Dunkel-Schetter C, Woo G, Hobel C. Modeling the types and timing of stress in pregnancy. *Anxiety, Stress Coping.* 2004; 17:87–102.
- Rueda MR, Fan J, McCandliss BD, Halparin JD, Gruber DB, Lercari LP, Posner MI. Development of attentional networks in childhood. *Neuropsychologia.* 2004; 42:1029–1040. [PubMed: 15093142]
- Sandman CA, Davis EP, Buss C, Glynn LM. Exposure to prenatal psychobiological stress exerts programming influences on the mother and her fetus. *Neuroendocrinology.* 2011 Epub ahead of print.

- Sandman CA, Wadhwa PD, Chicz-DeMet A, Porto M, Garite TJ. Maternal corticotropin-releasing hormone and habituation in the human fetus. *Dev Psychobiol.* 1999; 34:163–173. [PubMed: 10204092]
- Santor DA, Coyne JC. Shortening the CES-D to improve its ability to detect cases of depression. *Psychol Assess.* 1997; 9:233–243.
- Schneider ML, Roughton EC, Koehler AJ, Lubach GR. Growth and development following prenatal stress exposure in primates: An examination of ontogenetic vulnerability. *Child Dev.* 1999; 70:263–274. [PubMed: 10218255]
- Seckl JR, Meaney MJ. Glucocorticoid programming. *Ann N Y Acad Sci.* 2004; 1032:63–84. [PubMed: 15677396]
- Sommer KS, Whitman TL, Borkowski JG, Gondoli DM, Burke J, Maxwell SE, Weed K. Prenatal maternal predictors of cognitive and emotional delays in children of adolescent mothers. *Adolescence.* 2000; 35:87–112. [PubMed: 10841299]
- Song L, Zheng J, Li H, Jia N, Cai Q, Bai Z, Cheng D, Zhu Z. Prenatal stress causes oxidative damage to mitochondrial DNA in hippocampus of offspring rats. *Neurochem Res.* 2008; 34:739–745. [PubMed: 18802752]
- Sorensen HJ, Mortensen EL, Reinisch JM, Mednick SA. Association between prenatal exposure to bacterial infection and risk of schizophrenia. *Schizophr Bull.* 2009; 35:631–637. [PubMed: 18832344]
- Sowell ER, Mattson SN, Kan E, Thompson PM, Riley EP, Toga AW. Abnormal cortical thickness and brain-behavior correlation patterns in individuals with heavy prenatal alcohol exposure. *Cereb Cortex.* 2008; 18:136–144. [PubMed: 17443018]
- Spielberger, C. Manual for the state-trait anxiety inventory. Consulting Psychologists Press, Inc.; Palo Alto, CA: 1983.
- Steyerberg EW, Eijkemans MJ, Harrell FE Jr, Habbema JD. Prognostic modelling with logistic regression analysis: A comparison of selection and estimation methods in small data sets. *Stat Med.* 2000; 19:1059–1079. [PubMed: 10790680]
- Thompson BL, Levitt P, Stanwood GD. Prenatal exposure to drugs: Effects on brain development and implications for policy and education. *Nat Rev Neurosci.* 2009; 10:303–312. [PubMed: 19277053]
- Toepper M, Markowitsch HJ, Gebhardt H, Beblo T, Thomas C, Gallhofer B, Driessen M, Sammer G. Hippocampal involvement in working memory encoding of changing locations: An fMRI study. *Brain Res.* 2011; 1354:91–99. [PubMed: 20678490]
- Van den Bergh BR. The influence of maternal emotions during pregnancy on fetal and neonatal behavior. *Pre Peri Nat Psychol J.* 1990; 5:119–130.
- Van den Bergh BR, Marcoen A. High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and 9-year-olds. *Child Dev.* 2004; 75:1085–1097. [PubMed: 15260866]
- van den Bergh BR, Mennes M, Stevens V, van der Meere J, Borger N, Stiers P, Marcoen A, Lagae L. ADHD deficit as measured in adolescent boys with a continuous performance task is related to antenatal maternal anxiety. *Pediatr Res.* 2006; 59:78–82. [PubMed: 16327007]
- Van den Hove DL, Steinbusch HW, Scheepens A, Van de Berg WD, Kooiman LA, Boosten BJ, Prickaerts J, Blanco CE. Prenatal stress and neonatal rat brain development. *Neuroscience.* 2006; 137:145–155. [PubMed: 16242847]
- Wadhwa PD, Entringer S, Buss C, Lu MC. The contribution of maternal stress to preterm birth: Issues and considerations. *Clin Perinatol.* 2011; 38:351–384. [PubMed: 21890014]
- Wadhwa PD, Sandman CA, Porto M, Dunkel-Schetter C, Garite TJ. The association between prenatal stress and infant birth weight and gestational age at birth: A prospective investigation. *Am J Obstet Gynecol.* 1993; 169:858–865. [PubMed: 8238139]
- Watson JB, Mednick SA, Huttunen M, Wang X. Prenatal teratogens and the development of adult mental illness. *Dev Psychopathol.* 1999; 11:457–466. [PubMed: 10532619]
- Weinberg J, Sliwowska JH, Lan N, Hellemans KG. Prenatal alcohol exposure: Foetal programming, the hypothalamic-pituitary-adrenal axis and sex differences in outcome. *J Neuroendocrinol.* 2008; 20:470–488. [PubMed: 18266938]

- Weinstock M. Gender differences in the effects of prenatal stress on brain development and behaviour. *Neurochem Res.* 2007; 32:1730–1740. [PubMed: 17406975]
- Wynne O, Horvat JC, Osei-Kumah A, Smith R, Hansbro PM, Clifton VL, Hodgson DM. Early life infection alters adult BALB/c hippocampal gene expression in a sex specific manner. *Stress.* 2011; 14:247–261. [PubMed: 21294648]
- Zohar I, Weinstock M. Differential effect of prenatal stress on the expression of corticotropin releasing hormone and its receptors in the hypothalamus and amygdala in male and female rats. *J Neuroendocrinol.* 2011; 23:320–328. [PubMed: 21306450]

Figure 1.

High mean maternal pregnancy-specific anxiety measured up to five times over the course of gestation was associated with lower inhibitory control measured with the Flanker task in girls (A, $N = 49$; $p < 0.05$) but not in boys (B, $N = 39$). The presented log-transformed measure of performance reflects interference control with higher scores indicating lower performance.

Figure 2.

High mean maternal pregnancy-specific anxiety measured up to five times over the course of gestation was associated with lower visuospatial working memory performance in boys and girls ($N = 87$; $p < 0.001$). The outcome measure is the longest sequence the child was able to memorize.

Figure 3.

In girls, high pregnancy-specific anxiety at 15, 19, and 25 but not at 31 and 37 weeks gestation was associated with lower performance on the Flanker task (A, $N = 49$; $p < 0.01$). No significant association between pregnancy-specific anxiety and performance on this task was observed in boys (B, $N = 39$). For visualization purposes, pregnancy-specific anxiety slopes predicted by the HLM model are presented based on Flanker test scores $1\text{ SD} \pm \text{mean}$.

Figure 4.

High maternal pregnancy-specific anxiety at all time points in gestation was associated with lower performance on the sequential memory task in boys and girls ($N = 88$; $p = 0.05$ – 0.001). For visualization purposes, pregnancy-specific anxiety slopes predicted by the HLM model are presented based on test scores $1\text{ SD} \pm \text{mean}$.

Table I

Sociodemographic characteristics and birth outcomes.

	Mother-child dyads (mean $\pm$ SD, <i>N</i> = 89 unless stated otherwise)
Maternal age (yrs)	31.6 $\pm$ 5.6
Race/ethnicity	
Non-Hispanic White	55.2%
Hispanic White	21.8%
African American	6.9%
Asian	13.8%
Other	2.3%
Annual household income	
US \$0 to \$30,000	10.4%
\$30,001 to \$60,000	21.8%
\$60,001 to \$100,000	37.9%
Over \$100,000	29.9%
Pregnancy-specific anxiety	
15 weeks gestation	19.8 $\pm$ 5.4 (<i>N</i> = 89)
19 weeks gestation	19.4 $\pm$ 5.4 (<i>N</i> = 88)
25 weeks gestation	18.2 $\pm$ 4.8 (<i>N</i> = 79)
31 weeks gestation	18.0 $\pm$ 4.3 (<i>N</i> = 86)
37 weeks gestation	17.9 $\pm$ 4.6 (<i>N</i> = 74)
Average across pregnancy	18.7 $\pm$ 4.1 (<i>N</i> = 89)
Prenatal state anxiety (STAI)	
15 weeks gestation	22.8 $\pm$ 2.9 (<i>N</i> = 88)
19 weeks gestation	22.8 $\pm$ 3.1 (<i>N</i> = 88)
25 weeks gestation	19.7 $\pm$ 6.2 (<i>N</i> = 78)
31 weeks gestation	21.9 $\pm$ 2.8 (<i>N</i> = 88)
37 weeks gestation	19.6 $\pm$ 6.4 (<i>N</i> = 72)
Average across pregnancy	21.5 $\pm$ 3.0 (<i>N</i> = 89)
Prenatal depression (CESD)	
19 weeks gestation	15.5 $\pm$ 5.3 (<i>N</i> = 88)
25 weeks gestation	15.6 $\pm$ 4.3 (<i>N</i> = 79)
31 weeks gestation	15.8 $\pm$ 4.8 (<i>N</i> = 88)
37 weeks gestation	16.4 $\pm$ 4.6 (<i>N</i> = 72)
Average across pregnancy	15.7 $\pm$ 4.0 (<i>N</i> = 89)
Maternal postpartum depression (CESD)	14.1 $\pm$ 4.6 (<i>N</i> = 71)
Maternal concurrent depression (BDI)	5.8 $\pm$ 6.2 (<i>N</i> = 89)
Primiparous	52%
Child sex	
Male	56.2%
Female	43.8%

	Mother-child dyads (mean $\pm$ SD, $N = 89$ unless stated otherwise)
Length of gestation (weeks)	39.2 $\pm$ 1.6 (11% 34-36.9 weeks)
Birth weight (grams)	3494.4 $\pm$ 484.6 (3.4% ,2500g)

Table II

Performance on the Flanker and sequential memory tasks by child sex.

	Males (mean $\pm$ SD, $N = 39$)	Females (mean $\pm$ SD, $N = 49$)
Flanker	$N = 39$	$N = 49$
Congruent trials		
Reaction time (ms)	720 $\pm$ 166	778 $\pm$ 253
# Correct (max. 24)	22.2 $\pm$ 1.5	22.4 $\pm$ 2.5
# Missed	0.2 $\pm$ 0.6	0.3 $\pm$ 1.0
# False alarms	1.6 $\pm$ 1.4	1.3 $\pm$ 2.12
Performance efficiency (RT/#correct)		
Raw scores	32.7 $\pm$ 8.5	35.6 $\pm$ 13.9
Log-transformed scores ^A	3.49 $\pm$ 0.26	3.54 $\pm$ 0.34
Incongruent trials		
Reaction time (ms)	821 $\pm$ 246	897 $\pm$ 340
# Correct (max. 24)	21.5 $\pm$ 2.2	21.5 $\pm$ 2.6
# Missed	0.2 $\pm$ 0.5	0.4 $\pm$ 0.9
# False alarms	2.4 $\pm$ 2.0	2.1 $\pm$ 2.3
Performance efficiency (RT/#correct)		
Raw scores	38.6 $\pm$ 12.2	43.12 $\pm$ 20.6
Log-transformed scores ^B	3.63 $\pm$ 0.31	3.70 $\pm$ 0.40
Interference control (B-A) [*]	0.15 $\pm$ 0.14	0.16 $\pm$ 0.15
Sequential memory	$N = 39$	$N = 48$
Longest sequence (max. 6) [*]	4.41 $\pm$ 0.88	4.21 $\pm$ 1.11

^{*} Performance measure used in all statistical analyses.