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

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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).

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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 \pm 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 \pm 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 (Toepper 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.

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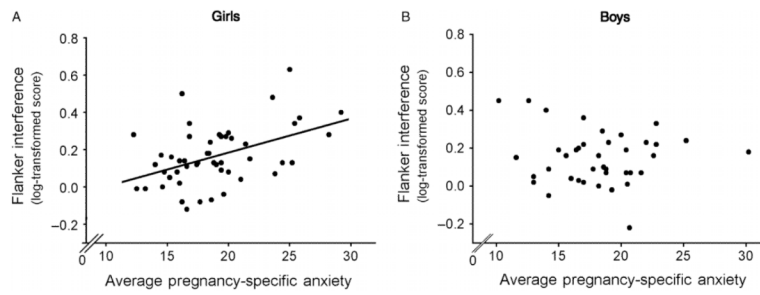


Figure 1.

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.

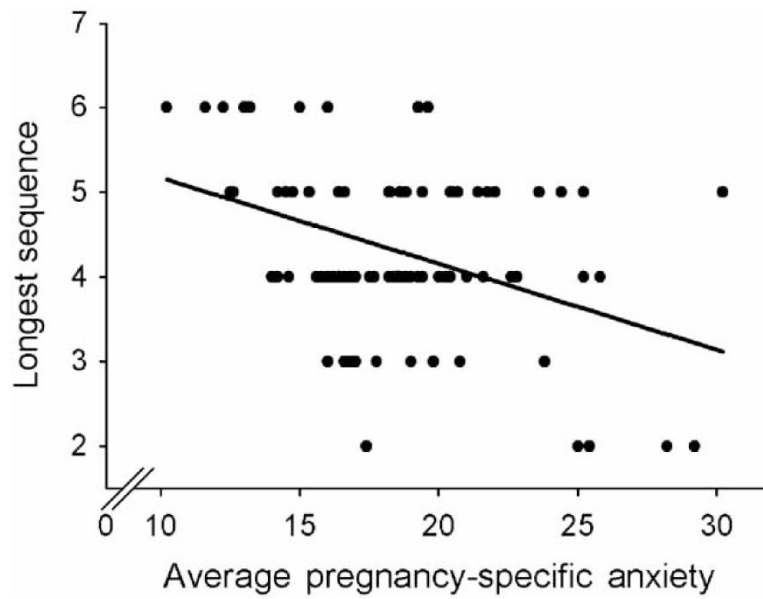


Figure 2. High mean maternal pregnancy-specific anxiety measured up to five times over the course of gestation was associated with lower visuospatial working memory performance in boys and girls ($N = 87$; $p < 0.001$). The outcome measure is the longest sequence the child was able to memorize.

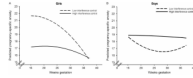


Figure 3.

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 $1 \text{ SD} \pm \text{mean}$.

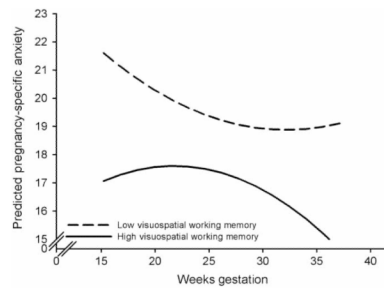


Figure 4.

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

* Performance measure used in all statistical analyses.